Clinical Study Protocol

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

Study Number TV48125-MH-40142

NCT04041284

Protocol with Amendment 04 Approval Date: 04 May 2020

Clinical Study Protocol with Amendment 04

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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

A Randomized, Double-Blind, Placebo-Controlled Study on Efficacy and Safety of Fremanezumab for Preventing Migraine in Patients with MDD

A Study to Assess if Fremanezumab is Effective in Preventing Migraine in Patients with Major Depressive Disorder

Efficacy and Safety Study (Phase 4)

IND number: 106533; NDA number: Not applicable; BLA number: 761089;
EudraCT number: 2019-001989-15

EMA Decision number of Pediatric Investigation Plan: Not applicable
Article 45 or 46 of 1901/2006 does not apply

Protocol Approval Date: 03 May 2019

Protocol with Amendment 01 Approval Date: 04 June 2019

Protocol with Amendment 02 Approval Date: 10 October 2019

Protocol with Amendment 03 Approval Date: 04 November 2019

Protocol with Amendment 04 Approval Date: 04 May 2020

Sponsor

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

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

COVID-19 pandemic-related operational updates are provided in Appendix P

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

AMENDMENT HISTORY

The protocol for study TV48125-MH-40142 (original protocol dated 03 May 2019) has been amended and reissued as follows:

Amendment 04	04 May 2020 24 patients randomized/enrolled to date The management of study activities during the COVID-19 pandemic are detailed in Appendix P. The following sections are affected: Section 3.5 Schedule of Study Procedures and Assessments (Table 4) Appendix D. Ethics
Administrative Letter 02	14 February 2020
Amendment 03	04 November 2019 0 patients randomized/enrolled to date
Amendment 02	10 October 2019 0 patients randomized/enrolled to date
Letter of Clarification 01	26 August 2019 0 patients randomized/enrolled to date
Amendment 01	04 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 03 May 2019

Clinical Study Protocol with Amendment 04

IND number: 106533; NDA number: Not applicable; BLA number: 761089; EudraCT number: 2019-001989-15

EMA Decision number of Pediatric Investigation Plan: Not applicable

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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

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 04 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

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

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

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

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]	[redacted]	

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 03 May 2019

Clinical Study Protocol with Amendment 04

IND number: 106533; NDA number: Not applicable; BLA number: 761089; EudraCT number: 2019-001989-15

EMA Decision number of Pediatric Investigation Plan: Not applicable Article 45 or 46 of 1901/2006 does not apply

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

I have read the protocol with Amendment 04 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national 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 Good Clinical Practice (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]

Title: [redacted]

Address of Investigational Center: [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 04

Study TV48125-MH-40142

Title of Study: 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

Sponsor:

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

Investigational New Drug Number: 106533; New Drug Application Number: Not applicable; Biological License Application Number: 761089; EudraCT Number: 2019-001989-15

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Name of Test Investigational Medicinal Product (IMP): Fremanezumab, TEV-48125, LBR-101, PF-04427429, and RN307.

EudraVigilance code for the IMP, if applicable: Not applicable

Type of the Study: Efficacy and Safety Study (Phase 4)

Indication: Fremanezumab is indicated for preventive treatment of migraine in adults.

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

Number of Investigational Centers Planned: The study is planned to be conducted in approximately 65 investigational centers.

Countries Planned: The study is planned to be conducted in approximately 13 countries.

Planned Study Period: The study is expected to start in approximately September 2019 and last until approximately August 2021.

Number of Patients Planned (total): Approximately 340 patients (approximately 170 patients per treatment group) are planned to be enrolled in this study to have approximately 288 completers (approximately 144 completers per treatment group). A 15% drop-out rate is anticipated.

Study Population:

The study population will be composed of female and male patients, aged 18 to 70 years, inclusive, with a diagnosis of migraine and major depressive disorder (MDD). Patients must have been diagnosed with migraine (as defined by the International Classification of Headache Disorders, 3rd revision [ICHD-3] criteria [IHS, 2013], see Appendix I) at least 12 months prior to the screening visit (visit [V] 1). The diagnosis of migraine will be prospectively confirmed via a

review of migraine data recorded daily during a 28-day baseline period in an electronic diary device. Patients must also have a history of MDD as diagnosed according to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria at least 12 months prior to the screening visit (V1) and have active symptoms of depression as assessed by a Patient Health Questionnaire-9 (PHQ-9) score of at least 10 at the screening visit (V1). Investigators must document that patients had the diagnosis of migraine and MDD for at least 12 months prior to the screening visit (V1).

For migraine, patients using no more than 1 preventive medication at the time of the screening visit (V1) will be allowed to remain on the medication. The total number of patients receiving concomitant migraine preventive medication during the study will not exceed 30% of the total sample size of the study. For depression, patients using no more than 1 medication for the treatment of depression at the time of the screening visit (V1) will be allowed to remain on the medication. Patients on a concomitant migraine preventive medication and/or an antidepressant must be on a stable dose for at least 8 weeks of consecutive use prior to study entry (ie, before the 28-day baseline period), without anticipated changes during the study. If in the clinical judgment of the investigator or qualified psychiatrist, the patient's antidepressant medication needs to be changed or dose-adjusted during the 28-day baseline period, the patient will be screen failed. Any changes made during the treatment period will be recorded in the electronic data capture system. The percentage of patients with these changes will be analyzed at the end of the study.

All concomitant medications prescribed or 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. Complete discontinuation criteria are provided in the full protocol in Section 4.3.

During the 28-day baseline period, patients must fulfill the following criteria for migraine:

- on ≥4 days, headache attacks qualified as migraine based on the following ICHD-3 criteria:
  - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura
  - ICHD-3 criteria B and C for 1.2 Migraine with aura
  - probable migraine (a migraine subtype where only 1 migraine criterion is missing)
  - triptan or ergot derivative used to treat an established headache

Patients who fulfill the criteria for migraine will be further delineated as patients with chronic migraine (CM) or episodic migraine (EM), for stratification and other analyses.

CM is defined as:

Patient fulfills the following criteria for CM in prospectively collected baseline information during the 28-day baseline period:

- headache occurring on ≥15 days
- on ≥8 days, fulfilling any 1 of the following:

- ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix I)
- ICHD-3 criteria B and C for 1.2 Migraine with aura (Appendix I)
- probable migraine (a migraine subtype where only 1 migraine criterion is missing)
- triptan or ergot derivative used to treat established headache

EM is defined as:

The patient fulfills the following criteria for EM in prospectively collected baseline information during the 28-day baseline period:

- headache occurring ≥4 days but <15
- on ≥4 days, fulfilling any 1 of the following:
  - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix I)
  - ICHD-3 criteria B and C for 1.2 Migraine with aura (Appendix I)
  - probable migraine (a migraine subtype where only 1 migraine criterion is missing)
  - triptan or ergot derivative used to treat an established headache

Primary and Secondary Objectives and Endpoints

The primary and secondary study objectives and endpoints are in Table 1.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD	Mean change in the monthly average number of migraine days from the 28-day baseline period during the 12-week period after the first dose of study drug
Key secondary objective: To evaluate the efficacy of monthly 225 mg sc of fremanezumab in adult patients with migraine and MDD on the reduction of MDD symptoms	Mean change in depression symptoms from randomization (day 1) to week 8 after the first dose of study drug as measured by: • HAM-D 17
Secondary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD in terms of responder rates in monthly migraine days	Number of patients with 50% or more reduction from the 28-day baseline period in the monthly average number of migraine days at 12 weeks after the first dose of study drug
Secondary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD in terms of improving quality of life	Mean change in quality of life from randomization (day 1) to week 12 after the first dose of study drug as measured by: • MSQoL questionnaire, role function-restrictive and role function-preventive domains
Secondary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD in terms of improving disability	Mean change from randomization (day 1) in disability score for overall impact as measured by CGI-S and HIT-6 to the following time points after administration of the first dose of study drug: • weeks 4 and 8 (CGI-S) • week 12 (CGI-S and HIT-6)

Table 1: Primary and Secondary Objectives and Endpoints (Continued)

Objectives	Endpoints
Safety and tolerability objective (Secondary objective): To evaluate the safety and tolerability of monthly 225 mg sc and quarterly 675 mg sc fremanezumab in adult patients with migraine and MDD	• occurrence of adverse events throughout the study • changes from randomization visit (day 1) in vital signs (pulse, systolic and diastolic blood pressure, body temperature, and respiratory rate) measurements • abnormal physical examination findings including body weight • use of concomitant medication for adverse events during the study • number (%) of patients who did not complete the study due to adverse events • occurrence of severe hypersensitivity/anaphylaxis reactions • suicidal ideation and behavior as suggested by eC-SSRS

CGI-S = Clinical Global Impression-Severity; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; HAM-D 17 = Hamilton Depression Rating Scale-17 items; HIT-6 = 6-item Headache Impact Test; MDD = major depressive disorder; MSQoL = Migraine-Specific Quality of Life; sc = subcutaneous.

Exploratory Objectives and Endpoints

[redacted]

[redacted]

General Study Design:

This is an approximately 28-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fremanezumab self-administered at monthly doses of 225 mg sc and a quarterly dose of 675 mg sc (ie, one dose using 3 prefilled syringes with 225 mg each) in adult patients with migraine and MDD. The study will consist of a 28-day (ie, 4-week) baseline period, a 12-week double-blind treatment phase followed by a 12-week open-label extension phase, and an end-of-treatment visit (approximately 12 weeks after the final dose of study drug).

The total duration of patient participation in the study is planned to be approximately 28 weeks. Patients are expected to complete the entire duration of the study.

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

The main purpose of this study is to test if fremanezumab is effective in preventing migraine in patients with MDD. Researchers will first look at 2 different groups of patients: 1 group of patients who take the study drug and 1 group of patients who take the placebo. This part of the study is "double-blind," which means patients and researchers will not know who takes fremanezumab or placebo. This ensures that the results are not influenced in any way. At the end of 12 weeks, researchers will combine these groups and give all patients the study drug for 12 more weeks. This part of the study will not be blinded. Researchers will test how effective the drug is at helping reduce the number of monthly migraine days.

Method of Randomization and Blinding:

For the first phase of this study, the sponsor, investigators, study staff, and patients will be blinded to treatment assignment. A computer-generated master randomization list will be provided to drug packaging facilities. The packaging vendor(s) will package active drug and placebo into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance and contain 1 prefilled syringe with either active drug or placebo.

Patients will be stratified based on sex, country, migraine classification (ie, CM or EM), and PHQ-9 score category (10 to 14, 15 to 19, and ≥20) to ensure balance for the covariates.

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list using electronic interactive response technology (IRT). This system is used to ensure a balance across treatment groups. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

At the randomization visit (day 1), each patient will be randomized in a 1:1 ratio within the stratum to which he or she belongs to receive monthly 225 mg sc fremanezumab or placebo, as assigned by the IRT. In the open-label extension phase starting at week 12, however, all patients will receive active treatment with a quarterly dose of 675 mg sc fremanezumab.

The IRT will manage initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At each study visit where study drug is administered, the IRT will be queried, the site personnel will retrieve the study drug from refrigerated storage, and the patient will self-administer treatment with the 1 or 3 prefilled syringes, depending on the study visit, contained in the appropriately numbered kit.

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

The safety and tolerability of fremanezumab (intravenous [iv] doses ranging from 0.2 to 2000 mg and sc doses of 225 mg and 900 mg) has been well characterized in the Phase 1 development program. Furthermore, the safety and efficacy of fremanezumab has been demonstrated in a randomized double-blind, placebo-controlled Phase 2 study of 2 sc dosing regimens of fremanezumab (monthly 900 mg fremanezumab or 675 mg fremanezumab followed by monthly 225 mg fremanezumab) in patients with CM and a randomized, double-blind, placebo-controlled Phase 2 study of 2 sc dosing regimens of fremanezumab (monthly dose of 675 or 225 mg fremanezumab) in patients with EM. Furthermore, the efficacy and tolerability profile have been confirmed in the Phase 3 development program, which included a quarterly dose of 675 mg.

A randomized, double-blind, parallel-group, placebo-controlled design is appropriate given the objectives of this study. Furthermore, this design is consistent with the recommendations of the Classifications Committee of the International Headache Society for controlled trials of preventive drugs in migraine.

Patients will receive experimental medicinal product fremanezumab (visit 2, visit 3, and visit 4) or matching placebo reference medicinal product (visit 2, visit 3, and visit 4) in monthly doses from the sponsor. Patients will receive a quarterly dose of 675 mg sc fremanezumab at visit 5.

Prefilled syringes (active or placebo) will be contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. (See details in Table 2). Active prefilled syringes will

contain 225 mg of TEV-48125 in 1.5 mL solution, and placebo prefilled syringes will contain the same vehicle and excipients as those for active injections. Each kit will contain 1 prefilled syringe.

Adequate kit supply for upcoming study visits will be managed by the IRT and kept (refrigerated at 2°C to 8°C) on site.

Treatment self-administration (active or placebo) will occur at visit 2 (day 1), visit 3 (day 29), and visit 4 (day 57). Only active treatment will be administered on visit 5 (day 85), which is the beginning of the open-label extension phase. Final study assessments will be performed at the end-of-treatment visit (visit 6), approximately 12 weeks after administration of the last dose of study treatment.

Table 2: Investigational Medicinal Products Used in the Study

IMP name **Recombinant humanized IgG2a/kappa mAb**	**Fremanezumab**	**Placebo**
Trade name and INN, if applicable, or company-assigned number	AJOVY, fremanezumab Also known as: TEV-48125, LBR-101, PF-04427429, RN307	Placebo
Formulation	Prefilled syringes containing 1.5 mL solution for injection of 225 mg of the active ingredient fremanezumab Inactive ingredients include L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate-80, EDTA, and water for injection	Prefilled syringes containing 1.5 mL solution for injection of the same vehicle and excipients as those for active injection Inactive ingredients include L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate-80, EDTA, and water for injection
Unit dose strength(s)/Dosage level(s)	225 mg/1.5 mL per unit	None
Route of Administration	sc injection	sc injection
Dosing instructions	**Double-blind treatment phase**: a dose of 225 mg fremanezumab as an active injection (225 mg/ 1.5 mL) at visit 2 (day 1), visit 3 (day 29), and visit 4 (day 57) **Open-label extension phase**: a quarterly dose of 675 mg fremanezumab as 3 active injections (225 mg/ 1.5 mL) at visit 5 (day 85)	**Double-blind treatment phase**: 1.5 mL placebo injection at visit 2 (day 1), visit 3 (day 29), and visit 4 (day 57) **Open-label extension phase**: not applicable
Packaging	A kit uniquely numbered containing 1 prefilled syringe stored (refrigerated at 2°C to 8°C) on site	A kit uniquely numbered containing 1 prefilled syringe stored (refrigerated at 2°C to 8°C) on site

Table 2: Investigational Medicinal Products Used in the Study (Continued)

IMP name **Recombinant humanized IgG2a/kappa mAb**	**Fremanezumab**	**Placebo**
Manufacturer	**Drug substance**: [redacted] **Drug product**: [redacted]	[redacted]

EDTA = ethylenediaminetetraacetate; IgG2a = immunoglobulin G2a; IMP = investigational medicinal product; INN = international non-proprietary name; mAb = monoclonal antibody; sc = subcutaneous.

Duration of Patient Participation and Maximal Exposure to IMP:

The total duration of patient participation in the study is planned to be approximately 28 weeks. Patients are expected to complete the entire duration of the study.

Patients initially randomized to fremanezumab will receive a total of 1350 mg sc fremanezumab in the study (one 225 mg dose monthly for 3 months in the double-blind treatment phase and a quarterly dose of 675 mg in the open-label extension phase). Patients initially randomized to placebo will receive a quarterly dose of 675 mg sc in the open-label extension.

Study Duration: The study duration will be approximately 24 months, from approximately September 2019 (first patient screened) to approximately August 2021 (last visit of the last patient).

End of Study: End of study is defined as the last visit (end-of-treatment/early withdrawal visit [visit 6]) of the last patient.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study:

No treatment is planned by the sponsor after completion of the study. Patients should be treated with standard of care after withdrawal from or termination of the study, as appropriate.

