Clinical Study Protocol

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age

Study Number TV48125-CNS-30083

NCT04458857

Protocol with Amendment 09 Approval Date: 24 September 2023

Clinical Study Protocol with Amendment 09

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Randomized, Double-Blind, Placebo-Controlled Study of Fremanezumab in Patients (6 to 17 Years) with Episodic Migraine

A Study to Test if Fremanezumab is Effective in Preventing Episodic Migraine in Patients 6 to 17 Years of Age

Efficacy, Safety, and Tolerability Study (Phase 3)

IND number: 106,533

NDA number: Not Applicable

BLA number: 761089

EudraCT number: 2019-002055-42

EMA Decision number of Pediatric Investigation Plan: P/0378/2023

Article 46 of Regulation (EC) No 1901/2006 applies

Protocol Approval Date: 28 March 2019

Protocol with Amendment 01 Approval Date: 21 June 2019

Protocol with Amendment 02 Approval Date: 05 December 2019

Protocol with Amendment 03 Approval Date: 03 February 2020

Protocol with Amendment 04 Approval Date: 20 April 2020

Protocol with Amendment 05 Approval Date: 27 June 2020

Protocol with Amendment 06 Approval Date: 27 July 2020

Protocol with Amendment 07 Approval Date: 20 August 2020

Protocol with Amendment 08 Approval Date: 09 December 2021

Protocol with Amendment 09 Version Date: 24 September 2023

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 and Regulations (as applicable in the

region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

Confidentiality Statement

This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, Inc. and/or its affiliates. The recipient agrees that no information contained herein may be published or disclosed without written approval from the sponsor.

AMENDMENT HISTORY

The protocol for Study TV48125-CNS-30083 (original protocol dated 28 March 2019) has been amended and reissued as follows:

Amendment 09	24 September 2023 217 patients randomized to date
Administrative Letter 06	21 December 2021
Amendment 08	09 December 2021 51 patients randomized/enrolled to date
Administrative Letter 05	10 May 2021
Administrative Letter 04	04 February 2021
Administrative Letter 03	05 November 2020
Amendment 07	20 August 2020 0 patients randomized/enrolled to date The management of study activities during the COVID-19 pandemic are detailed in Appendix O. The following sections are affected: Section 3.1 General Study Design and Study Schematic Section 3.5 Schedule of Study Procedures and Assessments Section 4.4 Replacement of Patients Section 9.5 Efficacy Analysis Table 1 Study Procedures and Assessments Appendix E. Quality Control and Quality Assurance Appendix F. Ethics
Amendment 06	27 July 2020 0 patients randomized/enrolled to date
Administrative Letter 02	07 July 2020
Amendment 05	27 June 2020 0 patients randomized/enrolled to date
Amendment 04	20 April 2020 0 patients randomized/enrolled to date
Administrative Letter 01	10 March 2020

Amendment 03	03 February 2020 0 patients randomized/enrolled to date
Amendment 02	05 December 2019 0 patients randomized/enrolled to date
Amendment 01	21 June 2019 0 patients randomized/enrolled to date

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 28 March 2019

Clinical Study Protocol with Amendment 09

IND number: 106,533; NDA number: Not Applicable; BLA number: 761089; EudraCT number: 2019-002055-42

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A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 09 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, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local GCP regulations as well as all other national and international laws and regulations.

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

Executed signature pages are maintained within the Investigator Site File and Trial Master File.

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]		

Executed signature pages are maintained within the Trial Master File.

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 28 March 2019
Clinical Study Protocol with Amendment 09

IND number: 106,533; NDA number: Not Applicable; BLA number: 761089;
EudraCT number: 2019-002055-42

EMA Decision number of Pediatric Investigation Plan: P/0378/2023

Article 46 of Regulation (EC) No 1901/2006 applies

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age

I have read the protocol with Amendment 09 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 and local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel 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 patient information, IMPs shipment and return forms, and other information collected during the study, in accordance with my responsibilities under the function of the coordinating investigator and in accordance with national and local GCP regulations as well as all other national and international laws and regulations. In addition, I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator [redacted]

[redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

[redacted]

[redacted]

Tel: [redacted]

Coordinating Investigator	Signature	Date
[redacted]		

Executed signature pages are maintained within the Investigator Site File and Trial Master File.

CLINICAL STUDY PROTOCOL SYNOPSIS

with Amendment 09

Study Number: TV48125-CNS-30083

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age

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

Investigational New Drug (IND) Number: 106,533

New Drug Application (NDA) Number: Not Applicable (NA)

Biological License Application (BLA) Number: 761089

EudraCT Number: 2019-002055-42

EMA Decision number of Pediatric Investigation Plan: P/0378/2023

Article 46 of Regulation (EC) No 1901/2006 applies.

Name of Test Investigational Medicinal Product (IMP): Fremanezumab

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

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

Indication: Preventive treatment of migraine in pediatric patients (6 to 17 years of age)

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

Number of Investigational Centers Planned: Approximately 85

Countries Planned: 6 to 10 countries

Planned Study Period: Quarter (Q)1 2020 to Q2 2024

Number of Patients Planned (total): Approximately 230 randomized episodic migraine (EM) patients.

Study Population: Female and male patients aged 6 to 17 years (inclusive) with a diagnosis of migraine for at least 6 months before screening, consistent with the International Classification of Headache Disorders, 3rd revision (ICHD-3) criteria (Headache Classification Committee of the IHS 2013), and a history of ≤14 migraine days per month in each of the 3 months prior to screening, prospectively confirmed by review of headache data recorded daily in an electronic headache diary device during a 28-day baseline period.

Because headache consortium guidelines recommend preventive therapies for patients with EM occurring on 4 or more days per month due to the frequency of headaches and high degree of disability, approximately 30% of EM patients using no more than 2 migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication if the medication has at least moderate evidence of efficacy for migraine (Silberstein et al 2012). Patients on concomitant preventive medications must have been on a stable, well-tolerated dose for at least 2 months prior to screening (visit 1), without anticipated changes during the study. A list of migraine preventive medications allowed for any condition for the duration of the study is presented in Appendix C. Randomization will be stratified by patients with and without preventive medications.

Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
The **primary objective** of the study is to evaluate the efficacy of fremanezumab as compared to placebo for the preventive treatment of episodic migraine (EM).	The **primary efficacy endpoint** is the mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of study drug.
A **secondary objective** is to evaluate the safety and tolerability of fremanezumab in the preventive treatment of EM.	The **safety and tolerability endpoints** are as follows: • occurrence of adverse events throughout the study, including local injection site reaction/pain • abnormal standard 12-lead electrocardiogram (ECG) findings • changes from baseline in vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate), height, and weight measurements • changes from baseline in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results • abnormal physical examination findings • suicidal ideation and behavior as suggested by the Columbia-Suicide Severity Rating Scale (C-SSRS)
A **secondary objective** of the study is to further demonstrate the efficacy of fremanezumab as compared to placebo for the preventive treatment of EM.	The **secondary efficacy endpoints** are as follows: • mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug • proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of study drug • mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug • mean change from baseline (day 1) in migraine-related disability score, as measured by the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire, at 12 weeks after administration of the first dose of study drug • mean change from baseline (day 1) in quality of life, as measured by the Pediatric Quality of Life Inventory

Objectives	Endpoints
	(PedsQL), at 12 weeks after administration of the first dose of study drug
A **secondary objective** of the study is to evaluate the immunogenicity of fremanezumab and the impact of antidrug antibodies (ADAs) on clinical outcomes in patients exposed to fremanezumab.	• proportion of patients developing ADAs throughout the study. The impact of ADAs on safety and efficacy will be analyzed if the number of ADA-positive patients allows.

Exploratory Objective and Endpoints

[redacted]

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

General Study Design: This is a 4-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of 2 different doses (dependent on patients' body weight) of subcutaneous (sc) fremanezumab and placebo. Enrollment will include male and female patients (6 to 17 years of age, inclusive).

An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (standard deviation [SD]) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients have completed at least 3 months of treatment or have withdrawn from the study early.

Patients will be randomly assigned in a 1:1 ratio between fremanezumab and placebo treatment groups:

- monthly sc administration of fremanezumab
- monthly sc administration of matching placebo

The dose of fremanezumab to be administered will be determined by the patient's weight at randomization (visit 2):

- Patients weighing ≥45.0 kg will receive monthly sc administration of fremanezumab at 225 mg.
- Patients weighing <45.0 kg will receive monthly sc administration of fremanezumab at 120 mg.

The enrollment target is approximately 230 EM patients, with a goal of approximately 20% of those patients in the 6- through 11-year-old age group.

The study consists of a screening visit, a 28-day baseline period, and a 12-week (84-day) treatment period, including a final evaluation at week 12 (end-of-treatment [EOT] visit, approximately 4 weeks [28 days] after the final dose of study drug).

Blinded treatment will be administered sc once monthly (approximately every 28 days) for a total of 3 doses. Randomization and first treatment administration will occur at visit 2 (day 1), and additional doses will be administered at visits 3 and 4 (approximately every 28 days) until the third dose is completed. Final study assessments will be performed at visit 5 (EOT visit), approximately 28 days after the third (last) dose of study drug. Overall, patients will participate in the current study for up to 4 months (including a 28-day baseline period and a 12-week, double-blind treatment period).

Approximately 30% of EM patients will be allowed to remain on no more than 2 migraine preventive medications for any condition, provided the medication is recognized to have at least moderate evidence of efficacy or is commonly used. Additional details on concomitant medication information are provided in Appendix C. Patients must have been on a stable, well-tolerated dose of this preventive medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining approximately 70% of EM patients, these medications are not allowed for migraine or for any other indications. As-needed (PRN) use of these medications are allowed during the course of the study. PRN use of these medications should be reported in the electronic case report form as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the prescribing information or local treatment guidelines.

Patients will be allowed to use acute medications to treat acute migraine attacks, as needed, with the exception of medications containing opioids and barbiturates.

Upon completion of the final study assessments, all eligible patients will be offered enrollment in a long-term safety and tolerability study (Study TV48125-CNS-30084), consisting of 9 months (36 weeks) of open-label treatment and 5 months of follow-up commencing from the last study drug administration. In the long-term safety extension study, patients rolling over from the current study will be weighed at visit 2 and will receive monthly fremanezumab with dose adjusted per weight category (225 mg in patients ≥45.0 kg or 120 mg in patients <45.0 kg). Patients who do not complete this study and patients who complete this study but do not wish to continue treatment may enroll in Study TV48125-CNS-30084 for the purpose of attending a follow-up visit for safety and ADA assessments approximately 5 months (150 days [5 half-lives]) after receiving the last dose of study drug.

Study procedures and assessments with their time points are shown in Table 1. The study schematic diagram is shown in Figure 1.

In the case that a patient is not able to go to the investigational center or the investigational center staff are not able to see patients at the investigational center, certain assessments/procedures, as detailed in Table 1, may be performed remotely.

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

Method of Randomization and Blinding: 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 into single-visit kits according to Good Manufacturing Practice procedures. The active drug and placebo kits for each dose will be identical in appearance and will contain 1 pre-filled syringe (PFS) (for the 225 mg dose and its matching placebo) or 2 vials (for the 120 mg dose and its matching placebo). Adequate kit supply for upcoming study visits will be managed by interactive response technology (IRT) and kept (refrigerated at 2°C to 8°C) on site.

This is a randomized study. Randomization will be stratified by country, sex, puberty status (Tanner staging scale, see Section 7.5), and preventive medication use at baseline (Yes/No). Each patient will undergo randomization in a 1:1 ratio within the stratum to which he or she belongs to receive fremanezumab or placebo, as assigned by the IRT. The IRT will manage

initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At the time of each study visit, the IRT will be queried, and site personnel will retrieve and administer a 1.5 mL volume for patients weighing ≥45.0 kg at randomization (visit 2) or a 0.8 mL volume for patients weighing <45.0 kg at randomization (visit 2) from each PFS or 2 vials contained in the appropriately numbered kit(s).

Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate: Pre-filled syringes or single-use vials (active or placebo) will be contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Active PFS/vials will contain 150 mg/mL of fremanezumab, and placebo PFS/vials will contain the same vehicle and excipients as those for active injections. Each kit will contain 1 PFS (1.5 mL) or 2 single-use vials (2 mL vials each containing 0.5 mL).

Study drug will be administered by qualified study personnel as sc injections approximately every 4 weeks (28 days) for a total of 3 doses, as follows:

- Patients with body weight ≥45.0 kg at randomization (visit 2) who are randomized to receive fremanezumab will receive 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) at visits 2, 3, and 4.
- Patients with body weight ≥45.0 kg at randomization (visit 2) who are randomized to receive placebo will receive a single 1.5 mL placebo injection at visits 2, 3, and 4.
- Patients with body weight <45.0 kg at randomization (visit 2) who are randomized to receive fremanezumab will receive 120 mg of fremanezumab as 1 active injection (120 mg/0.8 mL) at visits 2, 3, and 4.
- Patients with body weight <45.0 kg at randomization (visit 2) who are randomized to receive placebo will receive a single 0.8 mL placebo injection at visits 2, 3, and 4.

Fremanezumab is approved for the preventive treatment of migraine in adults. The recommended sc injection sites follow the National Institutes of Health (NIH) Clinical Center Patient Education Materials (NIH Clinical Center Patient Education Materials 2016). The suggested injection site locations for sc administration are the following: back of upper arms, lower abdomen/belly/waistline, and front of thighs. The sc injection and location will be recorded for each administration visit (visits 2, 3, and 4).

A 1.5 mL volume (patients weighing ≥45.0 kg at randomization [visit 2]) or 0.8 mL (patients weighing <45.0 kg at randomization [visit 2]) from each visit kit(s) (the full dose given with a PFS or taken from the vials) must be injected sc for administration to be considered complete. Patients randomized to the placebo group will receive volume-matched doses of placebo.

See the table below for a description of the test investigational medicinal product (IMP) and placebo.

IMP name	Test IMP	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	Fremanezumab	None
Formulation	Sterile, clear to opalescent, colorless to slightly yellow solution for injection	Sterile, clear to opalescent, colorless to slightly yellow solution for injection
Unit dose strength(s)/dosage level(s)	225 mg monthly in patients with body weight ≥45.0 kg at randomization (visit 2) 120 mg monthly dose in patients with body weight <45.0 kg at randomization (visit 2)	Not applicable
Route of administration	Subcutaneous injection	Subcutaneous injection
Dosing instructions	Patients with body weight ≥45.0 kg at randomization (visit 2): fremanezumab 225 mg: 1 active injection (225 mg/1.5 mL) at visits 2, 3, and 4 Patients with body weight <45.0 kg at randomization (visit 2): fremanezumab 120 mg: 1 active injection (120 mg/0.8 mL) at visits 2, 3, and 4	Patients with body weight ≥45.0 kg at randomization (visit 2): Placebo: single 1.5-mL injection at visits 2, 3, and 4 Patients with body weight <45.0 kg at randomization (visit 2): Placebo: single 0.8-mL injection at visits 2, 3, and 4.
Packaging	IMP will be provided as follows: • 225 mg dose: PFS for single-use administration • 120 mg dose: taken from two 2-mL vials each containing 0.5 mL of IMP for single use administration	Placebo will be provided as follows: • 1.5-mL injection: PFS for single-use administration • 0.8-mL injection: taken from two 2-mL vials each containing 0.5 mL of placebo for single-use administration
Manufacturer	[redacted]	[redacted]

IMP=investigational medicinal product; INN=international nonproprietary name; PFS=pre-filled syringe.

Test IMP: Fremanezumab

Placebo IMP: Same vehicle and excipients as those for fremanezumab active injection

Reference IMP: NA

Duration of Patient Participation and Maximal Exposure to IMP: Patient participation will last for up to 4 months (including a 28-day baseline period and a 12-week, double-blind treatment period), after which all eligible patients will be offered enrollment in an open-label, long-term safety and tolerability study. Patients who do not complete this study and patients who complete this study but do not wish to continue treatment may enroll in Study TV48125-CNS-30084 for the purpose of attending a follow-up visit for safety and ADA assessments approximately 5 months (150 days [5 half-lives]) after receiving the last dose of study drug.

Study Duration: 51 months, from Q1 2020 to Q2 2024

End of Study: End of study is defined as the date the last patient attends the EOT/early withdrawal visit (visit 5).

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: All eligible patients completing the study will be offered enrollment in the long-term extension Study TV48125-CNS-30084, unless it is decided to stop the treatment.

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

a. The patient is a male or female between the ages of 6 to 17 years (inclusive) on the day of randomization to study drug/IMP.

b. The patient's parent(s) or legal guardian(s) must give written informed consent, and the patient must give assent (in accordance with local regulations).

   Note: In some countries, patients aged 15 to 17 years (inclusive) may give written informed consent; however, the patient's parent(s) or legal guardian(s) must be informed, per local regulations.

c. The patient has a clinical history of recurrent headache consistent with the diagnosis of migraine for at least 6 months before screening, consistent with ICHD-3 criteria (Headache Classification Committee of the IHS 2013), and a history of ≤14 headache days per month in each of the 3 months prior to screening (visit 1).

d. The patient or parent/caregiver has maintained a prospectively collected headache diary during a 28-day baseline period in which at least 4 migraine days and ≤14 headache days were recorded. Migraine days have at least 1 of the following migraine characteristics:

   – head pain of moderate to severe intensity lasting for 2 or more hours in duration and accompanied by either throbbing quality, predominantly unilateral location, or aggravation with normal activities.

   – headache is accompanied by a migraine-associated symptom, such as photophobia, phonophobia, abdominal pain, nausea, or vomiting.

   – headache is preceded by an aura, as described by ICHD-3 criteria.

   – headache was treated by a nonsteroidal anti-inflammatory drug (NSAID), paracetamol, triptan, or ergot preparation.

e. The patient does not have chronic daily headache. For the purposes of this study, chronic daily headache is operationally defined as <4 headache-free days during the 28-day baseline period.

f. [Revision 01] Not using preventive migraine medications (listed in Appendix C) or using no more than 2 preventive migraine medications (listed in Appendix C) for migraine or other medical conditions, as long as the dose and regimen have been stable for at least 2 months prior to screening (visit 1). A list of migraine preventive medications allowed for any condition for the duration of the study for approximately 30% of patients is presented in Appendix C.

   Note: A person is considered to be not using migraine preventive medications (listed in Appendix C) when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinium toxin A or B prior to screening (visit 1). The use of other agents that are not included in Appendix C but used for migraine prevention is permitted during the study; however, these patients will not be counted toward the approximately 30% patient limit threshold.

g. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at baseline or are sterile. Definitions of females of childbearing potential and females who are not of childbearing potential are given in Appendix G.

h. Females who are postmenarchal or ≥12 years of age and sexually active must use highly effective birth control methods with their male partners for the duration of the study (ie, starting at screening) and for 6 months after the last dose of IMP. Males who are sexually active with female partners must use a condom for the duration of the study and for 6 months after the last administration of IMP. Further details are included in Appendix G.

i. The patient/caregiver has demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 21 out of 28 days (approximately 75% diary compliance).

j. The patient is in good health, as determined by a medical and psychiatric history, medical examination, 12-lead ECG, serum chemistry, hematology, coagulation, urinalysis, and serology.

k. The patient/caregiver must be willing and able to comply with study requirements and return to the clinic as required for the duration of the study.

l. The patient weighs at least 17.0 kg on the day of randomization to study drug/IMP.

m. The patient has a body mass index ranging from the 5th to 120% of the 95th percentile, inclusive, at screening based on the local standard.

n. The patient has received all recommended age-appropriate vaccines according to local standard of care and schedule prior to screening.

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

a. The patient is using medications containing opioids (including codeine) or barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) for the treatment of migraine during the 3 months prior to the day of the screening visit.

b. The patient has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine or in the head or neck area for any condition during the 2 months prior to the day of the screening visit.

c. The patient has any clinically significant cardiovascular (including congenital cardiac anomalies or thromboembolic events), endocrine, gastrointestinal, genitourinary, hematologic, hepatic, immunologic, neurologic, ophthalmic, pulmonary, renal disease, or complications of an infection, at the discretion of the investigator.

d. [Revision 01] The patient has a current history of a clinically significant psychiatric condition, at the discretion of the investigator. Any prior history of a suicide attempt, or a history of suicidal ideation with a specific plan within the past 2 years, must be excluded

e. The patient has an ongoing infection or a known history of human immunodeficiency virus infection, tuberculosis, Lyme disease, chronic hepatitis B or C, or a known active infection of coronavirus disease 2019 (COVID-19).

f. The patient has a past or current history of cancer.

g. The patient is pregnant or nursing.

h. The patient has a history of hypersensitivity reactions to injected proteins, including monoclonal antibodies (mAbs), or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome, or the patient is concomitantly using lamotrigine.

i. The patient has participated in another study of an IMP (or a medical device) within the 30 days (or 90 days for biologics) or 5 half-lives previous to the day of the screening visit (whichever is longer), or is currently participating in another study of an IMP (or a medical device).

j. The patient has had exposure to a mAb targeting the calcitonin gene-related peptide (CGRP) pathway (erenumab, eptinezumab, galcanezumab, fremanezumab) during the 6 months previous to the day of the screening visit.

k. Previous participation in the Phase 1 pharmacokinetics study (Study TV48125-CNS-10141).

l. In the judgment of the investigator, the patient has an abnormal finding on the baseline 12-lead ECG considered clinically significant.

m. In the judgment of the investigator, the patient has a significantly abnormal finding during the 28-day baseline period, including hematology, blood chemistry, coagulation tests, or urinalysis values/findings (abnormal tests may be repeated for confirmation).

n. The patient has hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]) more than 1.5× the upper limit

of normal (ULN) during the 28-day baseline period, after confirmation in a repeat test, or suspected hepatocellular damage that fulfills the criteria for Hy's law.

o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <75 mL/min/1.73m^2, as calculated by the revised Schwartz formula (eGFR=[0.413×Ht]/serum creatinine), or evidence of renal disease during the 28-day baseline period.

p. The patient has any history of alcohol or drug abuse. The definition of alcohol or drug abuse, including marijuana, is based on the investigator's clinical judgment.

q. In the judgment of the investigator, the patient cannot fully participate in or successfully complete the study for its full duration for any of the following reasons:

- The patient is mentally or legally incapacitated or unable to give assent/consent for any reason.
- The patient is in custody due to an administrative or a legal decision or is in residential treatment.
- The patient/caregiver is unable to be contacted in case of emergency.
- The patient has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study.
- The patient is a relative of a study center or sponsor employee who is directly involved in the study.

r. Vulnerable patients (eg, people kept in detention) whose vulnerability is based on a condition other than the age required for study eligibility.

s. The patient received a live attenuated vaccine (eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine) within the 12-week period prior to screening.

Note: If a medical need arises during the study, the patient may receive a live attenuated vaccine.

t. The patient has a known hypersensitivity to the active substance or to any of the excipients of the study drug.

u. The patient has a current or past medical history of hemiplegic migraine.

Statistical Considerations

Sample Size Rationale: The sample size planned is approximately 220 patients (110 evaluable patients completing the study per treatment group). Assuming a treatment difference of 1.8 days (reduction in monthly average number of migraine days) and a common SD of 4.31, a sample size of 110 patients per treatment group gives at least 87% power for the study to succeed at an alpha level of 0.05. Assuming a 4% discontinuation rate, approximately 230 patients (115 patients per treatment group) will be randomized. Patients will be randomized to receive either monthly sc administration of fremanezumab or placebo.

Analysis Sets

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.

Safety Analysis Set: The safety analysis set will include all randomized 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.

Full Analysis Set: The full analysis set will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 10 days of diary entries postbaseline for efficacy assessments on the primary endpoint.

Per-Protocol Analysis Set: The per-protocol analysis set will consist of all patients in the Full Analysis Set who have completed the study without any important deviations such as, important inclusion/exclusion criteria deviations, important deviation or omissions of the IMP administration, or unexpected drug concentration findings, and who have at least 75% diary compliance after the start of treatment.

Analysis of Primary Endpoint: The primary efficacy endpoint, the mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of study drug, will be analyzed using an analysis of covariance method. The model will include treatment, sex, puberty status, region, baseline weight category (<45.0 kg or ≥45.0 kg), and preventive medication use at baseline (Yes/No) as fixed effects and baseline number of migraine days as a covariate. Ninety-five percent confidence intervals will be constructed for the least squares mean differences between the fremanezumab group and the placebo group. An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (SD) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients have completed at least 3 months of treatment or have withdrawn from the study early. For the purpose of this study, a migraine day will be defined as a calendar day where the patient reports either of the following:

- headache pain that lasts ≥2 hours and is accompanied by ≥1 migraine symptom(s)
- the patient used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration

The detailed algorithm for deriving migraine days will be described in the statistical analysis plan.

Analysis of Secondary Endpoints: The same analysis used for the primary efficacy endpoint will be performed for the continuous secondary efficacy endpoints. For the proportion of responders, defined as at least 50% reduction from baseline in the monthly average number of migraine days, a logistic regression model will be used with the following factors: treatment, sex, region, puberty status, baseline weight category (<45.0 kg or ≥45.0 kg), and preventive medication use at baseline (Yes/No). The odds ratio, 95% confidence interval for the odds ratio, and p-value for the treatment comparison will be presented.

Sensitivity Analysis: A sensitivity analysis for the primary efficacy endpoint will be conducted by using multiple imputation method for missing data. Sensitivity analysis using Mixed-Effect Model Repeated Measure method also will be conducted for change from baseline to months 1 through 3 in migraine days. The details will be described in the statistical analysis plan.

Multiple Comparisons and Multiplicity: A fixed-sequence (hierarchical) testing procedure will be implemented to control the Type 1 error rate at 0.05. The sequence of comparisons will start with the analysis of the primary endpoint and will follow with the secondary efficacy endpoints.

Analysis of Exploratory Endpoints: [redacted]

Safety Analyses: Safety analyses will be performed on the safety analysis set.

Safety assessments and time points are provided in Table 1.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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 (and/or PFS) (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, serious adverse device effects, protocol-defined adverse events of special interest, and adverse events and adverse device effects causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events, serious adverse device effects, adverse events, and adverse device effects 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.

Suicidal ideation and behavior will be measured using the C-SSRS. Data for patients with positive findings 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 study drug.

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 clinical study report.

Assessment of Local Tolerability and Pain and Tolerability Analysis: Assessment of injection site will be performed after administration of each dose of study drug, before the patient

leaves the investigational site. Injection site reactions will be recorded as adverse events according to the following severity assessment criteria:

- Assessment of injection site erythema, induration, and ecchymosis will be recorded after administration of each dose of study drug according to measurements: 5 to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe).
- Injection site pain will be recorded using the 11-point numerical rating scale and will be mapped to mild, moderate, or severe, according to patient's self-report of pain intensity.
- Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.

Pharmacokinetic Analysis: Pharmacokinetic plasma concentration results (fremanezumab) will be tabulated descriptively at each planned sampling time point by weight cutoff.

In addition, the most appropriate population pharmacokinetic model will be developed. This analysis will be reported separately, as appropriate.

Pharmacokinetic/Pharmacodynamic Analysis: The pharmacokinetic/pharmacodynamic relationship may be estimated by compartmental techniques. The pharmacokinetic parameters will be based on fremanezumab measurements. The pharmacodynamic measures will be the efficacy/safety responses.

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

Immunogenicity Analysis:

Summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. The impact of immunogenicity on the pharmacokinetic profile, drug efficacy, and clinical safety will be evaluated if data allows. This analysis will be reported separately.

Planned Interim Analysis:

An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (SD) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients have completed at least 3 months of treatment or have withdrawn from the study early.

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LIST OF ABBREVIATIONS

Abbreviation	Term
β-HCG	Beta-human chorionic gonadotropin
ADAs	antidrug antibodies
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
BLA	Biological License Application
BP	blood pressure
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CGRP	calcitonin gene-related peptide
CH	cluster headache
CM	chronic migraine
COVID-19	coronavirus disease 2019
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EM	episodic migraine
EMA	European Medicines Agency
EOT	end-of-treatment
EU	European Union
EudraCT	European Clinical Trials
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPSP	Global Patient Safety and Pharmacovigilance
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd revision

Abbreviation	Term
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgG2	immunoglobulin G2
IHS	International Headache Society
IMP	investigational medicinal product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous
LSO	local safety officer
mAb	monoclonal antibody
n	number
NDA	New Drug Application
NIH	National Institutes of Health
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
PedMIDAS	Pediatric Migraine Disability Assessment
PedsQL	Pediatric Quality of Life Inventory
PEF	peak expiratory flow
PFS	pre-filled syringe
PGI-I	Patient Global Impression of Improvement
PPTH	persistent posttraumatic headache
PRN	as-needed
RBC	red blood cell
RTSM	Randomization and Trial Supply Management
SAR	serious adverse reaction
sc	subcutaneous
SD	standard deviation
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US or USA	United States or United States of America

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

Fremanezumab is a humanized immunoglobulin G2 (IgG2) Δa/kappa monoclonal antibody (mAb) derived from a murine precursor. In September 2018, fremanezumab was approved in the United States of America (US) for the preventive treatment of migraine in adults and marketed under the trade name AJOVY®. Fremanezumab has also been approved in the European Union (EU) and a number of countries worldwide. Fremanezumab is a potent, selective calcitonin gene-related peptide (CGRP) binder and blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor. While the precise mechanism of action by which fremanezumab prevents migraine is unknown, it is believed that blocking CGRP prevents activation of the trigeminal system. Fremanezumab is highly specific for CGRP and does not bind to closely related family members (eg, amylin, calcitonin, intermedin, and adrenomedullin). Two mutations were introduced into the constant region of the fremanezumab heavy chain to limit antibody effector functions. This loss of function prevents fremanezumab from stimulating antibody-dependent cell-mediated cytotoxicity and triggering complement-mediated lysis; these activities can lead to unwanted consequences, such as cell lysis, opsonization, and cytokine release and inflammation (Armour et al 1999, Zeller et al 2008).

The safety and tolerability of fremanezumab (intravenous [iv] doses of 0.2 to 2000 mg and subcutaneous [sc] doses of 225 to 900 mg) as well as the pharmacokinetic profile of 225 to 900 mg sc and iv have been well characterized in the Phase 1 development program in adults.

Furthermore, the safety and effectiveness of fremanezumab have been demonstrated in 2 Phase 2b studies and 3 Phase 3 studies in adult patients with migraine. The 2 Phase 2b studies were a randomized, double-blind, placebo-controlled Phase 2b study of 2 sc dosing regimens of fremanezumab (monthly fremanezumab at 900 mg or fremanezumab at 675 mg followed by monthly fremanezumab at 225 mg) in patients with chronic migraine (CM) and a randomized, double-blind, placebo-controlled Phase 2b study of 2 sc dosing regimens of fremanezumab (monthly fremanezumab at 675 or 225 mg) in patients with episodic migraine (EM).