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

a. The patient is capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in this protocol.
b. The patient is male or female and 18 to 70 years of age, inclusive.
c. The patient has a diagnosis of migraine with onset at ≤50 years of age.
d. Prior to the screening visit (V1), the patient has a 12-month history of either:
   - migraine (according to ICHD-3 criteria [IHS, 2013]) or
   - headache consistent with migraine (ie, migraine diagnosis not better accounted for by another ICHD-3 diagnosis)
e. The patient fulfills the following criteria for migraine in a prospectively collected diary during the 28-day baseline period:
   - on ≥4 days, headache attacks qualified as migraine based on the following ICHD-3 criteria:
     - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura

       headache has at least 2 of the following 4 characteristics: unilateral location; pulsating quality; moderate or severe pain intensity; and aggravation by, or causing avoidance of, routine physical activity (eg, walking or climbing stairs)

       during headache, at least one of the following: nausea and/or vomiting; photophobia and phonophobia
     - ICHD-3 criteria B and C for 1.2 Migraine with aura

       1 or more of the following fully reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, retinal

       at least 2 of the following 4 characteristics: at least 1 aura symptom spreads gradually over ≥5 minutes, and/or 2 or more symptoms occur in succession; each individual aura symptom lasts 5 to 60 minutes; at least 1 aura symptom is unilateral; the aura is accompanied, or followed within 60 minutes, by headache not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded
     - probable migraine (a migraine subtype where only 1 migraine criterion is missing)
     - triptan or ergot derivative used to treat an established headache.

f. The patient agrees not to initiate any migraine preventive medications (as defined in Appendix G) during the study. Up to 30% of patients, however, may take a single such medication previously prescribed for the treatment of migraine.
g. The patient has a history of MDD according to the DSM-V criteria at least 12 months prior to the screening visit (V1). Patients may take a single medication prescribed for the treatment of depression as long as the dose of that medication has been stable for at least 8 weeks prior to the screening visit (V1) and expects to remain at the stable dose throughout the study (Appendix G).
h. The patient has a PHQ-9 score of at least 10 at the screening visit (V1).
i. The patient has a Mini Mental State Examination score of at least 26 points at the screening visit (V1).
j. The patient is in good health in the opinion of the investigator as determined by medical evaluation, including medical and psychiatric history, physical examination, laboratory tests, and cardiac monitoring.
k. The patient has a body weight ≥45 kg and a body mass index within the range of 17.5 to 34.9 kg/m^2, inclusive.
l. The patient demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 21 days cumulative during the 28-day baseline period (~75% diary compliance).
m. Women may be included only if they have a negative serum beta-human chorionic gonadotropin test at the screening visit (V1), are sterile or postmenopausal, and are not lactating (not applicable for patients participating in safety follow-up only). Definitions of sterile and postmenopausal are given in Appendix E.
n. Women of child-bearing potential whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study and for 6 months after discontinuation of IMP (for details see Appendix E).
o. Men must be sterile or, if they are potentially fertile/reproductively competent (not congenitally sterile) and their female partners are of child-bearing potential, must use a condom for the duration of the study and for 6 months after discontinuation of IMP. For the purpose of this study, vasectomized men must use a condom if their partners are of child-bearing potential. Definitions of women of non-child-bearing potential, sterile and postmenopausal women; male contraception; and highly effective birth control methods, including examples, are given in Appendix E.
p. The patient must be willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study, and to return to the clinic for the follow-up evaluations, as specified in this protocol.

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

a. The patient uses medications containing opioids (including codeine) or barbiturates (including butalbital/aspirin/caffeine [Fiorinal®, Actavis plc], butalbital/paracetamol/caffeine [Fioricet®, Cardinal Health], or any other combination containing butalbital) on more than 4 days during the 28-day baseline period for the treatment of migraine or for any other reason.

b. The patient has failed 4 or more different medication classes to treat depression in their lifetime (Appendix G).
c. If in the clinical judgment of the investigator or qualified psychiatrist, the patient's antidepressant medication needs to be changed or dose-adjusted during the 28-day baseline period.
d. The patient has used an intervention/device (eg, scheduled nerve blocks, implantable vagal nerve stimulation, and transcranial magnetic stimulation) for migraine or depression during the 2 months prior to screening.
e. The patient has used electroconvulsive therapy at any time.
f. The patient suffers from constant or nearly constant headache, defined as having headaches for more than 80% of the time he/she is awake, and less than 4 days without headache per month. Daily headache is acceptable if patient has headaches 80% or less of the time he/she is awake on most days.
g. The patient has clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, ocular disease, or complications of an infection, at the discretion of the investigator.
h. The patient has a clinical history of a severe or uncontrolled psychiatric disorder, to include the following, or at the discretion of the investigator for any clinically significant psychiatric history that would likely interfere with full participation in the study:
   - Lifetime exclusion: suicide attempt
   - In the past 6 months exclusion: suicidal ideation, or other psychoactive spectrum disorders including schizoaffective disorder, delusional disorder, depression with psychotic features, and catatonic disorder
i. The patient has a history of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism.
j. The patient has a known infection or history of human immunodeficiency virus, tuberculosis, any history of Lyme disease, or chronic hepatitis B or C infection.
k. The patient has a past or current history of cancer, except for appropriately treated non-melanoma skin carcinoma.
l. The patient is a pregnant or nursing female or plans to become pregnant during the study, including the 6-month period after the administration of the last dose.
m. The patient has a history of hypersensitivity reactions to injected proteins, including monoclonal antibodies, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome.
n. The patient has participated in a clinical study of a new chemical entity or a prescription medicine within 2 months of the screening visit (V1) or 3 months in case of biologics if the half-life of the biologics is unknown or 5 half-lives, whichever is longer, or is currently participating in another study of an IMP (or a medical device).
o. The patient has failed treatment (based on tolerability and/or a lack of efficacy) with any monoclonal antibodies targeting the calcitonin gene-related peptide pathway (erenumab, eptinezumab, galcanezumab, or fremanezumab) or have taken the

medications within 5 half-lives of the screening visit (V1) or take them during the study.

p. The patient has any finding in the baseline 12-lead electrocardiogram considered clinically significant in the judgment of the investigator.
q. The patient has any finding that, in the judgment of the investigator, is a clinically significant abnormality, including serum chemistry, hematology, coagulation, and urinalysis test values (abnormal tests may be repeated for confirmation).
r. The patient has hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) >1.5 × the upper limit of the normal range after confirmation in a repeat test or suspected hepatocellular damage that fulfills the criteria for Hy's law at the screening visit (V1).
s. The patient has serum creatinine >1.5 × the upper limit of normal range, clinically significant proteinuria, or evidence of renal disease at the screening visit (V1).
t. The patient has any clinically significant uncontrolled medical condition (treated or untreated).
u. The patient has a history of alcohol or drug abuse in the opinion of the investigator.
v. The patient cannot participate or successfully complete the study, in the opinion of their healthcare provider or the investigator, for any of the following reasons:
   - mentally or legally incapacitated or unable to give consent for any reason
   - in custody due to an administrative or a legal decision, under tutelage, or being admitted to a sanitarium or social institution
   - unable to be contacted in case of emergency
   - has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study
w. The patient is a study center or sponsor employee who is directly involved in the study or the relative of such an employee.
x. The patient has any disorder that may interfere with the absorption, distribution, metabolism, or excretion of IMP.
y. The patient is vulnerable (eg, people kept in detention).
z. The patient has previously participated in this study.
aa. The patient has evidence or medical history of psychotic symptoms as per DSM-V criteria such as delusions, hallucinations, or disorganized speech in the past 1 month.
bb. Patient has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 3 months before screening visit.

Statistical Considerations

Sample Size Rationale:

A sample size of 288 (144 per treatment group) evaluable patients completing the study will provide 90% power to detect a treatment difference of 2 days with a common standard deviation of 5.2 days in changes from the 28-day baseline period in monthly average migraine days between active and placebo groups at a 2-sided alpha level of 0.05. This sample size will provide approximately 80% power to detect a treatment difference of 2 points with a common standard

deviation of 6 points in the change from randomization (day 1) in HAM-D 17 total score at a 2-sided alpha level of 0.05. Assuming a 15% drop-out rate, approximately 340 patients (approximately 170 patients per treatment group) will be randomized.

Primary Efficacy Analysis:

The primary efficacy endpoint, change from the 28-day baseline period in the monthly average number of migraine days, will be analyzed using analysis of covariance model with sex, region (United States, European, or rest of world), migraine classification (ie, CM or EM), baseline PHQ-9 score category, and treatment as factors and baseline number of migraine days as a covariate. The treatment difference, the 95% confidence interval for the treatment difference, and the associated p-value will be generated from this model.

Sensitivity Analysis:

Sensitivity analysis using multiple imputation for missing data imputation may be conducted.

Secondary Efficacy Analysis:

The continuous secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint. Analyses using the mixed-effect model repeated measure method will be conducted for continuous variables assessed at multiple time points. For the proportion of responders, defined as 50% or more reduction from the 28-day baseline period in the monthly average number of migraine days, a logistic regression model will be used with the following effects: treatment, sex, region (United States, European, or rest of world), migraine classification (ie, CM or EM), and baseline PHQ-9 score category. The odds ratios (ORs), 95% confidence intervals (for ORs), and p-values will be presented for fremanezumab comparing to placebo.

Other Efficacy Analysis:

[redacted]

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 is detailed in the statistical analysis plan.

Safety Analyses:

Safety analyses will be performed on the safety analysis set. All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP, serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of deaths, serious adverse events, and adverse events leading to withdrawal will be presented. Changes in laboratory, electrocardiogram, and vital signs measurements data will be summarized descriptively.

Tolerability Analysis:

Tolerability findings will be listed and summarized descriptively.

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Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ALT	alanine aminotransferase (SGPT)
ALP	alkaline phosphatase
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration-time curve
CDMS	clinical data management system
21CFR	Title 21 Code of Federal Regulations (USA)
CGI-S	Clinical Global Impression-Severity
CGRP	calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Sciences
CM	chronic migraine
C_{max}	maximum observed plasma drug concentration
COVID-19	Coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
DSM-V	Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
ECT	electroconvulsive therapy
EM	episodic migraine
GCP	Good Clinical Practice
GPSP	Global Patient Safety and Pharmacovigilance
HAM-A	Hamilton Anxiety Scale
HAM-D 17	Hamilton Depression Rating Scale-17 items
HIT-6	6-item Headache Impact Test
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council on Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd revision
IEC	Independent Ethics Committee
IHS	International Headache Society

Abbreviation	Term
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous
LSO	local safety officer
MDD	major depressive disorder
mITT	modified intent-to-treat
MSQoL	Migraine-Specific Quality of Life
OR	odds ratio
PHQ-9	Patient Health Questionnaire-9
PP	per-protocol
sc	subcutaneous
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	elimination half-life
t_{max}	time to maximum observed concentration
ULN	upper limit of normal
V	visit
V_z/F	apparent total volume of distribution (except for metabolites)
WPAI:GH	Work Productivity and Activity Impairment Questionnaire General Health

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

1.1.1. Disease Overview: Migraine

Migraine is a prevalent disease characterized by attacks of headache and associated symptoms (such as nausea, vomiting, photophobia, or phonophobia). The most common form of migraine occurs on less than 15 days per month and is referred to as episodic migraine (EM) (Lipton, 2007). However, 3% to 6% of individuals with EM evolve, in any given year, to a significantly more disabling condition called chronic migraine (CM) (Scher, 2003). Individuals with CM present with headaches of any severity on 15 or more days per month and have migraine on at least 8 days per month. A sizable proportion of individuals with CM experience daily headaches and, therefore, face considerable disability (Bigal, 2008).

1.1.2. Disease Overview: Major Depressive Disorder

Migraine and major depressive disorder (MDD) are frequently comorbid, with a lifetime prevalence of MDD in migraine of 40.7% and an odds ratio (OR) of 3.51 compared to nonmigraine controls (Breslau, 2000). Patients with CM are almost twice as likely to have received a medical diagnosis of depression and to meet criteria for depression based on Patient Health Questionnaire-9 (PHQ-9) compared to those with EM (Buse, 2013). As the frequency of attacks in migraine increases from low-frequency EM through high-frequency EM and on to CM, the frequency of depression symptoms increases as well (Chu, 2018). Depression has also been identified in multiple studies as a risk factor for the progression from EM to CM, and a "dose response" has been noted, with increased severity of depression increasing the risk for progression (Ashina, 2012). Additionally, there appears to be a bidirectional association between migraine and MDD, with migraine at baseline predicting onset of MDD within 2 years (OR 5.8) and MDD at baseline predicting onset of migraine within 2 years (OR 3.4) (Breslau, 2003).

1.1.3. Rationale for Fremanezumab Development as a Preventive Treatment for Migraine in Patients with Comorbid Major Depressive Disorder

The goals of migraine treatment are to relieve pain, to restore function, to reduce headache frequency, and to prevent progression of EM to CM. Pharmacological interventions for the treatment of migraine include acute (symptomatic) treatments and preventive medications.

Preventive drug treatment may be appropriate in a number of instances, including where frequency of attacks per month is 2 or higher, or where a patient's quality of life is severely impaired (Evers, 2009). A number of drugs from different pharmacological categories (eg, beta blockers, anticonvulsants) have been approved for migraine prevention or have class A evidence to support their use. However, adherence to and persistence on these medications can be poor, and there is a need for preventive medications that are more effective and better tolerated than the current standard of care (Puledda, 2017).

Calcitonin gene-related peptide (CGRP) is a well-studied neuropeptide involved in both central and peripheral processes underlying the pathophysiology of migraine (Eftekhari, 2010). Jugular levels of CGRP are increased during migraine attacks, and intravenous CGRP administration

induces migraine-like headache in most individuals with migraine (Ashina, 2000; Hansen, 2010). CGRP is involved in the pathophysiology of migraine at all levels, peripherally (neuronal, sensitization, vasodilation, inflammation and protein extravasation), at the trigeminal ganglion, and inside the brain (Ho, 2010). Studies have shown that inhibition of CGRP was efficacious in the treatment of EM (Bigal, 2015a; Dodick, 2018a; Dodick, 2018b; Reuter, 2018) and CM (Bigal, 2015a; Silberstein, 2008).

Fremanezumab (TEV-48125 [formerly LBR-101, PF-04427429, and RN307]) is a fully humanized IgG 2(delta) a/kappa monoclonal antibody, which has been developed for administration by the subcutaneous (sc) route for the preventive treatment of migraine. Fremanezumab was approved in the United States in September 2018, received positive opinion from EMA/CHMP in January 2019, and marketing authorization applications have been submitted in a number of countries worldwide. Fremanezumab potently and selectively binds to both CGRP isoforms (α- and β-CGRP) to prevent them from binding to the CGRP receptor. Fremanezumab is 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, which can lead to unwanted consequences such as cell lysis, opsonization, and cytokine release and inflammation (Armour, 1999; Zeller, 2008).

The safety and tolerability of fremanezumab (intravenous [iv] doses ranging from 0.2 to 2000 mg and sc doses of 225 mg and 900 mg) has been well characterized in the Phase 1 development program. Additional Phase 1 studies completed include Study TV48125-PK-10078 to assess the pharmacokinetics, safety, and tolerability of single-dose sc administration of fremanezumab in Japanese and Caucasian healthy subjects, and Study TV48125-BE-10114 to compare the pharmacokinetics of fremanezumab administered sc using an autoinjector in reference to a prefilled syringe. Furthermore, the safety and efficacy of fremanezumab have been demonstrated in a randomized double-blind, placebo-controlled Phase 2b study of 2 fremanezumab sc dosing regimens (fremanezumab 900 mg monthly or fremanezumab 675 mg followed by 225 mg monthly) in patients with CM, and a randomized, double-blind, placebo-controlled Phase 2 study of 2 fremanezumab sc dosing regimens (fremanezumab 675 mg monthly or fremanezumab 225 mg monthly) in patients with EM. Furthermore, the efficacy and tolerability profile have been confirmed in the Phase 3 development program, which included fremanezumab 225 mg sc monthly and fremanezumab 675 mg sc quarterly.

Post hoc analyses of data from Study TV48125-CNS-30049 (the HALO CM study) demonstrated significant reductions in migraine and headache days in patients with comorbid depression, significant reductions in disability, and significant improvements in quality of life. Additionally, patients with a baseline PHQ-9 of 10 to 19 experienced reductions in PHQ-9 of 9.5 to 10.5 points on average over the 12 weeks of the study when treated with fremanezumab quarterly or monthly. Based on these data and the bidirectional relationship of migraine and MDD, fremanezumab offers the potential benefit of improvement in migraine in patients with comorbid MDD as well as the possibility of improvement in depression.

In these post hoc analyses from the HALO CM study, 241 patients with migraine and PHQ-9 scores of ≥10, consistent with moderate to severe depression, had similar demographics to those

with scores <10, but had higher numbers of headache days of at least moderate severity, migraine days, and 6-item Headache Impact Test (HIT-6) scores at baseline, suggesting that patients with comorbid moderate to severe depression also had more severe migraine disease burden than those with mild or no depression. Patients with PHQ-9 scores of ≥10 showed significant reductions in migraine days over 12 weeks of fremanezumab treatment compared with placebo treatment (-5.4 quarterly, -5.5 monthly, -2.4 placebo, p <0.002 for both monthly and quarterly dosing compared with placebo). Significant reductions were also noted for headache days of at least moderate severity, as early as 4 weeks after the first dose. These reductions were greater than those seen in the overall study population. Adverse events in this subgroup were similar to the overall study population, with no serious adverse events thought to be related to treatment by investigators. There were no cases of suicide or suicide attempt in this subgroup. The most common adverse events in this subgroup were injection site reactions at similar rates seen in the overall population.

The demonstrated efficacy, favorable safety, and tolerability, long terminal elimination half-life ($t_{½}$, approximately 30 days), and dosing regimen choices (quarterly or monthly) of fremanezumab provide substantial therapeutic potential for patients with CM or EM and comorbid MDD.

1.1.4. Study Purpose

The purpose of the study is to assess if fremanezumab is effective in preventing migraine in patients with MDD.

1.2. Findings from Nonclinical and Clinical Studies

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

1.2.1. Nonclinical Studies

In vivo pharmacology studies of fremanezumab in animal models indicate that fremanezumab prevented an increase in blood flow in rat paw skin and the middle meningeal artery after electrical stimulation and produced a dose-dependent inhibition of the capsaicin-induced skin flare response in cynomolgus monkey.