Two completed, randomized, double-blind, placebo-controlled Phase 3 studies (Studies TV48125-CNS-30049 in CM and TV48125-CNS-30050 in EM) and 1 completed, randomized, double-blind Phase 3 long-term safety study (Study TV48125-CNS-30051 in migraine [EM and CM]) were conducted to further evaluate the efficacy, safety, and tolerability of various dose regimens of fremanezumab in the preventive treatment of migraine. Additional studies within the migraine development program of fremanezumab include the completed Phase 3b study (Study TV48125-CNS-30068) in patients from the EU and US to evaluate the safety and efficacy of fremanezumab in migraine patients who have failed multiple preventive medications, 2 ongoing Phase 2b/3 studies in Japanese and Korean EM and CM patients (Studies 406-102-00002 and 406-102-00001, respectively), and 1 ongoing long-term safety study (Study 406-102-00003) in CM and EM to evaluate the safety and efficacy of fremanezumab. One Phase 4 study (Study TV48125-MH-40142) was conducted to evaluate the efficacy and safety of fremanezumab in adult patients with migraine and comorbid major depressive disorder.

The pediatric migraine development program includes a completed Phase 1, single-dose, open-label study with administration of single sc doses of 75 mg in pediatric migraine patients 6 to 11 years of age, inclusive (Study TV48125-CNS-10141).

Fremanezumab is further studied for the preventive treatment of persistent posttraumatic headache (PPTH) in 1 Phase 2 study (Study TV48125-CNS-20024) that is comparing the efficacy and safety of the sc dose regimen of fremanezumab versus placebo in patients with PPTH. Fremanezumab was being studied for the preventive treatment of cluster headache (CH) in 3 Phase 3 studies: Study TV48125-CNS-30056 in patients with episodic CH, Study TV48125-CNS-30057 in patients with chronic CH, and a long-term safety Study TV48125-CNS-30058 in CH. All 3 studies were terminated by Teva because a prespecified futility analysis showed that the primary endpoint of mean change from baseline in the monthly average number of CH attacks during the 12-week treatment period was unlikely to be met.

Migraine is a prevalent condition characterized by attacks of headache and associated symptoms (such as nausea, photophobia, or phonophobia). Among populations of children of all ages, migraine prevalence ranges from 8% to 11% (Abu-Arefeh and Russell 1994, Abu-Arafeh et al 2010, Laurell et al 2004, Ozge et al 2013, Stovner and Andree 2010). The prevalence of migraine is substantially lower among children younger than 7 years, ranging from 1% to 3% (Lewis 2009). The prevalence of migraine in children younger than 12 years is less than one-third of the prevalence among adolescents (Fendrich et al 2007, Ozge et al 2013, Stovner and Andree 2010, Unalp et al 2007). Therefore, the prevalence of migraine increases throughout childhood, with estimates for adolescents comparable to the 12% to 15% prevalence estimates cited for adult populations (Buse et al 2013, Burch et al 2015, Stovner and Andree 2010, Victor et al 2010).

Migraine has been classified by headache frequency in the International Classification of Headache Disorders, 3rd revision (ICHD-3) and is described as EM, which is defined as headaches occurring on less than 15 days per month, and CM, which is defined as headaches on at least 15 days per month for at least 3 months, with the features of migraine on at least 8 days per month (Headache Classification Committee of the IHS 2013, Lipton and Silberstein 2015).

Treatment options for migraine include non-pharmacological biobehavioral strategies and pharmacological strategies. Topiramate is the only migraine preventive medication approved for pediatric populations, but it is not approved in all regions of the EU and is limited to adolescents ages 12 through 17. Non-pharmacological strategies for adults and children with migraine include sleep hygiene, exercise, dietary modifications, biofeedback, and stress management (O'Brien et al 2012, Silberstein 2000). Pharmacologic agents used for the treatment of migraine can be classified as acute (ie, to alleviate the acute migraine attack) or prophylactic (ie, preventing headache recurrence). Preventive therapy is indicated for all individuals with CM and for those with EM that have high frequency of attacks (Lipton and Silberstein 2015). If given during CM, prophylactic treatments could revert the patients to EM and continue to provide benefit after remission is achieved (Manack et al 2011). Most specialists require that a child experience a minimum of 1 headache per week or 3 to 4 headaches per month to justify prophylactic medication. Children who report intensive and prolonged headaches (lasting more than 48 hours), even if infrequent, may also be offered prophylactic therapy (Kacperski 2015). It is recommended that an adequate trial of at least 6 to 8 weeks should be sustained before abandoning a treatment (Kacperski 2015).

Overall, authorized medications for the acute and prophylactic treatment of migraine in children and medications that are being used off-label in children have limited evidence to support their use, require ongoing patient monitoring, or are associated with undesirable or intolerable adverse effects (Barnes 2015, Kacperski 2015). Therefore, there is an unmet medical need for a safe and effective prophylactic treatment for EM and CM in the pediatric population.

The purpose of the study is to determine whether fremanezumab is safe and effective in the preventive treatment of migraine in pediatric patients with EM.

1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical 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

The safety of fremanezumab was established in repeat-dose toxicity studies in rats for the duration of 3 months and in chronic toxicity studies in cynomolgus monkeys for the duration of 6 months. Both the iv and sc routes were tested with dose administration once every week. Reproduction toxicity studies consisting of fertility and early embryonic development in rats, embryo-fetal development in rats and in rabbits, and pre- and postnatal development in rats were conducted. In support of the pediatric clinical program, juvenile toxicity studies in rats were conducted.

The pharmacokinetics of fremanezumab were consistent with a typical humanized IgG2 molecule with a low plasma clearance, low steady state volume of distribution, and a long elimination half-life in both rats and monkeys.

[redacted]

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. [redacted]

Safety pharmacology endpoints were also included in the general toxicology studies, in addition to the stand-alone safety pharmacology studies (cardiovascular in monkeys and respiratory and central nervous system in rats). [redacted]

In an embryo-fetal development study in rabbits, sc injection of dosing fremanezumab to pregnant rabbits was well tolerated and did not induce any maternal toxicity at any dose level. No evidence of embryo-fetal toxicity was noted in any dose group. In addition, in a combined fertility and embryo-fetal development study in rats, no treatment-related effects were noted on

estrus cycle, mating behavior, reproductive performance, or on embryo-fetal survival and development in any of the experimental animals' tested dose levels. Additionally, no treatment related findings were noted in a pre- and postnatal development study in rats.

[redacted]

Overall, no toxicological concerns were identified, and the program is considered supportive for repeated (monthly) administration of fremanezumab in pediatric subjects.

Further details may be found in the current IB.

1.2.2. Clinical Studies

Overall in the fremanezumab migraine clinical development program, 2853 patients with migraine and 474 healthy subjects have received at least 1 dose of fremanezumab in the completed clinical studies. In addition, 142 and 380 patients in the 3 CH Phase 3 blinded studies (TV48125-CNS-30056, TV48125-CNS-30057, and TV48125-CNS-30058) were treated with placebo and fremanezumab, respectively.

The adult migraine clinical development program is composed of 15 studies with healthy subjects and patients with migraine (EM and CM): 9 Phase 1 studies, 2 Phase 2b studies (double-blind, placebo-controlled), 3 Phase 3 studies (2 double-blind, placebo-controlled studies and 1 long-term, double-blind safety study [Study TV48125-CNS-30051], and 1 Phase 4 study). All studies have been completed.

[redacted]

Six studies in adult migraine patients (2 Phase 2b studies, 3 Phase 3 studies, and 1 Phase 4 study) examining the safety and efficacy of fremanezumab have been completed. The Phase 2b CM study (Study LBR-101-021) was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study comparing 3 sc monthly doses of fremanezumab

[redacted]

[redacted]

1.2.2.1. Clinical Pharmacology Studies

Two relevant clinical pharmacology studies have been completed: a Phase 1 bioequivalence study comparing the pharmacokinetics of 225 mg of fremanezumab administered sc using an autoinjector referenced to a PFS (TV48125-BE-10145) in healthy adult subjects, and a Phase 1, single-dose, open-label study with administration of single sc doses of [redacted] in pediatric migraine patients 6 to 11 years of age, inclusive (Study TV48125-CNS-10141).

1.2.2.2. Clinical Safety and Efficacy Studies

The safety and tolerability of fremanezumab have been studied in all of the studies in the adult migraine clinical development program (ie, 9 Phase 1 studies in healthy subjects, 2 Phase 2b studies, and 3 Phase 3 studies in patients with migraine. Additional studies are the Phase 3b FOCUS study [TV48125-CNS-30068], the Japanese [Otsuka] registration studies, and the Phase 4 UNITE study [TV48125-MH-40142]). Safety results from these studies are presented in the IB.

Based on the safety results of the completed studies, the safety profile was assessed to include the following events as identified risks qualifying as adverse drug reactions: injection site induration, injection site erythema, injection site pruritus, injection site rash, and injection site pain. None of the identified risks was serious or considered as an important risk.

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

1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s) and/or Device

1.3.1.1. Identified Risks

The identified risks of fremanezumab are the following:

- Injection site induration
- Injection site erythema
- Injection site pruritus
- Injection site rash

- Injection site pain

None of these risks impact the benefit-risk profile.

1.3.1.2. Important Potential Risk

Mild and moderate drug hypersensitivity events were observed infrequently and with similar incidence in placebo and fremanezumab in the clinical development program, but no anaphylaxis or severe hypersensitivity reactions were seen. However, it cannot be excluded that severe events may occur in the future. For additional details, refer to the IB.

Based on the available efficacy and safety data for fremanezumab, the benefit-risk profile is favorable.

1.3.2. Overall Benefit and Risk Assessment for This Study

Based on the current safety profile and the demonstrated efficacy of the sc fremanezumab dosage form as observed in adults, the overall risk and benefit assessment for this study is favorable.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

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

Objectives	Endpoints
The **primary objective** of the study is to evaluate the efficacy of fremanezumab as compared to placebo for the preventive treatment of episodic migraine (EM).	The **primary efficacy endpoint** is the mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of study drug.
A **secondary objective** is to evaluate the safety and tolerability of fremanezumab in the preventive treatment of EM.	The **secondary safety and tolerability endpoints** are as follows: • occurrence of adverse events throughout the study, including local injection site reaction/pain • abnormal standard 12-lead electrocardiogram (ECG) findings • changes from baseline in vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate), height, and weight measurements • changes from baseline in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results • abnormal physical examination findings • suicidal ideation and behavior as suggested by the Columbia-Suicide Severity Rating Scale (C-SSRS)
A **secondary objective** of the study is to further demonstrate the efficacy of fremanezumab as compared to placebo for the preventive treatment of EM.	The **secondary efficacy endpoints** are as follows: • mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug • proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of study drug • mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug • mean change from baseline (day 1) in migraine-related disability score, as measured by the

Objectives	Endpoints
	Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire, at 12 weeks after administration of the first dose of study drug • mean change from baseline (day 1) in quality of life, as measured by the Pediatric Quality of Life Inventory (PedsQL), at 12 weeks after administration of the first dose of study drug
A **secondary objective** of the study is to evaluate the immunogenicity of fremanezumab and the impact of antidrug antibodies (ADAs) on clinical outcomes in patients exposed to fremanezumab.	• proportion of patients developing ADAs throughout the study. The impact of ADAs on safety and efficacy will be analyzed if the number of ADA-positive patients allows.

2.1.1. Justification of Primary Endpoint

This design is consistent with the recommendations of the International Headache Society (IHS) for controlled trials of preventive drugs in migraine (Tfelt-Hansen et al 2012).

By definition, the IHS diagnostic criteria for EM include patients who suffer 6 to 14 headache days per month and/or treat the headache with an acute migraine-specific medication. Headache and migraine days are defined differently in the protocol. For the inclusion criteria, the minimal requirement for migraine days during a 28-day baseline period is 4. This requirement is consistent with migraine preventive treatment guidelines and also with the Teva adult EM study inclusion criteria.

As per the guidelines for controlled trials of preventive treatment of EM of the IHS, Teva considers that the most appropriate primary endpoint to capture is the change from baseline on the monthly average number of migraine days. Pain is a very subjective experience, and its perception changes among patients. Therefore, it is most important to capture the individual manifestation and perception of migraine in every patient examined. Patients will subjectively rate their headaches as mild, moderate, or severe and record this information using the electronic headache diary device. This endpoint (decrease from baseline on the monthly average number of migraine days) is a classical endpoint used in most prior studies of EM, and it is recommended by the IHS (Tfelt-Hansen et al 2012). This is the same primary endpoint used in the adult migraine clinical development program, which showed significant results. Consistent with past trials in EM and the recommendation of the IHS, migraine day or probable migraine day requires meeting the ICHD-3 criteria or days treated with acute migraine therapies (triptans or ergot compounds). Teva will follow these guidelines and recommendations.

2.2. Exploratory Objective and Endpoints

[redacted]

[redacted]

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a 4-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of 2 different doses (dependent on patients' body weight) of sc fremanezumab and placebo. Enrollment will include male and female patients (6 to 17 years of age, inclusive).

An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (standard deviation [SD]) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients have completed at least 3 months of treatment or have withdrawn from the study early. If the pooled SD is <4.8, there will be no change in enrollment; if the pooled SD is >5.2, the sample size will increase to approximately 400 patients; and if the pooled SD is between 4.8 and 5.2, the sample size will increase to approximately 340 patients total.

The total duration of the study is planned to be 51 months (from Q1 2020 to Q2 2024).

Patients will be randomly assigned in a 1:1 ratio between fremanezumab and placebo treatment groups:

- monthly sc administration of fremanezumab
- monthly sc administration of matching placebo

The dose of fremanezumab to be administered will be determined by the patient's weight at randomization (visit 2):

- Patients weighing ≥45.0 kg will receive monthly sc administration of fremanezumab at 225 mg.
- Patients weighing <45.0 kg will receive monthly sc administration of fremanezumab at 120 mg.

The enrollment target is approximately 230 EM patients, with a goal of approximately 20% of those patients in the 6- through 11-year-old age group.

The study consists of a screening visit, a 28-day baseline period, and a 12-week (84-day) treatment period, including a final evaluation at week 12 (end-of-treatment [EOT] visit, approximately 4 weeks [28 days] after the final dose of study drug).

Blinded treatment will be administered sc once monthly (approximately every 28 days) for a total of 3 doses. Randomization and first treatment administration will occur at visit 2 (day 1), and additional doses will be administered at visits 3 and 4 (approximately every 28 days) until the third dose is completed. Final study assessments will be performed at visit 5 (EOT visit), approximately 28 days after the third (last) dose of study drug. Overall, patients will participate in the current study for up to 4 months (including a 28-day baseline period and a 12-week, double-blind treatment period).

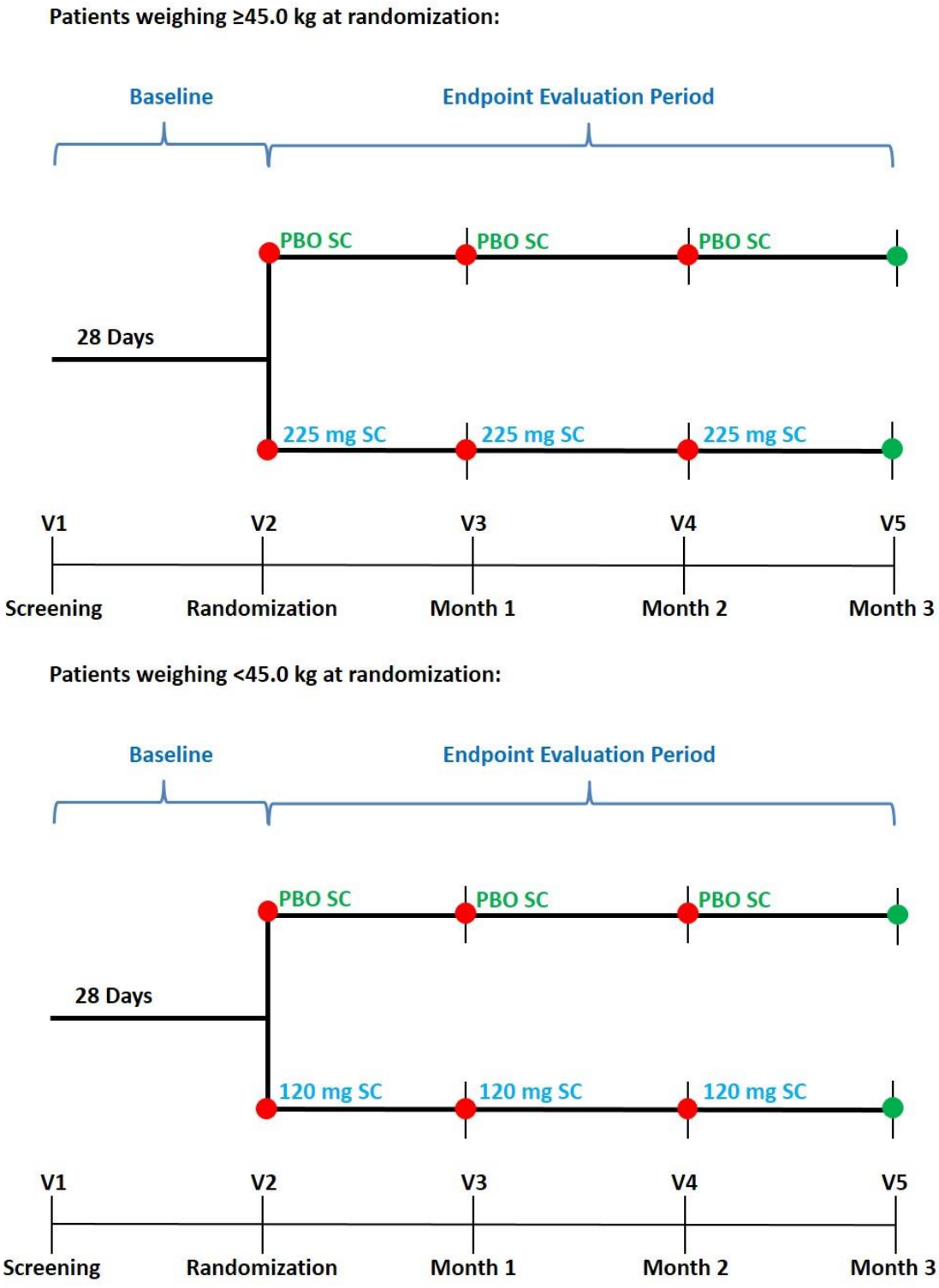
Patients will be allowed to use acute medications to treat acute migraine attacks, as needed, with the exception of medications containing opioids and barbiturates.

Upon completion of the final study assessments, all eligible patients will be offered enrollment in a long-term safety and tolerability study (Study TV48125-CNS-30084), consisting of 9 months (36 weeks) of open-label treatment and 5 months of follow-up commencing from the last study drug administration. In the long-term safety extension study, patients rolling over from the current study will be weighed at visit 2 and will receive monthly fremanezumab with dose adjusted every 3 months per weight category (225 mg in patients ≥45.0 kg or 120 mg in patients <45.0 kg). Patients who do not complete this study and patients who complete this study but do not wish to continue treatment may enroll in Study TV48125-CNS-30084 for the purpose of attending a follow-up visit for safety and ADA assessments approximately 5 months (150 days [5 half-lives]) after receiving the last dose of study drug.

Study procedures and assessments with their time points are shown in Table 1. The study schematic diagram is shown in Figure 1.

The end of study is defined as the date the last patient attends the EOT/early withdrawal visit (visit 5).

Figure 1: Overall Study Schematic Diagram



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

3.2. Planned Number of Patients and Countries

The number of evaluable patients is planned to be approximately 220 (110 evaluable patients completing the study per treatment group). Details on definition of evaluable patients and sample size are given in Section 9.

The total number of randomized patients planned is approximately 230.

The study is planned to be conducted in 6 to 10 countries in approximately 85 investigational centers. The study is expected to start in Q1 2020 and last until Q2 2024.

3.3. Justification for Study Design and Selection of Population

A multicenter, randomized, double-blind, placebo-controlled, parallel-group design is appropriate, given the objectives of this study. This design is consistent with the recommendations of the IHS for controlled trials of preventive drugs in migraine (Tfelt-Hansen et al 2012). Furthermore, this study is planned and designed in accordance with International Council for Harmonisation (ICH) E11 Guidance - Clinical Investigation of Medicinal Products in the Pediatric Population, 2017.

Migraine is a condition that starts from childhood or adolescence and progresses into adulthood. Among populations of children of all ages, migraine prevalence ranges from 8% to 11% (Abu-Arafeh et al 2010, Abu-Arefeh and Russell 1994, Laurell et al 2004, Ozge et al 2013, Stovner and Andree 2010). Additionally, there is an unmet need for the treatment of migraine in pediatric patients as there are limited therapy options available for this patient population. Throughout Teva's development program for adults, fremanezumab had demonstrated statistically and clinically significant superior efficacy over placebo. It is also well tolerated in the adult migraine population. Given the progression of the disease and the knowledge gained from the adult population, it is reasonable and important to evaluate fremanezumab in the pediatric population.

Because headache consortium guidelines recommend preventive therapies for patients with EM occurring on 4 or more days per month due to the frequency of headaches and high degree of disability, patients using no more than 2 migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication if the medication has at least moderate evidence of efficacy for migraine (Silberstein et al 2012). Patients on concomitant migraine preventive medications must be on a stable dose for at least 2 months prior to screening (visit 1), without anticipated changes during the study. A list of migraine preventive medications allowed for any condition for the duration of the study for approximately 30% of patients is presented in Appendix C. The total number of patients receiving concomitant migraine preventive medication during the study will be approximately 30% of the total number of patients randomized. Randomization will be stratified by patients with and without preventive medications.

3.4. Stopping Rules for the Study

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (Section 7.1.7) as they are reported from the investigational centers to identify safety concerns.

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

- new toxicological or pharmacological findings or safety issues that invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the investigational medicinal product (IMP)

If the study will be stopped, the patients that are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.3).

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 (Assessment of Safety), and Section 8 (Assessment of Pharmacokinetics and Immunogenicity). Study procedures and assessments by visit, including unscheduled visits, are listed in Appendix B.

Table 1: Study Procedures and Assessments

Study period	**Pretreatment period (incl. screening visit and baseline period)**	**Double-blind treatment period**			
Visit number	**V1**[a]	**V2**	**V3**	**V4**	**V5**[b]
Month number	**Month −1**	**Month 0**	**Month 1**	**Month 2**	**Month 3**
Procedures and assessments[c]	**Screening Days −28 to −1**	**Randomization Dose 1 Day 1**[d] **(+3 days)**	**Dose 2 Day 29**[d] **(±3 days)**	**Dose 3 Day 57**[d] **(±3 days)**	**EOT or early withdrawal Day 85**[d] **(±3 days)**
Informed consent and assent[e]	X				
Inform patients of study restrictions and compliance requirements[f]	X				
Medical and psychiatric history[f]	X				
Headache history[f]	X				
Lifetime prior medication and treatment history[f]	X				
Record demographic characteristics[f]	X				
Inclusion and exclusion criteria	X	X[g]			
Physical examination, including weight and height[h]	X	X			X
Puberty assessment[i,f]		X			X
Randomization[j]		X			
Triplicate 12-lead ECG[k]	X	X	X	X	X
Vital signs measurement[l]	X	X	X	X	X
Adverse events[m,f]	X	X	X	X	X
Concomitant medication inquiry[f]	X	X	X	X	X
Clinical laboratory tests[c,n]	X		X		X

Study period	**Pretreatment period (incl. screening visit and baseline period)**	**Double-blind treatment period**			
Visit number	**V1**[a]	**V2**	**V3**	**V4**	**V5**[b]
Month number	**Month −1**	**Month 0**	**Month 1**	**Month 2**	**Month 3**
Procedures and assessments[c]	**Screening Days −28 to −1**	**Randomization Dose 1 Day 1**[d] **(+3 days)**	**Dose 2 Day 29**[d] **(±3 days)**	**Dose 3 Day 57**[d] **(±3 days)**	**EOT or early withdrawal Day 85**[d] **(±3 days)**
Pregnancy test[o]	X	X	X	X	X
Electronic headache diary device dispensation[p]	X				
Review electronic headache diary entries[p,f]		X	X	X	X
Electronic headache diary device return[p]					X
Blood samples for plasma drug concentration[c]		X	X		X
Blood samples for serum ADA assessment[c]		X	X		X
C-SSRS[q,f]	X	X	X	X	X
PedMIDAS[f]		X			X
PedsQL[f]		X	X	X	X
PGI-I questionnaire[f]					X
Administration of study drug[r]		X	X	X	
Injection site assessment[c]		X	X	X	

[a] Patients will complete the screening visit no more than 28 (+3) days before the randomization visit (visit 2 [day 1]).
[b] After completing EOT assessments/procedures, all eligible patients will be offered enrollment in the long-term safety and tolerability study (Study TV48125-CNS-30084).
[c] Electrocardiograms will be performed, weight will be recorded (visit 2 only), urine pregnancy tests will be performed at all visits prior to dosing, and blood samples will be collected before study drug administration. Assessment of injection site reactions will be performed after administration of each dose of study drug, before the patient leaves the investigational site. All other study procedures can be performed at any time during the visit.
[d] The date of the next visit will be calculated based on the actual date of the last administration of study drug.
[e] Must be performed prior to any study procedure.

[f] This procedure/assessment may be performed remotely for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center due to unforeseen circumstances.
[g] Eligibility criteria will be confirmed prior to randomization.
[h] Physical examination, including height and weight, will be performed at screening, randomization, and EOT. Body mass index will be calculated at screening and randomization.
[i] Puberty status (Tanner staging scale, see Section 7.5) will be assessed at randomization (visit 2) and EOT either by patients' self report or by physical examination according to the Tanner staging card provided.
[j] Patients will be randomized to receive placebo or 1 of 2 fremanezumab doses (based on body weight).
[k] Twelve-lead ECGs will be performed in triplicate at any time during the visit, prior to study drug administration.
[l] The method for measuring temperature in an individual patient must be the same at each timepoint.
[m] Inquiries about adverse events will be made before and after study drug administration.
[n] Serum chemistry, hematology, coagulation, and urinalysis.
[o] Females who are postmenarchal or ≥12 years of age only. Serum β-HCG tests will be performed at screening (visit 1) and visit 5; urine β-HCG tests will be performed at all visits. Inquire and record start/stop date of menstrual period at each visit.
[p] Eligible patients will be given an electronic headache diary device and they or a parent/caregiver will be trained in its use and compliance requirements on the day of screening. Patients or parents/caregivers will complete electronic headache diary entries about the previous day daily beginning on day -27 through the EOT/early withdrawal visit. If the patient is unable to complete the diary themselves, then a parent/caregiver will complete the diary for them.
[q] The C-SSRS will be completed by a qualified rater trained to administer the scale at the investigational center based on discussion with the patient/caregiver at the time points described. Any patient who demonstrates suicidal ideation and/or any suicidal behavior at any point during the study should be withdrawn from the study and discontinued from study treatment. In addition, if a patient endorses suicidal ideation or behavior at any point during the study (including during screening), the investigator must explain to the patient/caregiver the need for follow-up with a mental health professional and make any necessary referrals.
[r] The location of the sc injection should be recorded at each administration visit.

β-HCG=beta-human chorionic gonadotropin; ADA=antidrug antibody; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=end-of-treatment; PedMIDAS=Pediatric Migraine Disability Assessment; PedsQL=Pediatric Quality of Life Inventory; PGI-I=Patient Global Impression of Improvement; sc=subcutaneous; 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 E).

4.1. Patient Inclusion Criteria

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

a. The patient is a male or female between the ages of 6 to 17 years (inclusive) on the day of randomization to study drug/IMP.

b. The patient's parent(s) or legal guardian(s) must give written informed consent, and the patient must give assent (in accordance with local regulations).

   Note: In some countries, patients aged 15 to 17 years (inclusive) may give written informed consent; however, the patient's parent(s) or legal guardian(s) must be informed, per local regulations.

c. The patient has a clinical history of recurrent headache consistent with the diagnosis of migraine for at least 6 months before screening, consistent with the ICHD-3 criteria (Headache Classification Committee of the IHS 2013), and a history of ≤14 headache days per month in each of the 3 months prior to screening (visit 1).

d. The patient or parent/caregiver has maintained a prospectively collected headache diary during a 28-day baseline period in which at least 4 migraine days and ≤14 headache days were recorded. Migraine days have at least 1 of the following migraine characteristics:

   – head pain of moderate to severe intensity lasting for 2 or more hours in duration and accompanied by either throbbing quality, predominantly unilateral location, or aggravation with normal activities.

   – headache is accompanied by a migraine-associated symptom, such as photophobia, phonophobia, abdominal pain, nausea, or vomiting.

   – headache is preceded by an aura, as described by ICHD-3 criteria.

   – headache was treated by a nonsteroidal anti-inflammatory drug (NSAID), paracetamol, triptan, or ergot preparation.

e. The patient does not have chronic daily headache. For the purposes of this study, chronic daily headache is operationally defined as <4 headache-free days during the 28-day baseline period.

f. [Revision 01] Not using migraine preventive medications (listed in Appendix C) or using no more than 2 migraine preventive medications (listed in Appendix C) for migraine or other medical conditions, as long as the dose and regimen have been stable for at least 2 months prior to screening (visit 1). A list of migraine preventive medications allowed for any condition for the duration of the study for approximately 30% of patients is presented in Appendix C.

Note: A person is considered to be not using migraine preventive medications (listed in Appendix C) when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinium toxin A or B prior to screening (visit 1). The use of other agents that are not included in Appendix C but used for migraine prevention is permitted during the study; however, these patients will not be counted toward the approximately 30% patient limit threshold.

g. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at baseline or are sterile. Definitions of females of childbearing potential and females who are not of childbearing potential are given in Appendix G.

h. Females who are postmenarchal or ≥12 years of age and sexually active must use highly effective birth control methods with their male partners for the duration of the study (ie, starting at screening) and for 6 months after the last dose of IMP. Males who are sexually active with female partners must use a condom for the duration of the study and for 6 months after the last administration of IMP. Further details are included in Appendix G.

i. The patient/caregiver has demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 21 out of 28 days (approximately 75% diary compliance).

j. The patient is in good health, as determined by a medical and psychiatric history, medical examination, 12-lead ECG, serum chemistry, hematology, coagulation, urinalysis, and serology.

k. The patient/caregiver must be willing and able to comply with study requirements and return to the clinic as required for the duration of the study.

l. The patient weighs at least 17.0 kg on the day of randomization to study drug/IMP.

m. The patient has a body mass index ranging from the 5th to 120% of the 95th percentile, inclusive, at screening, based on the local standard.

n. The patient has received all recommended age-appropriate vaccines according to local standard of care and schedule prior to screening.

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 is using medications containing opioids (including codeine) or barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) for the treatment of migraine during the 3 months prior to the day of the screening visit.

b. The patient has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine or in the head or neck area for any condition during the 2 months prior to the day of the screening visit.

c. The patient has any clinically significant cardiovascular (including congenital cardiac anomalies or thromboembolic events), endocrine, gastrointestinal, genitourinary, hematologic, hepatic, immunologic, neurologic, ophthalmic, pulmonary, renal disease, or complications of an infection, at the discretion of the investigator.

d. [Revision 01] The patient has a current history of a clinically significant psychiatric condition, at the discretion of the investigator. Any prior history of a suicide attempt, or a history of suicidal ideation with a specific plan within the past 2 years, must be excluded.

e. The patient has an ongoing infection or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, chronic hepatitis B or C, or a known active infection of coronavirus disease 2019 (COVID-19).

f. The patient has a past or current history of cancer.

g. The patient is pregnant or nursing.

h. The patient has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome, or the patient is concomitantly using lamotrigine.

i. The patient has participated in another study of an IMP (or a medical device) within the 30 days (or 90 days for biologics) or 5 half-lives previous to the day of the screening visit (whichever is longer), or is currently participating in another study of an IMP (or a medical device).

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

k. Previous participation in the Phase 1 pharmacokinetics study (Study TV48125-CNS-10141).

l. In the judgment of the investigator, the patient has an abnormal finding on the baseline 12-lead ECG considered clinically significant.

m. In the judgment of the investigator, the patient has a significantly abnormal finding during the 28-day baseline period, including hematology, blood chemistry, coagulation tests, or urinalysis values/findings (abnormal tests may be repeated for confirmation).

n. The patient has hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]) more than 1.5× the upper limit of normal (ULN) during the 28-day baseline period, after confirmation in a repeat test, or suspected hepatocellular damage that fulfills the criteria for Hy's law.

o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <75 mL/min/1.73m^2, as calculated by the revised Schwartz formula (eGFR=[0.413×Ht]/serum creatinine), or evidence of renal disease during the 28-day baseline period.

p. The patient has any history of alcohol or drug abuse. The definition of alcohol or drug abuse, including marijuana, is based on the investigator's clinical judgment.

q. In the judgment of the investigator, the patient cannot fully participate in or successfully complete the study for its full duration for any of the following reasons:

   – The patient is mentally or legally incapacitated, or unable to give assent/consent for any reason.

   – The patient is in custody due to an administrative or a legal decision or is in residential treatment.

   – The patient/caregiver is unable to be contacted in case of emergency.

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

   – The patient is a relative of a study center or sponsor employee who is directly involved in the study.

r. Vulnerable patients (eg, people kept in detention) whose vulnerability is based on a condition other than the age required for study eligibility.

s. The patient received a live attenuated vaccine (eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine) within the 12-week period prior to screening.

   Note: If a medical need arises during the study, the patient may receive a live attenuated vaccine.

t. The patient has a known hypersensitivity to the active substance or to any of the excipients of the study drug.

u. The patient has a current or past medical history of hemiplegic migraine.

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:

- Patient withdraws consent or requests discontinuation from the IMP or withdrawal from the study for any reason.
- Patient develops an illness that would interfere with his/her continued participation.
- Patient is noncompliant with the study procedures and assessments or administration of IMPs in the opinion of the investigator.
- Patient takes prohibited concomitant medications chronically.
- A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.
- The sponsor requests withdrawal of the patient.

- Patient experiences an adverse event or other medical condition indicating to the investigator that continued participation is not in the best interest of the patient.
- Any patient who demonstrates suicidal ideation and/or any suicidal behavior at any point during the study should be withdrawn from the study and discontinued from study 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 IMP.

See Appendix H 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 health care professional, or until a determination of a cause unrelated to the IMP [and/or PFS] 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.

The patient will be monitored as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the test IMP or study procedure is made). The investigator must inform the Study Leader as soon as possible of each patient who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that also include adverse events, the relevant 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.

All protocol-specified procedures/assessments should be performed at the EOT/early withdrawal visit (see Table 1). Patients who withdraw from the study or have an early termination will be invited to enter the long-term safety extension (within Study TV48125-CNS-30084) for the purpose of safety follow-up and evaluating ADA approximately 5 months (150 days [5 half-lives]) after receiving the last dose of study drug in this study.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient’s medical records and transcribed to the CRF.

4.3.1. Study-Specific Patient Withdrawal Criteria and Procedures

In the following circumstances for patients with abnormal hepatic laboratory values (eg, ALT, AST, ALP, gamma-glutamyl transpeptidase, total bilirubin, or International Normalized Ratio [INR]), IMP should be discontinued immediately:

1. any increase in ALT or AST to ≥3× the ULN, combined with INR >1.5× the ULN or total bilirubin ≥2× the ULN
2. 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, or eosinophilia) and not deemed related to other diseases (eg, vomiting or nausea triggered by migraine)
3. any increase in ALT or AST to levels ≥5 but <8× the ULN, which is persistent for ≥2 weeks of repeated measurements
4. any increase in ALT or AST to levels ≥8× the ULN
5. in any case where monitoring of liver enzymes cannot be performed according to the protocol guidance

The patient must be withdrawn from the study drug if the patient experiences a severe hypersensitivity reaction or anaphylaxis.

Additionally, IMP should be discontinued if the patient experiences an adverse event or other medical condition indicating to the investigator that continued participation is not in the best interest of the patient.

4.4. Replacement of Patients

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

Study enrollment assumes up to a 4% discontinuation rate The number of patients randomized (230) was selected to achieve the estimated 220 patients completing the study (110 patients per treatment group).

4.5. Rescreening

A patient who is screened but not enrolled (eg, because study eligibility criteria were not met [inclusion criteria not met or exclusion criteria met]) due to any of the following reasons: technical issues (eg, diary malfunction), out of visit 2 window due to an emergency situation (eg, pandemic or potential pandemic), a change in the patient's medical background, a modification of study inclusion and exclusion criteria, or upon the sponsor's discretion on a case-by-case basis, may be considered for rescreening 1 time. If the history of migraine classification (EM or CM) as taken by the investigator differs from the classification determined by the diary data (28-day baseline period), the patient may be rescreened one time; this information should be recorded in the CRF.

Patients may have individual parameters retested at the discretion of both the investigator and the sponsor.

Patients may be rescreened once if the repeated values for the laboratory, vital sign, or ECG screening criteria are within acceptable limits as judged by the investigator or if repeated values show normalization of the out-of-range values, but their initial baseline period has expired.

If the patient is rescreened, an informed consent form (ICF) will need to be re-signed, and a new screening number will be assigned.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screening failure information will be entered in the CRF. 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 IMPs and matching placebo IMPs to the respective test IMPs.

5.1.1. Test Investigational Medicinal Product

The formulation of fremanezumab to be used for clinical investigations in the pediatric population will be identical to the sc formulation of fremanezumab that will be used in the clinical program for adults. Information on the test IMP and placebo are shown in Table 2.

Additional details may be found in the IB for fremanezumab.

5.1.1.1. Starting Dose and Dose Levels

Patients will be randomly assigned in a 1:1 ratio between fremanezumab and placebo treatment groups:

- monthly sc administration of fremanezumab
- monthly sc administration of matching placebo

The dose of fremanezumab to be administered will be determined by the patient's weight at randomization (visit 2):

- Patients weighing ≥45.0 kg at randomization (visit 2) will receive monthly sc administration of fremanezumab at 225 mg.
- Patients weighing <45.0 kg at randomization (visit 2) will receive monthly sc administration of fremanezumab at 120 mg.

(Note: For this study, monthly dosing refers to dosing approximately every 4 weeks [28 days].)

The recommended sc injection sites follow the National Institutes of Health (NIH) Clinical Center Patient Education Materials (NIH Clinical Center Patient Education Materials 2016). The suggested injection site locations for sc administration are the following: back of upper arms, lower abdomen/belly/waistline, and front of thighs. The sc injection and location will be recorded for each administration visit (visits 2, 3, and 4).

A 1.5 mL volume (patients weighing ≥45.0 kg at randomization [visit 2]) or a 0.8 mL volume (patients weighing <45.0 kg at randomization [visit 2]) from each visit kit(s) (the full dose given with a PFS or taken from the vials) must be injected sc for administration to be considered complete. Patients randomized to the placebo group will receive volume-matched doses of placebo.

5.1.1.2. Dose Modification and Dose Stratification

Not applicable.

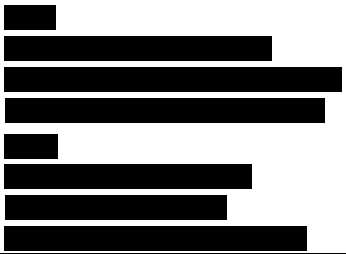
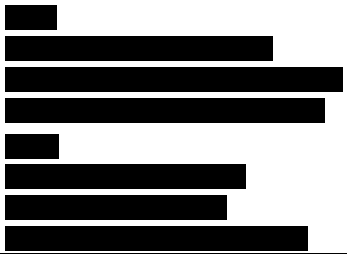
5.1.2. Reference Investigational Medicinal Product

Not applicable.

5.1.3. Placebo Investigational Medicinal Product

The placebo will match the test IMP in appearance and volume. See Table 2 for a description of the placebo.

Table 2: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	Fremanezumab	None
Formulation	Sterile, clear to opalescent, colorless to slightly yellow solution for injection	Sterile, clear to opalescent, colorless to slightly yellow solution for injection
Unit dose strength(s)/dosage level(s)	225 mg monthly in patients with body weight ≥45.0 kg at randomization (visit 2) 120 mg monthly dose in patients with body weight <45.0 kg at randomization (visit 2)	Not applicable
Route of administration	Subcutaneous injection	Subcutaneous injection
Dosing instructions	Patients with body weight ≥45.0 kg at randomization (visit 2): fremanezumab 225 mg: 1 active injection (225 mg/1.5 mL) at visits 2, 3, and 4 Patients with body weight <45.0 kg at randomization (visit 2): fremanezumab 120 mg: 1 active injection (120 mg/0.8 mL) at visits 2, 3, and 4	Patients with body weight ≥45.0 kg at randomization (visit 2): Placebo: single 1.5 mL injection at visits 2, 3, and 4 Patients with body weight <45.0 kg at randomization (visit 2): Placebo: single 0.8 mL injection at visits 2, 3, and 4
Packaging	IMP will be provided as follows: • 225 mg dose: PFS for single-use administration • 120 mg dose: taken from two 2-mL vials each containing 0.5 mL of IMP for single-use administration	Placebo will be provided as follows: • 1.5 mL injection: PFS for single-use administration • 0.8 mL injection: taken from two 2-mL vials each containing 0.5 mL of placebo for single-use administration
Manufacturer		

IMP=investigational medicinal product; INN=international nonproprietary name; PFS=pre-filled syringe.

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

5.2.1. Storage Conditions and Handling

Fremanezumab should be stored refrigerated at 2°C to 8°C (36°F to 46°F) in the original container until it is used. Protect from light. Do not freeze, and do not use if frozen. Do not shake vigorously. Refrigerated fremanezumab remains suitable for use until the expiration date printed on the primary container and/or carton. Do not use fremanezumab if the liquid is cloudy, discolored, or contains visible flakes or particles. Fremanezumab should be equilibrated to room temperature for 30 minutes prior to administration.

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

Further guidance is provided in the Pharmacy Manual.

5.2.2. Labeling

Supplies of IMPs will be labeled according to 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.

5.2.3. 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/or local regulations, and used in accordance with this protocol.

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

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

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused PFS and vials of IMP will be destroyed at the investigational center in accordance with investigational center Standard Operating Procedures (SOPs) or will be disposed of, retained, or returned to the sponsor or designee per sponsor instructions.

Further guidance and information are provided in the Study Reference Manual, Pharmacy Manual, or other specified location.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product and/or Device

[redacted]

[redacted]

[redacted]

5.3.2. Justification for Use of Placebo Investigational Medicinal Product

A multicenter, randomized, double-blind, placebo-controlled, parallel-group design is appropriate, given the objectives of this study. Furthermore, this design is consistent with the recommendations of the IHS for controlled trials of preventive drugs in migraine (Tfelt-Hansen et al 2012).

The use of a placebo rather than an active comparator is justified in this study because of the limited availability of a suitable comparator. Topiramate is the only migraine preventive medication approved for pediatric populations, but it is not approved in all regions of the EU and is limited to adolescents ages 12 through 17, so this medication would be off-label for those subjects ages 6 through 11.

5.4. Treatment After the End of the Study

Upon completion of the final study assessments, all eligible patients will be offered enrollment in a long-term safety and tolerability study (Study TV48125-CNS-30084), consisting of 9 months (36 weeks) of open-label treatment and 5 months of follow-up commencing from the last study drug administration. In the long-term safety extension study, patients rolling over from the current study will be weighed at visit 2 and will receive monthly fremanezumab with dose adjusted per weight category (225 mg in patients ≥45.0 kg or 120 mg in patients <45.0 kg). Patients who do not complete this study and patients who complete this study but do not wish to continue treatment may enroll in Study TV48125-CNS-30084 for the purpose of attending a follow-up visit for safety and ADA assessments approximately 5 months (150 days [5 half-lives]) after receiving the last dose of study drug.

5.5. Restrictions

Medications prohibited before and/or during the study are described in Section 5.6 and the exclusion criteria (Section 4.2). Restrictions with regard to pregnancy and required laboratory values are provided in the inclusion and exclusion criteria (Section 4.1 and Section 4.2, respectively). Restrictions regarding contraception methods are detailed in the inclusion and exclusion criteria (Section 4.1 and Section 4.2, respectively) and are also described in Appendix G.

Patients must remain at the site, for safety observation, for at least 30 minutes after injection or longer if deemed necessary by medical judgment.

There are no additional restrictions in this study.

5.6. Prior and Concomitant Medication or Therapy

All prior therapy, medication, or procedure (ie, procedures for the treatment of migraine [eg, nerve blocks]) for the treatment of migraine a patient has had during their lifetime will be recorded on the CRF. In addition, all concomitant medications taken during the study will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary.

The following medications are prohibited for regular chronic use during the study: opioids (including codeine), barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital), and lamotrigine.

Approximately 30% of EM patients will be allowed to remain on no more than 2 migraine preventive medications in Appendix C for any condition, provided the medication is recognized to have at least moderate evidence of efficacy or is commonly used. Additional details on migraine preventive medication information are provided in Appendix C. For chronic use of these medications for any indication, patients must have been on a stable, well-tolerated dose of this migraine preventive medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining approximately 70% of EM patients, these medications are not allowed for migraine or for any other indications. As-needed (PRN) use of these medications are allowed during the course of the study for any indications and do not have to have established dosing regimens. PRN use of these medications should be reported in the electronic case report form as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the prescribing information or local treatment guidelines.

Patients will be allowed PRN use of to use acute medications to treat acute migraine attacks, as needed, with the exception of regular use of medications containing opioids and barbiturates.

The chronic use of concomitant therapies not listed in Appendix C for any indication is allowed throughout the course of the study. All patients must have been on a stable dose of these concomitant medications for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. PRN use of medications for adverse events or intercurrent acute situations are allowed.

Patients must have received all recommended age-appropriate vaccines according to local standard of care and schedule prior to screening. Live attenuated vaccines (eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine) are disallowed within the 12-week period prior to screening. If a medical need arises during the study, the patient may receive a live attenuated vaccine.

All concomitant medications taken during the study, including over-the-counter medications, vitamins, or herbal or nutritional supplements, must be recorded with indication, daily dose, and start and stop dates of administration. All patients will be questioned about concomitant medication use at each visit.

Concomitant medication and treatment will be recorded until visit 5.

5.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. 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. The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) should be notified.

5.8. Randomization and Blinding

This is a double-blind study. 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 into single-visit kits according to Good Manufacturing Practice procedures. The active drug and placebo kits for each dose will be identical in appearance and will contain 1 PFS (for the 225 mg dose and its matching placebo) or 2 vials (for the 120 mg dose and its matching placebo). Adequate kit supply for upcoming study visits will be managed by interactive response technology (IRT) and kept (refrigerated at 2°C to 8°C) on site.

This is a randomized study. Randomization will be stratified by country, sex, puberty status, and preventive medication use at baseline (Yes/No). Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics. Each patient will undergo randomization in a 1:1 ratio within the stratum to which he or she belongs to receive fremanezumab or placebo, as assigned by the IRT. The IRT will manage initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At the time of each study visit, the IRT will be queried, and site personnel will retrieve and administer a 1.5 mL volume for patients weighing ≥45.0 kg at randomization (visit 2) or a 0.8 mL volume for patients weighing <45.0 kg at randomization (visit 2) from each PFS or 2 vials contained in the appropriately numbered kit(s).

The sponsor’s clinical personnel (and delegates) involved in the study will be blinded to the identity of the IMPs until the database is locked for analysis and the IMP assignment is known. However, if a prioritized sample analysis is needed, bioanalytical and clinical pharmacology personnel may be unblinded.

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

5.9. Maintenance of Randomization and Blinding

5.9.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of analysis (after the end of study), after receiving

unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant SOP.

5.9.2. Blinding and Unblinding

Blinded pharmacokinetic data may be assessed during the study. For patients who have pharmacokinetic sample bioanalysis or data analysis conducted, the individuals responsible for sample bioanalysis and other responsible personnel will know who received test IMP and who received placebo IMP during the study (of those patients only). Personnel responsible for bioanalysis 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).

In case of a serious adverse event, pregnancy, or in cases when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes, indicating the IMP assignment for each randomized patient, will be available to the investigator(s) or pharmacist(s) at the investigational center via the RTSM, both via telephone and internet. Breaking of the treatment code can always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified following breaking of the treatment code. The patient's IMP assignment should not be revealed to 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 SUSAR (ie, reasonable possibility; see Section 7.1.6), 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 analysis and reporting of the data.

5.9.3. Data Monitoring Committee

There will be no Data Monitoring Committee in this study.

5.10. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 48 mL. See Appendix J.

6. ASSESSMENT OF EFFICACY

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

6.1. Assessments of Efficacy

6.1.1. Electronic Headache Diary

The primary efficacy endpoint (and some secondary and exploratory efficacy endpoints as well) will be derived from headache variables collected daily using an electronic headache diary device. Eligible patients and parents/caregivers will receive comprehensive training from site personnel on the use of the electronic headache diary device. Site personnel will also instruct patients and parents/caregivers on the requirement for timely and daily completion of the electronic diary. Patients will complete an electronic headache diary. If the patient is unable to complete the diary themselves then a parent/caregiver will complete the diary for them.

On each day, the patient or parent/caregiver will be asked to record diary data for the previous 24-hour period. Patients and parents/caregivers may be asked about their (child's) performance at school and when doing household chores (ie, functional assessments). Patients or parents/caregivers who report headache on the previous day will answer questions about the headache (ie, the number of hours with headache, headache severity, presence of associated symptoms, and use of acute migraine medications). Additional details regarding the questions patients or parents/guardians will answer can be found in the electronic headache diary training manual.

If a patient or parent/caregiver fails to complete the diary for the preceding day, the patient will be prompted to enter the missed day's information the next time he/she accesses the electronic diary, provided no more than 48 hours have elapsed since the end of the missed day. If more than 48 hours have elapsed since completion of a diary day, the patient or parent/caregiver will not be allowed to enter diary information for that day, and it will be considered a missed day.

Rating of headache severity and headaches lasting ≥2 hours for each day will be completed in the electronic diary.

If headache is reported, then headache severity will be subjectively rated by the patient or parent/caregiver on an 11-point numerical rating scale, where 0 is no pain and 10 is the most severe pain. Each headache severity rating from the 11-point numerical rating scale will be mapped to mild (1 to 3), moderate (4 to 6), or severe (7 to 10) for endpoint analyses (McCaffery and Beebe 1989). Patients or parents/caregivers will also record whether photophobia, phonophobia, nausea, and vomiting are present, and they will record any migraine medications (name of drug, number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day. Diary compliance of less than 75% after the start of treatment will be recorded as a protocol deviation.

6.1.2. Pediatric Migraine Disability Assessment

The PedMIDAS questionnaire is a 6-item instrument to assess migraine-related disability in pediatric patients, which can be self-administered by the patient or administered by a caregiver. It has been validated in patients aged 4 through 18 years (Hershey et al 2001) and includes

questions related to the impact of headache on school performance, disability at home (eg, inability to do chores or homework), and social/sport functioning.

6.1.3. Patient Global Impression of Improvement Scale

The PGI-I scale is a 7-item questionnaire designed to assess the patient's global impression of improvement. It aims at evaluating all aspects of patients' health and determining if there has been an improvement or not. The patient has to select the 1 response that gives the most accurate description of his/her state of health (overall status).

The patient is instructed to select a response option on a 7-point scale in which a score of 1 indicates that the patient's condition is "very much better," a score of 4 indicates that the participant has experienced "no change," and a score of 7 indicates that the participant is "very much worse."

- 1=Very much better
- 2=Much better
- 3=A little better
- 4=No change
- 5=A little worse
- 6=Much worse
- 7=Very much worse

6.1.4. Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) 4.0 is a brief 23-item health-related quality of life instrument that evaluates quality of life in 4 areas of functioning: physical, emotional, social, and school functioning. The PedsQL 4.0 has 4 age ranges: toddlers (2 through 4 years), young child (5 through 7 years), child (8 through 12 years), and adolescent (13 through 18 years). This study will use the young child, child, and adolescent formats. The PedsQL version that will be used for the patient for the duration of the study will be based on the age of the patient at visit 2 and will not change during the course of the study.

The PedsQL 4.0 asks respondents to indicate how much of a problem each item has been during the past month. For the child and adolescent self-report (8 through 18 years of age) and the parent report forms, respondents use a 5-point Likert scale to rate the item severity (0=never a problem;1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem). For younger children (5 through 7 years of age), a simplified 3-point Likert scale, anchored with a happy and a sad face, is used (0=not at all a problem; 2=sometimes a problem; 4=a lot of a problem) to increase further the developmental sensitivity of the measure.

The PedsQL 4.0 yields a total quality of life score and 2 summary scores: Physical Health Summary Score and Psychosocial Health Summary Score. To obtain scores, items are reverse scored, transformed to a 0 through 100 scale (0=100, 1=75, 2=50, 3=25, 4=0), and averaged; total scores near 0 indicate lower quality of life, while scores approaching 100 indicate higher quality of life.

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 and height measurements), suicidal ideation and behavior (as suggested by the C-SSRS), 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 IMP. 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 (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event.)
- drug/drug or drug device interactions
- events occurring during diagnostic procedures of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study drug are not considered adverse events.)

Migraine exacerbations, including acute headache, requiring headache medications will be collected as part of the efficacy assessment in this study. Migraine exacerbations (including acute headache) should be recorded as an adverse event only if the presentation and/or outcome is more severe than would typically be expected from the normal course of the disease in a particular patient or if they are severe enough to require hospitalization of the patient, in which case they are recorded as serious adverse events.

7.1.2. Definition of an Adverse Device Effect

An adverse device effect is an adverse event related to the use of an investigational medical device or a combination product. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device, including any event resulting from user error or from intentional misuse of the investigational medical device. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

7.1.3. Recording and Reporting of Adverse Events

For adverse event recording, the study period is defined for each patient as the time period from signature of the ICF through completion of visit 5 or the early withdrawal visit (for patients who withdraw from the study for any reason). Adverse events will be collected at each visit via adverse event inquiry.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity of the event or judged relationship to the study drug (and/or PFS). For serious adverse events and protocol-defined adverse events of special interest for expedited reporting to GPSP, the Serious Adverse Event and Protocol-Defined Adverse Events of Special Interest Form must be completed, and the serious adverse event and the protocol-defined adverse events of special interest must be reported immediately (see Section 7.1.7.4.1). The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events 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 7.1.7.4.1.

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, also on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until it resolves, stabilizes, or returns to baseline; until the patient is referred for continued care to another health care professional; or until a determination of a cause unrelated to the study drug (and/or PFS)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 study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF.

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

Further details are given in the Safety Monitoring Plan.

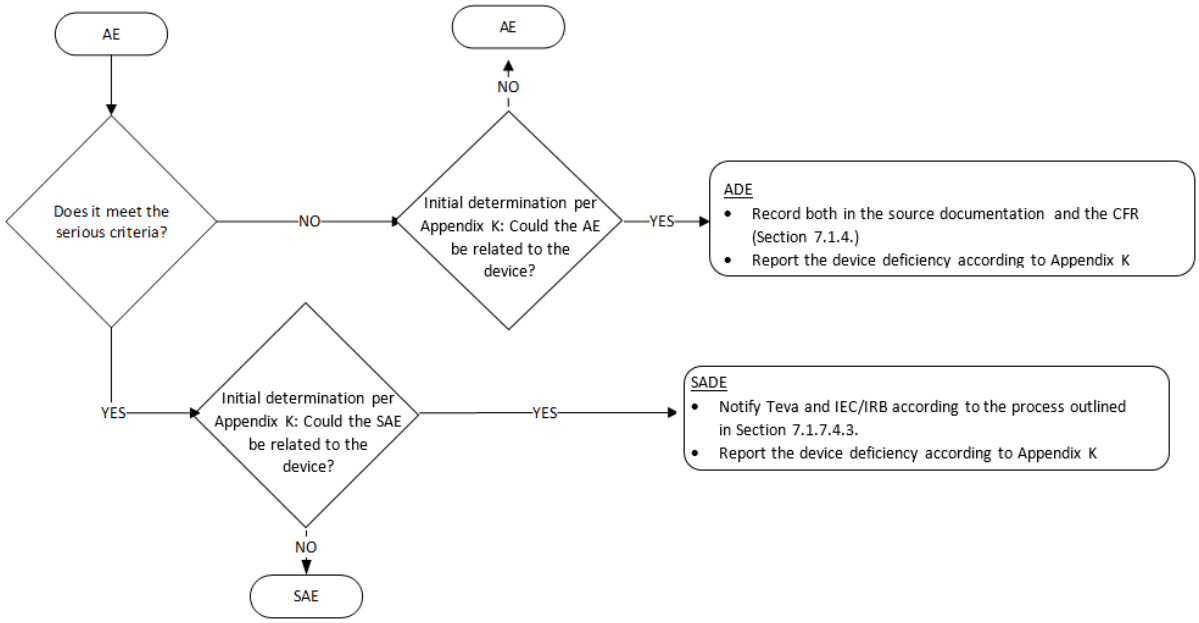
7.1.4. Recording and Reporting of Adverse Device Effect

Adverse device effects (Figure 2) must be recorded on both the source documentation and the CRF.

The investigator and sponsor will record all relevant information regarding every adverse device effect/serious adverse device effect and device deficiency and will categorize each as guided in Figure 2.

The investigator should make an initial determination whether the adverse event may be related to a device deficiency.

Figure 2: Decision Tree for Adverse Events and Adverse Device Effects Classification



AE=adverse event; ADE=adverse device effect; CRF=case report form; IEC=Independent Ethics Committee; IRB=Institutional Review Board; SADE=serious adverse device effect;SAE=serious adverse event.

7.1.5. Severity of an Adverse Event

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

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

7.1.6. Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device

The relationship of an adverse event to the IMP (and/or PSF) is characterized as described in Table 3.

Table 3: The Relationship of an Adverse Event to the IMP and/or Device

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP (and/or PFS).	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 (and/or PFS). • 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 (and/or PFS). • It does not reappear or worsen when the IMP (and/or PFS) 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 (and/or PFS) 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 (and/or PFS). • 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 (and/or PFS), yet an IMP (and/or PFS) relationship clearly exists. • It follows a known pattern of response to the IMP (and/or PFS).

IMP=investigational medicinal product.

7.1.7. Serious Adverse Events and Serious Adverse Device Effects

For recording of serious adverse events and serious adverse device effects, the study period is defined for each patient as that time period from signature of the ICF to visit 5 (EOT visit). Serious adverse events and serious adverse device effects occurring in a patient after the end of study should be reported to the sponsor if the investigator occurring in a patient after visit 5 (EOT visit) should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.7.4.1.

7.1.7.1. 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 pre-existing 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:

- ALT or AST increase of >3× the ULN
- total bilirubin increase of >2× ULN
- absence of initial findings of cholestasis (ie, no substantial increase of ALP)

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

Refer to Appendix I for guidance regarding monitoring patients with elevated liver function tests.

7.1.7.2. Definition of a Serious Adverse Device Effect

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (Section 7.1.7.1).

7.1.7.3. Expectedness

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

The sponsor's Pharmacovigilance Department will determine the expectedness for all serious adverse events.

For the purpose of SUSAR reporting, the version of the reference safety information document at the moment of the occurrence of the SUSAR applies.

An unanticipated serious adverse device effect is a serious adverse device effect that, by its nature, incidence, severity, or outcome, has not been listed in Appendix K (Appendix Table 1 and Appendix Table 2).

7.1.7.4. Reporting a Serious Adverse Event

7.1.7.4.1. Investigator Responsibility

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

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

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

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

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

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness

- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

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

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

For all countries, the sponsor's 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, IEC/IRBs, and investigators, according to regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Blinding will be maintained for the people who are involved directly in the study. Therefore, in case of a SUSAR, only the LSO or CRO personnel involved with safety regulatory submissions 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).

7.1.7.4.2. Sponsor Responsibility

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

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

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent form and informing all study participants of new findings

- modifying listings of expected toxicities to include adverse events newly identified as related to fremanezumab

7.1.7.4.3. Reporting a Serious Adverse Device Effect

The process and contact details for serious adverse device effect reporting are the same as for serious adverse event reporting provided in Section 7.1.7.4.

Events shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor using the appropriate form according to national and local regulations.

The investigator should use Appendix K (Appendix Table 1 and Appendix Table 2) to make an initial determination whether the serious adverse event may be related to a device deficiency

7.1.8. Protocol-Defined Adverse Events of Special Interest

Adverse events of special interest for pediatric patients are not listed in the Pediatric Investigation Plan or Pediatric Study Plan. 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 and severe hypersensitivity or anaphylactic reactions. Hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al 2006). The clinical criteria for diagnosing anaphylaxis are provided in Appendix D. In the event of suspected anaphylaxis, vital signs (including oxygen saturation and respiration rate) will be measured.

The process for reporting a protocol-defined adverse event of interest is the same as that for reporting a serious adverse event (Section 7.1.7.4). Protocol-defined adverse events of special interest to be reported to GPSP can be either serious or nonserious, according to the criteria outlined in Section 7.1.7.1.

7.1.9. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol are allowed based on the investigator's clinical judgment. 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 be withdrawn from the study.

All pregnancies of females participating in the study and consenting female partners of males participating in the study that occur during the study or within 6 months after the last dose of study drug in this study 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 7.1.7.4).

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 consenting female partners of male patients participating in the study) who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). 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.

Consenting female partners of men participating in the study who become pregnant will be asked to sign an ICF.

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

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

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

Any administration of IMP that is not in accordance with the study protocol should be reported in the patient's source documents, regardless of whether or not an adverse event occurs 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 health care 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.
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.

4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.
7. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.

7.4. Clinical Laboratory Tests

Details on sample handling, storage, shipment, and analysis are given in Appendix N and in the Laboratory Manual.

7.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis

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 adverse event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic work-up. (Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

In addition, potentially clinically significant values will be predefined by the sponsor for selected laboratory parameters and will be detailed in the statistical analysis plan.

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected hepatitis, HIV, or Lyme disease, a blood sample may be taken at screening at the discretion of the investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below (Table 4). Note, reflex tests (eg, red blood cell [RBC] shapes, RBC morphology, and other microscopic findings) may be triggered automatically.