Safety pharmacology parameters of fremanezumab were assessed in the pivotal toxicology studies in Sprague Dawley rats and cynomolgus monkeys and a separate cardiovascular safety pharmacology study in male cynomolgus monkeys. There were no treatment-related changes in electrocardiograms (ECGs) and heart rates in the 1- and 3-month toxicity studies, and a single iv dose of fremanezumab at 100 mg/kg did not result in changes in cardiovascular parameters or body temperature in monkeys. Additionally, no target organ toxicity was identified. In these referenced studies, the no-observed-adverse-effect level ranged from 100 to 300 mg/kg dosed either iv or sc. In a 3-month monkey study, perivascular inflammation of the ciliary artery was observed in a few animals at doses ≥100 mg/kg. The inflammation was suspected to be the result of immune complex formation/deposition from the monkeys' immunogenic response to the drug (fremanezumab). In the pivotal 6-month chronic toxicity study in monkeys following once-weekly sc dosing at dosage levels of up to 300 mg/kg/week, achieving high exposure throughout

the study, no microscopic findings were noted in any of the organs, including the ciliary vessels of the eyes, and the no-observed-adverse-effect level of the chronic toxicity study was determined to be the highest dose tested, 300 mg/kg/week. Thus, it is believed that in view of the low frequency (ie, observed in very few animals) and minimal severity, the finding (perivascular inflammation) that was only recorded in the 3-month toxicity study, and had been resolved during the recovery period, is an incidental finding.

The pharmacokinetics of fremanezumab in animals (rats and monkeys) is typical of a humanized IgG2 molecule, with low mean plasma clearance, low volume of distribution at steady state, and a long $t_{½}$. Exposure as defined by the maximum observed plasma drug concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) increased linearly across doses following single and repeated once-weekly dosing. No sex differences in exposure were observed in rats or monkeys.

Additionally, pivotal reproductive and developmental toxicity studies in rabbits and rats with fremanezumab were conducted and completed. Preliminary data suggest that weekly dosing with fremanezumab was well tolerated and did not induce any obvious maternal toxicity at any dose level. No apparent evidence of embryo-fetal toxicity was noted in any dose group.

Overall, no toxicological concerns were identified following up to 6 months of dosing to the experimental animals.

Further details may be found in the current Investigator's Brochure.

1.2.2. Clinical Studies

The clinical program to date is composed of 7 completed Phase 1 clinical studies in healthy subjects (Studies B0141001, B0141002, B0141006, B0141007, LBR-101-008, LBR-101-011, and TV48125-PK-10078), 1 completed Phase 1 bioequivalence study (TV48125-BE-10114), 2 completed Phase 2b clinical studies in patients with migraine (Studies LBR-101-021 and LBR-101-022), and 2 completed Phase 3 clinical studies in patients with migraine (Studies TV48125-CNS-30049 and TV48125-CNS-30050).

A total of 3196 subjects/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 clinical program, 2013 patients with migraine and 256 healthy subjects have received at least 1 dose of fremanezumab in completed and ongoing clinical studies. Two Phase 3 studies (Studies TV48125-CNS-30051 and TV48125-CNS-30068) are currently ongoing to further evaluate the efficacy, safety, and tolerability of various dose regimens of fremanezumab in the preventive treatment of migraine (CM and EM).

In addition, 2 Phase 3 studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) and 1 Phase 2 study (Study TV48125-CNS-20024) are ongoing, and 1 Phase 3 study (Study TV48125-CNS-30058) is planned to evaluate the efficacy, safety, and tolerability of various dose regimens of fremanezumab in the preventive treatment of cluster headache.

Two Phase 2/3 studies in Japanese and Korean EM and CM patients (406-102-00002 and 406-102-00001, respectively) to evaluate the efficacy and safety of fremanezumab as part of the complete clinical development plan, and one Phase 3b study (TV48125-CNS-30068) to evaluate migraine patients who had inadequate response to 2 to 4 other previous preventive treatments have started.

A brief summary of clinical pharmacology and clinical safety and efficacy studies of fremanezumab follows.

1.2.2.1. Clinical Pharmacology Studies

A total of 118 healthy subjects received fremanezumab across 8 completed Phase 1 studies in doses ranging from 0.2 to 2000 mg.

Six of these studies were 2 single-ascending-dose pharmacokinetic and pharmacodynamic studies in healthy men (Studies B0141001 and B0141002); a 2-cohort, placebo-controlled crossover study to examine the acute effects of administration of fremanezumab on capsaicin flare response in healthy men (Study B0141006); a parallel-group, repeat-dose study of fremanezumab in healthy subjects (Study B0141007); a single-dose study evaluating the safety, tolerability, and pharmacokinetics of doses up to 2000 mg administered iv in healthy women (Study LBR-101-008 [formerly referred to as Study B0141008]); and a study assessing the safety, tolerability, absolute bioavailability, and pharmacokinetics of single iv or sc doses of fremanezumab in healthy subjects (Study LBR-101-011). These Phase 1 studies were analyzed using the original bioanalytical method that has been determined to be unreliable and underestimate measured plasma concentrations compared to the current validated assay.

Another completed Phase 1 study that investigated pharmacokinetics was Study TV48125-BE-10114, an open-label, single-dose, randomized, bioequivalence study in healthy subjects designed to compare the pharmacokinetics of fremanezumab administered sc using 2 modes of administration: the test autoinjector and a prefilled syringe.

A pharmacokinetic, safety, and tolerability study was conducted in healthy Japanese and Caucasian subjects (Study TV48125-PK-10078) dosed with fremanezumab as an sc dose of 225, 675, or 900 mg. Plasma concentration-time profile was measured using the current validated bioanalytical method, and the pharmacokinetic results are described below. The pharmacokinetics (non-compartmental analysis) of fremanezumab demonstrated an increase in C_{max} and AUC values slightly greater than dose proportionality over sc dose range of 225 to 900 mg. Median time to maximum observed concentration (t_{max}) values generally occurred 5 to 7 days following sc doses. Mean values for apparent volume of distribution (V_z/F) after a single sc dose ranged from 5.7 to 6.4 L at 225 to 900 mg sc doses. The mean apparent total body clearance ranged from 0.0777 to 0.0895 mL/min at this dose range. The mean $t_{½}$ ranged from 32.23 to 36.15 days. Fremanezumab exposure parameters and overall pharmacokinetic profile were similar for healthy Japanese and Caucasian subjects. Absolute bioavailability following sc administration of fremanezumab was approximately 54% to 57%.

1.2.2.2. Clinical Safety and Efficacy Studies

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

Fremanezumab was well tolerated with favorable safety profile across the 8 completed Phase 1 studies, 2 completed Phase 2b studies, and 2 completed Phase 3 studies in patients with migraine. The treatment-emergent adverse events reported in the Phase 1, Phase 2b, and Phase 3 studies were predominantly mild to moderate in severity. A specific "pattern of adverse events" that

could be associated with a dose or a dose range of fremanezumab has not been identified, nor has a maximally tolerated dose been identified. Overall, the nature and occurrence of the reported treatment-related adverse events across the clinical program have not raised any specific safety concerns.

Two pivotal Phase 3 studies in CM and EM patients (Studies TV48125-CNS-30049 and TV48125-CNS-30050), confirmed efficacy findings in Phase 2. Study TV48125-CNS-30049 was a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy, safety, and tolerability of 2 dose regimens of sc fremanezumab (fremanezumab 675 mg quarterly [675 mg/placebo/placebo; N=379] and a starting dose of fremanezumab 675 mg followed by fremanezumab 225 mg monthly [675/225/225 mg; N=376]) and placebo (N=375) in adults (18 through 70 years of age) with CM. Patients who were on monotherapy (79%) and patients on stable doses of preventive medications (21%) were included in the study. The study consisted of a screening visit, a baseline period lasting approximately 4 weeks (~28 days), and a treatment period lasting approximately 12 weeks.

The analysis of the primary efficacy endpoint, the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug, demonstrated statistically significant differences from placebo in favor of fremanezumab ($p<0.0001$) for both active treatment groups. The median for the overall change from baseline of -4.2 and -4.5 (mean reduction of 4.7 and 4.9 days) versus -2.5 (mean reduction of 2.9 days) headache days of at least moderate severity for the 675 mg/placebo/placebo and 675/225/225 mg treatment groups versus the placebo group, respectively. The least square (LS) mean difference from placebo was 1.8 days for 675 mg/placebo/placebo and 2.1 days for 675/225/225 mg.

Statistically significant improvements ($p<0.0001$ for both comparisons versus placebo) were evident as early as month 1 (secondary endpoint), [redacted] (exploratory endpoints). The results of the analyses of each of the other secondary endpoints further support the efficacy of both fremanezumab dose regimens; all comparisons versus placebo were statistically significant. Thus, patients treated with fremanezumab were significantly more likely to be responders (≥50% reduction in the number of headache days of at least moderate severity), had significantly fewer migraine days and days with use of acute headache medication, and reported significantly less disability than patients treated with placebo. In addition, the overall treatment effect on headache days of at least moderate severity was also observed in the subset of patients (79% of patients) who were not receiving concomitant preventive medication.

Fremanezumab at the doses tested was generally safe and well tolerated for 3 months in patients with CM. Serious adverse events and adverse events leading to discontinuation from the study occurred infrequently and with similar incidence across the treatment groups. Most adverse events were mild to moderate. Injection site-related adverse events were the most frequent treatment-related adverse events and were overall comparable across all treatment groups.

Study TV48125-CNS-30050 was a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy, safety, and tolerability of 2 dose regimens of sc fremanezumab (quarterly dose of 675 mg fremanezumab [675-mg/placebo/placebo; N=291] and doses monthly 225 mg fremanezumab [225/225/225-mg; N=290]) and placebo (N=294) in adults (18 through 70 years of age) with EM. Patients who

were on monotherapy (79%) and patients on stable doses of preventive medications (21%) were included in the study. The study consisted of a screening visit, a baseline period lasting approximately 4 weeks (~28 days), and a treatment period lasting approximately 12 weeks.

The analysis of the primary efficacy endpoint, the mean change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug, demonstrated statistically significant differences from placebo in favor of fremanezumab ($p<0.0001$) for both active treatment groups. The median for the overall change from baseline was -4.0 and -4.2 days (mean reduction of 3.9 and 4.0 days) versus -2.7 days (mean reduction 2.6 days) for the 675 mg/placebo/placebo and 225/225/225 mg treatment groups versus the placebo group, respectively. The LS mean difference from placebo was 1.3 days for 675 mg/placebo/placebo and 1.5 days for 225/225/225 mg.

Statistically significant improvements ($p<0.0001$ for both comparisons versus placebo) were evident as early as month 1 (secondary endpoint), [redacted] (exploratory endpoints). The results of the analyses of each of the other secondary endpoints further support the efficacy of both fremanezumab dose regimens; all comparisons versus placebo were statistically significant. Thus, patients treated with fremanezumab were significantly more likely to be responders (≥50% reduction in the number of migraine days), had significantly fewer days with use of acute headache medication, and reported significantly less disability than patients treated with placebo. In addition, the overall treatment effect on migraine days was also observed in the subset of patients (79% of patients) who were not receiving concomitant preventive medication.

Fremanezumab at the doses tested was generally safe and well tolerated for 3 months in patients with EM. Serious adverse events and adverse events leading to discontinuation from the study occurred infrequently and with similar frequency across the treatment groups. Injection site-related adverse events were the most frequent treatment-related adverse events and were comparable across all treatment groups.

One Phase 3 study (Study TV48125-CNS-30051) was conducted to further evaluate long-term efficacy, safety, and tolerability of various dose regimens of fremanezumab in the preventive treatment of migraine (CM and EM). For the placebo rollover and the new patients, the efficacy profile during the first 3 month was similar to what was seen in Studies TV48125-CNS-30049 and TV48125-CNS-33050 for patients treated with fremanezumab. For all patients, efficacy was sustained for over 6 months in the long-term treatment period when patients received fremanezumab without interruption.

No clinically relevant changes in clinical laboratory values, vital signs measurements, or 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)

Additional information regarding benefits and risks to patients may be found in the IB.

1.3.1.1. Identified Risks

1.3.1.1.1. General Disorders and Administrative Site Conditions

Reports of transient administration site reactions, including injection site bruising, injection site swelling, injection site pain, injection site pruritus, injection site induration, injection site erythema, injection site inflammation, injection site warmth, injection site dermatitis, injection site rash, injection site edema, injection site discomfort, injection site hemorrhage, injection site irritation, injection site mass, and injection site hematoma, have occurred with sc administration. Among these events, the following have been identified as adverse drug reactions (identified risks): injection site erythema, injection site induration, injection site pruritus, injection site pain, and injection site rash. None of the identified risks were considered important risks.

1.3.1.1.2. Injury, Poisoning, and Procedural Complications/Immune System Disorders

The general risks of infusion reactions with monoclonal antibody administration include fever, headache, nausea, vomiting, and hypotension. These adverse events are generally ascribed to lysis of cellular targets, cytokine release, or complement activation.

Type I hypersensitivity or allergic reactions (eg, shortness of breath, urticaria, anaphylaxis, and angioedema) are theoretically possible with any injected protein.

Type III hypersensitivity reactions occur as a consequence of an antibody response to the injected protein resulting in immune complex formation. Such immune complex formation and subsequent deposition in tissues may result in symptoms, including rash, urticaria, polyarthritis, myalgias, polysynovitis, fever, neuritis, or angioedema, and if untreated and severe, can progress to glomerulonephritis.

Infusion-related reaction and drug hypersensitivity have occurred rarely with fremanezumab. In all patients in the placebo controlled studies, drug hypersensitivity occurred in 2 patients (<1%) who received placebo and 2 patients (<1%) who received fremanezumab (1 moderate event and 1 mild event). Among all fremanezumab-treated patients, 3 additional patients who received fremanezumab had adverse events of drug hypersensitivity (2 moderate events and 1 mild event).

1.3.1.2. Potential Risks

1.3.1.2.1. Perivascular Inflammation

In the 3-month monkey toxicology study, inflammation around the ciliary vessel of the eye was observed. Based on the low-grade increase in immune complex deposits observed in the intima and/or media of ciliary vessels in the animals with perivascular inflammation, these events were assessed as being due to the monkeys' immunogenic response to humanized monoclonal antibody rather than a pharmacologic toxicity and are not likely to be relevant in a clinical setting. Moreover, a confirmatory 6-month study could not repeat the findings.

1.3.1.2.2. Consequences of Calcitonin Gene-Related Peptide Inhibition

Because CGRP is a vasodilator, there is a theoretical risk of unfavorable cardiovascular effects with CGRP inhibition. Extensive research conducted with the CGRP receptor antagonists has not identified relevant safety cardiovascular concerns in humans. Dedicated studies conducted in monkey and humans using fremanezumab have not identified clinically relevant changes in heart

rate, blood pressure, or other cardiovascular parameters. No relevant cardiovascular event has been seen in the completed studies.

1.3.2. Overall Benefit and Risk Assessment for This Study

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are in Table 3:

Table 3: Primary and Secondary Study Objectives and Endpoints

Objectives	Endpoints
Primary objective: To evaluate the efficacy of monthly 225 mg subcutaneous (sc) fremanezumab in adult patients with migraine and major depressive disorder (MDD)	Mean change in the monthly average number of migraine days from the 28-day baseline period during the 12-week period after the first dose of study drug
Key secondary objective: To evaluate the efficacy of monthly 225 mg sc of fremanezumab in adult patients with migraine and MDD on the reduction of MDD symptoms	Mean change in depression symptoms from randomization (day 1) to week 8 after the first dose of study drug as measured by: • Hamilton Depression Rating Scale-17 items (HAM-D 17)
Secondary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD in terms of responder rates in monthly migraine days	Number of patients with 50% or more reduction from the 28-day baseline period in the monthly average number of migraine days at 12 weeks after the first dose of study drug
Secondary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD in terms of improving quality of life	Mean change in quality of life from randomization visit (day 1) to week 12 after the first dose of study drug as measured by: • Migraine-Specific Quality of Life (MSQoL) questionnaire, role function-restrictive and role function-preventive domains

Table 3: Primary and Secondary Study Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD in terms of improving disability	Mean change from randomization visit (day 1) in disability score for overall impact as measured by Clinical Global Impression-Severity (CGI-S) and 6-item Headache Impact Test (HIT-6) to the following time points after administration of the first dose of study drug: • weeks 4 and 8 (CGI-S) • week 12 (CGI-S and HIT-6)
Safety and tolerability objective (Secondary objective): To evaluate the safety and tolerability of monthly 225 mg sc and quarterly 675 mg sc fremanezumab in adult patients with migraine and MDD	• occurrence of adverse events throughout the study • changes from randomization visit (day 1) in vital signs (pulse, systolic and diastolic blood pressure, body temperature, and respiratory rate) measurements • abnormal physical examination findings including body weight • use of concomitant medication for adverse events during the study • number (%) of patients who did not complete the study due to adverse events • occurrence of severe hypersensitivity/anaphylaxis reactions • suicidal ideation and behavior as suggested by eC-SSRS

CGI-S = Clinical Global Impression-Severity; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; HAM-D 17 = Hamilton Depression Rating Scale-17 items; HIT-6 = 6-item Headache Impact Test; MDD = major depressive disorder; MSQoL = Migraine-Specific Quality of Life; sc = subcutaneous.

2.1.1. Justification of Primary Endpoint

The primary endpoint was chosen based on the International Headache Society (IHS) guidelines for trials in migraine, which suggest that the most appropriate primary endpoint to capture efficacy of treatment is the change from baseline in the monthly average number of migraine days (Silberstein, 2008).

2.2. Exploratory Objective and Endpoints

[redacted]

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is an approximately 28-week, multicenter, randomized, double-blind, placebo investigational medicinal product (IMP)-controlled, parallel-group study to evaluate the efficacy and safety of fremanezumab self-administered at monthly doses of 225 mg sc and a quarterly dose of 675 mg sc (ie, one dose using 3 prefilled syringes with 225 mg each) in adult patients with migraine and MDD. The study will consist of a 28-day (ie, 4-week) baseline period, a 12-week double-blind treatment phase followed by a 12-week open-label extension phase, and an end-of-treatment visit (approximately 12 weeks after the final dose of study drug).

The total duration of patient participation in the study is planned to be approximately 28 weeks. Patients are expected to complete the entire duration of the study.

This study will include female and male patients, aged 18 to 70 years, inclusive, with a diagnosis of migraine and MDD. Patients must have been diagnosed with migraine at least 12 months prior to the screening visit (visit [V] 1). The diagnosis of migraine (as defined by the International Classification of Headache Disorders, 3rd revision [ICHD-3] criteria [IHS, 2013], see Appendix I) will be prospectively confirmed via a review of migraine data recorded daily during a 28-day baseline period in an electronic diary device. Patients must also have a history of MDD according to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria at least 12 months prior to the screening visit (V1) and have active symptoms of depression as assessed by a PHQ-9 score of at least 10 at screening. Investigators must document that patients had the diagnosis of migraine and MDD for at least 12 months prior to the screening visit (V1).

During the 28-day baseline period, patients must fulfill the following criteria for migraine:

- on ≥4 days, headache attacks qualified as migraine based on the following ICHD-3 criteria:
  - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura
  - ICHD-3 criteria B and C for 1.2 Migraine with aura
  - probable migraine (a migraine subtype where only 1 migraine criterion is missing)
  - triptan or ergot derivative used to treat an established headache.

Patients who fulfill the criteria for migraine will be further delineated as patients with CM or EM, for stratification and other analyses.

CM is defined as:

Patient fulfills the following criteria for CM in prospectively collected baseline information during the 28-day baseline period:

- headache occurring on ≥15 days

- on ≥8 days, fulfilling any 1 of the following:
  - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix I)
  - ICHD-3 criteria B and C for 1.2 Migraine with aura (Appendix I)
  - probable migraine (a migraine subtype where only 1 migraine criterion is missing)
  - triptan or ergot derivative used to treat established headache.

EM is defined as:

The patient fulfills the following criteria for EM in prospectively collected baseline information during the 28-day baseline period:

- headache occurring ≥4 days but <15
- on ≥4 days, fulfilling any 1 of the following:
  - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix I)
  - ICHD-3 criteria B and C for 1.2 Migraine with aura (Appendix I)
  - probable migraine (a migraine subtype where only 1 migraine criterion is missing)
  - triptan or ergot derivative used to treat an established headache

At the randomization visit (day 1), patients will be randomly assigned to 1 of 2 treatment groups of 225 mg sc fremanezumab or placebo in a 1:1 ratio. Patients will receive their assigned study treatment on visit 2 (day 1), visit 3 (day 29), and visit 4 (day 57) and then continue into the open-label extension phase in which all patients will receive a quarterly dose of 675 mg sc fremanezumab on visit 5 (day 85). Investigators can contact patients in between study visits per their clinical judgment.

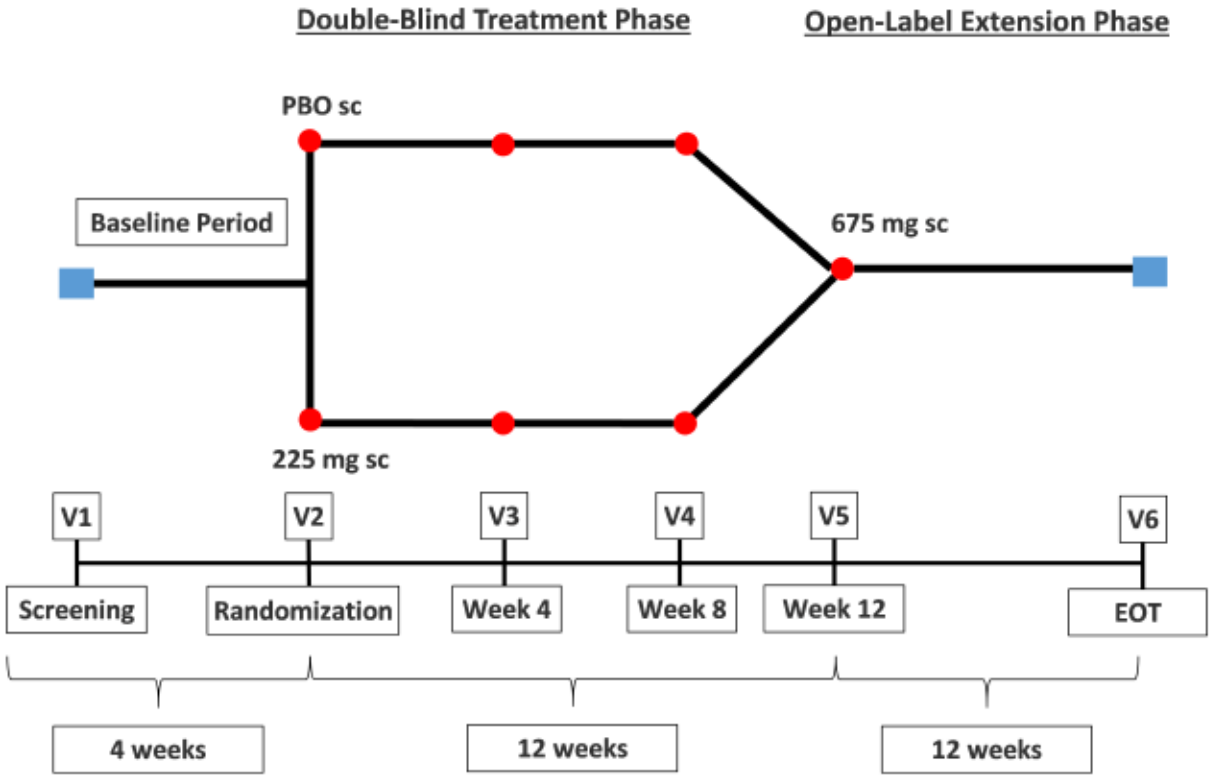
Patients who complete all scheduled visits will have procedures and assessments performed at visit 6 (end of treatment). Patients who withdraw from the study before completing the 24-week treatment phase will have visit 6 (end of treatment) procedures and assessments performed at their final visit.

Study procedures and assessments with their time points are shown in Table 4. The study schematic diagram is shown in Figure 1.

The end of study is defined as the last visit (end-of-treatment/early withdrawal visit [visit 6]) of the last patient.

The study duration will be approximately 24 months, from approximately September 2019 (first patient screened) to approximately August 2021 (last visit of the last patient).

Figure 1: Overall Study Schematic Diagram



EOT = end of treatment; PBO = placebo; sc = subcutaneous; V = visit.
A red circle indicates a study site visit when study medication is self-administered. A blue square indicates a study site visit when study medication is not administered.

3.2. Planned Number of Patients and Countries

Approximately 340 patients (approximately 170 patients per treatment group) are planned to be enrolled in this study to have approximately 288 completers (144 completers per treatment group). A 15% drop-out rate is anticipated.

Details on definition of evaluable patients and sample size are given in Section 9.

The study is planned to be conducted in approximately 13 countries in approximately 65 investigational centers. The study is expected to start in approximately September 2019 and last until approximately August 2021.

3.3. Justification for Study Design and Selection of Population

The study population will be composed of female and male patients, aged 18 to 70 years, inclusive, with a diagnosis of migraine and MDD. Patients must have been diagnosed with migraine (as defined by the ICHD-3 criteria [IHS, 2013], see Appendix I) at least 12 months prior to the screening visit (V1). The diagnosis of migraine will be prospectively confirmed via a review of migraine data recorded daily during a 28-day baseline period in an electronic diary device. Patients must also have a history of MDD according to the DSM-V criteria at least 12 months prior to the screening visit (V1) and have active symptoms of depression as assessed

by a PHQ-9 score of at least 10 at the screening visit (V1). Investigators must document that patients had the diagnosis of migraine and MDD for at least 12 months prior to the screening visit (V1). MDD is a common comorbidity with migraine. Post hoc analyses of the HALO CM study indicated that depressive symptoms improved in migraine patients with baseline PHQ-9 of 10 to 19. This study is designed to further evaluate the efficacy of fremanezumab in this population.

Commercially approved dosing regimens will be investigated in the double-blind treatment phase. Both the monthly dose of 225 mg and quarterly dose of 675 mg, which will be used in the current study in the double-blind and the open-label periods, respectively, were equally efficacious in the pivotal trials. For treatment details, see Section 5.1.

One objective of this study is to determine whether migraine and depression are affected independently by fremanezumab or whether improvement in one disease precedes and may causally improve the other disease via their bidirectional association (see Section 1.1.2 for further background information). By assessing both migraine and depression symptoms at multiple time points and by having placebo patients cross over to active treatment, we will have more data points by which to make this assessment. Additionally, the open-label extension phase is intended to provide the placebo-treated patients the opportunity to receive potential benefit from therapeutic doses. It also provides an opportunity to further explore efficacy and tolerability in this patient population and to generate data on switching from the monthly to the quarterly dose.

To provide additional expertise in depression, anxiety, and suicidality assessments and management, psychiatrists will be included in the study team at the investigational site.

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

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 7.1.5) as they are reported from the investigational centers to identify safety concerns.

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

- new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, or adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, important protocol deviations as defined in Appendix C, noncompliance, or adverse event). In addition, patients with positive suicidality findings or abnormal hepatic laboratory values (eg, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma glutamyl transpeptidase, bilirubin

[total, direct, or indirect], or international normalized ratio) may meet the criteria for discontinuation from the IMP (Section 7.1.1 and Section 7.1.5.1).

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 4. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments) and Section 7 (safety assessments). Study procedures and assessments by visit are listed in Appendix B. Investigators can contact patients in between study visits per their clinical judgment.

For Coronavirus disease 2019 (COVID-19) updates, see Appendix P.

Table 4: Study Procedures and Assessments

Study period	Pretreatment (screening and baseline)	Double-blind treatment phase			Open-label extension phase	End of treatment/ Early termination[a]/ Follow-up period
Visit number	V1	V2[b]	V3	V4	V5[c]	V6
Day and allowed time windows	Days -28 to -1	Day 1 +3 day(s)	Day 29 ±3 day(s)	Day 57 ±3 day(s)	Day 85 ±3 day(s)	Day 169 ±3 day(s)
Procedures and assessments	Screening	Randomization	Week 4	Week 8	Week 12	Week 24
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Assign randomization/treatment number		X				
Medical and psychiatric history	X					
Record demographic characteristics	X					
Prior medication and treatment history[d]	X					
Physical examination, including height and weight[e]	X[f]	X	X	X	X	X
12-Lead ECG	X	X[g]	X[g]	X[g]	X[g]	X
Vital signs measurement[h]	X	X	X	X	X	X
Safety laboratory assessments	X	X	X	X	X	X
Serum β-HCG test[i]	X					
Urine β-HCG test[i,j]		X	X	X	X	X
FSH[k]	X					
Inform patients of study restrictions and compliance requirements	X					
Review study compliance[l]		X	X	X	X	X
MMSE[j]	X					
PHQ-9[j]	X		X	X	X	X
eC-SSRS[j,m]	X	X	X	X	X	X
HAM-D 17[j,n]		X	X	X	X	X

Table 4: Study Procedures and Assessments (Continued)

Study period	Pretreatment (screening and baseline)	Double-blind treatment phase			Open-label extension phase	End of treatment/ Early termination[a]/ Follow-up period
Visit number	V1	V2[b]	V3	V4	V5[c]	V6
Day and allowed time windows	Days -28 to -1	Day 1 +3 day(s)	Day 29 ±3 day(s)	Day 57 ±3 day(s)	Day 85 ±3 day(s)	Day 169 ±3 day(s)
Procedures and assessments	Screening	Randomization	Week 4	Week 8	Week 12	Week 24
HAM-A[j,n]		X	X	X	X	X
HIT-6[j]		X	X	X	X	X
CGI-S[j]		X	X	X	X	X
MSQoL[j]		X	X	X	X	X
WPAI:GH[j]		X	X	X	X	X
Provide electronic headache diary[o]	X					
Complete electronic headache diary entries[p]	X	———				X
Review electronic headache diary[l]		X	X	X	X	X
Return headache diary						X
Adverse events and health care resource utilization inquiry[l]	X[q]	X	X	X	X	X
Dispensing of IMP		X	X	X	X	
Administration of IMP[r]		X	X	X	X	
Hypersensitivity/ anaphylaxis[s]		X	X	X	X	X
Concomitant medication and therapy inquiry[l]	X	X	X	X	X	X

[a] In the case of early termination, site personnel should perform a follow-up phone call to ensure the patient does not report suicidal ideation or behavior. Phone calls should be performed once weekly for 2 weeks. If signs of suicidality are identified during the follow-up phone call, the site personnel should provide direction to the patient for further psychiatric evaluation at the site or at a community psychiatrist referenced by the site. Relevant emergency psychiatric care services should be notified in the event that the patient is deemed to be a threat to themself.

[b] Patients will complete the screening visit not more than 28 (+3) days before the randomization visit (V2 [day 1]). All visit 2 procedures must be performed before study drug administration.

[c] Patients will continue into the open-label extension phase at week 12 and will all receive a quarterly dose of 675 mg sc fremanezumab.

[d] Collection of prior medications for migraine and/or depression is limited to those medications administered within the past 10 years or for any indication with the past 5 months before screening (V1).
[e] In addition, inquire and record start/stop date of menstrual period for women of child-bearing potential only at each visit as part of physical examination assessments.
[f] Height will be measured only at the screening visit (V1).
[g] This assessment will be done predose. A single ECG will be performed. If results are abnormal, the ECG will be repeated 1 time.
[h] 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.
[i] For details see Appendix E.
[j] On dosing days, the test or questionnaire should be completed before study drug administration.
[k] The FSH assessment applies only to women thought to be postmenopausal at the screening visit (V1). If the results show an elevated FSH (>35 U/L) and the patient has had no menses for at least 12 months, they do not need urine pregnancy testing.
1 This is a required procedure for unscheduled visits. See further details in Appendix B.
[m] Patients will complete the eC-SSRS Lifetime version at V1 and will complete the eC-SSRS Since Last Visit version at all other visits. The eC-SSRS will be used in conjunction with a qualified clinician's clinical judgment to assess the patient's suicidal ideation (severity and intensity) and behavior.
[n] A qualified staff member (ie, the investigator or a medically qualified person designated by the investigator) will perform this assessment.
[o] Eligible patients will be given an electronic headache diary device and will be trained in its use and compliance requirements on the day of the screening visit (V1).
[p] Patients will complete electronic headache diary entries about the previous day daily beginning on day -27 through the EOT/early withdrawal visit.
[q] Inquiries about adverse events will be made before administering questionnaires on non-dosing days and before and after study drug administration on dosing days. Post-dose inquiries will be made before the patient leaves the study center.
[r] Patients will be assessed for severe hypersensitivity/anaphylaxis reaction during and after administration of the IMP. Oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity. See further details in Appendix H.

β-HCG = beta-human chorionic gonadotropin; ECG = electrocardiography; eCRF = electronic case report form; CT = electroconvulsive therapy; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; EOT = end of treatment; FSH = follicle-stimulating hormone; HAM-A = Hamilton Anxiety Scale; HAM-D 17 = Hamilton Depression Rating Scale-17 items; HIT-6 = 6-item Headache Impact Test; IMP = investigational medicinal product; MMSE = Mini Mental State Examination; MSQoL = Migraine-Specific Quality of Life; PHQ-9 = Patient Health Questionnaire-9; WPAI:GH = Work Productivity and Activity Impairment Questionnaire General Health V2.0; V = visit.