Table 4: Clinical Laboratory Tests

Serum chemistry	Hematology and coagulation	Urinalysis
Calcium	Hemoglobin	Color and appearance
Phosphate	Hematocrit	Protein
Sodium	RBC count	Glucose
Potassium	RBC indices	Ketones
Chloride	– mean corpuscular volume	Blood
Creatinine	– mean corpuscular hemoglobin concentration	Leukocyte esterase
Glucose	– RBC distribution width	Nitrite
BUN	Platelets	Bilirubin
ALT	Leukocytes	pH
AST	– neutrophils	Specific gravity
LDH	– lymphocytes	Microscopic tests
GGT	– eosinophils	– bacteria
Alkaline phosphatase	– monocytes	– erythrocytes
Creatine phosphokinase	– basophils	– leukocytes
Carbon dioxide	Prothrombin time	– crystals
Magnesium	Partial thromboplastin time	– casts
Protein	INR	
Albumin		
Bilirubin (total and direct)		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyl transpeptidase; INR=International Normalized Ratio; LDH=lactate dehydrogenase; RBC=red blood cell.

7.4.2. Other Clinical Laboratory Tests

7.4.2.1. Human Chorionic Gonadotropin Tests

Serum β-HCG tests will be performed for all female patients who are postmenarchal or ≥12 years of age at screening (visit 1) and visit 5; urine β-HCG tests will be performed at all visits (Table 1). Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.5. Physical Examinations

Physical examinations, including height and weight (to be obtained at the screening visit, randomization visit, and EOT only) and puberty status (at randomization and EOT only) will be performed at the time points detailed in Table 1. Body mass index will be calculated at screening and randomization.

While the onset of puberty is generally associated with the onset of adolescence, a globally accepted age range for the onset of puberty and adolescence cannot be easily defined (World Health Organization 1986). Because randomization will be stratified by puberty status, the Tanner puberty staging scale (Finegold 1992) will be used to assess puberty status at that time. Puberty status will be assessed either by patients' self report or by physical examination according to the Tanner staging card provided.

A complete physical examination will include the following organ systems: general appearance; head, eyes, ears, nose, and throat; chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Any physical examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.6. Vital Signs

Vital signs (pulse, systolic and diastolic blood pressure, temperature, and respiratory rate) will be measured at any time during the visit, as detailed in Table 1. The method for measuring temperature in an individual patient must be the same at each time point.

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

7.7. Electrocardiography

Twelve-lead ECGs will be conducted at any time during the visit, prior to study drug administration, as detailed in Table 1. The ECGs should be performed after the patient has been supine for at least 5 minutes. The ECGs will be performed in triplicate, with at least 1 minute between recordings.

A qualified physician at a central diagnostic center will be responsible for interpreting the ECG. ECGs 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 clinical sites.

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

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

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

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

Any ECG finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the

source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

7.8. Assessment of Local Tolerability and Pain

Injection site assessment will be performed after administration of each dose of study drug, before the patient leaves the investigational site. The injection site will be assessed by site personnel for erythema, induration, and ecchymosis and categorized according to measurements: 5 to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation, avoiding placing pressure on or squeezing the injection site.

Reports of pain will be recorded as adverse events and will be graded using the 11-point numerical rating scale according to patient's self-report of pain intensity and then mapping to mild, moderate, or severe.

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

Injection site reactions will be recorded as adverse events as described in Section 7.1 and Section 9.8.

7.9. Assessment of Suicidality

The C-SSRS, combined with the investigator's clinical evaluation, will be used to assess whether the patient has suicidal ideation or behavior and its severity (Posner et al 2011). The C-SSRS will be completed by a qualified rater trained to administer the scale at the investigational center based on discussion with the patient/caregiver at the time points described in Table 1. Any patient who demonstrates suicidal ideation and/or any suicidal behavior at any point during the study should be withdrawn from the study and discontinued from study treatment. In addition, if a patient endorses suicidal ideation or behavior at any point during the study (including during screening), the investigator must explain to the patient/caregiver the need for follow-up with a mental health professional and make any necessary referrals.

7.10. Concomitant Therapy or Medication

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

8. ASSESSMENT OF PHARMACOKINETICS 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 from the clinical study report.

Samples from patients who receive active study drug will be analyzed for fremanezumab using a validated method. Samples from patients who receive placebo will not be analyzed.

8.1.1. Specimen Sampling, Handling, and Shipment

Blood samples (2 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 study drug administration and each pharmacokinetic sample will be recorded on the source documentation and transcribed onto the CRF.

Details on sample handling, storage, shipment, and analysis are given in Appendix N and in the Laboratory Manual.

8.2. Pharmacodynamics Assessment

Not applicable.

8.3. Immunogenicity Testing

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

Blood samples (4 mL) will be collected via venipuncture or indwelling catheter at the time points detailed in Table 1 for immunogenicity testing.

Details on sample handling, storage, shipment, and analysis are given in Appendix N and in the Laboratory Manual.

8.4. Assessment of Exploratory Biomarkers

Not applicable.

9. STATISTICS

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy, safety, and tolerability of sc administration of fremanezumab versus placebo for preventive treatment of EM in pediatric patients 6 through 17 years of age. Eligible patients will be randomized in a 1:1 ratio between fremanezumab and placebo treatment groups. Patients weighing ≥45.0 kg at randomization (visit 2) will receive a 225 mg administration of fremanezumab or matching placebo. Patients weighing <45.0 kg at randomization (visit 2) will receive a 120 mg administration of fremanezumab or matching placebo. Randomization will be stratified by country, sex, puberty status, and preventive medication use at baseline (Yes/No).

9.1. Sample Size and Power Considerations

The sample size planned is approximately 220 patients (110 evaluable patients completing the study per treatment group). Assuming a treatment difference of 1.8 days (reduction in monthly average number of migraine days) and a common SD of 4.31, a sample size of 110 patients per treatment group gives at least 87% power for the study to succeed at an alpha level of 0.05. Assuming a 4% discontinuation rate, approximately 230 patients (115 patients per treatment group) will be randomized. Patients will be randomized to receive either monthly sc administration of fremanezumab or placebo.

The enrollment target is approximately 230 patients in total, with a goal of approximately 20% of those patients in the 6- through 11-year-old age group.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

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

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

9.2.2. Safety Analysis Set

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

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

9.2.3. Full Analysis Set

The full analysis set (FAS) will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 10 days of diary entries postbaseline for efficacy assessments on the primary endpoint.

9.2.4. Per-Protocol Analysis Set

The per-protocol analysis set will consist of all patients in the FAS who have completed the study without any important deviations, such as important inclusion/exclusion criteria deviations,

important deviations or omissions of the IMP administration, or unexpected drug concentration findings, and who have at least 75% diary compliance after the start of treatment.

9.3. Data Handling Conventions

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

9.3.1. Handling Withdrawals and Missing Data

Efficacy variables based on diary data will be prorated to monthly rate. Sensitivity analysis for primary efficacy endpoint will be conducted using multiple imputation method for missing data.

9.4. Study Population

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

9.5. Efficacy Analysis

For the purpose of this study, a migraine day will be defined as a calendar day where the patient reports either of the following:

- headache pain that lasts ≥2 hours and is accompanied by ≥1 migraine symptom(s)
- the patient used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration

The detailed algorithm for deriving migraine days will be described in the statistical analysis plan.

9.5.1. Primary Endpoint

The primary efficacy endpoint is the mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of study drug.

9.5.1.1. Estimand for the Primary Endpoint

The primary estimand for this study is the difference in means between the fremanezumab group and the placebo group in the target population who have received at least 1 dose of study drug and have at least 10 days of electronic diary efficacy data for the mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of study drug as if there were no intercurrent events. Data collected after treatment discontinuation or prohibited therapy will not be used for assessing the primary estimand.

9.5.2. Secondary Endpoints

The secondary efficacy endpoints are as follows:

- mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug
- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of study drug
- mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug
- mean change from baseline (day 1) in migraine-related disability score, as measured by the PedMIDAS questionnaire, at 12 weeks after administration of the first dose of study drug
- mean change from baseline (day 1) in quality of life, as measured by the PedsQL, at 12 weeks after administration of the first dose of study drug
- proportion of patients developing ADAs throughout the study. The impact of ADAs on safety and efficacy will be analyzed if the number of ADA-positive patients allows.

9.5.3. Exploratory/Other Endpoints

[redacted]

[redacted]

9.5.4. Planned Method of Analysis

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

9.5.4.1. Primary Efficacy Analysis

The primary efficacy endpoint, the mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of study drug, will be analyzed using an analysis of covariance method. The model will include treatment, sex, puberty status, region, baseline weight category (<45.0 kg or ≥45.0 kg), and preventive medication use at baseline (Yes/No) as fixed effects and baseline number of migraine days as a

covariate. Ninety-five percent confidence intervals will be constructed for the least squares mean differences between the fremanezumab group and the placebo group. A hierarchical procedure will be used to control Type 1 error rate, as described in Section 9.6. An interim analysis with blinded sample size re-estimation will be conducted as described in Section 9.12.

9.5.4.2. Sensitivity and Supplementary Analyses

A sensitivity analysis for the primary efficacy endpoint will be conducted by using multiple imputation method for missing data. Sensitivity analysis using Mixed-Effect Model Repeated Measure method also will be conducted for change from baseline to months 1 through 3 in migraine days. A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint. Additional subgroup analyses will be performed to investigate treatment effect among relevant sub-populations, such as sex, region, receiving preventive migraine therapy or not, receiving 2 preventive medications from Appendix C, and receiving alternative preventive medications that belong to the same classes but are not listed in Appendix C. The details will be described in the statistical analysis plan.

9.5.4.3. Secondary Efficacy Analysis

The same analysis used for the primary efficacy endpoint will be performed for the continuous secondary efficacy endpoints. For the proportion of responders, defined as at least 50% reduction from baseline in the monthly average number of migraine days, a logistic regression model will be used with the following factors: treatment, sex, region, puberty status, baseline weight category (<45.0 kg or ≥45.0 kg), and preventive medication use at baseline (Yes/No). The odds ratio, 95% confidence interval for the odds ratio, and p-value for the treatment comparison will be presented.

9.5.4.4. Exploratory Efficacy Analysis

[redacted]

9.6. Multiple Comparisons and Multiplicity

A fixed-sequence (hierarchical) testing procedure will be implemented to control the Type 1 error rate at 0.05. The sequence of comparisons will start with the analysis of the primary endpoint and will follow with the secondary efficacy endpoints.

The order of secondary endpoint analyses will in general follow the sequence listed in Section 9.5.2. Final order and details will be confirmed in the statistical analysis plan, which will be finalized before database lock.

9.7. Safety Analysis

Safety analyses will be performed on the safety analysis set.

Safety assessments and time points are provided in Table 1.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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 (and/or PFS) (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, serious adverse device effects, and adverse events and adverse device effects 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.

Suicidal ideation and behavior will be measured using the C-SSRS. Data for patients with positive findings 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 study drug.

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 clinical study report.

9.8. Tolerability Analysis

Injection site reactions will be recorded as adverse events according to the following severity assessment criteria:

- Assessment of injection site erythema, induration, and ecchymosis will be recorded according to measurements: 5 to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe).
- Injection site pain will be recorded using the 11-point numerical rating scale and will be mapped to mild, moderate, or severe, according to patient's self-report of pain intensity, as described for the recording of headache pain in Section 6.1.1.
- Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.

Tolerability will be assessed by the following:

- the number (%) of patients who fail to complete the study (day 85, final assessment)
- the number (%) of patients who fail to complete the study due to adverse events

Local tolerability findings will be listed and summarized descriptively.

9.9. Pharmacokinetic Analysis

Pharmacokinetic plasma concentration results (fremanezumab) will be tabulated descriptively at each planned sampling time point by weight cutoff.

In addition, the most appropriate population pharmacokinetic model will be developed. This analysis will be reported separately, as appropriate.

9.10. Pharmacokinetic/Pharmacodynamic Analysis

The pharmacokinetics/pharmacodynamic relationship may be estimated by compartmental techniques. The pharmacokinetic parameters will be based on fremanezumab measurements. The pharmacodynamic measures will be the efficacy/safety responses.

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

9.11. Immunogenicity Analysis

Summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. The impact of immunogenicity on the pharmacokinetic profile, drug efficacy, and clinical safety will be evaluated if data allows. This analysis will be reported separately.

9.12. Planned Interim Analysis

An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (SD) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients have completed at least 3 months of treatment or have withdrawn from the study early. If the pooled SD is <4.8, there will be no change in enrollment; if the pooled SD is >5.2, the sample size will increase to approximately 400 patients; and if the pooled SD is between 4.8 and 5.2, the sample size will increase to approximately 340 patients total. Details of the interim analysis will be provided in the statistical analysis plan.

9.13. Reporting Deviations from the Statistical Plan

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix E 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 K 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, Guideline for Good Clinical Practice E6 and ISO 14155: Clinical investigation of medical devices for human subjects – Good clinical practice, and any applicable national and local laws and regulations (eg, 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 F 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 L 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.

This clinical study is insured in accordance with the corresponding local 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 21 CFR 54), the investigator will provide the sponsor with financial information required to complete FDA 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. PUBLICATION POLICY

See Appendix M for information regarding the publication policy.

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 09 Dated 24 September 2023

The primary reason for this amendment is to reduce the size of the study population and update the inclusion criteria in order to help with enrollment and study completion. Text relating to device vigilance was also added. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Table 1 (Study Procedures and Assessments) and Table 3 (The relationship of an adverse event to the IMP and/or Device) have been revised to reflect the changes described below. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/justification for change
Title page, Investigator Agreement, and Coordinating Investigator Agreement		
EMA Decision number of Pediatric Investigation Plan: ~~P/0411/2019~~ P/0378/2023	EMA Decision number of Pediatric Investigation Plan: P/0378/2023	Alignment with agreed modified paediatric investigation plan for fremanezumab
1.1. Introduction		
… in CM and EM to evaluate the safety and efficacy of fremanezumab. One Phase 4 study (Study TV48125-MH-40142) was conducted to evaluate the efficacy and safety of fremanezumab in adult patients with migraine and comorbid major depressive disorder.	… in CM and EM to evaluate the safety and efficacy of fremanezumab. One Phase 4 study (Study TV48125-MH-40142) was conducted to evaluate the efficacy and safety of fremanezumab in adult patients with migraine and comorbid major depressive disorder.	Updated text with info of completed Phase 4 Study.

Original text with changes shown	New wording	Reason/justification for change
1.2.2. Clinical Studies		
Overall in the fremanezumab migraine clinical development program, ~~2512~~2853 patients with…	Overall in the fremanezumab migraine clinical development program, 2853 patients with…	Updated text with info of completed Phase 4 Study
…composed of ~~14~~ 15 studies…blind, placebo-controlled), ~~and~~ 3 Phase 3 studies (2 double-blind, placebo-controlled studies and 1 long-term, double-blind safety study [Study TV48125-CNS-30051], and 1 Phase 4 study)~~])~~….	…composed of 15 studies …blind, placebo-controlled), 3 Phase 3 studies (2 double-blind, placebo-controlled studies and 1 long-term, double-blind safety study [Study TV48125-CNS-30051], and 1 Phase 4 study). …	Updated text with info of completed Phase 4 Study.
Six~~Five~~ studies in adult migraine patients (2 Phase 2b studies, ~~and~~ 3 Phase 3 studies, and 1 Phase 4 study) examining the safety…	Six studies in adult migraine patients (2 Phase 2b studies, 3 Phase 3 studies, and 1 Phase 4 study) examining the safety…	Updated text with info of completed Phase 4 Study.
…dose regimens of fremanezumab in the preventive treatment of migraine (CM and EM). The Phase 4 Study TV48125-MH-40142 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study followed by an open-label extension to evaluate the efficacy and safety of fremanezumab for preventive treatment of migraine in patients with major depressive disorder.	…dose regimens of fremanezumab in the preventive treatment of migraine (CM and EM). The Phase 4 Study TV48125-MH-40142 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study followed by an open-label extension to evaluate the efficacy and safety of fremanezumab for preventive treatment of migraine in patients with major depressive disorder.	Updated text with info of completed Phase 4 Study.
1.2.2.2. Clinical Safety and Efficacy Studies		
…3 Phase 3 studies in patients with migraine. Additional studies are the Phase 3b FOCUS study [TV48125-CNS-30068], the Japanese [Otsuka] registration studies, and the Phase 4 UNITE study [TV48125-MH-40142]). Safety results from these studies are presented in the IB.	…3 Phase 3 studies in patients with migraine. Additional studies are the Phase 3b FOCUS study [TV48125-CNS-30068], the Japanese [Otsuka] registration studies, and the Phase 4 UNITE study [TV48125-MH-40142]). Safety results from these studies are presented in the IB.	Update
None of the identified risks was serious or considered as an important risk. ~~No serious adverse reactions (SARs) are considered expected by the sponsor for the purpose of expedited reporting of suspected unexpected serious adverse reactions (SUSAR)~~.	None of the identified risks was serious or considered as an important risk.	Statement not relevant for protocol as can be quicklu outdated. The IB includes this information.
1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s) and/or Device		

Original text with changes shown	New wording	Reason/justification for change
1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s) and/or Device	1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s) and/or Device	Updated according to template and added device vigilance text throughout protocol.
1.3.1.2. Important Potential Risk		
~~Severe hypersensitivity reactions are regarded as a potential risk for fremanezumab.~~ Mild and moderate drug hypersensitivity events …	Mild and moderate drug hypersensitivity events…	Updated as hypersensitivity reaction are no longer a potential risk
For additional details, refer to the IB~~current IB, Section 7.5.5~~.	For additional details, refer to the IB.	Update
2.2. Exploratory Objective and Endpoints		
[redacted]	[redacted]	Clarification
3.1. General Study Design and Study Schematic Diagram		
An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (standard deviation [SD]) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients have completed…	An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (standard deviation [SD]) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients have completed…	Clarification
The total duration of the study is planned to be 51~~36~~ months (from Q1 2020 to Q2 2024~~Q4 2022~~).	The total duration of the study is planned to be 51 months (from Q1 2020 to Q2 2024).	Updated study timelines according to new projections and reduced study population.
The enrollment target is approximately 230 EM patients,~~288 patients in total with potential increase (up to approximately 400 patients total), depending on the planned interim analysis of blinded sample size re-estimation (Section 9.12)~~, with a goal of approximately 20~~at least 30~~% of those patients in the 6- through 11-year-old age group. ~~The goal in the 12- through 17-year-old age group is to enroll similar numbers of patients who are 12 through 14 years old and 15 through 17 years old.~~	The enrollment target is approximately 230 EM patients, with a goal of approximately 20% of those patients in the 6- through 11-year-old age group.	Updated text to reduce study population and study criteria in order to aid timely study completion.
3.2. Planned Number of Patients and Countries		

Original text with changes shown	New wording	Reason/justification for change
~~Approximately 412 patients will be screened to achieve 288 randomized patients.~~ The number of evaluable patients is planned to be approximately 220 (110~~approximately 244(122~~ evaluable patients completing the study per treatment group). Details on definition of evaluable patients and sample size are given in Section 9. The total number of randomized patients planned is approximately 230.~~288 with potential increase (up to approximately 400 patients total), depending on the planned interim analysis of blinded sample size re-estimation (Section 9.12).~~ … The study is expected to start in Q1 2020 and last until Q2 2024~~Q4 2022~~.	The number of evaluable patients is planned to be approximately 220 (110 evaluable patients completing the study per treatment group). Details on definition of evaluable patients and sample size are given in Section 9. The total number of randomized patients planned is approximatly 230. … The study is expected to start in Q1 2020 and last until Q2 2024.	Updated text to reflect reduced study population, projections, and currently observed drop-out rate. Removed text on interim analysis here, as analysis was already conducted and based on variations sample size does not need to be increased.
3.3. Justification for Study Design and Selection of Population		
Patients on concomitant migraine preventive medications must be on a stable dose for at least 2…	Patients on concomitant migraine preventive medications must be on a stable dose for at least 2…	Clarification
…A list of migraine preventive medications allowed for any condition for the duration of the study for approximately~~up to~~ 30% of patients is presented in Appendix C. The total number of patients receiving migraine concomitant preventive medication during the study will be approximately~~not exceed~~ 30% of the total number of patients randomized.	…A list of migraine preventive medications allowed for any condition for the duration of the study for approximately 30% of patients is presented in Appendix C. The total number of patients receiving concomitant preventive medication during the study will be approximately 30% of the total number of patients randomized.	Aid with recruitement and clarification
3.5 Schedule of Study Procedures and Assessments		
Table 1 Study Procedures and Assessments		
[d] The~~In case of an out-of-window visit, the~~ date of the next visit will be calculated based on the actual date of the last administration of study drug.	[d] The date of the next visit will be calculated based on the actual date of the last administration of study drug.	Clarification that the date of the next dosing visit is always calculated based on the actual date of the last investigational medicinal product administration; regardless of whether the visit is out-of-window or not.
4.1. Patient Inclusion Criteria		
[f.] [Revision 01] Not using migraine preventive medications (listed in Appendix C)… no more than 2	[f.] [Revision 01] Not using migraine preventive medications (listed in Appendix C)… no more than 2	Aid with recruitement and clarification

Original text with changes shown	New wording	Reason/justification for change
migraine preventive medications (listed in Appendix C)…A list of migraine preventive medications allowed for any condition for the duration of the study for approximately~~up to~~ 30% of patients is presented in Appendix C. … **Note:** A person is considered to be not using migraine preventive medications (listed in Appendix C)…but used for migraine prevention is permitted during the study; however, these patients will not be counted toward the approximately 30% patient limit threshold.	migraine preventive medications (listed in Appendix C)…A list of migraine preventive medications allowed for any condition for the duration of the study for approximately 30% of patients is presented in Appendix C. … **Note:** A person is considered to be not using migraine preventive medications (listed in Appendix C)… but used for migraine prevention is permitted during the study; however, these patients will not be counted toward the approximately 30% patient limit threshold.	
4.2. Patient Exclusion Criteria		
d. [Revision 01] The patient has a current history of a clinically significant psychiatric condition, at the discretion of the investigator. A~~a~~ny prior history of a suicide attempt, or a history of suicidal ideation with a specific plan within the past 2 years, must be excluded~~at the discretion of the investigator~~.	d. [Revision 01] The patient has a current history of a clinically significant psychiatric condition, at the discretion of the investigator. Any prior history of a suicide attempt, or a history of suicidal ideation with a specific plan within the past 2 years must be excluded.	Clarification
e. … known active infection of coronavirus disease 2019 (COVID-19).	e. … known active infection of coronavirus disease 2019 (COVID-19).	Formatting update
4.3. Withdrawal Criteria and Procedures for the Patient		
… • Patient takes prohibited concomitant medications ~~as defined in the protocol~~ chronically. …• Any patient who demonstrates suicidal ideation and/or any suicidal behavior…should be withdrawn from the study and discontinued from study treatment.	… •Patient takes prohibited concomitant medications chronically • Any patient who demonstrates suicidal ideation and/or any suicidal behavior…should be withdrawn from the study and discontinued from study treatment	Alignment with Section 7.9
…or until a determination of a cause unrelated to the IMP [and/or PFS] or study procedure is made).	…or until a determination of a cause unrelated to the IMP [and/or PFS] or study procedure is made).	Updated according to template and added device vigilance text throughout protocol.
4.4. Replacement of Patients		
Study enrollment assumes up to a 4~~15~~% discontinuation rate. The number of patients randomized (230~~288~~) was selected to achieve the	Study enrollment assumes up to a 4% discontinuation rate. The number of patients randomized (230) was selected to achieve the estimated 220 patients	Updated text to reflect reduced study population and currently observed drop-out rate.

Original text with changes shown	New wording	Reason/justification for change
estimated 220~~244~~ patients completing the study (110~~122~~ patients per treatment group).	completing the study (110 patients per treatment group).	
5.3.1. Justification for Dose of Test Investigational Medicinal Product and/or Device		
5.3.1. Justification for Dose of Test Investigational Medicinal Product and/or Device	5.3.1. Justification for Dose of Test Investigational Medicinal Product and/or Device	Updated according to template and added device vigilance text throughout protocol.
5.6. Prior and Concomitant Medication or Therapy (Other sections affected by this change: Appendix C)		
The following medications are prohibited for regular chronic use during…	The following medications are prohibited for regular chronic use during…	Clarification
Approximately~~Up to~~ 30% of EM patients will be allowed to remain on no more than 2 migraine preventive medications in Appendix C …Additional details on ~~concomitant~~ migaine preventive medications are provided in Appendix C. ~~Patients~~ For chronic use of these medications for any indication, patients must have been on a stable, well-tolerated dose of this migraine preventive…For the remaining approximately 70% of EM patients…	Approximately 30% of EM patients will be allowed to remain on no more than 2 migraine preventive medications in Appendix C… Additional details on migaine preventive medications are provided in Appendix C. For chronic use of these medications for any indication, patients must have must have been on a stable, well-tolerated dose of this migraine preventive …For the remaining approximately 70% of EM patients…	Aid with recruitement
As-needed (PRN) use of these medications are allowed during the course of the study for any indications and do not have to have established dosing regimens.	As-needed (PRN) use of these medications are allowed during the course of the study for any indications and do not have to have established dosing regimens	Clarification
Patients will be allowed PRN use of to use acute medications to treat acute migraine attacks, as needed, with the exception of regular use of medications…	Patients will be allowed PRN use of to use acute medications to treat acute migraine attacks, as needed, with the exception of regular use of medications…	Clarification
The chronic use of concomitant therapies not listed in Appendix C for any indication~~s other than migraine prevention~~ is allowed throughout the course of the study~~, provided they are not known to be effective for migraine or they meet the criteria for permitted concomitant migraine preventive medication for any condition for up to 30% of patients~~.	The chronic use of concomitant therapies not listed in Appendix C for any indication is allowed throughout the course of the study.	Clarification
All patients must have been on a stable dose of these ~~all their~~ concomitant medications for at least 2	All patients must have been on a stable dose of these concomitant medications for chronic conditions for at least 2	Clarification

Original text with changes shown	New wording	Reason/justification for change
months…PRN use of medications for adverse events or intercurrent acute situations are allowed.	months…PRN use of medications for adverse events or intercurrent acute situations are allowed.	
7.1.1. Definition of an Adverse Event		
• drug/drug or drug device interactions	• drug/drug or drug device interactions	Updated according to template and added device vigilance text throughout protocol.
7.1.2. Definition of an Adverse Device Effect		
Not applicable	New Section added	Updated according to template and added device vigilance text throughout protocol.
7.1.3. Recording and Reporting of Adverse Events		
…regardless of the severity of the event or judged relationship to the study drug (and/or PFS). For serious adverse events and protocol-defined adverse events of special interest for expedited reporting to GPSP, the serious adverse event Protocol-Defined Adverse Events of Special Interest Form must be completed, and the serious adverse event and the protocol-defined adverse events of special interest must be reported…	…regardless of the severity of the event or judged relationship to the study drug (and/or PFS). For serious adverse events and protocol-defined adverse events of special interest for expedited reporting to GPSP, the serious adverse event Protocol-Defined Adverse Events of Special Interest Form must be completed, and the serious adverse event and the protocol-defined adverse events of special interest must be reported…	Updated according to template and added device vigilance text throughout protocol.
…or until a determination of a cause unrelated to the study drug (and/or PFS) or study procedure is made.	or until a determination of a cause unrelated to the study drug (and/or PFS) or study procedure is made.	Updated according to template and added device vigilance text throughout protocol.
7.1.4. Recording and Reporting of Adverse Device Effect		
Not applicable	New Section added (including Figure 2: Decision Tree for Adverse Events and Adverse Device Effects Classification).	Updated according to template and added device vigilance text throughout protocol.
7.1.6. Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device		
7.1.6. Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device	7.1.6. Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device	Updated according to template and added device vigilance text throughout protocol.
The relationship of an adverse event to the IMP (and/or PSF) is characterized as described in…	The relationship of an adverse event to the IMP (and/or PSF) is characterized as described in….	Updated according to template and added device vigilance text throughout protocol.
Table 3: The Relationship of an Adverse Event to the IMP and/or	Table 3: The Relationship of an Adverse Event to the IMP and/or	Updated according to template and added device

Original text with changes shown	New wording	Reason/justification for change
Device	Device Text in the table was updated in accordance with the title.	vigilance text throughout protocol.
7.1.7. Serious Adverse Events and Serious Adverse Device Effects		
7.1.7.Serious Adverse Events and Serious Adverse Device Effects	7.1.7. Serious Adverse Events and Serious Adverse Device Effects	Updated according to template and added device vigilance text throughout protocol.
For recording of serious adverse events and serious adverse device effects, the study period is defined for each patient as that time period from signature of the ICF to visit 5 (EOT visit). Serious adverse events and serious adverse device effects occurring…	For recording of serious adverse events and serious adverse device effects, the study period is defined for each patient as that time period from signature of the ICF to visit 5 (EOT visit). Serious adverse events and serious adverse device effects occurring…	Updated according to template and added device vigilance text throughout protocol.
7.1.7.2.Definition of a Serious Adverse Device Effect		
Not applicable	New Section added	Updated according to template and added device vigilance text throughout protocol.
7.1.7.3. Expectedness		
An unanticipated serious adverse device effect is a serious adverse device effect that, by its nature, incidence, severity, or outcome, has not been listed in Appendix K (Appendix Table 1 and Appendix Table 2).	An unanticipated serious adverse device effect is a serious adverse device effect that, by its nature, incidence, severity, or outcome, has not been listed in Appendix K (Appendix Table 1 and Appendix Table 2).	Updated according to template and added device vigilance text throughout protocol.
7.1.7.4.3. Reporting a Serious Adverse Device Effect		
Not applicable	New Section added	Updated according to template and added device vigilance text throughout protocol.
7.1.8. Protocol-Defined Adverse Events of Special Interest		
…anaphylactic reactions. ~~Although treatment with fremanezumab is not expected to impact the course or severity of COVID-19, suspected or confirmed COVID-19, based on local standard of care, will be considered a protocol-defined adverse event of special interest to be sent to the sponsor's GPSP for the purpose of timely and robust adverse event data collection.~~ Hypersensitivity reactions will be..	…ophthalmic-related adverse events of at least moderate severity and severe hypersensitivity or anaphylactic reactions. Hypersensitivity reactions will be…	COVID-19 is no longer adverse event of special interest and doesn't need to be reported via same procedure as serious adverse events.

Original text with changes shown	New wording	Reason/justification for change
7.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis		
…listed below (Table 4). Note, reflex tests (eg, red blood cell [RBC] shapes, RBC morphology, and other microscopic findings) may be triggered automatically.	…listed below (Table 4). Note, reflex tests (eg, red blood cell [RBC] shapes, RBC morphology, and other microscopic findings) may be triggered automatically.	Clarification
7.4.2.1. Human Chorionic Gonadotropin Tests		
Serum β-HCG tests will be performed for all female patients who are postmenarchal or ≥12 years of age at screening (visit 1) and visit 5; urine β-HCG tests will be performed at all ~~other~~ visits (Table 1).	Serum β-HCG tests will be performed for all female patients who are postmenarchal or ≥12 years of age at screening (visit 1) and visit 5; urine β-HCG tests will be performed at all visits (Table 1).	Clarification (and alignment with Table 1) that urine pregnancy tests are performed at all visits.
9.1. Sample Size and Power Considerations		
The sample size planned is approximately 220~~244~~ patients (110~~122~~ evaluable patients completing… a sample size of 110~~122~~ patients per treatment group gives at least 87~~90~~% power for the study to succeed at an alpha level of 0.05. Assuming a 4~~15~~% discontinuation rate, approximately 230~~288~~ patients (115~~144~~ patients… … The enrollment target is approximately 230~~288~~ patients in total, ~~with potential increase (up to approximately 400 patients total), depending on the planned interim analysis of blinded sample size re-estimation (Section 9.12),~~ with a goal of approximately 20~~at least 30~~% of those patients in the 6- through 11-year-old age group. ~~The goal in the 12- through 17-year-old age group is to enroll similar numbers of patients who are 12 through 14 years old and 15 through 17 years old.~~	The sample size planned is approximately 220 patients (110 evaluable patients completing… a sample size of 110 patients per treatment group gives at least 87% power for the study to succeed at an alpha level of 0.05. Assuming a 4% discontinuation rate, approximately 230 patients (115 patients… … The enrollment target is approximately 230 patients in total, with a goal of approximately 20% of those patients in the 6- through 11-year-old age group.	Updated text to reflect reduced study population, projections, power, and currently observed drop-out rate. Removed text on interim analysis here, as analysis was already conducted and based on variations sample size does not need to be increased.
9.2.4. Per-Protocol Analysis Set		
The per-protocol analysis set will consist of all patients in the FAS who have completed the study without any important deviations, such as important ~~violations of the~~ inclusion/exclusion criteria deviations, important deviations~~or any violations~~ or omissions of the IMP~~drug~~	The per-protocol analysis set will consist of all patients in the FAS who have completed the study without any important deviations, such as important inclusion/exclusion criteria deviations, important deviations or omissions of the IMP administration, or unexpected drug concentration findings, and who	Clarification

Original text with changes shown	New wording	Reason/justification for change
administration, or unexpected drug concentration findings, and who have at least 75% diary compliance after the start of treatment~~, or who have unexpected drug concentration findings~~.	have at least 75% diary compliance after the start of treatment.	
9.5.4.1. Primary Efficacy Analysis		
The model will include treatment, sex, puberty status, region, baseline weight category (<45.0 kg or ≥45.0 kg), and preventive medication use at baseline…	The model will include treatment, sex, puberty status, region, baseline weight category (<45.0 kg or ≥45.0 kg), and preventive medication use at baseline…	Clarification and alignment with Statistical Analysis Plan
9.5.4.3. Secondary Efficacy Analysis		
…region, puberty status, baseline weight category (<45.0 kg or ≥45.0 kg), and preventive medication use at baseline (Yes/No).	…region, puberty status, baseline weight category (<45.0 kg or ≥45.0 kg), and preventive medication use at baseline (Yes/No).	Clarification and alignment with Statistical Analysis Plan
9.7. Safety Analysis		
…adverse events determined by the investigator to be related to test IMP (and/or PFS) (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, serious adverse device effects, and adverse events and adverse device effects causing withdrawal from the study.	…adverse events determined by the investigator to be related to test IMP (and/or PFS) (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, serious adverse device effects, and adverse events and adverse device effects causing withdrawal from the study.	Updated according to template and added device vigilance text throughout protocol
9.11. Immunogenecity Analysis		
…The impact of immunogenicity on the pharmacokinetic profile, drug efficacy, and clinical safety will be evaluated if data allows. This analysis will be reported separately.	…The impact of immunogenicity on the pharmacokinetic profile, drug efficacy, and clinical safety will be evaluated if data allows. This analysis will be reported separately.	Clarification
9.12. Planned Interim Analysis		
… of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients…	… of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% (±10%) of patients…	Clarification (ie, interim analysis was already conducted and based on variations sample size did not need be be increased)
11. COMPLIANCE STATEMENT		
This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6 and ISO 14155: Clinical investigation of	This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6 and ISO 14155: Clinical investigation of	Updated according to template and added device vigilance text throughout protocol.

Original text with changes shown	New wording	Reason/justification for change
medical devices for human subjects – Good clinical practice, and any applicable…	medical devices for human subjects – Good clinical practice, and any applicable…	
APPENDIX A CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
[redacted] Global Patient Safety and Pharmacovigilance Teva Pharmaceuticals~~Pharmaceutical Industries Ltd.~~ ~~Tel:~~ [redacted] Cell: [redacted] [redacted]	[redacted] Global Patient Safety and Pharmacovigilance Teva Pharmaceuticals Cell: [redacted] [redacted]	Updated contact details for Sponsor's Representative of Global Patient Safety and Pharmacovigilance
Clario~~eResearch Technology, Inc~~ 1818 Market Street #1000 Philadelphia, PA 19103 United States	Clario 1818 Market Street #1000 Philadelphia, PA 19103 United States	Updated contact details for Central Electrocardiogram Evaluation
APPENDIX B STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
1. Procedures for Screening (Visit 1, Days -28 to -1) …• serum beta human chorionic gonadotropin (β-HCG) and urine pregnancy tests (only female patients who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period …	1. Procedures for Screening (Visit 1, Days -28 to -1) …• serum beta human chorionic gonadotropin (β-HCG) and urine pregnancy tests (only female patients who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period …	Alignment with Section 7.4.2.1
4. End of Treatment/Early Withdrawal (Visit 5 [Day 85±3 days]) …• serum β-HCG and urine pregnancy tests (only female patients who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period …	4. End of Treatment/Early Withdrawal (Visit 5 [Day 85±3 days]) …• serum β-HCG and urine pregnancy tests (only female patients who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period …	Alignment with Section 7.4.2.1
APPENDIX C. PREVENTIVE MIGRAINE MEDICATIONS FOR ANY CONDITION ALLOWED FOR THE DURATION OF THE STUDY FOR APPROXIMATELY 30% OF PATIENTS		
For the remaining approximately 70% of EM patients, the chronic use of these ~~following~~ medications are not allowed…	For the remaining approximately 70% of EM patients, the chronic use of these medications are not allowed	Clarification
PRN use of the following medications are allowed during the course of the study for any indication and do not have to have established dosing regimens.	PRN use of the following medications are allowed during the course of the study for any indication and do not have to have established dosing regimens.	Clarification

Original text with changes shown	New wording	Reason/justification for change
Patients will be allowed PRN ~~to~~ use of acute medications to treat acute migraine attacks, as needed, with the exception of regular use of medications containing opioids and barbiturates.	Patients will be allowed PRN use of acute medications to treat acute migraine attacks, as needed, with the exception of regular use of medications containing opioids and barbiturates	Clarification
APPENDIX K. PRODUCT COMPLAINTS		
Clinical Product Complaints/Device Deficieny	Clinical Product Complaints/Device Deficieny	Updated according to template and added device vigilance text throughout protocol.
For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (or item) be sent	For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (or item) be sent.	Updated according to template and added device vigilance text throughout protocol.
*Please refer to Appendix Table 1 and Appendix Table 2.	*Please refer to Appendix Table 1 and Appendix Table 2.	Updated according to template and added device vigilance text throughout protocol.
Handling of Investigational Medicinal Product(s)/Devices at the Investigational Center(s)	Handling of Investigational Medicinal Product(s)/Devices at the Investigational Center(s)	Updated according to template and added device vigilance text throughout protocol.
If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP (and/or PFS). If it is determined that the investigational center must return all IMP (and/or PFS), the sponsor will provide the information needed to handle the return.	If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP (and/or PFS). If it is determined that the investigational center must return all IMP (and/or PFS), the sponsor will provide the information needed to handle the return.	Updated according to template and added device vigilance text throughout protocol.
The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (see below: Assessment of Device Performance), and any actions	The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (see below: Assessment of Device Performance), and any actions	Updated according to template and added device vigilance text throughout protocol.
Not applicable	Added new subsection “Assessment of Device Performance”. Including Appedix Figure 1: Decision Tree for Device Deficiencies, Appendix Table 1: Potential Use-Related Deficiencies That Could Lead to Serious Adverse Events, and Appendix Table 2: Potential Design	Updated according to template and added device vigilance text throughout protocol.

Original text with changes shown	New wording	Reason/justification for change
	Related Deficiencies That Could Lead to Serious Adverse Events.	
APPENDIX O. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19		
Appendix O and its internal cross refrences were removed thoughout document		No longer relevant as pandemic passed.

16.2. Administrative Letter Dated 21 December 2021

ADMINISTRATIVE LETTER 06

Study number: TV48125-CNS-30083

Clinical Study Protocol with Amendment 08

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age, approved date 09 December 2021

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002055-42

21 December 2021

Dear Investigator:

The purpose of this letter is to correct inconsistencies and/or provide clarification for the protocol sections outlined below. Where applicable, changes made to the text (in italics) are shown (revisions and additions are shown in bold; deletions are shown in strikethrough).

In Section 3.5. Schedule of Study Procedures and Assessments, it is clarified that the date of the next dosing visit is always calculated based on the actual date of the last investigational medicinal product administration; regardless of whether the visit is out-of-window or not. Calculations, however, already account for this via the Interactive Response Technology System. Therefore, footnote "*d*", under the table of Study Procedures and Assessments (Table 1), is revised as shown in the table below.

Before	After
In case of an out-of-window visit, the date of the next visit will be calculated based on the actual date of the last administration of study drug.	~~*In case of an out-of-window visit, t*~~*The date of the next visit will be calculated based on the actual date of the last administration of study drug.*

In Section 7.4.2.1., the word "*other*" will be deleted from the sentence (as shown in the table below) in order to correct the discrepancy with pregnancy tests. Thus, clarifying that urine pregnancy tests are performed at all visits. The table of Study Procedures and Assessments (Table 1), however, correctly reflects the intent of the protocol, which is to perform urine pregnancy tests at all visits and serum beta-human chorionic gonadotropin (β-HCG) tests at screening (visit 1) and visit 5.

Before	After
Serum β-HCG tests will be performed for all female patients who are postmenarchal or ≥12 years of age at screening (visit 1) and visit 5; urine β-HCG tests will be performed at all other visits (Table 1).	*Serum β-HCG tests will be performed for all female patients who are postmenarchal or ≥12 years of age at screening (visit 1) and visit 5; urine β-HCG tests will be performed at all* ~~*other*~~ *visits (Table 1).*

To align Appendix B Study Procedures and Assessments by Visit, with Section 7.4.2.1. (as mentioned above), the discrepancy with pregnancy tests is revised under visit 1 and 5 as shown in the table below.

Before	After
1. Procedures for Screening (Visit 1, Days -28 to -1): • *serum beta-human chorionic gonadotropin (β-HCG) pregnancy test (only female patients who are postmenarchal or ≥12 years of age); inquire and record start / stop date of menstrual period.*	*1. Procedures for Screening (Visit 1, Days -28 to -1):* • *serum beta-human chorionic gonadotropin (β-HCG) **and urine** pregnancy tests (only female patients who are postmenarchal or ≥12 years of age); inquire and record start / stop date of menstrual period.*
4. End of Treatment/Early Withdrawal (Visit 5 [Day 85±3 days]): • *serum β-HCG pregnancy test (only female patients who are postmenarchal or ≥12 years of age); inquire and record start / stop date of menstrual period.*	*4. End of Treatment/Early Withdrawal (Visit 5 [Day 85±3 days]):* • *serum β-HCG **and urine** pregnancy tests (only female patients who are postmenarchal or ≥12 years of age); inquire and record start / stop date of menstrual period.*

To align Section 4.3. Withdrawal Criteria and Procedures for the Patient, with the existing wording in Section 7.9. Assessment of Suicidality, regarding the withdrawal of patients who demonstrate suicidal ideation / behavior from the study, a new bullet point is added in Section 4.3., as shown in the table below.

Before	After
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: (New bullet added)	*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:* • ***Any patient who demonstrates suicidal ideation and/or any suicidal behavior at any point during the study should be withdrawn from the study and discontinued from study treatment.***

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your Institutional Review Board/Independent Ethics Committee for review and acknowledgment.

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

Sincerely,

DocuSigned by:
[redacted]

[redacted]
Teva Branded Pharmaceutical Products R&D, Inc.

16.3. Amendment 08 Dated 09 December 2021

The primary reason for this amendment is to revise the protocol to allow combined oral progestin and estrogen contraceptives, expand the BMI upper limit to 120% of the 95th percentile in order reflect the real-world patient population, and to clarify potential sample size changes subsequent to the planned interim analysis. This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment and Written Request agreements. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/justification for change
3.1. General Study Design and Study Schematic (Other sections affected by this change: 3.2, 9.1, and 9.12)		
An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (SD) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% of patients have completed at least 3 months of treatment or have withdrawn from the study early. If the pooled SD is <4.8, there will be no change in enrollment; if the pooled SD is >5.2, the sample size will increase to approximately 400 patients; and if the pooled SD is between 4.8 and 5.2, the sample size will increase to approximately 340 patients total.	An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (SD) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% of patients have completed at least 3 months of treatment or have withdrawn from the study early. If the pooled SD is <4.8, there will be no change in enrollment; if the pooled SD is >5.2, the sample size will increase to approximately 400 patients; and if the pooled SD is between 4.8 and 5.2, the sample size will increase to approximately 340 patients total.	Added interim analysis language.
The enrollment target is approximately 288 patients in total with potential increase (up to approximately of 400 patients total) depending on the planned interim analysis of blinded sample size re-estimation (Section 9.12), with a goal of at least 30% of those patients in the 6- through 11-year-old age group. The goal in the 12- through 17-year-old age group is to enroll similar numbers of patients who are 12 through 14 years old and 15 through 17 years old.	The enrollment target is approximately 288 patients in total with potential increase (up to approximately of 400 patients total), depending on the planned interim analysis of blinded sample size re-estimation (Section 9.12), with a goal of at least 30% of those patients in the 6- through 11-year-old age group. The goal in the 12- through 17-year-old age group is to enroll similar numbers of patients who are 12 through 14 years old and 15 through 17 years old.	Added interim analysis language.

Original text with changes shown	New wording	Reason/justification for change
3.3. Justification for Study Design and Selection of Population (Other sections affected by this change: 4.1)		
A list of migraine preventive medications allowed for any condition for the duration of the study for up to 30% of patients is presented in Appendix C.	A list of migraine preventive medications allowed for any condition for the duration of the study for up to 30% of patients is presented in Appendix C.	Clarification
Table 1: Study Procedures and Assessments		
[c] Electrocardiograms will be performed, weight will be recorded (visit 2 only), urine pregnancy tests will be performed at all visits prior to dosing, and blood samples will be collected before study drug administration. Assessment of injection site reactions will be performed after administration of each dose of study drug, before the patient leaves the investigational site. All other study procedures can be performed at any time during the visit.	[c] Electrocardiograms will be performed, weight will be recorded (visit 2 only), urine pregnancy tests will be performed at all visits prior to dosing, and blood samples will be collected before study drug administration. Assessment of injection site reactions will be performed after administration of each dose of study drug, before the patient leaves the investigational site. All other study procedures can be performed at any time during the visit.	Clarification.
4.1. Patient Inclusion Criteria		
d. The patient or parent/caregiver has maintained a prospectively collected headache diary during a 28-day baseline period in which at least 4 migraine days and ≤14 headache days were recorded ~~on 6 to 14 days inclusive~~. Migraine days have at least 1 of the following migraine characteristics:	d. The patient or parent/caregiver has maintained a prospectively collected headache diary during a 28-day baseline period in which at least 4 migraine days and ≤14 headache days were recorded. Migraine days have at least 1 of the following migraine characteristics:	Change in the amount of migraine days for entry criteria
-headache was treated by a nonsteroidal anti-inflammatory drug (NSAID), paracetamol, triptan, or ergot preparation.	-headache was treated by a nonsteroidal anti-inflammatory drug (NSAID), paracetamol, triptan, or ergot preparation.	Paracetamol is added as it is a commonly used acute medication
f. Note: A person is considered to be not using preventive medications when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinum toxin A or B prior to screening (visit 1). The use of other agents that are not included in Appendix C but used for migraine prevention is permitted during the study; however, these patients will not be counted towards the 30% patient limit threshold.	f. Note: A person is considered to be not using preventive medications when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinum toxin A or B prior to screening (visit 1). The use of other agents that are not included in Appendix C but used for migraine prevention is permitted during the study; however, these patients will not be counted toward the 30% patient limit threshold.	Clarification

Original text with changes shown	New wording	Reason/justification for change
m. The patient has a body mass index ranging from the 5th to 120% of the 95th percentile, inclusive, at screening, based on the local standard.	m. The patient has a body mass index ranging from the 5th to 120% of the 95th percentile, inclusive, at screening, based on the local standard.	Expansion of patient body mass index to allow representation of real-world patient population
4.2. Patient Exclusion Criteria		
b. The patient has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine or in the head or neck area for any condition during the 2 months prior to the day of the screening visit.	b. The patient has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine or in the head or neck area for any condition during the 2 months prior to the day of the screening visit.	Clarification
g. The patient is pregnant~~, nursing, or taking a combined estrogen and progestogen hormonal contraceptive~~ or nursing.	g. The patient is pregnant or nursing.	Changes to reflect allowance of combination contraception
o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <~~90~~ 75 mL/min/1.73m^2, as calculated by the revised Schwartz formula (~~CrCl=[ke~~ eGFR=[0.413×Ht]/Serum Creatinine), or evidence of renal disease during the 28-day baseline period.	o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <75 mL/min/1.73m2, as calculated by the revised Schwartz formula (eGFR=[0.413×Ht]/Serum Creatinine), or evidence of renal disease during the 28-day baseline period.	Clarification of Schwartz formula, reflecting the administrative letter
p. The patient has any history of alcohol or drug abuse. The definition of alcohol or drug abuse, including marijuana, is based on investigator's clinical judgement.	p. The patient has any history of alcohol or drug abuse. The definition of alcohol or drug abuse, including marijuana, is based on the investigator's clinical judgment.	Clarification on alcohol and drug abuse, including marijuana.
See New wording column.	u. The patient has a current or past medical history of hemiplegic migraine.	Added an exclusion criterion
5.1.3. Placebo Investigational Medicinal Product		
Table 2: Investigational Medicinal Products Used in the Study		
[redacted]	[redacted]	Change updating manufacturer name for the test and placebo investigational medicinal products
5.6. Prior and Concomitant Medication or Therapy		

Original text with changes shown	New wording	Reason/justification for change
All prior therapy, medication, or procedure (ie, procedures for the treatment of migraine [eg, nerve blocks]) for the treatment of migraine a patient has had during their lifetime will be recorded on the CRF.	All prior therapy, medication, or procedure (ie, procedures for the treatment of migraine [eg, nerve blocks]) for the treatment of migraine a patient has had during their lifetime will be recorded on the CRF.	Clarification
6.1.4. Pediatric Quality of Life Inventory		
The Pediatric Quality of Life Inventory (PedsQL) 4.0 is a brief 23-item health-related quality of life instrument that evaluates quality of life in 4 areas of functioning: physical, emotional, social, and school functioning. The PedsQL 4.0 has 4 age ranges: toddlers (2 through 4 years), young child (5 through 7 years), child (8 through 12 years), and adolescent (13 through 18 years). This study will use the young child, child, and adolescent formats. The PedsQL version that will be used for the patient for the duration of the study will be based on the age of the patient at visit 2 and will not change during the course of the study.	The Pediatric Quality of Life Inventory (PedsQL) 4.0 is a brief 23-item health-related quality of life instrument that evaluates quality of life in 4 areas of functioning: physical, emotional, social, and school functioning. The PedsQL 4.0 has 4 age ranges: toddlers (2 through 4 years), young child (5 through 7 years), child (8 through 12 years), and adolescent (13 through 18 years). This study will use the young child, child, and adolescent formats. The PedsQL version that will be used for the patient for the duration of the study will be based on the age of the patient at visit 2 and will not change during the course of the study.	Clarification
9.5.4.2. Sensitivity and Supplementary Analyses		
A sensitivity analysis for the primary efficacy endpoint will be conducted by using multiple imputation method for missing data. Sensitivity analysis using Mixed-Effect Model Repeated Measure method also will be conducted for change from baseline to months 1 through 3 in headache days of at least moderate severity. A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint. Additional subgroup analyses will be performed to investigate treatment effect among relevant sub-populations, such as sex, region, receiving preventive migraine therapy or not, receiving 2 preventive medications from Appendix C, and receiving alternative preventive medications that belong to the same classes but are not listed in Appendix C. The details will be described in the statistical analysis plan.	A sensitivity analysis for the primary efficacy endpoint will be conducted by using multiple imputation method for missing data. Sensitivity analysis using Mixed-Effect Model Repeated Measure method also will be conducted for change from baseline to months 1 through 3 in headache days of at least moderate severity. A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint. Additional subgroup analyses will be performed to investigate treatment effect among relevant sub-populations, such as sex, region, receiving preventive migraine therapy or not, receiving 2 preventive medications from Appendix C, and receiving alternative preventive medications that belong to the same classes but are not listed in Appendix C. The details will be described in the statistical analysis plan.	Clarification of additional subgroup analyses

Original text with changes shown	New wording	Reason/justification for change
Appendix C. PREVENTIVE MIGRAINE MEDICATIONS FOR ANY CONDITION ALLOWED FOR THE DURATION OF THE STUDY FOR UP TO 30% OF PATIENTS (Other sections affected by this change: 3.3, 4.1, 5.6)		
The chronic use of two of the following concomitant ~~preventive migraine~~ medications are allowed in up to ~~20~~ 30% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients using no more than 2 migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication. Patients must have been on a stable, well-tolerated dose of this medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 70% of patients, the chronic use of these medications are not allowed for migraine or for any other indications. As-needed (PRN) use of these medications are allowed during the course of the study. PRN use of these medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary PRN use is defined as any treatment regimen outside of the locally approved prescribing information or local treatment guidelines.	The chronic use of two of the following concomitant medications are allowed in up to 30% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients using no more than 2 migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication. Patients must have been on a stable, well-tolerated dose of this medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 70% of patients, the chronic use of the following medications is not allowed for migraine or for any other indications. As-needed (PRN) use of these medications are allowed during the course of the study. PRN use of the following medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the locally approved prescribing information or local treatment guidelines.	Clarification of preventative migraine medications to reflect real-world use
~~• Other: riboflavin, magnesium~~	See Original text with changes shown column.	Removal of riboflavin and magnesium from the Appendix C as they are not prescribed medicines
Other agents that are not on this list but used for migraine prevention that may be used per local guidelines or clinical practice preference are considered to have doubtful evidence for migraine prevention and therefore are treated the same as other concomitant medications and DO NOT need to be captured in eCRF pages specific for migraine preventive medications.	Other agents that are not on this list but used for migraine prevention that may be used per local guidelines or clinical practice preference are considered to have doubtful evidence for migraine prevention and therefore are treated the same as other concomitant medications and DO NOT need to be captured in eCRF pages specific for migraine preventive medications.	Clarification

Original text with changes shown	New wording	Reason/justification for change
APPENDIX G. BIRTH CONTROL METHODS AND PREGNANCY TESTING		
• Progestin and estrogen contraceptives (oral only) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP	• Progestin and estrogen contraceptives (oral only) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP	Changes to allow for oral progestin and estrogen contraceptives.
Appendix O. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19		
See New wording column.	Section 5.6 Prior and Concomitant Medication or Therapy There are currently no data available regarding the concomitant use of fremanezumab and the new COVID-19 vaccines. Based on Teva's knowledge of both fremanezumab and what has been published about the respective vaccines, Teva has no reason to believe there would be an interaction. However, the investigator should use his/her medical judgment regarding any concerns related to an individual patient. We do recommend not giving the 2 injections, the study drug, and the vaccines in the same arm if the injections are administered close together in time, as it would be difficult to tell which one caused any potential reaction. If logistically possible, we would recommend waiting at least 72 hours between the receipt of the vaccine and the subsequent dose of fremanezumab in order to allow for better attribution of causality should an adverse event occur after administration. As with any concomitant medication, the vaccine should be recorded in the source documentation and in the electronic data capture.	Clarification regarding the COVID-19 vaccination

16.4. Administrative Letter Dated 10 May 2021

ADMINISTRATIVE LETTER 05

Study number: TV48125-CNS-30083

Clinical Study Protocol with Amendment 07

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age, version date 20 August 2020

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002055-42

10 May 2021

Dear Investigator:

The purpose of this letter is to provide a clarification to the upper bound of estimated glomerular filtration rate for exclusion criterion o in the protocol. The current exclusionary limit of <90 mL/min/1.73m^2 was based on the original Schwartz formula that utilized the Jaffe method to measure serum creatinine level. In the original Schwartz formula (CrCl=[k×Ht]/Serum Creatinine), the k is dependent on age and gender. The laboratory vendor for this study, ICON Laboratories, informed the Sponsor that in recent years, the industry does not use the Jaffe method any longer and a different enzymatic assay is used to measure serum creatinine levels. As a result, the original Schwartz formula is not applicable for this study any longer. The new assay method ICON Laboratories uses is for the revised Schwartz formula (eGFR=[k×Ht]/Serum Creatinine), where k=0.413 regardless of age or gender. The appropriate exclusionary limit per the revised Schwartz formula is estimated glomerular filtration rate of <75 mL/min/1.73m^2. The clarification to exclusion criterion o is provided below:

Before	After
o. The patient has a serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <90 mL/min/1.73m^2, as calculated by the Schwartz formula (CrCl=[k×Ht]/Serum Creatinine), or evidence of renal disease during the 28-day baseline period.	o. The patient has a serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of **<75** mL/min/1.73m^2, as calculated by the **revised** Schwartz formula (**eGFR**=[**0.413**×Ht]/Serum Creatinine), or evidence of renal disease during the 28-day baseline period.

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your Institutional Review Board/Independent Ethics Committee for review and acknowledgment.

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

Sincerely,

DocuSigned by:

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

5/10/2021 | 1:15:52 PM EDT

16.5. Administrative Letter Dated 04 February 2021

ADMINISTRATIVE LETTER 04

Study number: TV48125-CNS-30083

Clinical Study Protocol with Amendment 07

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age, version date 20 August 2020

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002055-42

04 February 2021

Dear Investigator:

The purpose of this letter is (1) to clarify that the determination of the body mass index percentile will be based on local standard of practice and (2) to update the manufacturer's name for the vial presentation of the investigational medicinal product (IMP). The manufacturer itself remains the same. The clarification and update are provided below:

1. The determination of body mass index percentile for protocol inclusion criterion "m" in Section 4.1 and in the Synopsis will be based on the local standard of practice.
2. The change in the manufacturer's name for the vial presentation of the IMP in Protocol Table 2 and in the Synopsis is shown in the table below with new text in underline:

Before	After
Vial: [redacted]	Vial: [redacted]

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your Institutional Review Board/Independent Ethics Committee for review and acknowledgment.

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

Sincerely,

DocuSigned by:
[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

2/4/2021 | 12:21:16 PM EST

16.6. Administrative Letter Dated 05 November 2020

ADMINISTRATIVE LETTER 03

Study number: TV48125-CNS-30083

Clinical Study Protocol with Amendment 07

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age, version date 20 August 2020

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002055-42

05 November 2020

Dear Investigator:

The purpose of this letter is to clarify that chronic use of one of the concomitant medications listed in Protocol Appendix C, that are commonly used for migraine prevention, are allowed in up to 20% of patients. For the remaining 80% of patients, the chronic use of those medications are not allowed for migraine or for any other indications. As-needed (PRN) use of those medications listed in Protocol Appendix C are allowed during the course of the study. PRN use of those medications should be reported in the electronic case report form as concomitant medications.

The wording of Protocol Appendix C (and throughout the protocol as applicable) will be revised as follows to reflect this clarification (additions in underline font and deletions in strikethrough font):

"The chronic use of one of the following concomitant ~~preventive migraine~~ medications are allowed in up to 20% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients must have been on a stable, well tolerated dose of this ~~preventive~~ medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 80% of patients, the chronic use of these medications are not allowed for migraine or for any other indications. As-needed (PRN) use of these medications are allowed during the course of the study. PRN use of these medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary."

The final wording without tracked changes will be as follows:

"The chronic use of one of the following concomitant medications are allowed in up to 20% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine

preventive medication. Patients must have been on a stable, well tolerated dose of this medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 80% of patients, the chronic use of these medications are not allowed for migraine or for any other indications. As-needed (PRN) use of these medications are allowed during the course of the study. PRN use of these medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary."

The clarifying wording will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

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

[redacted]

Sincerely,

Signed by: [redacted]
Reason: I approved and digitally signed this document.
Date & Time: 05 Nov 2020 18:17 -05:00

[redacted]
Teva Branded Pharmaceutical Products R&D, Inc.

16.7. Amendment 07 Dated 20 August 2020

The primary reason for this amendment is to provide guidance for remote assessments to minimize the time that patients and caregivers are required to spend at the study site. This consideration was triggered by the COVID-19 pandemic; however, remote assessments can be carried out on a regular basis to provide flexibility for patients, caregivers, and site staff. Patient reported outcomes assessed in this study, including the PedMIDAS, PedsQL, and PGI-I, as well as the C-SSRS, are valid to be conducted remotely, as confirmed by the scale authors. Instructions on remote data collection are available in the site operational manual. This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment and Written Request agreements. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Additionally, COVID-19 pandemic-related operational updates were added to the study protocol as a new appendix (Appendix O). Administrative changes have been applied, including updating the Table of Contents.

Changes to the Protocol

Original text with changes shown	New wording	Reason/justification for change
TITLE PAGE		
See New wording column.	**COVID-19 pandemic-related operational updates are provided in Appendix O.**	Sentence was added to provide a link to the operational guidance for COVID-19 contained in Appendix O.
1.1. Introduction		
See New wording column.	In September 2018, fremanezumab was approved in the United States of America (US) for the preventive treatment of migraine in adults and marketed under the trade name AJOVY®. Fremanezumab has also been approved in the European Union (EU) and a number of countries worldwide.	Sentences were added to provide context regarding the regulatory status of fremanezumab in the adult population.
3.1. General Study Design and Study Schematic (Other sections affected by this change: 3.5)		
The total duration of the study is planned to be 36 months (from ~~approximately~~ Q1 2020 to Q4 2022).	The total duration of the study is planned to be 36 months (from Q1 2020 to Q4 2022).	Revised as quarter is an approximation.
See New wording column.	For coronavirus disease 2019 (COVID-19) updates, see Appendix O.	Updated sections to cross-references the addition of Appendix O.