4. SELECTION AND WITHDRAWAL OF PATIENTS

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

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

4.1. Patient Inclusion Criteria

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

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

b. The patient is male or female and 18 to 70 years of age, inclusive.

c. The patient has a diagnosis of migraine with onset at ≤50 years of age.

d. Prior to the screening visit (V1), the patient has a 12-month history of either:

   – migraine (according to ICHD-3 criteria [IHS, 2013]) or

   – headache consistent with migraine (ie, migraine diagnosis not better accounted for by another ICHD-3 diagnosis)

e. [Revision 1] The patient fulfills the following criteria for migraine in prospectively collected baseline information during the 28-day baseline period:

   – on ≥4 days, headache attacks qualified as migraine based on the following ICHD-3 criteria:

      ○ ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura

         headache has at least 2 of the following 4 characteristics: unilateral location; pulsating quality; moderate or severe pain intensity; and aggravation by, or causing avoidance of, routine physical activity (eg, walking or climbing stairs)

         during headache, at least one of the following: nausea and/or vomiting; photophobia and phonophobia

      ○ ICHD-3 criteria B and C for 1.2 Migraine with aura

         1 or more of the following fully reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, retinal

         at least 2 of the following 4 characteristics: at least 1 aura symptom spreads gradually over ≥5 minutes, and/or 2 or more symptoms occur in succession; each individual aura symptom lasts 5 to 60 minutes; at least 1 aura symptom is unilateral; the aura is accompanied, or followed within 60 minutes, by headache not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

      ○ probable migraine (a migraine subtype where only 1 migraine criterion is missing)

- triptan or ergot derivative used to treat an established headache.

f. The patient agrees not to initiate any migraine preventive medications (as defined in Appendix G) during the study. Up to 30% of patients, however, may take such a single medication previously prescribed for the treatment of migraine.
g. The patient has a history of MDD according to the DSM-V criteria at least 12 months prior to the screening visit (V1). Patients may take a single medication prescribed for the treatment of depression as long as the dose of that medication has been stable for at least 8 weeks prior to the screening visit (V1) and expects to remain at the stable dose throughout the study (Appendix G).
h. The patient has a PHQ-9 score of at least 10 at the screening visit (V1).
i. The patient has a Mini Mental State Examination score of at least 26 points at the screening visit (V1).
j. The patient is in good health in the opinion of the investigator as determined by medical evaluation, including medical and psychiatric history, physical examination, laboratory tests, and cardiac monitoring.
k. The patient has a body weight ≥45 kg and a body mass index within the range of 17.5 to 34.9 kg/m^2, inclusive.
l. [Revision 2] The patient demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 21 days cumulative during the 28-day baseline period (~75% diary compliance).
m. Women may be included only if they have a negative serum beta-human chorionic gonadotropin (β-HCG) test at the screening visit (V1), are sterile or postmenopausal, and are not lactating (not applicable for patients participating in safety follow-up only). Definitions of sterile and postmenopausal are given in Appendix E.
n. Women of child-bearing potential whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study and for 6 months after discontinuation of IMP (for details see Appendix E).
o. Men must be sterile or, if they are potentially fertile/reproductively competent (not congenitally sterile) and their female partners are of child-bearing potential, must use a condom for the duration of the study and for 6 months after discontinuation of IMP. For the purpose of this study, vasectomized men must use a condom if their partners are of child-bearing potential. Definitions of women of non-child-bearing potential, sterile and postmenopausal women; male contraception; and highly effective birth control methods, including examples, are given in Appendix E.
p. The patient must be willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study and to return to the clinic for the follow-up evaluations, as specified in this protocol.

4.2. Patient Exclusion Criteria

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

a. [Revision 1] The patient uses medications containing opioids (including codeine) or barbiturates (including butalbital/aspirin/caffeine [Fiorinal®, Actavis plc], butalbital/paracetamol/caffeine [Fioricet®, Cardinal Health], or any other combination containing butalbital) on more than 4 days during the 28-day baseline period for the treatment of migraine or for any other reason.

b. [Revision 1] The patient has failed 4 or more different medication classes to treat depression in their lifetime (Appendix G).

c. [Revision 1] If in the clinical judgment of the investigator or qualified psychiatrist, the patient's antidepressant medication needs to be changed or dose-adjusted during the 28-day baseline period.

d. [Revision 1] The patient has used an intervention/device (eg, scheduled nerve blocks, implantable vagal nerve stimulation, and transcranial magnetic stimulation) for migraine or depression during the 2 months prior to screening.

e. The patient has used electroconvulsive therapy (ECT) at any time.

f. The patient suffers from constant or nearly constant headache, defined as having headaches for more than 80% of the time he/she is awake, and less than 4 days without headache per month. Daily headache is acceptable if the patient has headaches 80% or less of the time he/she is awake on most days.

g. [Revision 1] The patient has clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, ocular disease, or complications of an infection, at the discretion of the investigator.

h. [Revision 2] The patient has a clinical history of a severe or uncontrolled psychiatric disorder, to include the following, or at the discretion of the investigator for any clinically significant psychiatric history that would likely interfere with full participation in the study:

   – Lifetime exclusion: suicide attempt

   – In the past 6 months exclusion: suicidal ideation, or other psychoactive spectrum disorders including schizoaffective disorder, delusional disorder, depression with psychotic features, and catatonic disorder

i. The patient has a history of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism.

j. The patient has a known infection or history of human immunodeficiency virus, tuberculosis, any history of Lyme disease, or chronic hepatitis B or C infection.

k. The patient has a past or current history of cancer, except for appropriately treated non-melanoma skin carcinoma.

l. The patient is a pregnant or nursing female or plans to become pregnant during the study, including the 6-month period after the administration of the last dose.

m. [Revision 1] The patient has a history of hypersensitivity reactions to injected proteins, including monoclonal antibodies, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome.

n. The patient has participated in a clinical study of a new chemical entity or a prescription medicine within 2 months of the screening visit (V1), or 3 months in case of biologics if the half-life of the biologics is unknown or 5 half-lives, whichever is longer, or is currently participating in another study of an IMP (or a medical device).

o. [Revision 1] The patient has failed treatment (based on tolerability and/or a lack of efficacy) with any monoclonal antibodies targeting the CGRP pathway (erenumab, eptinezumab, galcanezumab, or fremanezumab) or have taken the medications within 5 half-lives of the screening visit (V1) or take them during the study.

p. The patient has any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator.

q. The patient has any finding that, in the judgment of the investigator, is a clinically significant abnormality, including serum chemistry, hematology, coagulation, and urinalysis test values (abnormal tests may be repeated for confirmation).

r. The patient has hepatic enzymes (ALT, AST, and ALP) >1.5 × the upper limit of the normal range after confirmation in a repeat test or suspected hepatocellular damage that fulfills the criteria for Hy's law at the screening visit (V1).

s. The patient has serum creatinine >1.5 × the upper limit of normal range, clinically significant proteinuria, or evidence of renal disease at the screening visit (V1).

t. The patient has any clinically significant uncontrolled medical condition (treated or untreated).

u. [Revision 1] The patient has a history of alcohol or drug abuse in the opinion of the investigator.

v. The patient cannot participate or successfully complete the study, in the opinion of their healthcare provider or the investigator, for any of the following reasons:

   – mentally or legally incapacitated or unable to give consent for any reason
   – in custody due to an administrative or a legal decision, under tutelage, or being admitted to a sanitarium or social institution
   – unable to be contacted in case of emergency
   – has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study

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

x. The patient has any disorder that may interfere with the absorption, distribution, metabolism, or excretion of IMP.

y. The patient is vulnerable (eg, people kept in detention).

z. The patient has previously participated in this study.

aa. The patient has evidence or medical history of psychotic symptoms as per DSM-V criteria such as delusions, hallucinations, or disorganized speech in the past 1 month.

bb. Patient has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 3 months before screening visit.

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 IMP if any of the following events occur:

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

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 electronic case report form (eCRF) must document the primary reason for withdrawal from the study or discontinuation from IMP.

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

If 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 or study procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded on both the source documentation and the eCRF; both the adverse events page and the relevant page of the eCRF 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 or discontinues IMP for multiple reasons that also include adverse events, the relevant page of the eCRF 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.

In the case of patients lost to follow-up, attempts to contact the patient must be made. A patient should only be designated as lost to follow up if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (telephone, text, email, certified letter, etc).

4.4. Replacement of Patients

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

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, or require to screen fail as directed by the sponsor due to an emergency situation (eg, pandemic or potential pandemic), may be considered for rescreening 1 time.

Investigators may contact the sponsor's medical monitors or medical expert for additional guidance on rescreening. 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. Minimal information includes but is not limited to demography, screening failure details, eligibility criteria, and any serious adverse events.

5. TREATMENTS

5.1. Investigational Medicinal Products Used in the Study

Investigational medicinal product is defined as the test IMP and matching placebo IMP to the respective test IMP.

Patients will receive experimental medicinal product fremanezumab (visit 2, visit 3, and visit 4) or matching placebo reference medicinal product (visit 2, visit 3, and visit 4) in monthly doses from the sponsor. Patients will receive a single quarterly dose of fremanezumab at visit 5.

5.1.1. Test Investigational Medicinal Product

Refer to the Pharmacy Manual for full instructions for preparation and administration for the test IMP and placebo IMP.

Prefilled syringes (active or placebo) will be contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Active prefilled syringes will contain 225 mg of TEV-48125 in 1.5 mL solution, and placebo prefilled syringes will contain the same vehicle and excipients as those for active injections. Each kit will contain 1 prefilled syringe.

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.

Treatment self-administration (active or placebo) will occur at visit 2 (day 1), visit 3 (day 29), and visit 4 (day 57). Only active treatment will be administered on visit 5 (day 85), which is the beginning of the open-label extension phase. Final study assessments will be performed at the end-of-treatment visit (visit 6), approximately 12 weeks after administration of the last dose of study treatment.

IMPs are defined as the test IMP and placebo IMP (Table 5). Additional details may be found in the IB for fremanezumab.

5.1.1.1. Starting Dose and Dose Levels

The starting dose will be 225 mg fremanezumab as an active injection (225 mg/1.5 mL), or a 1.5 mL placebo injection. Treatment self-administration (active or placebo) will occur at visit 2 (day 1), visit 3 (day 29), and visit 4 (day 57). Only active treatment (a quarterly dose of 675 mg sc [ie, one dose using 3 prefilled syringes with 225 mg each]) will be administered on visit 5 (day 85), which is the beginning of the open-label extension phase.

5.1.1.2. Dose Modification and Dose Stratification

No dose modifications are allowed.

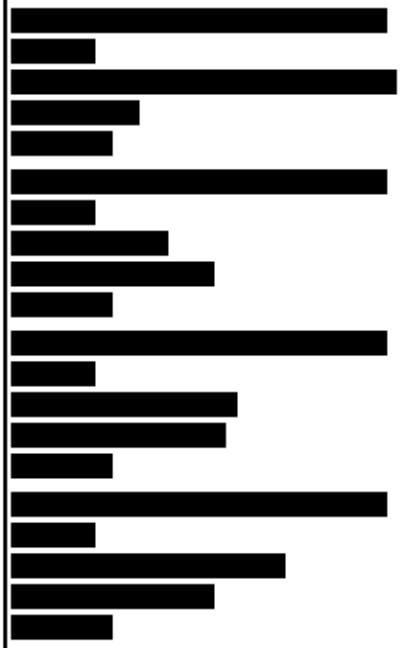
5.1.2. Placebo Investigational Medicinal Product

The placebo IMP is a placebo to the test IMP. Details on the placebo IMP are found in Section 5.1.1.

Table 5: Investigational Medicinal Products Used in the Study

IMP name **Recombinant humanized IgG2a/kappa mAb**	**Fremanezumab**	**Placebo**
Trade name and INN, if applicable, or company-assigned number	AJOVY, fremanezumab Also known as: TEV-48125, LBR-101, PF-04427429, RN307	Placebo
Formulation	Prefilled syringes containing 1.5 mL solution for injection of 225 mg of the active ingredient fremanezumab Inactive ingredients include L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate-80, EDTA, and water for injection	Prefilled syringes containing 1.5 mL solution for injection of the same vehicle and excipients as those for active injection Inactive ingredients include L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate-80, EDTA, and water for injection
Unit dose strength(s)/Dosage level(s)	225 mg/1.5 mL per unit	None
Route of administration	sc injection	sc injection
Dosing instructions	**Double-blind, treatment phase**: a dose of monthly 225 mg sc fremanezumab as an active injection (225 mg/1.5 mL) at visit 2 (day 1), visit 3 (day 29), and visit 4 (day 57) **Open-label extension phase**: a quarterly dose of 675 mg fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 5 (day 85)	**Double-blind, treatment phase**: monthly 1.5 mL placebo injection at visit 2 (day 1), visit 3 (day 29), and visit 4 (day 57) **Open-label extension phase**: not applicable
Packaging	A kit uniquely numbered containing 1 prefilled syringe stored (refrigerated at 2°C to 8°C) on site	A kit uniquely numbered containing 1 prefilled syringe stored (refrigerated at 2°C to 8°C) on site

Table 5: Investigational Medicinal Products Used in the Study (Continued)

IMP name Recombinant humanized IgG2a/kappa mAb	Fremanezumab	Placebo
Manufacturer	Drug substance:  Drug product: 	

EDTA = ethylenediaminetetraacetate; IgG2a = immunoglobulin G2a; IMP = investigational medicinal product; INN = international non-proprietary name; mAb = monoclonal antibody; sc = subcutaneous.

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

Individual, uniquely numbered visit kits containing 1 prefilled syringe with a staked 27-G, ½-inch needle will be provided.

At the time of each study visit, the IRT will be queried, and site staff will retrieve the IMP and oversee patient self-administration of 1.5 mL from each prefilled syringe contained in the appropriately numbered kit(s). Recommended sc injection sites follow the National Institutes of Health Patient Education Guidelines of June 2012 (see Appendix O).

The suggested sites of injection are back of upper arms, lower abdomen/belly/waistline, and front of thighs. Each of the injections should be given in a different location (eg, not in precisely the same place/not on top of the previous injection site), and study staff member(s) are responsible for overseeing patient self-administration of injections and inspecting previous injection sites to ensure that they are free of bruising and tenderness and that proper rotation of sites is performed.

Study drug should be removed from the refrigerator and allowed to equilibrate at room temperature for 30 minutes before study drug self-administration. A 1.5-mL volume from each prefilled syringe in each visit's kit(s) must be injected sc for dosing to be considered complete. The total number of sc injections and their locations will be recorded on the eCRF for each dosing visit (visits 2, 3, 4, and 5).

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

5.2.1. Storage and Security

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

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

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

5.2.2. 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 national and local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive and self-administer IMPs, and only authorized site staff at the investigational center may supply 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 site 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 disposal records).

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee,

with an account given for any discrepancies. Prefilled syringes should never be used partially. Empty syringes should be destroyed at the investigational center after reconciliation is performed. If the investigational center does not have the capability to destroy the empty syringes, they should be sent back to the sponsor. Unused prefilled syringes of IMP will be returned to the sponsor or designee.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

Three dose regimens of fremanezumab administered sc were tested during 2 Phase 3 pivotal studies in the EM and CM patient populations. Chronic migraine doses were 675 mg loading dose/monthly 225 mg or quarterly 675 mg and EM doses were monthly 225 mg or quarterly 675 mg.

During the Phase 2b studies, 4 dose regimens (ie, EM: monthly 225 mg or 675 mg, and CM: monthly 675 mg followed by 225 mg or monthly 900 mg sc fremanezumab) were tested and shown to be effective, safe, and well tolerated at the 3-month treatment period. Because it is considered best practice to select the lower dose for administration from 2 doses that show equivalence in efficacy (to avoid higher dose than necessary), the 2 monthly dose regimens of monthly 225 mg with 675 mg loading dose (CM) or without loading dose (EM) were used as 1 active arm in each of the Phase 3 studies. A second active arm included in both the EM and CM studies was 675 mg sc fremanezumab administration once every 3 months. Hence, each study retained the lowest effective dose from Phase 2 while exploring different intervals of administration. Furthermore, the addition of the quarterly dose regimen, which was a shared dose level across the migraine continuum, enabled the exploration of the choice of treatment convenience and flexibility for patients and physicians, the change in preference, and the likelihood of patients' demand for different treatment options.

The results of the Phase 3 studies, namely statistically significant differences, equally favoring monthly and quarterly fremanezumab compared with placebo for all primary and secondary endpoints, demonstrate the efficacy of fremanezumab as a preventive treatment for EM and CM in adults. In addition, all active dose regimens showed no significant difference in safety parameters.

The dose regimens included in this study are monthly 225 mg sc and quarterly 675 mg sc. The open-label extension phase with a quarterly dose of 675 mg sc fremanezumab is intended to provide the placebo-treated patients the opportunity to receive potential benefit from therapeutic doses. It also provides an opportunity to further explore efficacy and tolerability in this patient population and to generate data on switching from the monthly to the quarterly dose.

5.3.2. Justification for Use of Placebo Investigational Medicinal Product

A placebo-controlled design is appropriate, given the purpose and objectives of this clinical study. Inclusion of a placebo control group is consistent with guidelines for controlled trials of prophylactic treatment of migraine in adults (Silberstein, 2008) and the Classification Committee of the IHS guidelines for controlled trials of drugs in migraine, 3rd edition (Tfelt-Hansen, 2012).

5.4. Other Medicinal Products/Non-Investigational Medicinal Products

Not applicable.

5.5. Treatment after the End of the Study

At the end of the last study visit, patients will return to the care of their treating physicians.

No treatment is planned by the sponsor after completion of the study. Patients should be treated with standard of care after withdrawal from or termination of the study, as appropriate.

5.6. Restrictions

Patients will be required to comply with the following restrictions.

5.6.1. Activity

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

5.6.2. Blood Donation

Patients may not donate blood while taking IMP and for 5 half-lives (6.0 months) after the last IMP administration.

5.6.3. Pregnancy

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

5.7. Prior and Concomitant Medication or Therapy

Any prior or concomitant medication, treatment, psychotherapy, or procedure a patient has had for migraine and/or depression within the past 10 years or for any indication within the past 5 months before IMP administration and up to the end of study, including follow-up, will be recorded on the eCRF. Trade name and international nonproprietary name (if available), indication, dose, and start and end dates of the administered medication or treatment will be recorded. In addition, migraine and depression preventive medication listed in Appendix G that a patient took before study drug administration will be recorded on the eCRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all medication according to the World Health Organization drug dictionary (WHO Drug).