Original text with changes shown	New wording	Reason/justification for change
3.2. Planned Number of Patients and Countries		
The study is expected to start in Q1 2020 and last until ~~approximately~~ Q4 2022.	The study is expected to start in Q1 2020 and last until Q4 2022.	Revised as quarter is an approximation.
Table 1 Study Procedures and Assessments		
c Electrocardiograms will be performed, and blood samples will be collected before study drug administration. Assessment of injection site reactions will be performed after administration of each dose of study drug, before the patient leaves the investigational site. All other study procedures can be performed at any time during the visit.	c Electrocardiograms will be performed, and blood samples will be collected before study drug administration. Assessment of injection site reactions will be performed after administration of each dose of study drug, before the patient leaves the investigational site. All other study procedures can be performed at any time during the visit.	Footnote "c" was modified to specify that ECGs will be performed before study drug administration.
See New wording column.	f This procedure/assessment may be performed remotely for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center due to unforeseen circumstances.	Footnote "f" was added to identify the procedures/assessments that may be performed remotely.
k Twelve-lead ECGs will be performed in triplicate at any time during the visit, prior to study drug administration.	k Twelve-lead ECGs will be performed in triplicate at any time during the visit, prior to study drug administration.	Footnote "k" was modified to specify that ECGs will be performed before study drug administration.
m Inquiries about adverse events will be made before and after study drug administration. ~~Postdose inquiries will be made before the patient leaves the study center.~~	m Inquiries about adverse events will be made before and after study drug administration.	Revised as adverse event inquiries are not mandated to occur on site.
q The C-SSRS ~~Baseline/Screening version~~ will be completed by a qualified rater trained to administer the scale at the investigational center ~~the physician based on discussion with the patient/caregiver at visit 1 (screening visit), and the C-SSRS Since Last Visit version will be completed by the physician~~ based on discussion with the patient/caregiver at ~~all other~~ the time points described.	q The C-SSRS will be completed by a qualified rater trained to administer the scale at the investigational center based on discussion with the patient/caregiver at the time points described.	Revised for simplicity as the C-SSRS does not need to be completed specifically by a physician.
4.1. Patient Inclusion Criteria		
m. The patient has a body mass index ranging from the 5th to the ~~90~~95th percentile, inclusive, ~~on the day of randomization~~at screening.	m. The patient has a body mass index ranging from the 5th to the 95th percentile, inclusive, at screening.	This inclusion criterion was changed to allow patients at a higher BMI percentile to be included in the study, for greater enrollment.

Original text with changes shown	New wording	Reason/justification for change
4.2. Patient Exclusion Criteria (Other sections affected by this change: 5.6)		
s. The patient received a live attenuated vaccine (eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine) within the 12-week period prior to screening ~~or plans to receive a live attenuated vaccine at any time during the study and for 6 months after the last dose of IMP~~. **Note:** If a medical need arises during the study, the patient may receive a live attenuated vaccine.	s. The patient received a live attenuated vaccine (eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine) within the 12-week period prior to screening. **Note:** If a medical need arises during the study, the patient may receive a live attenuated vaccine.	Patient exclusion criterion was revised to add leniency in the requirements regarding live attenuated vaccines during the study.
4.3. Withdrawal Criteria and Procedures for the Patient (Other sections affected by this change: 3.1 and 5.4)		
Patients who withdraw from the study or have an early termination will be invited to enter the long-term safety extension (within Study TV48125-CNS-30084) for the purpose of safety follow-up and evaluating ADA approximately ~~6~~5 months (~~180~~150 days [~~more than~~ 5 half-lives]) after receiving the last dose of study drug.	Patients who withdraw from the study or have an early termination will be invited to enter the long-term safety extension (within Study TV48125-CNS-30084) for the purpose of safety follow-up and evaluating ADA approximately 5 months (150 days [5 half-lives]) after receiving the last dose of study drug.	The duration of the ADA follow-up period for patients rolling over for ADA assessment only in the long-term safety Study TV48125-CNS-30084 was changed to be approximately 150 days (5 half-lives) after the final dose of IMP to be in line with the duration of the ADA follow-up period for patients who roll over and continue receiving IMP.
4.3.1. Study-Specific Patient Withdrawal Criteria and Procedures		
The patient must be withdrawn from the study drug if the patient experiences a severe hypersensitivity reaction or anaphylaxis.	The patient must be withdrawn from the study drug if the patient experiences a severe hypersensitivity reaction or anaphylaxis.	This was revised as adverse events must still be followed in these patients and therefore, they will not be withdrawn from the study, rather the study drug.
7.1.5.1. Definition of a Serious Adverse Event		
~~An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.~~	Not applicable.	This sentence was deleted as it was inadvertently repeated twice in the section.
7.1.6. Protocol-Defined Adverse Events of Special Interest		
Although treatment with fremanezumab is not expected to impact the course or severity of COVID-19,~~COVID-19 is not suspected to be causally related to fremanezumab treatment,~~ suspected or confirmed COVID 19, based on local	Although treatment with fremanezumab is not expected to impact the course or severity of COVID-19, suspected or confirmed COVID 19, based on local standard of care, will be considered a protocol-defined adverse event of special	Clarification.

Original text with changes shown	New wording	Reason/justification for change
standard of care, will be considered a protocol-defined adverse event of special interest to be sent to the sponsor's GPSP for the purpose of timely and robust adverse event data collection.	interest to be sent to the sponsor's GPSP for the purpose of timely and robust adverse event data collection.	
7.7. Electrocardiography		
Twelve lead ECGs will be conducted at any time during the visit, prior to study drug administration, as detailed in Table 1.	Twelve lead ECGs will be conducted at any time during the visit, prior to study drug administration, as detailed in Table 1.	This sentence was modified to specify that ECGs will be performed before study drug administration.
The ECGs will be performed in triplicate, with ~~approximately~~ at least 1 ~~to 5~~ minute~~s~~ between recordings.	The ECGs will be performed in triplicate, with at least 1 minute between recordings.	The time frame between ECG recordings was revised to allow leniency.
7.9. Assessment of Suicidality		
The C-SSRS ~~Baseline/Screening version~~ will be completed by a qualified rater trained to administer the scale at the investigational center ~~the physician based on discussion with the patient/caregiver at visit 1 (screening visit), and the C-SSRS Since Last Visit version will be completed by the physician~~ based on discussion with the patient/caregiver ~~at all other time points, as~~at the time points described in Table 1.	The C-SSRS will be completed by a qualified rater trained to administer the scale at the investigational center based on discussion with the patient/caregiver at the time points described in Table 1.	Revised for simplicity as the C-SSRS does not need to be completed specifically by a physician.
Appendix B. Study Procedures and Assessments by Visit		
See New wording column.	In the case that a patient is not able to go to the investigational center or the investigational center staff are not able to see patients at the investigational center, certain assessments/procedures, as detailed in Table 1, may be performed remotely.	This sentence was provided to add clarity to refer to Table 1.
Appendix O. Management of Study Activities During COVID-19		
New appendix and text.	Additional text too numerous to include in this table; refer to Appendix O of this protocol.	Appendix O has been added to describe the management of the study during the COVID-19 pandemic.

16.8. Amendment 06 Dated 27 July 2020

The primary reason for this amendment is to revise the protocol in accordance with the conditions for approval of the clinical trial application received from the Voluntary Harmonisation Procedure (VHP). This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment and Written Request agreements. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Changes to the Protocol

Original text with changes shown	New wording	Reason/justification for change
2.2. Exploratory Objective and Endpoints (Other sections affected by this change: 9.5.3)		
[redacted]	[redacted]	Revision to the exploratory endpoint in accordance with Protocol Administrative Letter 02, which is a correction of a typo.
4.2. Patient Exclusion Criteria		
o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <90 mL/min/1.73m^2, as calculated by the Schwartz formula (CrCl=[k×Ht]/Serum Creatinine), or evidence of renal disease during the 28-day baseline period.	o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <90 mL/min/1.73m^2, as calculated by the Schwartz formula (CrCl=[k×Ht]/Serum Creatinine), or evidence of renal disease during the 28-day baseline period.	Clarification.
5.3.1. Justification for Dose of Test Investigational Medicinal Product		
Data from this study (TV48125-CNS-10141) were used to refine the current adult population pharmacokinetic model (which was based on adult data from 2 Phase 1 studies [Studies LBR-101-011 and TV48125-PK-10078], 2 Phase 2b studies [Studies LBR-101-021 and LBR-101-022], and 3 Phase 3 Studies [Studies TV48125-CNS-30049, TV48125-CNS-30050, and TV48125-CNS-30051 (cutoff date 30 May 2018)]), where allometric weight exponents for clearance and central volume were estimated, and a 2-compartment model with first-order absorption, elimination, and body	Data from this study (TV48125-CNS-10141) were used to refine the current adult population pharmacokinetic model (which was based on adult data from 2 Phase 1 studies [Studies LBR-101-011 and TV48125-PK-10078], 2 Phase 2b studies [Studies LBR-101-021 and LBR-101-022], and 3 Phase 3 Studies [Studies TV48125-CNS-30049, TV48125-CNS-30050, and TV48125-CNS-30051 (cutoff date 30 May 2018)]), where allometric weight exponents for clearance and central volume were estimated, and a 2-compartment model with first-order absorption, elimination, and body	Revised to provide additional context for the determination of the dose for patients weighing <45 kg.

Original text with changes shown	New wording	Reason/justification for change
weight effect on clearance and central volume adequately described the fremanezumab concentration-time data observed in pediatric patients with migraine.	weight effect on clearance and central volume adequately described the fremanezumab concentration-time data observed in pediatric patients with migraine.	
See New wording column.	Additional simulations of dose selection for pediatric patients weighing <45 kg was also performed with an alternative pediatric population pharmacokinetic model with the fixed allometric exponents (ie, 0.75 for clearance and 1.0 for volume). However, the apparent over prediction of observed exposures from the Phase 1 pharmacokinetic pediatric study (Study TV48125-CNS-10141) with this model led to an under prediction of the selected dose needed to achieve exposures comparable to those in adults receiving 225 mg sc fremanezumab. Considering the wide safety margin for fremanezumab with substantial evidence supporting the safety of the approved dose of 225 mg sc monthly in adults, the expected exposures in pediatric patients weighing <45 kg after administration of 120 mg sc monthly fall well within the exposure range of adults receiving doses up to 900 mg sc monthly; where 675 mg sc monthly and 900 mg sc monthly were administered in the adult Phase 2b studies and were found to be safe and well tolerated. Safety margin data from a nonclinical study in juvenile rats indicate that at the NOAEL dose of 450 mg/kg/week (see Section 1.2.1), calculated safety margins range from 16- to 22-fold higher than expected pediatric clinical exposure based on a population pharmacokinetic model. It is therefore concluded that in nonclinical studies, adequate safety margins are calculated even when considering higher exposure in the pediatric population.	Additional paragraphs detailing the selection of dose for patients weighing <45 kg have been added to inform investigators.
6.1.3. Patient Global Impression of Improvement Scale		
The PGI-I scale is a ~~1~~7-item questionnaire designed to assess the	The PGI-I scale is a 7-item questionnaire designed to assess the	Correction of a typo; updated in accordance with Protocol Administrative Letter 02.

Original text with changes shown	New wording	Reason/justification for change
patient's global impression of ~~change~~improvement.	patient's global impression of improvement.	
16. Summary of Changes to Protocol		
See New wording column.	**Section 16.2 Administrative Letter 02 Dated 07 July 2020**	Updated to include the Administrative Letter 02.

16.9. Administrative Letter 02 Dated 07 July 2020

ADMINISTRATIVE LETTER 02

Study number: TV48125-CNS-30083

Clinical Study Protocol with Amendment 05

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age
Version Date 27 June 2020

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002055-42

07 July 2020

Dear Investigator:

The purpose of this letter is to correct an inconsistency/editorial error in the study protocol relating to the exploratory endpoint of [redacted] and to correct a typo in Section 6.1.3, describing the [redacted]

The [redacted] only, as correctly described in Protocol Table 1 and Appendix B. The required changes to the exploratory endpoint throughout the protocol are provided below and apply to the Protocol Synopsis, Section 2.2, and Section 9.5.3:

[redacted]

The change to Section 6.1.3 is provided below:

[redacted]

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

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

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel. [redacted] www.tevapharm.com

16.10. Amendment 05 Dated 27 June 2020

The primary reason for this amendment is to revise the protocol in accordance with the Grounds for Non-Acceptance received from the Voluntary Harmonization Procedure (VHP). All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Changes to the Protocol

Original text with changes shown	New wording	Reason/justification for change
3.3. Justification for Study Design and Selection of Population		
Migraine is a condition that starts from childhood or adolescence and progresses into adulthood. Among populations of children of all ages, migraine prevalence ranges from 8% to 11% (Abu-Arafeh et al 2010, Abu-Arefeh and Russell 1994, Laurell et al 2004, Ozge et al 2013, Stovner and Andree 2010). Additionally, there is an unmet need for the treatment of migraine in pediatric patients as there are limited therapy options available for this patient population. Throughout Teva's development program for adults, fremanezumab had demonstrated statistically and clinically significant superior efficacy over placebo. It is also well tolerated in the adult migraine population. Given the progression of the disease and the knowledge gained from the adult population, it is reasonable and important to evaluate fremanezumab in the pediatric population.	Migraine is a condition that starts from childhood or adolescence and progresses into adulthood. Among populations of children of all ages, migraine prevalence ranges from 8% to 11% (Abu-Arafeh et al 2010, Abu-Arefeh and Russell 1994, Laurell et al 2004, Ozge et al 2013, Stovner and Andree 2010). Additionally, there is an unmet need for the treatment of migraine in pediatric patients as there are limited therapy options available for this patient population. Throughout Teva's development program for adults, fremanezumab had demonstrated statistically and clinically significant superior efficacy over placebo. It is also well tolerated in the adult migraine population. Given the progression of the disease and the knowledge gained from the adult population, it is reasonable and important to evaluate fremanezumab in the pediatric population.	This paragraph was added to provide context for conducting a study in vulnerable patients.
Section 4.1. Patient Inclusion Criteria		
b. The patient's parent(s) or legal guardian(s) must give written informed consent, and the patient must give assent (in accordance with local regulations). **Note:** In some countries, patients aged 15 to 17 years (inclusive) may give written informed consent; however, the patient's parent(s) or legal guardian(s) must be informed, per local regulations.	b. The patient's parent(s) or legal guardian(s) must give written informed consent, and the patient must give assent (in accordance with local regulations). **Note:** In some countries, patients aged 15 to 17 years (inclusive) may give written informed consent; however, the patient's parent(s) or legal guardian(s) must be informed, per local regulations.	Inclusion criterion b was revised to specify that some countries may allow patients aged 15 to 17 years to give written informed consent, per local regulations.
Section 4.2. Patient Exclusion Criteria		

Original text with changes shown	New wording	Reason/justification for change
d. The patient has a current history of a clinically significant psychiatric condition, any prior history of a suicide attempt, or a history of suicidal ideation with a specific plan within the past 2 years, at the discretion of the investigator.	d. The patient has a current history of a clinically significant psychiatric condition, any prior history of a suicide attempt, or a history of suicidal ideation with a specific plan within the past 2 years, at the discretion of the investigator.	Exclusion criterion was revised to specify that exclusion of a patient based on clinically significant psychiatric condition is at the discretion of the investigator.
e. The patient has an ongoing infection or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, ~~or~~ chronic hepatitis B or C, or a known active infection of coronavirus disease 2019 (COVID-19).	e. The patient has an ongoing infection or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, chronic hepatitis B or C, or a known active infection of coronavirus disease 2019 (COVID-19).	Exclusion criterion was revised to exclude those with a known active COVID-19 infection.
g. The patient is pregnant, nursing, or taking a combined estrogen and progestogen hormonal contraceptive.	g. The patient is pregnant, nursing, or taking a combined estrogen and progestogen hormonal contraceptive.	Revised to exclude patients taking a combined estrogen and progestogen hormonal contraceptive.
h. The patient has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome, or the patient is concomitantly using lamotrigine.	h. The patient has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome, or the patient is concomitantly using lamotrigine.	Revised to exclude patients concomitantly using lamotrigine.
o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <90 mL/min/1.73m2, or evidence of renal disease during the 28-day baseline period.	o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <90 mL/min/1.73m2, or evidence of renal disease during the 28-day baseline period.	An exclusion of patients with an estimated glomerular filtration rate of <90 mL/min/1.73m^2 was added as another means of evidence of renal disease.
t. The patient has a known hypersensitivity to the active substance or to any of the excipients of the study drug.	t. The patient has a known hypersensitivity to the active substance or to any of the excipients of the study drug.	This exclusion criteria was added to ensure patients with a known hypersensitivity are not enrolled in the study.
4.3.1. Study-Specific Patient Withdrawal Criteria and Procedures		
The patient must be withdrawn from the study if the patient experiences a severe hypersensitivity reaction or anaphylaxis.	The patient must be withdrawn from the study if the patient experiences a severe hypersensitivity reaction or anaphylaxis.	The sentence was added to specify that patients must be withdrawn if they experience a severe hypersensitivity reaction of anaphylaxis.
4.5. Rescreening		
If the history of migraine classification (EM or CM) as taken by the investigator differs from the classification determined by the diary data (28- day	If the history of migraine classification (EM or CM) as taken by the investigator differs from the classification determined by the diary data (28- day baseline period),	Clarification to avoid confusion by referencing a screening period.

Original text with changes shown	New wording	Reason/justification for change
~~screening~~baseline period), the patient may be rescreened one time; this information should be recorded in the CRF.	the patient may be rescreened one time; this information should be recorded in the CRF.	
Patients may be rescreened once if the repeated values for the laboratory, vital sign, or ECG screening criteria are within acceptable limits as judged by the investigator or if repeated values show normalization of the out-of-range values, but their initial ~~screening~~baseline period has expired.	Patients may be rescreened once if the repeated values for the laboratory, vital sign, or ECG screening criteria are within acceptable limits as judged by the investigator or if repeated values show normalization of the out-of-range values, but their initial baseline period has expired.	Clarification to avoid confusion by referencing a screening period.
5.3.1. Justification for Dose of Test Investigational Medicinal Product		
A 2013 investigation by Momper et al from the Food and Drug Administration (FDA) analyzed 92 products approved between 2007 and 2012 with similar adult and pediatric indications across different therapeutic areas, and 87 (94.5%) had equivalent dosing for adults and adolescent patients (Momper et al 2013~~The formulation of fremanezumab to be used for clinical investigations in the pediatric population will be identical to the sc formulation of fremanezumab that was used in the clinical program for adults.~~). Based on pharmacokinetic simulations, a body weight threshold of 40 kg can be generally used for pediatric patients to receive the same fixed adult dosage for mAbs (Yang et al 2019). In addition, mAbs tend to have wide therapeutic windows since they represent more targeted therapy with limited off-target toxicity; as a result, recommending a 40 kg threshold for receiving the adult dosage, with resultant pediatric exposure being within 20% to 30% above adult exposure, seems to be appropriate (Yang et al 2019). The fremanezumab weight cutoff is slightly higher (45 kg); hence, this reduces the likelihood to be above adult exposure. In addition, fremanezumab has a wide therapeutic dose range that was	A 2013 investigation by Momper et al from the Food and Drug Administration (FDA) analyzed 92 products approved between 2007 and 2012 with similar adult and pediatric indications across different therapeutic areas, and 87 (94.5%) had equivalent dosing for adults and adolescent patients (Momper et al 2013). Based on pharmacokinetic simulations, a body weight threshold of 40 kg can be generally used for pediatric patients to receive the same fixed adult dosage for mAbs (Yang et al 2019). In addition, mAbs tend to have wide therapeutic windows since they represent more targeted therapy with limited off-target toxicity; as a result, recommending a 40 kg threshold for receiving the adult dosage, with resultant pediatric exposure being within 20% to 30% above adult exposure, seems to be appropriate (Yang et al 2019). The fremanezumab weight cutoff is slightly higher (45 kg); hence, this reduces the likelihood to be above adult exposure. In addition, fremanezumab has a wide therapeutic dose range that was tested in Phase 2b and Phase 3 studies in adults of up to 900 mg sc monthly. Thus, based on considerable data available in adult patients with migraine weighing ≥45 kg, in	Additional information on the selected weight cutoff for the pediatric population has been added for investigator awareness.

Original text with changes shown	New wording	Reason/justification for change
tested in Phase 2b and Phase 3 studies in adults of up to 900 mg sc monthly. Thus, based on considerable data available in adult patients with migraine weighing ≥45 kg, in addition to the evidence supporting the lack of expected difference in pharmacokinetics between adults and adolescent patients, the use of 225 mg monthly was proposed in pediatric patients weighing ≥45 kg.	addition to the evidence supporting the lack of expected difference in pharmacokinetics between adults and adolescent patients, the use of 225 mg monthly was proposed in pediatric patients weighing ≥45 kg.	
This refined pediatric population pharmacokinetic model was used to simulate individual estimates of exposure for a virtual population of pediatric subjects over a range of possible fremanezumab doses. ~~Pediatric~~A population of 2400 virtual pediatric patients ~~virtual subjects~~ (6 to 17 years of age [inclusive]) was generated (200 patients per year of age) and used along with the final pediatric pharmacokinetic model estimates to simulate concentration-time data for monthly sc doses ranging from 60 to 225 mg. Virtual patients were assigned weight values based on a uniform distribution of age using growth chart data from the Centers for Disease Control. ~~The~~Simulated exposure measures were calculated at steady state for the virtual pediatric patients and compared to exposure measured at steady state in the adult population receiving fremanezumab 225 mg sc monthly. For virtual pediatric patients 6 to 17 years of age with baseline weight <45 kg administered 120 mg sc monthly, the simulated area under the concentration-time curve from time 0 to 28 days distribution was nearly identical to the adult patient distribution following administration of 225 mg sc monthly. Very similar patterns were observed for average concentration and minimum drug concentration. The simulated maximum concentration distribution following 120 mg sc monthly in the pediatric population suggests	This refined pediatric population pharmacokinetic model was used to simulate individual estimates of exposure for a virtual population of pediatric subjects over a range of possible fremanezumab doses. A population of 2400 virtual pediatric patients (6 to 17 years of age [inclusive]) was generated (200 patients per year of age) and used along with the final pediatric pharmacokinetic model estimates to simulate concentration-time data for monthly sc doses ranging from 60 to 225 mg. Virtual patients were assigned weight values based on a uniform distribution of age using growth chart data from the Centers for Disease Control. Simulated exposure measures were calculated at steady state for the virtual pediatric patients and compared to exposure measured at steady state in the adult population receiving fremanezumab 225 mg sc monthly. For virtual pediatric patients 6 to 17 years of age with baseline weight <45 kg administered 120 mg sc monthly, the simulated area under the concentration-time curve from time 0 to 28 days distribution was nearly identical to the adult patient distribution following administration of 225 mg sc monthly. Very similar patterns were observed for average concentration and minimum drug concentration. The simulated maximum concentration distribution following 120 mg sc monthly in the pediatric population suggests slightly higher maximum	Additional information on the pediatric population pharmacokinetic model to determine the dose for patients weighing <45 kg has been added for investigator awareness.

Original text with changes shown	New wording	Reason/justification for change
slightly higher maximum concentration than that achieved in the adult population following 225 mg sc monthly; however, overall, the upper exposure range extends only slightly above the upper range of the adult exposures. Given the wide safety margin of fremanezumab with considerable evidence supporting the safety of the approved dose of 225 mg sc monthly in adults, and to minimize the risk of decreased efficacy in this pediatric population, the 120 mg monthly dose level was selected for patients aged 6 to 17 years (inclusive) with weight values <45.0 kg based on targeting the achievement of a similar distribution of fremanezumab exposure levels (following multiple dosing) of 225 mg monthly in adult patients with EM and CM. The formulation of fremanezumab to be used for clinical investigations in the pediatric population will be identical to the sc formulation of fremanezumab that was used in the clinical program for adults.	concentration than that achieved in the adult population following 225 mg sc monthly; however, overall, the upper exposure range extends only slightly above the upper range of the adult exposures. Given the wide safety margin of fremanezumab with considerable evidence supporting the safety of the approved dose of 225 mg sc monthly in adults, and to minimize the risk of decreased efficacy in this pediatric population, the 120 mg monthly dose level was selected for patients aged 6 to 17 years (inclusive) with weight values <45.0 kg based on targeting the achievement of a similar distribution of fremanezumab exposure levels (following multiple dosing) of 225 mg monthly in adult patients with EM and CM. The formulation of fremanezumab to be used for clinical investigations in the pediatric population will be identical to the sc formulation of fremanezumab that was used in the clinical program for adults.	
5.5. Restrictions		
Patients must remain at the site, for safety observation, for at least 30 minutes after injection or longer if deemed necessary by medical judgment.	Patients must remain at the site, for safety observation, for at least 30 minutes after injection or longer if deemed necessary by medical judgment.	This sentence was added to provide a minimum time frame that the patient must be observed for safety evaluation.
5.6. Prior and Concomitant Medication or Therapy		
The following medications are prohibited during the study: opioids (including codeine), barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital), combined estrogen and progestogen hormonal contraceptives, and lamotrigine.	The following medications are prohibited during the study: opioids (including codeine), barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital), combined estrogen and progestogen hormonal contraceptives, and lamotrigine.	The sentence was added to specifically note which medications are prohibited during the study.
5.8. Randomization and Blinding		
~~Study personnel will be blinded to the results of the interim analysis other than the need (if any) for an adjustment in sample size.~~	-	This sentence was removed as the study personnel will not be unblinded to the results of the interim analysis.

Original text with changes shown	New wording	Reason/justification for change
7.4. Clinical Laboratory Tests (Other sections affected by this change: 8.1.1, 8.3)		
Details on sample handling, storage, shipment, and analysis are given in Appendix N and in the Laboratory Manual.	Details on sample handling, storage, shipment, and analysis are given in Appendix N and in the Laboratory Manual.	Reference to the newly added Appendix N has been added as it contains information on storage and destruction of samples.
9.5.1.1. Estimand for the Primary Endpoint		
The primary estimand for this study is the difference in means between the fremanezumab group and the placebo group in the target population who have received at least 1 dose of study drug and have at least 10 days of electronic diary efficacy data for the mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of study drug as if there were no intercurrent events. Data collected after treatment discontinuation or prohibited therapy will not be used for assessing the primary estimand.	The primary estimand for this study is the difference in means between the fremanezumab group and the placebo group in the target population who have received at least 1 dose of study drug and have at least 10 days of electronic diary efficacy data for the mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of study drug as if there were no intercurrent events. Data collected after treatment discontinuation or prohibited therapy will not be used for assessing the primary estimand.	Estimand language has been added to the protocol per recent ICH E9 guidance.
9.5.4.1. Primary Efficacy Analysis		
~~The group of patients 6 through 11 years of age will be analyzed descriptively.~~	-	This sentence was removed as patients aged 6 through 11 years will be analyzed as part of a subgroup analysis.
9.5.4.2. Sensitivity and Supplementary Analyses		
A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint.	A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint.	The sentence was added to provide information that a supplementary analysis using the ITT population will be conducted.
9.6. Multiple Comparisons and Multiplicity		
The order of secondary endpoint analyses will in general follow the sequence listed in Section 9.5.2. Final order and details will be confirmed in the statistical analysis plan, which will be finalized before database lock.	The order of secondary endpoint analyses will in general follow the sequence listed in Section 9.5.2. Final order and details will be confirmed in the statistical analysis plan, which will be finalized before database lock.	This sentence was added to provide clarity on the sequence of secondary efficacy endpoint comparisons.
9.8. Tolerability Analysis (Other sections affection by this change: 7.8)		
• Injection site pain will be recorded ~~as~~ using the 11-point numerical rating scale and will be mapped to mild, moderate, or severe, according to patient's self-	• Injection site pain will be recorded using the 11-point numerical rating scale and will be mapped to mild, moderate, or severe, according to patient's self-	Injection site pain assessments were revised to use the 11-point NRS to harmonize with the other pain assessments in the study.

Original text with changes shown	New wording	Reason/justification for change
report of pain intensity, as described for the recording of headache pain in Section 6.1.1.	report of pain intensity, as described for the recording of headache pain in Section 6.1.1.	
9.12. Planned Interim Analysis (Other sections affected by this change: 3.1 and 9.5.4.1)		
An interim analysis ~~for~~with blinded sample size re-estimation will be conducted by ~~an independent statistical group~~evaluating the pooled variability (SD) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% of patients have completed at least 3 months of treatment or have withdrawn from the study early. ~~The sample size re-estimation will be based on the interim analysis result. The conditional power for the primary efficacy variable will be calculated. If the conditional power is less than 25% or greater than 75%, the sample size will not be increased. If the conditional power is between 25% and 75%, the sample size will be increased by up to 25%.~~	An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (SD) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% of patients have completed at least 3 months of treatment or have withdrawn from the study early.	This sentence was revised to ensure it is clear that the sample size re-estimation will be blinded. Additionally, the conditional power description for the sample size re-estimation was removed as the planned sample size re-assess will use a more robust method to be described in the statistical analysis plan.
Appendix F. Ethics		
The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB).), per local regulations.	The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB).), per local regulations.	This stipulation was added as there may be different requirements for certain countries.
The investigator, or a qualified person designated by the investigator, should fully inform the patient and each parent/legally acceptable representative of all pertinent aspects of the study, including the written information approved by the IEC/IRB., per local regulations.	The investigator, or a qualified person designated by the investigator, should fully inform the patient and each parent/legally acceptable representative of all pertinent aspects of the study, including the written information approved by the IEC/IRB., per local regulations.	This stipulation was added as there may be different requirements for certain countries.
Appendix G. Birth Control Methods and Pregnancy Testing		
~~• Combined estrogen and progestogen hormonal contraception (oral, intravaginal, and transdermal) associated with inhibition of~~	-	This bullet was deleted from highly effective birth control methods as combined estrogen and progestogen hormonal contraception has been

Original text with changes shown	New wording	Reason/justification for change
~~ovulation; these should be initiated at least 1 month before the first dose of IMP~~		added as prohibited medications during the study.
Appendix L. Data Management and Record Keeping		
~~These data may also be sent electronically to the sponsor (or organization performing data management).~~	-	This sentence was deleted to avoid unintentional unblinding.
Appendix N. Storage and Destruction of Biological Samples		
Safety Samples Safety samples will be stored for a short period of time in the central laboratory until analysis and destruction. Specific details regarding central laboratory storage and destruction can be found in the study Laboratory Manual and the central laboratory's standard operating procedures (SOPs). **Pharmacokinetic and Immunogenicity Samples** Pharmacokinetic and immunogenicity samples will be stored at the sites at a temperature of 70°C ±20°C (or at/below -20°C if no 70°C freezer is available) in an upright position until they are shipped to the central laboratory. Samples will be stored at -70°C at the central laboratory, until shipped to the sponsor or designee for analysis, as described in the study Laboratory Manual. After analysis, the sponsor will store the residue (leftovers) from the pharmacokinetic and immunogenicity samples at 70°C at the designated bioanalytical archive facility for up to 5 years after the study results are submitted to the regulatory authorities. Destruction will take place at the sponsor's bioanalytical laboratory or designee, according to the applicable SOPs.	**Safety Samples** Safety samples will be stored for a short period of time in the central laboratory until analysis and destruction. Specific details regarding central laboratory storage and destruction can be found in the study Laboratory Manual and the central laboratory's standard operating procedures (SOPs). **Pharmacokinetic and Immunogenicity Samples** Pharmacokinetic and immunogenicity samples will be stored at the sites at a temperature of 70°C ±20°C (or at/below -20°C if no 70°C freezer is available) in an upright position until they are shipped to the central laboratory. Samples will be stored at -70°C at the central laboratory, until shipped to the sponsor or designee for analysis, as described in the study Laboratory Manual. After analysis, the sponsor will store the residue (leftovers) from the pharmacokinetic and immunogenicity samples at 70°C at the designated bioanalytical archive facility for up to 5 years after the study results are submitted to the regulatory authorities. Destruction will take place at the sponsor's bioanalytical laboratory or designee, according to the applicable SOPs.	Appendix N has been added to describe the storage and destruction of biological samples.