For migraine, patients using no more than 1 preventive medication at the time of the screening visit (V1) will be allowed to remain on the medication. The total number of patients receiving concomitant migraine preventive medication during the study will not exceed 30% of the total sample size of the study. For depression, patients using no more than 1 medication for the treatment of depression at the time of the screening visit (V1) will be allowed to remain on the medication. Patients on a concomitant migraine preventive medication and/or an antidepressant must be on a stable dose for at least 8 weeks of consecutive use prior to study entry (ie, before the 28-day baseline period), without anticipated changes during the study. If in the clinical

judgment of the investigator or qualified psychiatrist, the patient's antidepressant medication needs to be changed or dose-adjusted during the 28-day baseline period, the patient will be screen failed. Any changes made during the treatment period will be recorded in the electronic data capture system. The percentage of patients with these changes will be analyzed at the end of the study.

All concomitant medications prescribed or 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. Complete discontinuation criteria are provided in Section 4.3.

A list of preventive migraine medications that are allowed for up to 30% of the study population and antidepressant medications allowed for the whole study population for the duration of the study are given in Appendix G.

Concomitant medications that are not allowed for the duration of the study include other monoclonal antibodies that target the CGRP pathway (erenumab, eptinezumab, or galcanezumab), as described in Section 4.2.

If clinically indicated, patients' antidepressant medications and psychotherapy may be changed at any time during the treatment period at the discretion of the investigator, and all changes will be recorded in the eCRF. In such case, the patient's continued participation in the study will be reviewed by the medical monitors.

At each visit at the investigational center after the screening visit (V1), the investigator will ask patients whether they have taken any medications (other than IMP), including over-the-counter medications, vitamins, or herbal or nutritional supplements, or received any therapies (eg, ECT) since the previous visit.

Concomitant medication and treatment, including psychotherapy, will be recorded until visit 6, day 169.

5.8. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance until completion of the IMP administration according to the protocol or discontinuation from IMP. 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/Institutional Review Board (IEC/IRB) should be notified.

5.9. Randomization and Blinding

After the 28-day baseline period, the first 12 weeks of this study will be double-blind. Patients and investigators will remain blinded to IMP assignment during this part of the study. This will be followed by a 12-week open-label extension phase.

Patients will receive 225 mg sc fremanezumab (visit 2, visit 3, and visit 4) or matching placebo (visit 2) in monthly doses.

For the first phase of this study, the sponsor, investigators, study staff, and patients will be blinded to treatment assignment. A computer-generated master randomization list will be provided to drug packaging facilities. The packaging vendor(s) will package active drug and placebo into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance and contain 1 prefilled syringe with either active drug or placebo.

Patients will be stratified based on sex, country, migraine classification (ie, CM or EM), and PHQ-9 score category (10 to 14, 15 to 19, and ≥20) to ensure balance for the covariates.

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list using electronic IRT. This system is used to ensure a balance across treatment groups. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

At randomization visit (day 1), each patient will be randomized in a 1:1 ratio within the stratum to which he or she belongs to receive monthly 225 mg sc fremanezumab or placebo, as assigned by the IRT. In the open-label extension phase starting at week 12, however, all patients will receive active treatment with a quarterly dose of 675 mg sc fremanezumab.

The IRT will manage initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At each study visit where study drug is administered, the IRT will be queried, the site personnel will retrieve the study drug from refrigerated storage, and the patient will self-administer treatment with the 1 or 3 prefilled syringes, depending on the study visit, contained in the appropriately numbered kit.

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 IRT system. All investigational centers will be provided with details on 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.

The randomization list will be assigned to the relevant treatment groups through a qualified service provider, eg, via IRT system. The generation of the randomization list and management of the IRT system will be done by a qualified service provider under the oversight of the responsible function at Teva.

5.10. Maintenance of Randomization and Blinding

5.10.1. 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 Standard Operating Procedure (SOP).

5.10.2. Blinding and Unblinding

Double-Blind Treatment Phase

In case of a serious adverse event, pregnancy, or in cases when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations, through specialized access in the IRT system. Breaking of the treatment code can always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified that the code was broken, but the patient treatment 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 eCRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP should not be recorded in any study documents or source document.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study and the analysis and reporting of the data.

Open-Label Extension Phase

The open-label extension phase has no blinding.

5.10.3. Data Monitoring Committee

There will be no Data and Safety Monitoring Board in this study.

5.11. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 64.2 mL for scheduled tests. Details on total blood volume are provided in Appendix J.

6. ASSESSMENT OF EFFICACY

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

6.1. Assessments of Efficacy

See Appendix B for a detailed description of assessments and procedures. Questionnaires and the headache diary will be collected with an electronic handheld device.

6.1.1. Electronic Headache Diary

Patients will keep a daily headache diary to record the number of migraine days and headaches days they experience. These diary entries will be reviewed at clinic visits on visit 2 (randomization), visit 3 (day 29), visit 4 (day 57), visit 5 (day 85), and visit 6 (day 169) (see Table 4).

The primary efficacy endpoint (and secondary and exploratory efficacy endpoints as well) will be derived from headache variables collected daily using an electronic headache diary device. Eligible patients will receive comprehensive training from site personnel on the use of the electronic headache diary device. Site personnel will also instruct patients on the requirement for timely and daily completion of the electronic diary. Approximately 75% compliance is needed after the randomization period. Site personnel will monitor patient's compliance that approximately 75% diary entry is met during the double-blind treatment phase and open-label extension phase.

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

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

Rating of headache severity and duration of headache for each day will be completed in the electronic diary. Overall headache duration will be recorded numerically (in hours) as well as number of hours with headache of at least moderate severity.

If headache is reported, then headache severity will be subjectively rated by the patient as follows:

- mild headache

- moderate headache
- severe headache

Patients will also record whether photophobia, phonophobia, nausea, and/or 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.

6.1.2. Mini Mental State Examination

Patients will complete Mini Mental State Examination at the time points detailed in Table 4. This is a 30-point questionnaire to measure cognitive function.

6.1.3. Patient Health Questionnaire-9

The PHQ is a 9-item questionnaire with each item corresponding to 1 criterion of the Diagnostic and Statistical Manual for Mental Disorders 4th edition diagnostic criteria for MDD. Each of the items is scored on a scale of 0 ("not at all"), 1 ("several days"), 2 ("more than half the days"), and 3 ("nearly every day") based on the frequency of symptoms during the past 2 weeks (Spitzer, 1999). The PHQ-9 is a validated measure for detecting and monitoring depression, anxiety, and somatization (Kroenke, 2010).

Patients will complete the PHQ-9 at the time points detailed in Table 4.

6.1.4. Hamilton Depression Rating Scale-17

A qualified staff member (ie, the investigator or a medically qualified person designated by the investigator) will administer and record the HAM-D 17 at the time points detailed in Table 4. The HAM-D 17 is a list of 17 items used to determine a patient's level of depression. The HAM-D 17 questionnaire should be given at the same time of day for each visit. A psychiatrist will be a member of the site study team and should be consulted as appropriate.

6.1.5. Hamilton Anxiety Scale

A qualified staff member (ie, the investigator or a medically qualified person designated by the investigator) will administer and record the HAM-A at the time points detailed in Table 4. The HAM-A Scale is a tool for measuring the severity of a patient's anxiety. A psychiatrist will be a member of the site study team and should be consulted as appropriate.

6.1.6. 6-Item Headache Impact Test

The HIT-6 was developed by Kosinski et al, 2003 as a short form for reliably assessing the adverse headache impact in clinical practice and clinical research settings. The questionnaire measures the adverse impact of headache on social functioning, role functioning, vitality, cognitive functioning, and psychological distress. It also assesses headache severity. The HIT-6 has been shown to be a reliable and valid tool for assessment of headache impact in patients with migraine (Yang, 2011).

Patients will complete the HIT-6 at the time points detailed in Table 4.

6.1.7. Clinical Global Impression-Severity Scale

Patients will complete the CGI-S scale at the time points detailed in Table 4. The CGI-S is a short questionnaire filled out by the investigator that rates a patient's mental health from 1 (normal, not at all ill) to 7 (among the most extremely ill patients; Guy, 1976).

6.1.8. Migraine-Specific Quality of Life

The MSQoL version 2.1 is a 14-item questionnaire that assesses the impact of migraine and migraine treatment on a patient's quality of life during the previous 4 weeks, which has been shown to be a reliable and valid tool for use in CM and EM (Bagley, 2012). The MSQoL measures the degree to which performance of normal activities is limited by migraine (Role Function-Restrictive domain comprising 7 items), the degree to which performance of normal activities is prevented by migraine (Role Function-Preventive domain comprising 4 items), and the emotional effects of migraine (Emotional Function domain comprising 3 items). Scores range from 0 to 100, with higher scores indicating better health-related quality of life.

Patients will complete the MSQoL at the time points detailed in Table 4.

6.1.9. Work Productivity and Activity Impairment Questionnaire General Health V2.0

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

Patients will complete the WPAI questionnaire at the time points detailed in Table 4.

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 height and weight measurements), eC-SSRS scores, use of concomitant medication and therapy, and occurrence of severe hypersensitivity/anaphylactic reactions.

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, fremanezumab. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

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

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

  (Note: Abnormal laboratory or diagnostic test results at the screening visit (V1) that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)
- all events of possible drug-induced liver injury with hyperbilirubinemia (defined as AST or ALT ≥3 times the upper limit of normal [ULN], plus either total bilirubin

≥2 times the ULN or international normalized ratio >1.5) or Hy's Law events require immediate study treatment cessation.

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.

Worsening of depression will be collected as part of the efficacy assessment in this study and should be recorded as an adverse event only if the presentation or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse event, the study period is defined for each patient as the time period from signature of the ICF to the end of the follow-up period. The follow-up period of recording of adverse events is defined as 12 weeks after the last dose of IMP. The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered and until end of follow-up period on day 169 (±3 days).

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

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

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

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

The relationship of each adverse event to IMP and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described in Section 7.1.3 and Section 7.1.4.

Further details are given in the Safety Monitoring Plan.

7.1.3. Severity of an Adverse Event

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

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

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

The relationship of an adverse event to the IMP is characterized as follows:

Table 6: The Relationship of an Adverse Event to the IMP

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

7.1.5. Serious Adverse Events

For recording of serious adverse event, the study period is defined for each patient as that time period from signature of the ICF to the end of the follow-up period. Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

7.1.5.1. Definition of a Serious Adverse Event

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

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

  Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient's participation in this study.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

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

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

- ALT or AST increase of >3× 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.

7.1.5.2. 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 locally approved prescribing information for countries where fremanezumab is approved for the preventive treatment of migraine. For countries where fremanezumab is not yet approved, the reference safety information for this study is the IB.

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

For the purpose of SUSAR reporting, in countries where fremanezumab is approved for the preventive treatment of migraine, the locally approved prescribing information will be used. For countries where the IB is the reference safety information, the current version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the 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 department.

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 to underlying disease.

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

For all countries, the sponsor's GPSP department will distribute the Council for International Organizations of Medical Sciences (CIOMS) 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.

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

7.1.5.3.2. 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 the listings of expected toxicities to include adverse events newly identified as related to fremanezumab

7.1.6. Protocol-Defined Adverse Events of Special Interest

For purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to the sponsor's GPSP for evaluation:

- events of anaphylaxis and severe hypersensitivity reactions.
- ophthalmic events of at least moderate severity.

Anaphylaxis and severe hypersensitivity will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson, 2006) (also see Appendix H). In the event of suspected anaphylaxis and severe hypersensitivity, vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator. As a precaution, each site should have a resuscitation cart nearby.

The process for reporting a protocol-defined adverse event of interest is the same as that for reporting a serious adverse event (Section 7.1.5.3). 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 7.1.5.1.

7.1.7. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Pregnancy

Any female patient becoming pregnant during the study will discontinue IMP. All pregnancies of women participating in the study and female partners of men participating in the study that occur during the study or within at least 6 months after the last dose of IMP are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3). The investigator is not required to report patients who are found to be pregnant between the screening visit (V1) and randomization visit (V2 on day 1), provided no protocol-related procedures were applied.

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

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

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

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

Any administration of IMP that is not in accordance with the study protocol should be reported in the patients 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 healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.

7. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.

7.4. Clinical Laboratory Tests

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

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded on both the source documentation and the eCRF as an adverse event and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic work-up. (Note: Abnormal laboratory or diagnostic test results at the screening visit (V1) 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.

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 4. Clinical laboratory tests will be performed using the central laboratory. However, in case of abnormal coagulation during the 28-day baseline period, a local retest can be authorized by the sponsor on a case-by-case basis. Specific laboratory tests to be performed are provided in Appendix N.

7.4.2. Follicle-Stimulating Hormone

Follicle-stimulating hormone will be assessed at the time points detailed in Table 4. This assessment applies only to women thought to be postmenopausal at the screening visit (V1). If the results show an elevated FSH (>35 U/L) and the patient has had no menses for at least 12 months, they do not need urine pregnancy testing.

7.4.3. Human Chorionic Gonadotropin Tests

Serum β-HCG test will be administered at visit 1 (screening) for women of child-bearing potential and women thought to be postmenopausal. Urine β-HCG test will be administered at visit 2 (randomization), visit 3 (day 29), visit 4 (day 57), visit 5 (day 85), and visit 6 (day 169) for women of child-bearing potential and for women thought to be postmenopausal whose FSH results at the screening visit did not show an elevation (≤35 U/L) (see Table 4). On dosing days, the test should be completed before study drug administration.

7.5. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit [V1] only) and weight, will be performed at the time points detailed in Table 4. A full physical examination will

include, at a minimum, general appearance; head, eyes, ears, nose, and throat; chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Investigators should pay special attention to clinical signs related to previous serious diseases. Any physical examination finding that is judged by the investigator as clinically significant (except at the screening visit [V1]) will be considered an adverse event, recorded on the eCRF, and monitored as described in Section 7.1.2. For women of child-bearing potential only, inquire and record start/stop date of menstrual period at each visit as part of physical examination assessments.

7.6. Vital Signs

Vital signs (blood pressure [systolic/diastolic], temperature, respiratory rate, and pulse) will be measured at the time points detailed in Table 4. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

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

7.7. Electrocardiography

A single 12-lead ECG will be recorded at the time points detailed in Table 4.

A qualified physician at a central diagnostic center will be 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 the investigator's responsibility.

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

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

- abnormal and not clinically significant
- abnormal and clinically significant

If results are abnormal, the ECG will be repeated 1 time.

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 on the eCRF regardless of the central reading interpretation. Any ECG finding that is judged by the investigator as

clinically significant (except at the screening visit [V1]) will be considered an adverse event, recorded on the source documentation and the eCRF and monitored as described in Section 7.1.2.

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

7.8. Electronic Columbia-Suicide Severity Rating Scale

As part of the overall safety evaluation, the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (Posner, 2016) will be used in conjunction with a qualified clinician's (ie, the investigator or a medically qualified person designated by the investigator) clinical judgment to assess the patient's suicidal ideation (severity and intensity) and behavior. The eC-SSRS Lifetime version will be completed by the patient at visit 1, and the eC-SSRS Since Last Visit version will be completed by the patient at all other time points, as described in Table 4. Any positive findings on the eC-SSRS Since Last Visit version require evaluation by a qualified psychiatrist for potential exclusion and/or discontinuation from the study. Based on his/her medical judgment, a qualified psychiatrist will determine if the patient should be referred for further evaluation to another mental health specialist and if the patient should continue participation in the study.

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

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

8. ASSESSMENT OF PHARMACOKINETICS / PHARMACODYNAMICS / BIOMARKERS / PHARMACOGENOMICS / IMMUNOGENICITY / ANCILLARY STUDIES

Not applicable.

9. STATISTICS

This study is a Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fremanezumab monthly dosing compared with placebo for preventive treatment of EM and CM. Eligible patients will be randomized in a 1:1 ratio to receive monthly 225 mg sc fremanezumab or matching placebo. Patients will be stratified by sex, country, migraine classification (ie, CM or EM), and baseline PHQ-9 score category (10 to 14, 15 to 19, and ≥20).

9.1. Sample Size and Power Considerations

A sample size of 288 (144 per treatment group) evaluable patients completing the study will provide 90% power to detect a treatment difference of 2 days with a common standard deviation of 5.2 days in changes from the 28-day baseline period in monthly average migraine days between active and placebo groups at a 2-sided alpha level of 0.05. This sample size will provide approximately 80% power to detect a treatment difference of 2 points with a common standard deviation of 6 points in the change from randomization visit (day 1) in HAM-D 17 total score at a 2-sided alpha level of 0.05. Assuming a 15% drop-out rate, approximately 340 patients (approximately 170 patients per treatment group) will be randomized.

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.

Data collected from patients after treatment discontinuation will be included in the ITT analysis set.

9.2.2. Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP and have at least 10 days of postrandomization efficacy assessment on the primary endpoint.

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

9.2.3. Safety Analysis Set

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

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

Patients who begin prohibited therapies during the study will be included in the safety analysis set but not the per-protocol analysis set (Section 9.2.4).

9.2.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without important protocol deviations, including any deviation of the inclusion/exclusion criteria or any deviations or omissions of the IMP administration.

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

9.3. Data Handling Conventions

Efficacy variables from patients who do not have the electronic headache diary completed for the entire study period will be imputed using a prorated approach. Sensitivity analysis for the primary efficacy variable will be performed using multiple imputation methods for missing data. The detailed data imputation rules will be described in the statistical analysis plan.