16.11. Amendment 04 Dated 20 April 2020

The primary reason for this amendment is to revise an exclusion criterion to exclude patients with a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome. This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment and Written Request agreements. The amendment is considered to be substantial (ie, requires approval by competent authorities, 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.

Changes to the Protocol

Original text with changes shown	New wording	Reason/ justification for change
TITLE PAGE (Other sections affected by this change: Amendment History, Investigator Agreement, Coordinating Investigator Agreement)		
Protocol with Amendment 04 Approval Date: 20 April 2020	**Protocol with Amendment 04 Approval Date: 20 April 2020**	Updated for Amendment 04
4.2. Patient Exclusion Criteria		
c. The patient has any clinically significant cardiovascular (including congenital cardiac anomalies or thromboembolic events), endocrine, gastrointestinal, genitourinary, hematologic, hepatic, immunologic, neurologic, ophthalmic, pulmonary, ~~or~~ renal disease, or complications of an infection, at the discretion of the investigator. e. The patient has an ongoing infection~~,~~ or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, or chronic hepatitis B or C. h. The patient has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome.	c. The patient has any clinically significant cardiovascular (including congenital cardiac anomalies or thromboembolic events), endocrine, gastrointestinal, genitourinary, hematologic, hepatic, immunologic, neurologic, ophthalmic, pulmonary, renal disease, or complications of an infection, at the discretion of the investigator. e. The patient has an ongoing infection or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, or chronic hepatitis B or C. h. The patient has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome.	Updated to specifically exclude patients with a history of chronic hepatitis B or C, and to exclude patients with a history of Stevens-Johnson Syndrome/toxic epidermal necrolysis syndrome from this study. It was also specified that patients with clinically significant complications of an infection may be excluded at the discretion of the investigator
4.5. Rescreening		

Original text with changes shown	New wording	Reason/ justification for change
A patient who is screened but not enrolled (eg, because study eligibility criteria were not met [inclusion criteria not met or exclusion criteria met]) due to any of the following reasons: technical issues (eg, diary malfunction), out of visit 2 window due to an emergency situation (eg, pandemic or potential pandemic), a change in the patient's medical background, a modification of study inclusion and exclusion criteria, or upon the sponsor's discretion on a case-by-case basis, may be considered for rescreening 1 time. If the history of migraine classification (EM or CM) as taken by the investigator differs from the classification determined by the diary data (28-day screening period), the patient may be rescreened one time; this information should be recorded in the CRF.	A patient who is screened but not enrolled (eg, because study eligibility criteria were not met [inclusion criteria not met or exclusion criteria met]) due to any of the following reasons: technical issues (eg, diary malfunction), out of visit 2 window due to an emergency situation (eg, pandemic or potential pandemic), a change in the patient's medical background, a modification of study inclusion and exclusion criteria, or upon the sponsor's discretion on a case-by-case basis, may be considered for rescreening 1 time. If the history of migraine classification (EM or CM) as taken by the investigator differs from the classification determined by the diary data (28-day screening period), the patient may be rescreened one time; this information should be recorded in the CRF.	Clarification as a measure implementing to protect study participants and manage study conduct resulting from the COVID-19 or other potential pandemic.
7.1.6. Protocol-Defined Adverse Events of Special Interest		
Although coronavirus disease 2019 (COVID-19) is not suspected to be causally related to fremanezumab treatment, suspected or confirmed COVID-19, based on local standard of care, will be considered a protocol-defined adverse event of special interest to be sent to the sponsor's GPSP for the purpose of timely and robust adverse event data collection.	Although coronavirus disease 2019 (COVID-19) is not suspected to be causally related to fremanezumab treatment, suspected or confirmed COVID-19, based on local standard of care, will be considered a protocol-defined adverse event of special interest to be sent to the sponsor's GPSP for the purpose of timely and robust adverse event data collection.	Suspected or confirmed COVID-19 was added as an adverse event of special interest in order to manage study conduct resulting from the COVID-19 pandemic.
16. Summary of Changes to Protocol		
Section 16.2 Administrative Letter 01 Dated 10 March 2020	**Section 16.2 Administrative Letter 01 Dated 10 March 2020**	Updated to include the Administrative Letter 01.
Appendix A. Clinical Laboratories and Other Departments and Institutions		
[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	Updated as outlined in Administrative Letter 01.

Original text with changes shown	New wording	Reason/ justification for change
[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	Updated as outlined in Administrative Letter 01.

16.12. Administrative Letter 01 Dated 10 March 2020

ADMINISTRATIVE LETTER 01

Study number: TV48125-CNS-30083

Clinical Study Protocol with Amendment 03

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age
Version Date 03 February 2020

IND number: 106533; BLA number: 761089; EudraCT number: 2019-002055-42

10 March 2020

Dear Investigator:

The purpose of this letter is to provide the change of sponsor representative contact information. The changes are provided below:

1. Revise the telephone number of [redacted] in Appendix A from [redacted] to [redacted]
2. Revise the telephone number of [redacted] in Appendix A from [redacted] to [redacted]

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

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

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

16.13. Amendment 03 Dated 03 February 2020

The primary reason for this amendment is to update the sponsor's address. This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment and Written Request agreements. The amendment is considered to be substantial (ie, requires approval by competent authorities, 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.

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 03 **Approval Date: 03 February 2020**	**Protocol with Amendment 03** **Approval Date:** **03 February 2020**	To update for Amendment 03
Teva Branded Pharmaceutical Products R&D, Inc. ~~**41 Moores Road**~~ ~~**Frazer, Pennsylvania 19355**~~ **145 Brandywine Parkway** **West Chester, Pennsylvania 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.
© ~~2019~~2020 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	© 2020 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	To update for Amendment 03
3. STUDY DESIGN		
3.5. Schedule of Study Procedures and Assessments (Table 1) (Other sections affected by this change: Appendix B)		
Headache history	Headache history	Specific study procedure added for clarity to collect headache history data during screening.
Clinical laboratory tests[~~c~~,m]	Clinical laboratory tests[c,m]	To clarify that blood samples will be collected before study drug administration.
Blood samples for plasma drug concentration[~~c~~~~p~~]	Blood samples for plasma drug concentration[c]	Correction to simplify footnotes.
Blood samples for serum ADA assessment[~~c~~~~p~~]	Blood samples for serum ADA assessment[c]	Correction to simplify footnotes.
Injection site assessments[~~c~~]	Injection site assessments[c]	Footnote reference added to the injection site assessment row for clarity.
~~p Blood samples for plasma drug concentration and serum ADA determination must be collected prior to dosing as applicable.~~	-	The footnote was deleted as it was repetitive with footnote c.

Original text with changes shown	New wording	Reason/Justification for change
4. SELECTION AND WITHDRAWAL OF PATIENTS		
4.1. Patient Inclusion Criteria		
Note: A person is considered to be not using preventive medications when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinium toxin A <u>or B</u> prior to screening (visit 1).	Note: A person is considered to be not using preventive medications when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinium toxin A or B prior to screening (visit 1).	This note for inclusion criterion f was updated to include onabotulinumtoxinB to coincide with it being added as a preventive migraine medication allowed for up to 20% of patients during the study as per Appendix C.
4.2. Patient Exclusion Criteria (Other sections affected by this change: 5.6)		
s. The patient received a live attenuated vaccine <u>(eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine)</u> within the 12-week period prior to screening or plans to receive a live attenuated vaccine at any time during the study and for 6 months after the last dose of IMP.	s. The patient received a live attenuated vaccine (eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine) within the 12-week period prior to screening or plans to receive a live attenuated vaccine at any time during the study and for 6 months after the last dose of IMP.	Added a clarification to describe some potentially applicable live attenuated vaccines.
7. ASSESSMENT OF SAFETY		
7.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis		
Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected <u>hepatitis,</u> HIV<u>,</u> or Lyme disease, a blood sample may be taken at screening at the discretion of the investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below (Table 4).	Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected hepatitis, HIV, or Lyme disease, a blood sample may be taken at screening at the discretion of the investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below (Table 4).	To clarify that the investigator may take a blood sample at screening in case of suspected hepatitis.
Table 4 (urinalysis column)		
~~Albumin~~	-	Albumin was removed from Table 4 as it is included in the protein measurement and will not be evaluated separately by the central laboratory.
~~Hemoglobin~~<u>Blood</u>	Blood	Correction as the urinalysis will specifically assess for blood in urine.

Original text with changes shown	New wording	Reason/Justification for change
7.1.5.1. Definition of a Serious Adverse Event		
Refer to Appendix I for guidance regarding monitoring patients with elevated liver function tests. An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.	Refer to Appendix I for guidance regarding monitoring patients with elevated liver function tests. An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.	Refer to Appendix I for guidance regarding monitoring patients with elevated liver function tests. An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.
APPENDIX C. PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR THE DURATION OF THE STUDY FOR UP TO 20% OF PATIENTS		
OnabotulinumtoxinA or B	OnabotulinumtoxinA or B	OnabotulinumtoxinB was added as a preventive migraine medications allowed for the duration of the study for up to 20% of patients as outlined in Appendix C.
APPENDIX I. GUIDANCE ON SAFETY MONITORING	**APPENDIX I. GUIDANCE ON SAFETY MONITORING**	Appendix I was newly added to provide guidance to the investigator on monitoring patients with elevated liver function tests.

16.14. Amendment 02 Dated 05 December 2019

The primary reason for this amendment is to update the protocol with the dose to be used for patients <45.0 kg (120 mg sc monthly) following the completion of the Phase 1 pediatric pharmacokinetic study (TV48125-CNS-10141). This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment agreement. The amendment is considered to be substantial (ie, requires approval by competent authorities, 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.

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, Amendment History, Investigator Agreement, Coordinating Investigator Agreement)		
Clinical Study Protocol with Amendment ~~01~~02	**Clinical Study Protocol with Amendment 02**	To update for Amendment 02
Protocol with Amendment 02 Approval Date: 05 December 2019	**Protocol with Amendment 02 Approval Date: 05 December 2019**	To update for Amendment 02
1. INTRODUCTION AND BACKGROUND INFORMATION		
1.1. Introduction (Other sections affected by this change: 1.2.2, 1.2.2.1, 1.2.2.2)		
Two completed, randomized, double-blind, placebo-controlled Phase 3 studies (Studies TV48125-CNS-30049 in CM and TV48125-CNS-30050 in EM) and 1 ~~ongoing~~completed, randomized, double-blind Phase 3 long-term safety study (Study TV48125-CNS-30051 in migraine [EM and CM]) were conducted to further evaluate the efficacy, safety, and tolerability of various dose regimens of fremanezumab in the preventive treatment of migraine. ~~Study TV48125-CNS-30051 is ongoing, and as of the safety cutoff date of 30 May 2018, all patients (excluding 2) completed study treatment.~~ Additional studies within the migraine development program of fremanezumab include the completed Phase 3b study (Study TV48125-CNS-30068) in patients from the EU and US to evaluate the safety and efficacy of fremanezumab in migraine patients who have failed multiple preventive medications, 2 ongoing Phase 2b/3 studies in Japanese and Korean EM and CM patients (Studies 406-102-00002 and 406-102-00001, respectively), and 1 ongoing long-term safety study (Study 406-102-00003) in CM and EM to evaluate the safety and efficacy of fremanezumab.	Two completed, randomized, double-blind, placebo-controlled Phase 3 studies (Studies TV48125-CNS-30049 in CM and TV48125-CNS-30050 in EM) and 1 completed, randomized, double-blind Phase 3 long-term safety study (Study TV48125-CNS-30051 in migraine [EM and CM]) were conducted to further evaluate the efficacy, safety, and tolerability of various dose regimens of fremanezumab in the preventive treatment of migraine. Additional studies within the migraine development program of fremanezumab include the completed Phase 3b study (Study TV48125-CNS-30068) in patients from the EU and US to evaluate the safety and efficacy of fremanezumab in migraine patients who have failed multiple preventive medications, 2 ongoing Phase 2b/3 studies in Japanese and Korean EM and CM patients (Studies 406-102-00002 and 406-102-00001, respectively), and 1 ongoing long-term safety study (Study 406-102-00003) in CM and EM to evaluate the safety and efficacy of fremanezumab.	Updated to reflect that Study TV48125-CNS-30051 is now complete.
The pediatric migraine development program includes a completed Phase 1, single-dose, open-	The pediatric migraine development program includes a completed Phase 1, single-dose, open-	Updated to reflect that Study TV48125-CNS-10141 is now complete.

Original text with changes shown	New wording	Reason/Justification for change
label study with administration of single sc doses of 75 mg in pediatric migraine patients 6 to 11 years of age, inclusive (Study TV48125-CNS-10141).	label study with administration of single sc doses of 75 mg in pediatric migraine patients 6 to 11 years of age, inclusive (Study TV48125-CNS-10141).	
Fremanezumab is further studied for the preventive treatment of ~~cluster headache (CH) and~~ persistent posttraumatic headache (PPTH) in ~~the following ongoing studies:~~ 1 Phase 2 study (Study TV48125-CNS-20024) ~~to compare~~that is comparing the efficacy and safety of the sc dose regimen of fremanezumab versus placebo in patients with PPTH~~; 1 Phase 3 study (~~. Fremanezumab was being studied for the preventive treatment of cluster headache (CH) in 3 Phase 3 studies: Study TV48125-CNS-30056 in patients with episodic ~~cluster headache ([E~~CH~~]) to evaluate the efficacy and safety of various dose regimens of fremanezumab in the preventive treatment of ECH; and a third study evaluating long-term safety of fremanezumab (Study TV48125-CNS-30058 in CH). As of 15 June 2018~~, Study TV48125-CNS-30057 in patients with chronic ~~cluster headache (C~~CH~~) was~~, and a long-term safety Study TV48125-CNS-30058 in CH. All 3 studies were terminated by Teva~~,~~ because a prespecified futility analysis showed that the primary endpoint of mean change from baseline in the monthly average number of CH attacks during the 12-week treatment period was unlikely to be met. ~~At that time, participation in Study TV48125-CNS-30058 was also discontinued for patients with CCH who had completed Study TV48125-CNS-30057.~~	Fremanezumab is further studied for the preventive treatment of persistent posttraumatic headache (PPTH) in 1 Phase 2 study (Study TV48125-CNS-20024) that is comparing the efficacy and safety of the sc dose regimen of fremanezumab versus placebo in patients with PPTH. Fremanezumab was being studied for the preventive treatment of cluster headache (CH) in 3 Phase 3 studies: Study TV48125-CNS-30056 in patients with episodic CH, Study TV48125-CNS-30057 in patients with chronic CH, and a long-term safety Study TV48125-CNS-30058 in CH. All 3 studies were terminated by Teva because a prespecified futility analysis showed that the primary endpoint of mean change from baseline in the monthly average number of CH attacks during the 12-week treatment period was unlikely to be met.	Updated with the status of the 3 chronic headache studies.
1.2.2. Clinical Studies		
~~As of 26 September 2017, 3196 subjects and patients (318 healthy subjects and 2878 patients with migraine) have been enrolled in 13 studies in the fremanezumab migraine clinical development program.~~ Overall in the fremanezumab migraine clinical development program, ~~2013~~ 2512 patients	Overall in the fremanezumab migraine clinical development program, 2512 patients with migraine and 474 healthy subjects have received at least 1 dose of fremanezumab in the completed clinical studies. In addition, 142 and 380 patients in the 3 CH Phase 3 blinded studies (TV48125-CNS-30056,	Update to represent current exposure data.

Original text with changes shown	New wording	Reason/Justification for change
with migraine and ~~256~~ 474 healthy subjects have received at least 1 dose of fremanezumab in the completed ~~and ongoing~~ clinical studies. In addition, ~~as of 26 September 2018, 138~~ 142 and 380 patients in the 3 CH Phase 3 blinded studies (TV48125-CNS-30056, TV48125-CNS-30057, and TV48125-CNS-30058) were treated with ~~either~~ placebo ~~or~~and fremanezumab, respectively.	TV48125-CNS-30057, and TV48125-CNS-30058) were treated with placebo and fremanezumab, respectively.	
The ~~8~~9 completed Phase 1 studies include administration of single iv doses ranging from 0.2 to 2000 mg; among these studies are 1 completed Phase 1 study with administration of 2 doses via iv infusion (30 or 300 mg) administered 14 days apart; 1 completed Phase 1 study testing single iv and sc doses of 225 and 900 mg; 1 completed Phase 1 bioequivalence study comparing the pharmacokinetics of 225 mg of fremanezumab administered sc using an autoinjector referenced to a pre-filled syringe (PFS); and 1 completed Phase 1 study in Japanese and Caucasian subjects testing single sc doses of 225, 675, and 900 mg.	The 9 completed Phase 1 studies include administration of single iv doses ranging from 0.2 to 2000 mg; among these studies are 1 completed Phase 1 study with administration of 2 doses via iv infusion (30 or 300 mg) administered 14 days apart; 1 completed Phase 1 study testing single iv and sc doses of 225 and 900 mg; 1 completed Phase 1 bioequivalence study comparing the pharmacokinetics of 225 mg of fremanezumab administered sc using an autoinjector referenced to a pre-filled syringe (PFS); and 1 completed Phase 1 study in Japanese and Caucasian subjects testing single sc doses of 225, 675, and 900 mg.	Update for completion of Study TV48125-CNS-10141.
~~Four~~Five studies in adult migraine patients (2 Phase 2b studies and ~~2~~3 Phase 3 studies) examining the safety and efficacy of fremanezumab have been completed.	Five studies in adult migraine patients (2 Phase 2b studies and 3 Phase 3 studies) examining the safety and efficacy of fremanezumab have been completed.	Update for completion of Study TV48125-CNS-30051.
1.2.2.1. Clinical Pharmacology Studies		
Two relevant clinical pharmacology studies ~~in the pediatric migraine development program~~ have been completed: a Phase 1 bioequivalence study comparing the pharmacokinetics of 225 mg of fremanezumab administered sc using an autoinjector referenced to a PFS (TV48125-BE-10145) in healthy adult subjects, and a Phase 1, single-dose, open-label study with administration of single sc doses of 75 mg in pediatric migraine patients 6 to 11 years of age, inclusive (Study TV48125-CNS-10141).	Two relevant clinical pharmacology studies have been completed: a Phase 1 bioequivalence study comparing the pharmacokinetics of 225 mg of fremanezumab administered sc using an autoinjector referenced to a PFS (TV48125-BE-10145) in healthy adult subjects, and a Phase 1, single-dose, open-label study with administration of single sc doses of 75 mg in pediatric migraine patients 6 to 11 years of age, inclusive (Study TV48125-CNS-10141).	Update to the clinical pharmacology studies.

Original text with changes shown	New wording	Reason/Justification for change
3. STUDY DESIGN		
3.1. General Study Design and Study Schematic Diagram (Other sections affected by this change: 3.2, 5.1.1.1, 5.1.3, 5.3.1, 5.4, 5.8, 9, 9.1)		
The total duration of the study is planned to be 48 months (from approximately ~~Q4 2019~~Q1 2020 to Q4 2022).	The total duration of the study is planned to be 48 months (from approximately Q1 2020 to Q4 2022).	Updated the approximate start date of the study.
• Patients weighing <45.0 kg will receive monthly sc administration of fremanezumab at ~~a dose to be confirmed after pharmacokinetic analyses and safety and tolerability results become available from the Phase 1 pharmacokinetics study (Study TV48125-CNS-10141). The sponsor will communicate the dose selection for patients <45.0 kg when it becomes available~~120 mg.	• Patients weighing <45.0 kg will receive monthly sc administration of fremanezumab at 120 mg.	Updated dose for patients <45.0 kg.
The enrollment target is approximately 288 patients in total, with a goal of at least 30% of those patients in the 6- through 11-year-old age group. The goal in the 12- through 17-year-old age group is to enroll similar numbers of patients who are 12 through 14 years old and 15 through 17 years old. ~~The enrollment will start with patients weighing ≥45.0 kg. The enrollment of patients weighing <45.0 kg will commence after the dose level is finalized and approved by regulatory agencies.~~	The enrollment target is approximately 288 patients in total, with a goal of at least 30% of those patients in the 6- through 11-year-old age group. The goal in the 12- through 17-year-old age group is to enroll similar numbers of patients who are 12 through 14 years old and 15 through 17 years old.	No longer applicable to study enrollment
3.5. Schedule of Study Procedures and Assessments (Other sections affected by this change: 7.9, Appendix B)		
Lifetime p~~P~~rior medication and treatment history	Lifetime prior medication and treatment history	Clarification.
p Blood samples for plasma drug concentration and serum ADA ~~concentrations~~ determination must be collected prior to dosing as applicable.	p Blood samples for plasma drug concentration and serum ADA determination must be collected prior to dosing as applicable.	Clarification.
q The C-SSRS Baseline/Screening version will be completed by the physician based on discussion with the patient/caregiver at visit 1 (screening visit), and the C-SSRS Since Last Visit version will be completed by the physician based on discussion with the patient/caregiver at all other time points. ~~Any~~	q The C-SSRS Baseline/Screening version will be completed by the physician based on discussion with the patient/caregiver at visit 1 (screening visit), and the C-SSRS Since Last Visit version will be completed by the physician based on discussion with the patient/caregiver at all other time points.	Clarified who will be completing the C-SSRS and what occurs if there is a positive finding.

Original text with changes shown	New wording	Reason/Justification for change
~~positive finding on the C-SSRS Since Last Visit version requires evaluation by a physician or doctoral-level psychologist.~~ Any patient who demonstrates suicidal ideation and/or any suicidal behavior at any point during the study should be withdrawn from the study and discontinued from study treatment. In addition, if a patient endorses suicidal ideation or behavior at any point during the study (including during screening), the investigator must explain to the patient/caregiver the need for follow-up with a mental health professional and make any necessary referrals.	Any patient who demonstrates suicidal ideation and/or any suicidal behavior at any point during the study should be withdrawn from the study and discontinued from study treatment. In addition, if a patient endorses suicidal ideation or behavior at any point during the study (including during screening), the investigator must explain to the patient/caregiver the need for follow-up with a mental health professional and make any necessary referrals.	
r The location of the sc injection should be recorded at each administration visit.	r The location of the sc injection should be recorded at each administration visit.	Clarification.
4. SELECTION AND WITHDRAWAL OF PATIENTS		
4.3. Withdrawal Criteria and Procedures for the Patient		
All protocol-specified procedures/assessments should be performed at the EOT/early withdrawal visit (see Table 1). Patients who withdraw from the study or have an early termination will be invited to enter the long-term safety extension (within Study TV48125-CNS-30084) for the purpose of safety follow-up and evaluating ADA approximately 6 months (180 days [more than 5 half-lives]) after receiving the last dose of study drug in this study.	All protocol-specified procedures/assessments should be performed at the EOT/early withdrawal visit (see Table 1). Patients who withdraw from the study or have an early termination will be invited to enter the long-term safety extension (within Study TV48125-CNS-30084) for the purpose of safety follow-up and evaluating ADA approximately 6 months (180 days [more than 5 half-lives]) after receiving the last dose of study drug in this study.	Clarification.
5. TREATMENTS (Other sections affected by this change: 5.1.3, 5.8)		
5.1.1.1. Starting Dose and Dose Levels		
A 1.5 mL volume (patients weighing ≥45.0 kg at randomization [visit 2]) or a 0.8 mL volume ~~to be confirmed~~ (patients weighing <45.0 kg at randomization [visit 2]) from each visit kit(s) (the full dose given with a PFS or taken from the vials) must be injected sc for administration to be considered complete. Patients randomized to the	A 1.5 mL volume (patients weighing ≥45.0 kg at randomization [visit 2]) or a 0.8 mL volume (patients weighing <45.0 kg at randomization [visit 2]) from each visit kit(s) (the full dose given with a PFS or taken from the vials) must be injected sc for administration to be considered complete. Patients	Updated volume requirements for patients <45.0 kg.

Original text with changes shown	New wording	Reason/Justification for change
placebo group will receive volume-matched doses of placebo.	randomized to the placebo group will receive volume-matched doses of placebo.	
5.1.3. Placebo Investigational Medicinal Product		
~~dose to be confirmed for patients with body weight <45.0 kg~~120 mg dose: taken from two 2-mL vials each containing 0.5 mL of IMP for single-use administration	120 mg dose: taken from two 2-mL vials each containing 0.5 mL of IMP for single-use administration	Updated to reflect the dose selected for patients <45.0 kg was from the completed Study TV48125-CNS-10141.
0.8-mL injection ~~(volume to be confirmed)~~: taken from two 2-mL vials each containing 0.5 mL of placebo for single-use administration	0.8-mL injection: taken from two 2-mL vials each containing 0.5 mL of placebo for single-use administration	Updated to reflect the dose selected for patients <45.0 kg was from the completed Study TV48125-CNS-10141.
5.3.1. Justification for Dose of Test Investigational Medicinal Product		
~~It should be noted that~~The final dose for patients <45.0 kg ~~will be provided during protocol development,~~was determined by taking into account observed pharmacokinetic data from Study T~~E~~V48125-CNS-10141, a Phase 1 study in pediatric patients 6 to 11 years of age (inclusive). Data from this study (T~~E~~V48125-CNS-10141) ~~will be incorporated into~~were used to refine the ~~pooled dataset~~ current adult population pharmacokinetic model (~~currently~~which was based on adult data from 2 Phase 1 studies [Studies LBR-101-011 and TV48125-PK-10078], 2 Phase 2b studies [Studies LBR-101-021 and LBR-101-022], and 3 Phase 3 Studies [Studies TV48125-CNS-30049, TV48125-CNS-30050, and TV48125-CNS-30051 (cutoff date 30 May 2018)]). ~~and used to refine, as appropriate, the adult~~ This refined pediatric population pharmacokinetic model~~. This refined population pharmacokinetic model, based on adult and pediatric data, will then be~~was used to simulate individual estimates of exposure for a virtual population of pediatric subjects over a range of possible fremanezumab doses. Pediatric virtual subjects (6 to 17 years [inclusive]) ~~will be~~were assigned weight values based on a uniform distribution of age using	The final dose for patients <45.0 kg was determined by taking into account observed pharmacokinetic data from Study TV48125-CNS-10141, a Phase 1 study in pediatric patients 6 to 11 years of age (inclusive). Data from this study (TV48125-CNS-10141) were used to refine the current adult population pharmacokinetic model (which was based on adult data from 2 Phase 1 studies [Studies LBR-101-011 and TV48125-PK-10078], 2 Phase 2b studies [Studies LBR-101-021 and LBR-101-022], and 3 Phase 3 Studies [Studies TV48125-CNS-30049, TV48125-CNS-30050, and TV48125-CNS-30051 (cutoff date 30 May 2018)]). This refined pediatric population pharmacokinetic model was used to simulate individual estimates of exposure for a virtual population of pediatric subjects over a range of possible fremanezumab doses. Pediatric virtual subjects (6 to 17 years [inclusive]) were assigned weight values based on a uniform distribution of age using growth chart data from the Centers for Disease Control. The 120 mg monthly dose level was selected for patients age 6 to 17 years (inclusive) with weight values <45.0 kg based on targeting the achievement of a similar distribution of fremanezumab exposure levels	Updated to reflect the dose selected for patients <45.0 kg was from the completed Study TV48125-CNS-10141.

Original text with changes shown	New wording	Reason/Justification for change
growth chart data from the Centers for Disease Control. ~~A~~ The 120 mg monthly dose level ~~will be~~was selected for patients age 6 to 17 years (inclusive) with weight values <45.0 kg based on targeting the achievement of a similar distribution of fremanezumab exposure levels (following multiple dosing) of 225 mg monthly in adult patients with EM and CM.	(following multiple dosing) of 225 mg monthly in adult patients with EM and CM.	
5.10. Total Blood Volume		
The total blood volume to be collected for each patient in this study is approximately ~~6648~~ mL ~~(at maximum)~~. See Appendix I.	The total blood volume to be collected for each patient in this study is approximately 48 mL. See Appendix I.	Updated total blood volume.
6. ASSESSMENT OF EFFICACY		
6.1.1. Electronic Headache Diary		
On each day, the patient or parent/caregiver will be asked to record diary data for the previous 24-hour period. Patients and parents/caregivers may be asked about their (child's) performance at school and when doing household chores (ie, functional assessments). Patients or parents/caregivers who report headache on the previous day will answer questions about the headache (ie, the number of hours with headache, headache severity, presence of associated symptoms, and use of acute migraine medications). Additional details regarding the questions patients or parents/guardians will answer can be found in the electronic headache diary training manual.	On each day, the patient or parent/caregiver will be asked to record diary data for the previous 24-hour period. Patients and parents/caregivers may be asked about their (child's) performance at school and when doing household chores (ie, functional assessments). Patients or parents/caregivers who report headache on the previous day will answer questions about the headache (ie, the number of hours with headache, headache severity, presence of associated symptoms, and use of acute migraine medications). Additional details regarding the questions patients or parents/guardians will answer can be found in the electronic headache diary training manual.	Clarification.
If headache is reported, then headache severity will be subjectively rated by the patient or parent/caregiver on an 11-point numerical rating scale, where 0 is no pain and 10 is the most severe pain.~~as follows:~~ ~~• mild headache~~	If headache is reported, then headache severity will be subjectively rated by the patient or parent/caregiver on an 11-point numerical rating scale, where 0 is no pain and 10 is the most severe pain. Each headache severity rating from the 11-point numerical rating scale will be mapped to mild (1 to 3), moderate (4 to 6), or severe (7 to 10) for	Updated language to clarify how headache severity will be assessed.

Original text with changes shown	New wording	Reason/Justification for change
~~• moderate headache~~ ~~• severe headache~~ ~~An 11-point numerical scale will be used for the patients to rate their headache pain intensity.~~ Each headache s~~S~~everity rating from the 11-point numerical rating scale will be mapped to mild (1 to 3), moderate (4 to 6), or severe (7 to 10) for endpoint analyses (McCaffery and Beebe 1989). Patients or parents/caregivers will also record whether photophobia, phonophobia, nausea, and vomiting are present, and they will record any migraine medications (name of drug, number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day. Diary compliance of less than 75% after the start of treatment will be recorded as a protocol deviation.	endpoint analyses (McCaffery and Beebe 1989). Patients or parents/caregivers will also record whether photophobia, phonophobia, nausea, and vomiting are present, and they will record any migraine medications (name of drug, number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day. Diary compliance of less than 75% after the start of treatment will be recorded as a protocol deviation.	
7. ASSESSMENT OF SAFETY		
7.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis		
Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected HIV or Lyme disease, a blood sample ~~should~~may be taken at screening at the discretion of the investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below (Table 4).	Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected HIV or Lyme disease, a blood sample may be taken at screening at the discretion of the investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below (Table 4).	Virology sampling may be done at the discretion of the investigator.
9. STATISTICS		
9.7. Safety Analysis		
Suicidal ideation and behavior will be measured using the C-SSRS. Data for patients with positive findings will be listed.	Suicidal ideation and behavior will be measured using the C-SSRS. Data for patients with positive findings will be listed.	Clarification.
9.8. Tolerability Analysis		

Original text with changes shown	New wording	Reason/Justification for change
~~Subjective t~~Tolerability will be assessed by the following:	Tolerability will be assessed by the following:	Clarification.
15. REFERENCES		
McCaffery M, Beebe A. Pain: Clinical manual for nursing practice. St. Louis (MO): Mosby 1989. Available upon request.	McCaffery M, Beebe A. Pain: Clinical manual for nursing practice. St. Louis (MO): Mosby 1989. Available upon request.	Added in a reference for the pain severity scale.
APPENDIX A CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Legal Representative of the Sponsor in the European Union (EU) and Contact Person	Legal Representative of the Sponsor in the European Union (EU) and Contact Person	Clarification.
APPENDIX B CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
• review lifetime prior medication and treatment history	• review lifetime prior medication and treatment history	Clarification.
APPENDIX C PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR THE DURATION OF THE STUDY FOR UP TO 20% OF PATIENTS	**APPENDIX C PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR THE DURATION OF THE STUDY FOR UP TO 20% OF PATIENTS**	Clarification.
The following concomitant preventive migraine medications are allowed in up to 20% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients must have been on a stable, well-tolerated dose of this preventive medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 80% of patients, these medications are not allowed for migraine or for any other indications.	The following concomitant preventive migraine medications are allowed in up to 20% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients must have been on a stable, well-tolerated dose of this preventive medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 80% of patients, these medications are not allowed for migraine or for any other indications.	Clarification.

Original text with changes shown

APPENDIX I TOTAL BLOOD VOLUME

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)	10	3	30
Pharmacokinetics	2	3	6
ADA	4	3	12
~~Virology (hepatitis, HIV, Lyme disease, and tuberculosis)~~	~~18~~	~~1~~	~~18~~
Total			**~~66~~48**

ADA=antidrug antibody; β-HCG=beta-human chorionic gonadotropin~~; HIV=human immunodeficiency virus~~.

New wording

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)	10	3	30
Pharmacokinetics	2	3	6
ADA	4	3	12
Total			**48**

ADA=antidrug antibody; β-HCG=beta-human chorionic gonadotropin.

Reason/Justification for change

Updated blood samples to remove virology testing. Virology blood sampling will be done at the discretion of the investigator.

16.15. Amendment 01 Dated 21 June 2019

The primary reasons for this amendment are to improve the feasibility of the diary compliance requirement, clarify the exclusion criterion for nerve stimulation or device, and clarify the timing of injection site reaction assessment. None of these revisions impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment agreement. The amendment is considered to be substantial (ie, requires approval by competent authorities, 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.

Changes to the Protocol

Table 1 (Study Procedures and Assessments) has been revised to reflect the changes described below.

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE (Other sections affected by this change: Investigator Agreement, Coordinating Investigator Agreement)		
EudraCT number: ~~<TBD>~~2019-002055-42	EudraCT number: 2019-002055-42	This change was made to provide the EudraCT number.
Teva Branded Pharmaceutical Products R&D, Inc. ~~145 Brandywine Parkway~~ ~~West Chester, PA 19380~~ 41 Moores Road Frazer, Pennsylvania 19355 United States of America	Teva Branded Pharmaceutical Products R&D, Inc. 41 Moores Road Frazer, Pennsylvania 19355 United States of America	This change was made to update the addresses for the Sponsor.
SELECTION AND WITHDRAWAL OF PATIENTS		
Section 4.1		
i. The patient/caregiver has demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of ~~24~~21 out of 28 days (approximately ~~85~~75% diary compliance).	i. The patient/caregiver has demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 21 out of 28 days (approximately 75% diary compliance).	This change was made to harmonize the required diary compliance during the baseline and treatment periods across the 3 Phase 3 pediatric protocols. The change will not impact data quality or accuracy.
(Not applicable)	n. The patient has received all recommended age-appropriate vaccines according to local standard of care and schedule.	This inclusion criterion was added to protect study participants from preventable childhood illnesses in accordance with current medical recommendations for pediatric patients and to help prevent the spread of communicable infections to others at the investigational site.

Original text with changes shown	New wording	Reason/Justification for change
Section 4.2		
(Not applicable)	b. The patient has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine during the 2 months prior to the day of the screening visit.	This exclusion criterion was added to decrease the chances that previous nonpharmacologic treatments would confound the assessment of safety and efficacy of fremanezumab.
(Not applicable)	s. The patient received a live attenuated vaccine within the 12-week period prior to screening or plans to receive a live attenuated vaccine at any time during the study and for 6 months after the last dose of IMP.	This exclusion criterion was added to avoid an immune response elicited by administration of a live attenuated vaccine that could interfere with the accurate assessment of efficacy and safety of fremanezumab.
ASSESSMENT OF SAFETY		
Section 7.8		
Injection site assessments will be performed ~~immediately and 1 hour~~ after administration of each dose of study drug, d before patients leave the investigational site.	Injection site assessments will be performed after administration of each dose of study drug and before patients leave the investigational site.	This change was made to clarify the procedure for assessment of local tolerability and pain.
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Appendix A		
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	This change was made to add details for the Sponsor's Authorized Representative.

Original text with changes shown	New wording	Reason/Justification for change
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Tel: [redacted]	[redacted] Tel: [redacted]	This change was made to add details for the Legal Representative of the Sponsor in the European Union.
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	This change was made to add details for the Sponsor's Medical Expert.
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Tel: [redacted]	[redacted] Tel: [redacted]	This change was made to add details for the Coordinating Investigator.
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Teva Pharmaceutical Industries Ltd. Tel: [redacted] Cell: [redacted]	[redacted] Teva Pharmaceutical Industries Ltd. Tel: [redacted] Cell: [redacted]	This change was made to add details for the Sponsor's Representative of Global Patient Safety and Pharmacovigilance.
~~<Name of Company>~~ICON	ICON plc South County Business Park Leopardstown, Dublin 18, Ireland	This change was made to add the name and contact information of the Contract Research Organization.

Original text with changes shown	New wording	Reason/Justification for change
~~<Name of Company>~~Icon Laboratories 123 Smith Street Farmingdale, NY 11735 United States Icon Laboratories South County Business Park Leopardstown, Dublin 18, Ireland	Icon Laboratories 123 Smith Street Farmingdale, NY 11735 United States Icon Laboratories South County Business Park Leopardstown, Dublin 18, Ireland	This change was made to add the name and contact information of the Central Clinical Laboratories.
~~<Name of Company>~~ eResearch Technology, Inc 1818 Market Street #1000 Philadelphia, PA 19103 United States	eResearch Technology, Inc 1818 Market Street #1000 Philadelphia, PA 19103 United States	This change was made to add the name and contact information of the Central Electrocardiogram Evaluation site.
~~<Name of Company>~~ PAREXEL International Corp. 195 West Street Waltham, MA 02451 Tel: [redacted]	PAREXEL International Corp. 195 West Street Waltham, MA 02451 Tel:[redacted]	This change was made to add the name and contact information of the Randomization and Trial Supply Management (RTSM) vendor.

TOTAL BLOOD VOLUME

Appendix I (Other sections affected by this change: Section 5.10)

(Not applicable)				Virology (hepatitis, HIV, Lyme disease, and tuberculosis)				Added virology testing to Total Blood Volume table in order to align with exclusion criterion e: The patient has an ongoing infection, known history of HIV infection, tuberculosis, Lyme disease, or hepatitis.
(Not applicable)				Virology (hepatitis, HIV, Lyme disease, and tuberculosis)	18	1	18	Total blood draws were adjusted to reflect the addition of virology testing.
Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)	~~7.5~~ 10	3	~~22.5~~ 30	Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)	10	3	30	Blood draw volumes were adjusted to include β-HCG testing.
Total			**~~44.5~~ 5566**	**Total**			**66**	Total blood draws were updated to reflect the new total based on blood draw adjustments.

Changes to the Protocol

Table 1 (Study Procedures and Assessments) has been revised to reflect the changes described below.

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE (Other sections affected by this change: Investigator Agreement, Coordinating Investigator Agreement)		
EudraCT number: ~~<TBD>~~2019-002055-42	EudraCT number: 2019-002055-42	This change was made to provide the EudraCT number.
Teva Branded Pharmaceutical Products R&D, Inc. ~~145 Brandywine Parkway~~ ~~West Chester, PA 19380~~ 41 Moores Road Frazer, Pennsylvania 19355 United States of America	Teva Branded Pharmaceutical Products R&D, Inc. 41 Moores Road Frazer, Pennsylvania 19355 United States of America	This change was made to update the addresses for the Sponsor.
SELECTION AND WITHDRAWAL OF PATIENTS		
Section 4.1		
i. The patient/caregiver has demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of ~~24~~21 out of 28 days (approximately ~~85~~75% diary compliance).	i. The patient/caregiver has demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 21 out of 28 days (approximately 75% diary compliance).	This change was made to harmonize the required diary compliance during the baseline and treatment periods across the 3 Phase 3 pediatric protocols. The change will not impact data quality or accuracy.
(Not applicable)	n. The patient has received all recommended age-appropriate vaccines according to local standard of care and schedule.	This inclusion criterion was added to protect study participants from preventable childhood illnesses in accordance with current medical recommendations for pediatric patients and to help prevent the spread of communicable infections to others at the investigational site.

Original text with changes shown	New wording	Reason/Justification for change
Section 4.2		
(Not applicable)	b. The patient has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine during the 2 months prior to the day of the screening visit.	This exclusion criterion was added to decrease the chances that previous nonpharmacologic treatments would confound the assessment of safety and efficacy of fremanezumab.
(Not applicable)	s. The patient received a live attenuated vaccine within the 12-week period prior to screening or plans to receive a live attenuated vaccine at any time during the study and for 6 months after the last dose of IMP.	This exclusion criterion was added to avoid an immune response elicited by administration of a live attenuated vaccine that could interfere with the accurate assessment of efficacy and safety of fremanezumab.
ASSESSMENT OF SAFETY		
Section 7.8		
Injection site assessments will be performed ~~immediately and 1 hour~~ after administration of each dose of study drug, d before patients leave the investigational site.	Injection site assessments will be performed after administration of each dose of study drug and before patients leave the investigational site.	This change was made to clarify the procedure for assessment of local tolerability and pain.
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Appendix A		
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	This change was made to add details for the Sponsor's Authorized Representative.

Original text with changes shown	New wording	Reason/Justification for change
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Tel: [redacted]	[redacted] Tel: [redacted]	This change was made to add details for the Legal Representative of the Sponsor in the European Union.
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	This change was made to add details for the Sponsor's Medical Expert.
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Tel: [redacted]	[redacted] Tel: [redacted]	This change was made to add details for the Coordinating Investigator.
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Teva Pharmaceutical Industries Ltd. Tel: [redacted] Cell: [redacted]	[redacted] Teva Pharmaceutical Industries Ltd. Tel: [redacted] Cell: [redacted]	This change was made to add details for the Sponsor's Representative of Global Patient Safety and Pharmacovigilance.
~~<Name of Company>~~ICON	ICON plc South County Business Park Leopardstown, Dublin 18, Ireland	This change was made to add the name and contact information of the Contract Research Organization.

Original text with changes shown	New wording	Reason/Justification for change
~~<Name of Company>~~Icon Laboratories 123 Smith Street Farmingdale, NY 11735 United States Icon Laboratories South County Business Park Leopardstown, Dublin 18, Ireland	Icon Laboratories 123 Smith Street Farmingdale, NY 11735 United States Icon Laboratories South County Business Park Leopardstown, Dublin 18, Ireland	This change was made to add the name and contact information of the Central Clinical Laboratories.
~~<Name of Company>~~ eResearch Technology, Inc 1818 Market Street #1000 Philadelphia, PA 19103 United States	eResearch Technology, Inc 1818 Market Street #1000 Philadelphia, PA 19103 United States	This change was made to add the name and contact information of the Central Electrocardiogram Evaluation site.
~~<Name of Company>~~ PAREXEL International Corp. 195 West Street Waltham, MA 02451 Tel: [redacted]	PAREXEL International Corp. 195 West Street Waltham, MA 02451 Tel: [redacted]	This change was made to add the name and contact information of the Randomization and Trial Supply Management (RTSM) vendor.

TOTAL BLOOD VOLUME

Appendix I (Other sections affected by this change: Section 5.10)

(Not applicable)				Virology (hepatitis, HIV, Lyme disease, and tuberculosis)				Added virology testing to Total Blood Volume table in order to align with exclusion criterion e: The patient has an ongoing infection, known history of HIV infection, tuberculosis, Lyme disease, or hepatitis.
(Not applicable)				Virology (hepatitis, HIV, Lyme disease, and tuberculosis)	18	1	18	Total blood draws were adjusted to reflect the addition of virology testing.
Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)	~~7.5~~ 10	3	~~22.5~~ 30	Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)	10	3	30	Blood draw volumes were adjusted to include β-HCG testing.
Total			**~~44.5~~ 5566**	**Total**			**66**	Total blood draws were updated to reflect the new total based on blood draw adjustments.

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]
Legal Representative of the Sponsor in the European Union (EU) and Contact Person	[redacted] Tel: [redacted]
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]
Coordinating Investigator	[redacted] Tel: [redacted]
Sponsor's Representative of Global Patient Safety and Pharmacovigilance For **serious adverse events:** Send by email to the local safety officer/contract research organization (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.	[redacted] Teva Pharmaceuticals Cell: [redacted]
Contract Research Organization	ICON plc South County Business Park Leopardstown, Dublin 18 Ireland

Central Clinical Laboratory	Icon Laboratories 123 Smith Street Farmingdale, NY 11735 United States Icon Laboratories South County Business Park Leopardstown, Dublin 18 Ireland
Central Electrocardiogram Evaluation	Clario 1818 Market Street #1000 Philadelphia, PA 19103 United States
Bioanalytical Pharmacokinetics Evaluation	Specialty Bioanalytics Teva Branded Pharmaceutical Products R&D, Inc. 610 Brandywine Parkway West Chester, PA, 19380 United States
Bioanalytical Immunogenicity Evaluation	Specialty Bioanalytics Teva Branded Pharmaceutical Products R&D, Inc. 610 Brandywine Parkway West Chester, PA, 19380 United States
Pharmacogenomics/Biomarker Evaluation	Not Applicable
Randomization and Trial Supply Management (RTSM) vendor	Calyx - Perceptive eClinical Limited Castle Wharf, 4 Canal Street, Nottingham United Kingdom NG1 7EH Tel: [redacted]

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. **Procedures for Screening (Visit 1, Days -28 to -1)**

The screening visit (visit 1) will take place not more than 28 (+3) days before the randomization visit (visit 2). The following procedures will be performed at visit 1:

- obtain written informed consent from parent(s) or legal guardian(s) and assent (according to local regulations) from each patient before any study-related procedures are performed
- inform patients of study restrictions and compliance requirements
- review medical and psychiatric history
- review headache history
- review lifetime prior medication and treatment history
- review demographic characteristics
- review inclusion and exclusion criteria
- full physical examination (including height, weight, and body mass index)
- triplicate 12-lead electrocardiogram (ECG)
- vital signs measurements
- review adverse events
- review concomitant medications
- clinical laboratory tests
- serum beta-human chorionic gonadotropin (β-HCG) and urine pregnancy tests (only female patients who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period
- provide electronic headache diary device and instructions
- administer Columbia-Suicide Severity Rating Scale (C-SSRS)

2. **Visit 2 (Day 1+3 days)**

Patients who meet the inclusion and exclusion criteria at visit 1 will continue to visit 2. The following procedures will be performed at visit 2:

- review inclusion and exclusion criteria
- full physical examination (including height, weight, and body mass index)
- assessment of puberty status (Tanner staging scale) by patient's self-report or by physical examination
- assign randomization number and enter into case report form (CRF)
- triplicate 12-lead ECG

- vital signs measurements
- review adverse events
- review concomitant medications
- urine β-HCG pregnancy test (only female patients who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period
- review electronic headache diary
- collect blood samples for plasma drug concentration and serum antidrug antibodies (ADA) prior to dosing
- administer C-SSRS
- administer Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire
- administer Pediatric Quality of Life Inventory (PedsQL)
- administer study drug
- assess injection site

3. **Visits 3 and 4 (Day 29 [±3 days] and Day 57 [±3 days])**

The following procedures will be performed at visits 3 and 4:

- triplicate 12-lead ECG
- vital signs measurements
- review adverse events
- review concomitant medications
- clinical laboratory tests - **visit 3 only**
- collect blood samples for plasma drug concentration and serum ADA prior to dosing - **visit 3 only**
- urine β-HCG pregnancy test (only female patients who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period
- review electronic headache diary
- administer C-SSRS
- administer PedsQL
- administer study drug
- assess injection site

4. **End of Treatment/Early Withdrawal (Visit 5 [Day 85±3 days])**

The following procedures and assessments will be performed at visit 5 (End of Treatment or early withdrawal):

- full physical examination (including height and weight)
- assessment of puberty status (Tanner staging scale) by patient's self-report or by physical examination
- triplicate 12-lead ECG
- vital signs measurements
- review adverse events
- review concomitant medications
- clinical laboratory tests
- serum β-HCG and urine pregnancy tests (only female patients who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period
- review electronic headache diary
- return electronic headache diary device
- collect blood samples for plasma drug concentration and serum ADA prior to dosing
- administer C-SSRS
- administer PedMIDAS questionnaire
- administer PedsQL
- administer Patient Global Impression of Improvement questionnaire

5. **Unscheduled Visits**

An unscheduled procedure or visit may be performed at any time during the study at the subject's request or as deemed necessary by the investigator.

Unscheduled procedures may include the following:

- concomitant medication review
- vital signs measurements
- inquire and record start/stop date of menstrual period
- adverse event inquiry
- study compliance review

Other procedures may be performed at the discretion of the investigator, who may consult with the sponsor.

In the case that a patient is not able to go to the investigational center or the investigational center staff are not able to see patients at the investigational center, certain assessments/procedures, as detailed in Table 1, may be performed remotely.

APPENDIX C. PREVENTIVE MIGRAINE MEDICATIONS FOR ANY CONDITION ALLOWED FOR THE DURATION OF THE STUDY FOR APPROXIMATELY 30% OF PATIENTS

The chronic use of 2 of the following concomitant medications is allowed in approximately 30% of EM patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients using no more than 2 of the following migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication. Patients must have been on a stable, well-tolerated dose of this medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining approximately 70% of EM patients, the chronic use of these medications are not allowed for migraine or for any other indications. PRN use of the following medications are allowed during the course of the study for any indications and do not have to have established dosing regimens. PRN use of these medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the prescribing information or local treatment guidelines. Patients will be allowed PRN use of acute medications to treat acute migraine attacks, as needed, with the exception of regular use of medications containing opioids and barbiturates.

- **Antidepressants**: amitriptyline, nortriptyline, fluoxetine, desipramine, venlafaxine, duloxetine
- **Antiepileptics**: topiramate, valproic acid, levetiracetam, zonisamide, gabapentin, pregabalin
- **Antihistamines**: cyproheptadine, pizotifen
- **Beta blockers**: propranolol, metoprolol, nadolol, timolol
- **Calcium-channel blockers**: flunarizine, verapamil, nimodipine
- **Onabotulinumtoxin A or B**

Other agents that are not on this list but used for migraine prevention that may be used per local guidelines or clinical practice preference are considered to have doubtful evidence for migraine prevention and therefore are treated the same as other concomitant medications (ie, recorded as concomitant medications on the CRF) and DO NOT need to be captured in eCRF pages specific for migraine preventive medications.

Adapted from:

O'Brien HL, Kabbouche MA, Kacperski J, Hershey AD. Treatment of pediatric migraine. Curr Treat Options Neurol 2015;17(1):326.

Lewis DW, Winner P. The pharmacological treatment options for pediatric migraine: an evidence-based appraisal. NeuroRx 2006;3(2):181-91.

APPENDIX D. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

a. 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
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

b. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):
   - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

c. Reduced BP after exposure to known allergen for that subject (minutes to several hours):
   - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

Source: Modified from 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.[reprint in Ann Emerg Med 2006 Apr;47(4):373-80; PMID:16546624]. J Allergy Clin Immunol 2006 Feb;117(2):391-7.

APPENDIX E. 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/ Internal Review Board (IEC/IRB) and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

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 an important protocol deviation. Important protocol deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or Good Clinical Practice (GCP) guidelines; noncompliance to investigational medicinal product (IMP) administration; use of prohibited medications. Important protocol deviations will be identified and recorded by investigational center personnel in the source documents and reported to regulatory authorities as applicable. All important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important protocol deviation is reported, the investigator and the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If the 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 important 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 procedure (SOPs), the protocol, and other written instructions and regulatory guidelines.

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

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

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

Audit and Inspection

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

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

APPENDIX F. ETHICS

Informed Consent/Assent

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

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the informed consent form (ICF), which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

The investigator, or a qualified person designated by the investigator, should fully inform the patient and each parent/legally acceptable representative of all pertinent aspects of the study, including the written information approved by the IEC/IRB, per local regulations. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by each parent/legally acceptable representative and the patient. The patient and each parent/legally acceptable representative 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.

A personally signed and dated ICF will be obtained from each parent/legally acceptable representative, and a signed and dated assent form will be obtained from each patient (if the patient is able) before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained; according to IEC/IRB requirements. The forms will be signed and dated also by the person who conducted the informed consent discussion. The investigator will keep the original informed consent and assent forms, and copies will be given to the patients (and each parent/legally acceptable representative). It will also be explained to the patients (and each parent/legally acceptable representative) that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

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

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In 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 (GCA), or competent authorities. Personal medical information will always be treated as confidential.

Registration of the Clinical Study

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

APPENDIX G. BIRTH CONTROL METHODS AND PREGNANCY TESTING

Females of childbearing potential are defined as the following:

- not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- postmenarchal or ≥12 years of age

Females who are not of childbearing potential are defined as the following:

- premenarchal and <12 years of age

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 are considered. Such methods include the following:

- Progestogen-only hormonal contraception (oral, injectable, and implantable) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP
- Progestin and estrogen contraceptives (oral only) associated with inhibition of ovulation; these should be initiated at least 1 month 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 that he is the sole sexual partner and has received medical assessment of the surgical process
- Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

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 who are sexually active with female partners must always use a condom for the duration of the study and for 6 months after the last administration of IMP.

APPENDIX H. 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 and transcribed to the electronic case report forms.
- 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 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 bilirubin[1] will be measured at each study visits 1, 3, and 5.

In any case of elevated ALT or AST to a level exceeding ≥2× the upper limit of normal (ULN) (including patients whose baseline ALT or AST levels are ≥2× and ≤3× the ULN, who may be enrolled in the study), a thorough medical history and physical examination with a focus on liver disease should be undertaken.[2] In addition, the patient should be instructed to refrain from alcoholic beverages.

In case of symptoms compatible with drug-induced liver injury during the study, patients will be instructed to return to the 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 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, total bilirubin, CBC [with differential for eosinophil count, separate tube], and International Normalized Ratio [INR] [separate tube; not to be sent in a confirmatory test]). The investigator should also question the patient regarding symptoms.

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

The 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 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 Less Than 5× the ULN

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

ALT or AST ≥5× but Less Than 8× the ULN

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

- ALT, AST, GGT, ALP, total and direct bilirubin, CBC 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, eosinophilia) and not deemed related to other diseases (eg, vomiting or nausea triggered by migraine)
- any increase in ALT or AST to levels ≥5 but <8× the ULN, which is persistent for ≥2 weeks of repeated measurements
- any increase in ALT or AST to levels ≥8× the ULN
- in any case where monitoring of liver enzymes cannot be performed according to the protocol guidance

Follow-Up of Liver Enzymes After Stopping Rules Are Met

- A patient who meets the above criteria for discontinuation of the study drug should be invited to the site to return the study drug. 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.
- Every effort should be made to ensure that the patient continues to receive ongoing evaluation and treatment by their primary care physician after withdrawal from the study.

APPENDIX J. TOTAL BLOOD VOLUME

Total blood volume to be collected for each patient in this study is approximately 48 mL.

Total Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)	10	3	30
Pharmacokinetics	2	3	6
ADA	4	3	12
Total			**48**

ADA=antidrug antibody; β-HCG=beta-human chorionic gonadotropin.

APPENDIX K. PRODUCT COMPLAINTS

Clinical Product Complaints/Device Deficieny

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/combination product or other retrievable item, it is required that the device/combination product (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.

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.

*Please refer to Appendix Table 1 and Appendix Table 2.

Handling of Investigational Medicinal Product(s)/Devices 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 (and/or PFS).

If it is determined that the investigational center must return all IMP (and/or PFS), 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.

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 7.1.7.4, respectively).

Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (see below: Assessment of Device Performance), 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.

Assessment of Device Performance

A device deficiency is defined as any inadequacy of an investigational medical device or combination product with respect to its identity, quality, durability, reliability, usability, safety, or performance (Appendix Figure 1). This definition includes malfunctions, use errors, inadequate labeling (eg, unintelligible label, incorrect expiry date), and product complaints that are related to the IMP.

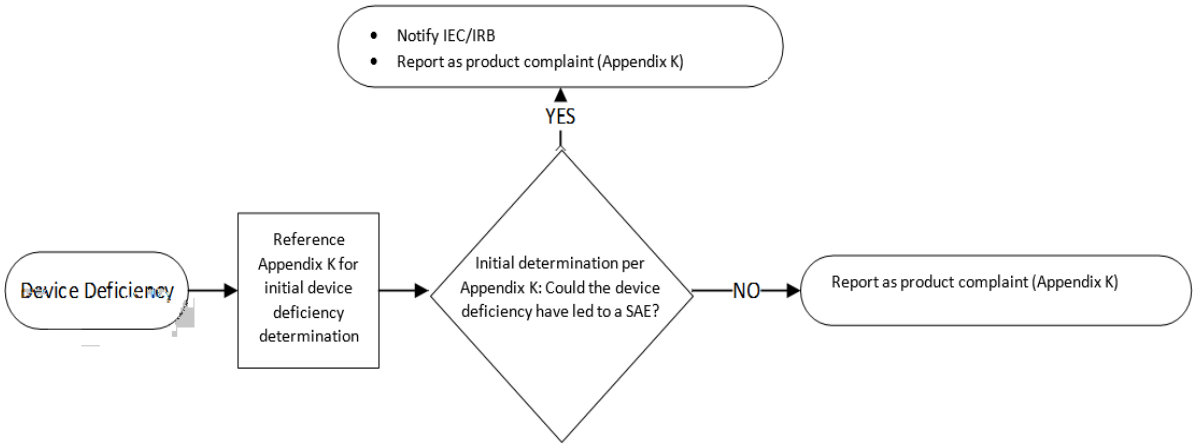
The investigator should use Appendix Table 1 and Appendix Table 2 to help make an initial determination whether the device deficiency could have led to a serious adverse event and include this assessment in the product complaint form.

Device deficiencies with potential serious adverse device effect are defined as deficiencies that might have led to a serious adverse device effect if (Appendix Figure 1):

- suitable action had not been taken (or)
- intervention had not been made (or)
- if circumstances had been less fortunate

These device deficiencies shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor according to the national and local regulations.

Appendix Figure 1: Decision Tree for Device Deficiencies



IEC=Independent Ethics Committee; IRB=Institutional Review Board; SAE=serious adverse event.

Appendix Table 1: Potential Use-Related Deficiencies That Could Lead to Serious Adverse Events

Use step	Use error	Potential hazard situation	Potential harm
Obtain sharps container and dispose of the device	Syringe not disposed of correctly after use	Needle stick third party	Third party death
Check that IMP name appears on device	Failure to check IMP information.	Incorrect medicament injected	Patient death
Store carton within the refrigerator	Fail to store product correctly	Patient exposed to toxic substance due to degraded drug	Permanent impairment or life threatening injury

Use step	Use error	Potential hazard situation	Potential harm
Inspect the device	Fail to perceive or recognize a need to visually inspect the device; Incorrect mental model of what would be considered to constitute 'damage'; Expiration date check not completed; Misread the expiration date; etc.	Inject degraded or expired IMP	Toxicity – Permanent impairment or life threatening injury

IMP=investigational new drug.

Appendix Table 2: Potential Design Related Deficiencies That Could Lead to Serious Adverse Events

Device component	Failure mode	Potential hazard situation	Potential harm
PFS components (Barrel-needle, RNS, plunger rod, backstop, syringe label)	PFS components are not biocompatible	User is exposed to an irritant, a toxic substance and/or a sensitizer	Toxicity - Permanent impairment or life threatening injury
PFS components (Barrel-needle, RNS, plunger rod, backstop, syringe label)	PFS components are not compatible with drug	User injects degraded drug. Patient exposed to a toxic substance	Toxicity - Permanent impairment or life threatening injury
RNS and syringe barrel with needle	RNS is smaller than needle leaving needle exposed	Needle sterility compromised. Drug is contaminated	Infection – Permanent impairment or life threatening injury
RNS and syringe barrel with needle	Too much radial clearance between needle and inside of RNS. RNS comes off easily.	Needle sterility compromised. Drug is contaminated.	Infection – Permanent impairment or life threatening injury
Syringe barrel	Barrel view is occluded	User is exposed to toxic substance	Toxicity - Permanent impairment or life threatening injury
Syringe label	Label is illegible	User is exposed to toxic substance	Toxicity - Permanent impairment or life threatening injury
Syringe label	Misinformation or label is incorrect.	User is exposed to toxic substance or degraded drug	Permanent impairment or life threatening injury
Product IFU	Misinformation or missing information. IFU is incorrect or incomplete.	User is exposed to toxic substance or degraded drug	Permanent impairment or life threatening injury

IFU=instructions for use; PFS=pre-filled syringe; RNS=rigid needle shield.

APPENDIX L. 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.

If data are processed from other institutions or by other means (eg, clinical laboratory, central image center, or electronic diary data) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol.

The medical experts, study monitors, auditors, Independent Ethics Committee/ Institutional Review Board (IEC/IRB), and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, 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 [ePRO] tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

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

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's SOPs for clinical studies. Day-to-day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

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

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

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

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

Investigator Responsibilities

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

- full case histories
- signed informed consent forms
- patient identification lists
- CRFs for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the 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 M. 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 (ICMJE 2014):

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

APPENDIX N. STORAGE AND DESTRUCTION OF BIOLOGICAL SAMPLES

Safety Samples

Safety samples will be stored for a short period of time in the central laboratory until analysis and destruction. Specific details regarding central laboratory storage and destruction can be found in the study Laboratory Manual and the central laboratory's standard operating procedures (SOPs).

Pharmacokinetic and Immunogenicity Samples

Pharmacokinetic and immunogenicity samples will be stored at the sites at a temperature of -70°C ±20°C (or at/below -20°C if no -70°C freezer is available) in an upright position until they are shipped to the central laboratory.

Samples will be stored at -70°C at the central laboratory, until shipped to the sponsor or designee for analysis, as described in the study Laboratory Manual.

After analysis, the sponsor will store the residue (leftovers) from the pharmacokinetic and immunogenicity samples at -70°C at the designated bioanalytical archive facility for up to 5 years after the study results are submitted to the regulatory authorities. Destruction will take place at the sponsor's bioanalytical laboratory or designee, according to the applicable SOPs.