9.3.1. Handling Withdrawals and Missing Data

Details for missing data imputation will be provided in the statistical analysis plan.

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

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications and therapies, and ECG findings, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, 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 a factor. The categorical variables of patient sex and race will be summarized using descriptive statistics for each variable category. Missing categories will be presented if necessary. Treatment groups will be compared for all categorical variables using a Pearson's chi-square test (or Fisher's exact test if cell sizes are too small).

9.5. Efficacy Analysis

Migraine days will be defined as follows. If the headache fulfills the criteria for migraine on any given day, the consecutive days are part of the same migraine attack and are therefore considered to be migraine days as well (even if they do not fulfill the criteria for migraine). These days only reflect normal fluctuations in migraine severity that lead to or represent the resolution of a full-blown migraine attack (IHS, 2004). Accordingly, for the purpose of this study, a migraine day is endorsed when at least one of the following situations occurs:

- a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting the criteria for migraine with or without aura
- a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting the criteria for probable migraine, a migraine subtype where only 1 migraine criterion is missing
- a calendar day (00:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds)
- a calendar day (00:00 to 23:59) that is immediately consecutive (happening 1 day before or 1 day after) of any day fulfilling the 3 criteria above, where individuals report headache of any duration

9.5.1. Primary Endpoint

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

9.5.2. Secondary Endpoints

The key secondary efficacy endpoint is the mean change in depression symptoms from randomization visit (day 1) to week 8 after the first dose of study drug as measured by HAM-D 17.

Other secondary endpoints include the following:

- Number of patients with 50% or more reduction from the 28-day baseline period until 12 weeks after the first dose of study drug, in the monthly average number of migraine days
- Mean change in quality of life from randomization visit (day 1) to week 12 after the first dose of study drug as measured by the MSQoL questionnaire, role function-restrictive and role function-preventive domains
- Mean change from randomization visit (day 1) in disability score for overall impact, as measured by CGI-S and HIT-6, to the following time points after administration of the first dose of study drug:
  - weeks 4 and 8 (CGI-S)
  - week 12 (CGI-S and HIT-6)

9.5.3. Exploratory/Other Endpoints

[redacted]

9.5.4. Planned Method of Analysis

The ITT analysis set (Sections 9.2.1, 9.2.2, and 9.2.4, respectively) 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, change from the 28-day baseline period in the monthly average number of migraine days, will be analyzed using analysis of covariance model with sex, region

(United States, European, or rest of world), migraine classification (ie, CM or EM), baseline PHQ-9 score category, and treatment as factors and baseline number of migraine days as a covariate. The treatment difference, the 95% confidence interval for the treatment difference, and the associated p-value will be generated from this model.

9.5.4.2. Sensitivity Analysis

Sensitivity analysis using multiple imputation for missing data imputation may be conducted.

9.5.4.3. Secondary Efficacy Analysis

The continuous secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint. Analyses using the mixed-effect model repeated measure method will be conducted for continuous variables assessed at multiple time points. For the proportion of responders, defined as 50% or more reduction from the 28-day baseline period in the monthly average number of migraine days, a logistic regression model will be used with the following effects: treatment, sex, region (United States, European, or rest of world), migraine classification (ie, CM or EM), and baseline PHQ-9 score category. The ORs, 95% confidence intervals (for ORs), and p-values will be presented for fremanezumab comparing to placebo.

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 is detailed in the statistical analysis plan.

9.7. Safety Analysis

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

Safety assessments and time points are provided in Table 4.

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

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

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include ECT and all medications taken while the patient

is treated with IMP. Patients who begin prohibited therapies during the study will be discontinued from the study (eg, ECT, vagus nerve stimulation, direct current therapy, transcutaneous supraorbital stimulation, and other forms of electrical stimulation). Complete discontinuation criteria are provided in Section 4.3.

Safety data will be summarized descriptively overall, by treatment group, and by study phase. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from randomization visit (day 1) to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events and patient withdrawals due to adverse events will be provided as well.

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

9.8. Tolerability Analysis

Tolerability findings will be listed and summarized descriptively.

9.9. Planned Interim Analysis

There will be no formal interim analysis.

9.10. Reporting Deviations from the Statistical Plan

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

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

See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IEC/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 eCRFs and source documents.

13. FINANCING AND INSURANCE

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

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

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

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

14. PUBLICATION POLICY

See Appendix M for information regarding the publication policy.

15. REFERENCES

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 04 Dated 04 May 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 and to allow rescreening of patients 1 time. These changes are reflected in the table below.

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

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.

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 Approval Date: 03 May 2019 **Protocol with Amendment 01 Approval Date: 04 June 2019** **Protocol with Amendment 02 Approval Date: 10 October 2019** **Protocol with Amendment 03 Approval Date: 04 November 2019** **Protocol with Amendment 04 Approval Date: 04 May 2020**	**Protocol Approval Date: 03 May 2019** **Protocol with Amendment 01 Approval Date: 04 June 2019** **Protocol with Amendment 02 Approval Date: 10 October 2019** **Protocol with Amendment 03 Approval Date: 04 November 2019** **Protocol with Amendment 04 Approval Date: 04 May 2020**	Updated for Amendment 04
COVID-19 pandemic-related operational updates are provided in Appendix P	**COVID-19 pandemic-related operational updates are provided in Appendix P**	Updated to manage study conduct during the COVID-19 pandemic.
© ~~2019~~ 2020 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	© 2020 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	Updated for Amendment 04
Teva Branded Pharmaceutical Products R&D, Inc. **145 Brandywine Parkway,** **West Chester, Pennsylvania 19380** **~~41 Moores Road~~** **~~Frazer, Pennsylvania 19355~~** **United States of America**	**Teva Branded Pharmaceutical Products R&D, Inc.** **145 Brandywine Parkway,** **West Chester, Pennsylvania 19380** **United States of America**	Updated as outlined in Administrative Letter 02

Original text with changes shown	New wording	Reason/ justification for change
3.5 Schedule of Study Procedures and Assessments (Table 4) and Appendix D. Ethics		
For Coronavirus disease 2019 (COVID-19) updates, see Appendix P.	For Coronavirus disease 2019 (COVID-19) updates, see Appendix P.	Updated sections to cross-reference the addition of Appendix P.
3.5. Schedule of Study Procedures and Assessments (Table 4)		
a. In the case of early termination, site personnel should perform a follow-up phone call to ensure the patient does not report suicidal ideation or behavior. Phone calls should be performed once weekly for 2 weeks. If signs of suicidality are identified during the follow-up phone call, the site personnel should provide direction to the patient for further psychiatric evaluation at the site or at a community psychiatrist referenced by the site. Relevant emergency psychiatric care services should be notified in the event that the patient is deemed to be a threat to themself.	a. In the case of early termination, site personnel should perform a follow-up phone call to ensure the patient does not report suicidal ideation or behavior. Phone calls should be performed once weekly for 2 weeks. If signs of suicidality are identified during the follow-up phone call, the site personnel should provide direction to the patient for further psychiatric evaluation at the site or at a community psychiatrist referenced by the site. Relevant emergency psychiatric care services should be notified in the event that the patient is deemed to be a threat to themself.	Additional follow-up for patients who early terminate were added to ensure the safety of these patients.
d. Collection of prior medications for migraine and/or depression is limited to those medications administered within the past 10 years or for any indication with the past 5 months before screening (V1).	d. Collection of prior medications for migraine and/or depression is limited to those medications administered within the past 10 years or for any indication with the past 5 months before screening (V1).	Clarification
4.2. Patient Exclusion Criteria		
g. [Revision 1] The patient has clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, ~~or~~ ocular disease, or complications of an infection, at the discretion of the investigator.	g. [Revision 1] The patient has clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, ocular disease, or complications of an infection, at the discretion of the investigator.	It has been specified that patients with clinically significant complications of an infection may be excluded at the discretion of the investigator

Original text with changes shown	New wording	Reason/ justification for change
h. The patient has a clinical history of a severe or uncontrolled psychiatric disorder, to include the following, or at the discretion of the investigator for any clinically significant psychiatric history that would likely interfere with full participation in the study: ~~evidence or medical history of other clinically significant psychiatric issues that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study including panic disorder, bipolar disorder, schizophrenia, or any~~ - **Lifetime exclusion:** suicide attempt ~~in the past,~~ - **In the past 6 months exclusion:** suicidal ideation, or other psychoactive spectrum disorders including schizoaffective disorder, delusional disorder, depression with psychotic features, and catatonic disorder ~~in the past 6 months.~~	h. The patient has a clinical history of a severe or uncontrolled psychiatric disorder, to include the following, or at the discretion of the investigator for any clinically significant psychiatric history that would likely interfere with full participation in the study: - Lifetime exclusion: suicide attempt - In the past 6 months exclusion: suicidal ideation, or other psychoactive spectrum disorders including schizoaffective disorder, delusional disorder, depression with psychotic features, and catatonic disorder	Updated to clarify exclusion of psychiatric disorders including suicide attempt and ideation
m. The patient has a history of hypersensitivity reactions to injected proteins, including monoclonal antibodies, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome.	m. The patient has a history of hypersensitivity reactions to injected proteins, including monoclonal antibodies, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome.	Updated to exclude patients with history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome per safety updates
bb. Patient has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 3 months before screening visit.	bb. Patient has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 3 months before screening visit.	Updated to exclude patients that received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 3 months before screening visit per safety updates
4.5. Rescreening		
~~A patient who is screened and does not meet study inclusion and exclusion criteria will not be considered for screening again.~~ A patient who is screened 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	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, or require to screen fail as directed by the sponsor due to an emergency situation (eg, pandemic	Updated rescreening criterion to account for extraordinary situations and technical problems

Original text with changes shown	New wording	Reason/ justification for change
visit 2 window due to an emergency situation, or require to screen fail as directed by the sponsor due to an emergency situation (eg, pandemic or potential pandemic), may be considered for rescreening 1 time. Investigators may contact the sponsor's medical monitors or medical expert for additional guidance on rescreening. If the patient is rescreened, an informed consent form (ICF) will need to be re-signed, and a new screening number will be assigned.	or potential pandemic), may be considered for rescreening 1 time. Investigators may contact the sponsor's medical monitors or medical expert for additional guidance on rescreening. If the patient is rescreened, an informed consent form (ICF) will need to be re-signed, and a new screening number will be assigned.	
5.7. Prior and Concomitant Medication or Therapy		
Any prior or concomitant medication, treatment, psychotherapy, or procedure a patient has had for migraine and/or depression within the past 10 years or for any indication within the past 5 months before IMP administration and up to the end of study, including follow-up, will be recorded on the eCRF.	Any prior or concomitant medication, treatment, psychotherapy, or procedure a patient has had for migraine and/or depression within the past 10 years or for any indication within the past 5 months before IMP administration and up to the end of study, including follow up, will be recorded on the eCRF.	Clarification
6.1.4. Hamilton Depression Rating Scale-17		
The HAM-D 17 is a list of ~~21~~ 17 items used to determine a patient's level of depression.	The HAM D 17 is a list of 17 items used to determine a patient's level of depression.	Clarification
7.7. Electrocardiography		
A single 12-lead ECG will be recorded at the time points detailed inTable 4. ~~This procedure will be performed before other assessments (eg, blood draws and administration of questionnaires).~~	A single 12-lead ECG will be recorded at the time points detailed inTable 4.	Updated to remove wording involving when the procedure is performed
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. Cell: [redacted]	Updated as outlined in Administrative Letter 02.

Original text with changes shown	New wording	Reason/ justification for change
[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] and [redacted] Cell: [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] and [redacted] Cell: [redacted]	Updated as outlined in Administrative Letter 02.
Appendix B. Study Procedures sand Assessments by Visit		
In the case of early termination, site personnel should perform a follow-up phone call to ensure the patient does not report suicidal ideation or behavior. Phone calls should be performed once weekly for 2 weeks. If signs of suicidality are identified during the follow-up phone call, the site personnel should provide direction to the patient for further psychiatric evaluation at the site or at a community psychiatrist referenced by the site. Relevant emergency psychiatric care services should be notified in the event that the patient is deemed to be a threat to themself.	In the case of early termination, site personnel should perform a follow-up phone call to ensure the patient does not report suicidal ideation or behavior. Phone calls should be performed once weekly for 2 weeks. If signs of suicidality are identified during the follow-up phone call, the site personnel should provide direction to the patient for further psychiatric evaluation at the site or at a community psychiatrist referenced by the site. Relevant emergency psychiatric care services should be notified in the event that the patient is deemed to be a threat to themself.	Additional follow-up for patients who early terminate were added to ensure the safety of these patients.
Appendix G. Preventive Migraine Medications Allowed for 30% of the Study Population and Anti Depressant Medications Allowed for the Whole Study Population for the Duration of the Study		
Patients are not permitted to use onabotulinumtoxinA for any indication for the duration of the study.	Patients are not permitted to use onabotulinumtoxinA for any indication for the duration of the study.	Clarification.
Appendix P. Management of Study Activities During COVID-19		
New appendix and text.	Additional text too numerous to include in this table; refer to Appendix P of this protocol.	Updated to manage study conduct during the COVID-19 pandemic.

16.2. Administrative Letter 02 Dated 14 February 2020

teva

ADMINISTRATIVE LETTER 02

Study number: TV48125-MH-40142

Clinical Study Protocol with Amendment 03

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, Version Date 04 November 2019

IND number: 106533; BLA number: 761089; EudraCT number: 2019-001989-15

14 February 2020

Dear Investigator:

The purpose of this letter is to provide the change of sponsor address and sponsor representative phone numbers. The clarifications are provided below:

1. Revise the sponsor address listed on the title page of the protocol and throughout from 41 Moores Road, Frazer, Pennsylvania 19355, USA to 145 Brandywine Parkway, West Chester, Pennsylvania 19380, USA. The sponsor has not changed and remains Teva Branded Pharmaceutical Products R&D, Inc.
2. Remove the office telephone number of [redacted] in Protocol Appendix A [redacted] To contact [redacted] please reach out to his cell phone number listed in Protocol Appendix A [redacted]
3. Revise the telephone number of [redacted] in Appendix A from [redacted] to [redacted] and [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 me, [redacted] (Tel: [redacted] and [redacted] Cell: [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

16.3. Amendment 03 Dated 04 November 2019

The primary reasons for this amendment are to update the protocol to allow a qualified staff member to complete the HAM-A and HAM-D 17 assessments and to allow a qualified clinician's judgment to be used in conjunction with the eC-SSRS instead of a psychiatrist. This amendment is considered to be substantial (ie, requires approval by competent authority, 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.

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 ~~02~~03 Approval Date: ~~10 October 2019~~ 04 November 2019	**Clinical Study Protocol with Amendment 03 Approval Date: 04 November 2019**	To update for Amendment 03
3. STUDY DESIGN		
3.2. Planned Number of Patients and Countries		
The study is planned to be conducted in approximately ~~10~~13 countries in approximately 65 investigational centers. The study is expected to start in approximately September 2019 and last until approximately August 2021.	The study is planned to be conducted in approximately 13 countries in approximately 65 investigational centers. The study is expected to start in approximately September 2019 and last until approximately August 2021.	To update the planned number of countries.
3.5. Schedule of Study Procedures and Assessments (Table 4) (Other sections affected by this change: 7.4.2, Appendix B, Appendix J)		
[j] On dosing days, the test or questionnaire should be ~~administered predose~~ completed before study drug administration.	[j] On dosing days, the test or questionnaire should be completed before study drug administration.	Clarification
[k] The FSH ~~this~~ assessment applies only to women thought to be postmenopausal at the screening visit (V1). If the results show an elevated FSH (>35 U/L) and the patient has had no menses for at least 12 months, they do not need urine pregnancy testing.	[k] The FSH assessment applies only to women thought to be postmenopausal at the screening visit (V1). If the results show an elevated FSH (>35 U/L) and the patient has had no menses for at least 12 months, they do not need urine pregnancy testing.	To clarify and update the FSH assessment
[n] A qualified ~~psychiatrist~~ staff member (ie, the investigator or a medically qualified person designated by the investigator) will perform this assessment.	[n] A qualified staff member (ie, the investigator or a medically qualified person designated by the investigator) will perform this assessment.	To update who can administer the HAM-A/ D 17
4. SELECTION AND WITHDRAWAL OF PATIENTS		
4.1. Patient Inclusion Criteria		

Original text with changes shown	New wording	Reason/ justification for change
1. [Revision ~~1~~ 2] The patient demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 21 ~~4~~–days cumulative during the 28-day baseline period (~75% diary compliance).	1. [Revision 2] The patient demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 21 days cumulative during the 28-day baseline period (~75% diary compliance).	To correct the minimum amount of days to 21
4.2. Patient Exclusion Criteria		
b. [Revision 1] The patient has failed 4 or more different medication classes to treat depression in their lifetime	b. [Revision 1] The patient has failed 4 or more different medication classes to treat depression in their lifetime	Clarification
d. [Revision 1] The patient has used an intervention/device (eg, scheduled nerve blocks, implantable vagal nerve stimulation, and transcranial magnetic stimulation) for migraine or depression ~~at any time~~during the 2 months prior to screening.	d. [Revision 1] The patient has used an intervention/device (eg, scheduled nerve blocks, implantable vagal nerve stimulation, and transcranial magnetic stimulation) for migraine or depression during the 2 months prior to screening.	To update the requirements for patients that have used an intervention/device.
o. [Revision 1] The patient has failed treatment (based on tolerability and/or a lack of efficacy) with any monoclonal antibodies targeting the CGRP pathway (erenumab, eptinezumab, galcanezumab, or fremanezumab) or have taken the medications within 5 half-lives of the screening visit (V1) or take them during the study.	o. [Revision 1] The patient has failed treatment (based on tolerability and/or a lack of efficacy) with any monoclonal antibodies targeting the CGRP pathway (erenumab, eptinezumab, galcanezumab, or fremanezumab) or have taken the medications within 5 half-lives of the screening visit (V1) or take them during the study.	Clarification
4.3. Withdrawal Criteria and Procedures for the Patient		
5. A female patient has a confirmation of pregnancy during the study from a positive urine pregnancy test.	5. A female patient has a confirmation of pregnancy during the study from a positive urine pregnancy test.	Clarification
5. TREATMENTS		
5.1.1.2. Dose Modification and Dose Stratification		
No dose modifications ~~were~~are allowed.	No dose modifications are allowed.	Clarification
5.1.2. Placebo Investigational Medicinal Product (Other sections affected by this change: 3.1, 5.1.1, 5.9)		
At the time of each study visit, the IRT will be queried, and site ~~personnel~~ staff will retrieve the IMP and oversee patient self-administration of 1.5 mL from each prefilled syringe contained in the appropriately numbered kit(s).	At the time of each study visit, the IRT will be queried, and site staff will retrieve the IMP and oversee patient self-administration of 1.5 mL from each prefilled syringe contained in the appropriately numbered kit(s).	Clarification
Study drug should be removed from the refrigerator and allowed to equilibrate at room temperature for ~~45 to 60~~ 30 minutes before study drug self-administration.	Study drug should be removed from the refrigerator and allowed to equilibrate at room temperature for 30 minutes before study drug self-administration.	Update the IP equilibration time to be in line with the US PI and the SmPC
5.2.3. Accountability		

Original text with changes shown	New wording	Reason/ justification for change
Only patients enrolled in the study may receive and self-administer IMPs, and only authorized site staff at the investigational center may supply 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 site staff at the investigational center.	Only patients enrolled in the study may receive and self-administer IMPs, and only authorized site staff at the investigational center may supply 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 site staff at the investigational center.	Clarification
5.11. Total Blood Volume (Other sections affected by this change: Appendix J)		
The total blood volume to be collected for each patient in this study is approximately ~~45~~ 64.2 mL for scheduled tests. Details on total blood volume are provided in Appendix J.	The total blood volume to be collected for each patient in this study is approximately 64.2 mL for scheduled tests. Details on total blood volume are provided in Appendix J.	Total blood volume updated
6. ASSESSMENT OF EFFICACY		
6.1.4. Hamilton Depression Rating Scale-17 (Other sections affected by this change: Appendix B)		
~~Patients will complete~~A qualified staff member (ie, the investigator or a medically qualified person designated by the investigator) will administer and record the HAM-D 17 at the time points detailed in Table 4. The HAM D-17 is a list of 21 items used to determine a patient's level of depression. The HAM-D 17 questionnaire should be given at the same time of day for each visit. A psychiatrist will be a member of the site study team and should be consulted as appropriate.	A qualified staff member (ie, the investigator or a medically qualified person designated by the investigator) will administer and record the HAM-D 17 at the time points detailed in Table 4. The HAM D-17 is a list of 21 items used to determine a patient's level of depression. The HAM-D 17 questionnaire should be given at the same time of day for each visit. A psychiatrist will be a member of the site study team and should be consulted as appropriate.	To update who can administer the HAM-D 17
6.1.5. Hamilton Anxiety Scale (Other sections affected by this change: Appendix B)		
~~Patients will complete~~A qualified staff member (ie, the investigator or a medically qualified person designated by the investigator) will administer and record the HAM-A at the time points detailed in Table 4. The HAM-A Scale is a tool for measuring the severity of a patient's anxiety. A psychiatrist will be a member of the site study team and should be consulted as appropriate.	A qualified staff member (ie, the investigator or a medically qualified person designated by the investigator) will administer and record the HAM-A at the time points detailed in Table 4. The HAM-A Scale is a tool for measuring the severity of a patient's anxiety. A psychiatrist will be a member of the site study team and should be consulted as appropriate.	To update who can administer the HAM-A
7. ASSESSMENT OF SAFETY		
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	Any administration of IMP that is not in accordance with the study protocol should be	To update wording from violation to

Original text with changes shown	New wording	Reason/ justification for change
be reported ~~on the eCRF either as a violation, if it meets the violation criteria specified in the protocol (Appendix C), or as a deviation,~~ in the patients source documents, regardless of whether or not an adverse event occurs as a result.	reported in the patients source documents, regardless of whether or not an adverse event occurs as a result.	important protocol deviation.
7.4.3. Human Chorionic Gonadotropin Tests (Other sections affected by this change: Appendix B and Appendix J.		
Serum β-HCG test will be administered at visit 1 (screening) for women of child-bearing potential and women thought to be postmenopausal. Urine β-HCG test will be administered at visit 2 (randomization), visit 3 (day 29), visit 4 (day 57), visit 5 (day 85), and visit 6 (day 169) for women of child-bearing potential and for women thought to be postmenopausal whose FSH results at the screening visit did not show an elevation (≤35 U/L) (see Table 4). On dosing days, the test should be completed before study drug administration.	Serum β-HCG test will be administered at visit 1 (screening) for women of child-bearing potential and women thought to be postmenopausal. Urine β-HCG test will be administered at visit 2 (randomization), visit 3 (day 29), visit 4 (day 57), visit 5 (day 85), and visit 6 (day 169) for women of child-bearing potential and for women thought to be postmenopausal whose FSH results at the screening visit did not show an elevation (≤35 U/L) (see Table 4). On dosing days, the test should be completed before study drug administration.	Clarification
7.8. Electronic Columbia-Suicide Severity Rating Scale (Other sections affected by this change: Section 3.5 (Table 4, Footnote l) and Appendix B)		
As part of the overall safety evaluation, the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (Posner, 2016) will be used in conjunction with a qualified ~~psychiatrist's~~ clinician's (ie, the investigator or a medically qualified person designated by the investigator) clinical judgment to assess the patient's suicidal ideation (severity and intensity) and behavior.	As part of the overall safety evaluation, the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (Posner, 2016) will be used in conjunction with a qualified clinician's (ie, the investigator or a medically qualified person designated by the investigator) clinical judgment to assess the patient's suicidal ideation (severity and intensity) and behavior.	Clarification
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] [redacted] ~~Teva Branded Pharmaceutical Products R&D, Inc.~~	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	To update Sponsor's Authorized Representative

Original text with changes shown	New wording	Reason/ justification for change
~~Tel:~~ [redacted] ~~Cell:~~ [redacted] [redacted]		
Legal Representative of the Sponsor in the EU and Contact Person	Legal Representative of the Sponsor in the EU and Contact Person	Clarification
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] [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]	To update Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study
Appendix B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
• ~~administer~~ complete Mini Mental State Examination • ~~administer~~ complete Patient Health Questionnaire-9 (PHQ-9) • ~~administer~~ complete the eC-SSRS Lifetime version (used in conjunction with qualified ~~psychiatrist's~~clinician's clinical judgment to assess the patient's suicidal ideation [severity and intensity] and behavior)	• complete Mini Mental State Examination • complete Patient Health Questionnaire-9 (PHQ-9) • complete the eC-SSRS Lifetime version (used in conjunction with qualified clinician's clinical judgment to assess the patient's suicidal ideation [severity and intensity] and behavior)	Clarification *similar changes applied to other scales/questionnaires in Appendix B*
Appendix C. QUALITY CONTROL AND QUALITY ASSURANCE (Other sections affected: Section 3.4 and 9.2.4)		
Important Protocol Deviations ~~Protocol Violations~~	Important Protocol Deviations	Rewording of protocol violation to important protocol deviation
Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered ~~a protocol violation~~ an important protocol	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	Rewording of protocol violation to important protocol deviation

Original text with changes shown	New wording	Reason/ justification for change
deviation. ~~Protocol violations~~ 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 IMP administration; and use of prohibited medications. ~~Protocol violations~~ Important protocol deviations will be identified and recorded by investigational center personnel on the electronic case report form (eCRF). All ~~protocol violations~~ important protocol deviations will be reported to the responsible IEC/IRB, as required.	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 IMP administration; and use of prohibited medications. Important protocol deviations will be identified and recorded by investigational center personnel on the electronic case report form (eCRF). All important protocol deviations will be reported to the responsible IEC/IRB, as required.	
When ~~a protocol violation~~ an important protocol deviation is reported, 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.	When an important protocol deviation is reported, 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.	Rewording of protocol violation to important protocol deviation
If investigational center personnel learn that a patient who did not meet the protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the ~~protocol violation~~ important protocol deviation. If such patient has already completed the study or has withdrawn early, no action will be taken but the ~~violation~~ deviation will be recorded.	If investigational center personnel learn that a patient who did not meet the 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.	Rewording of protocol violation to important protocol deviation

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/ justification for change</th></tr>
<tr><td colspan="3">Appendix J. TOTAL BLOOD VOLUME</td></tr>
<tr><td>
<table>
<tr><th>Type of samples</th><th>Volume per sample (mL)</th><th>Total number of samples</th><th>Total volume (mL)</th></tr>
<tr><td>Serum chemistry, hematology, ~~and~~ coagulation, serum β-HCG test[a] and FSH[b]</td><td>~~6.5~~10.7</td><td>~~6~~1</td><td>~~39~~10.7</td></tr>
<tr><td>~~Serum β-HCG test[a]~~Serum chemistry, hematology, and coagulation</td><td>~~3~~10.7</td><td>~~1~~5</td><td>~~3~~53.5</td></tr>
<tr><td>~~FSH[b]~~</td><td>~~3~~</td><td>~~1~~</td><td>~~3~~</td></tr>
<tr><td>Total</td><td></td><td>~~8~~6</td><td>~~15~~64.2</td></tr>
</table>
</td><td>
<table>
<tr><th>Type of samples</th><th>Volume per sample (mL)</th><th>Total number of samples</th><th>Total volume (mL)</th></tr>
<tr><td>Serum chemistry, hematology, coagulation, serum β-HCG test[a] and FSH[b]</td><td>10.7</td><td>1</td><td>10.7</td></tr>
<tr><td>Serum chemistry, hematology, and coagulation</td><td>10.7</td><td>5</td><td>53.5</td></tr>
<tr><td>Total</td><td></td><td>6</td><td>64.2</td></tr>
</table>
</td><td>Update to the volume of blood taken during the source of the study.</td></tr>
</table>

16.4. Amendment 02 Dated 10 October 2019

The primary reason for this amendment is to update the protocol based on feedback received from the Voluntary Harmonisation Procedure. This amendment is considered to be substantial (ie, requires approval by competent authority, 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.

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 Approval Date: ~~04~~10 October 2019	**Clinical Study Protocol with Amendment 02 Approval Date: 10 October 2019**	To update for Amendment 02
2. STUDY OBJECTIVES AND ENDPOINTS		
2.1. Primary and Secondary Study Objectives and Endpoint		
Key secondary objective: To evaluate the efficacy of monthly 225 mg sc of fremanezumab in adult patients with migraine and MDD on the reduction of MDD symptoms	**Key secondary objective:** To evaluate the efficacy of monthly 225 mg sc of fremanezumab in adult patients with migraine and MDD on the reduction of MDD symptoms	To fix an editorial mistake.
4. SELECTION AND WITHDRAWAL OF PATIENTS		
4.2. Patient Exclusion Criteria		
h. [Revision 1] The patient has evidence or medical history of other clinically significant psychiatric issues that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study including panic disorder, bipolar disorder, schizophrenia, or any suicide attempt in the past, ~~or~~ suicidal ideation, or other psychoactive spectrum disorders including schizoaffective disorder, delusional disorder, depression with psychotic features, and catatonic disorder in the past 6 months.	h. [Revision 1] The patient has evidence or medical history of other clinically significant psychiatric issues that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study including panic disorder, bipolar disorder, schizophrenia, or any suicide attempt in the past, suicidal ideation, or other psychoactive spectrum disorders including schizoaffective disorder, delusional disorder, depression with psychotic features, and catatonic disorder in the past 6 months.	Clarification to ensure no patients with evidence of psychosis are included in this study.
u. [Revision 1] The patient has a history of alcohol or drug abuse in the opinion of the investigator.	u. [Revision 1] The patient has a history of alcohol or drug abuse in the opinion of the investigator.	Clarification
aa. The patient has evidence or medical history of psychotic symptoms as per DSM-V criteria such as delusions, hallucinations, or disorganized speech in the past 1 month.	aa. The patient has evidence or medical history of psychotic symptoms as per DSM-V criteria such as delusions, hallucinations, or disorganized speech in the past 1 month.	Exclusion criterion "aa" was added to ensure no patients with evidence of psychosis are included in this

Original text with changes shown	New wording	Reason/ justification for change
		study.
5.7. Prior and Concomitant Medication or Therapy		
Any prior or concomitant medication, treatment, psychotherapy, or procedure a patient has had within the past 10 years before IMP administration and up to the end of study, including follow up, will be recorded on the eCRF. Trade name and international nonproprietary name (if available), indication, dose, and start and end dates of the administered medication or treatment will be recorded. In addition, migraine and depression preventive medication listed in Appendix G that a patient took before study drug administration will be recorded on the eCRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all medication according to the World Health Organization drug dictionary (WHO Drug).	Any prior or concomitant medication, treatment, psychotherapy, or procedure a patient has had within the past 10 years before IMP administration and up to the end of study, including follow up, will be recorded on the eCRF. Trade name and international nonproprietary name (if available), indication, dose, and start and end dates of the administered medication or treatment will be recorded. In addition, migraine and depression preventive medication listed in Appendix G that a patient took before study drug administration will be recorded on the eCRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all medication according to the World Health Organization drug dictionary (WHO Drug)..	Clarified that any ongoing psychotherapy or changes to the patients' psychotherapy is to be recorded throughout the study.
A list of preventive migraine medications that are allowed for up to 30% of the study population and antidepressant medications allowed for the whole study population for the duration of the study are given in Appendix G. Concomitant medications that are not allowed for the duration of the study include other monoclonal antibodies that target the CGRP pathway (erenumab, eptinezumab, or galcanezumab), as described in Section 4.2. If clinically indicated, patients' antidepressant medications and psychotherapy may be changed at any time during the treatment period at the discretion of the investigator, and all changes will be recorded in the eCRF. In such case, the patient's continued participation in the study will be reviewed by the medical monitors.	A list of preventive migraine medications that are allowed for up to 30% of the study population and antidepressant medications allowed for the whole study population for the duration of the study are given in Appendix G. Concomitant medications that are not allowed for the duration of the study include other monoclonal antibodies that target the CGRP pathway (erenumab, eptinezumab, or galcanezumab), as described in Section 4.2. If clinically indicated, patients' antidepressant medications and psychotherapy may be changed at any time during the treatment period at the discretion of the investigator, and all changes will be recorded in the eCRF. In such case, the patient's continued participation in the study will be reviewed by the medical monitors.	Clarification of medications that are allowed and disallowed for the duration of the study and that patients may change their antidepressant medication or psychotherapy during the study.
Concomitant medication and treatment, including psychotherapy, will be recorded until visit 6, day 169.	Concomitant medication and treatment, including psychotherapy, will be recorded until visit 6, day 169.	Clarified that any changes to the patients' psychotherapy is to be recorded throughout the study.
7. ASSESSMENT OF SAFETY		
7.1.5.2. Expectedness		
A serious adverse event that is not included in	A serious adverse event that is not included in	Clarification of

Original text with changes shown	New wording	Reason/ justification for change
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 and Development Safety Update Report~~locally approved prescribing information for countries where fremanezumab is approved for the preventive treatment of migraine. For countries where fremanezumab is not yet approved, the reference safety information for this study is the IB. The sponsor's GPSP will determine the expectedness for all serious adverse events. For the purpose of SUSAR reporting, in countries where fremanezumab is approved for the preventive treatment of migraine, the locally approved prescribing information will be used. For countries where the IB is the reference safety information, the current version of the IB at the time of occurrence of the SUSAR applies.	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 locally approved prescribing information for countries where fremanezumab is approved for the preventive treatment of migraine. For countries where fremanezumab is not yet approved, the reference safety information for this study is the IB. The sponsor's GPSP will determine the expectedness for all serious adverse events. For the purpose of SUSAR reporting, in countries where fremanezumab is approved for the preventive treatment of migraine, the locally approved prescribing information will be used. For countries where the IB is the reference safety information, the current version of the IB at the time of occurrence of the SUSAR applies.	what document should be used as the reference safety information.
9. STATISTICS		
9.1. Sample Size and Power Considerations		
A sample size of 288 (144 per treatment group) evaluable patients completing the study will provide 90% power to detect a treatment difference of 2 days with a common standard deviation of 5.2 days in changes from the 28-day baseline period in monthly average migraine days between active and placebo groups at a 2-sided alpha level of 0.05. This sample size will provide approximately 80% power to detect a treatment difference of 2 points with a common standard deviation of 6 points in the change from randomization visit (day 1) in HAM-D 17 total score at a 2-sided alpha level of 0.05. Assuming a 15% drop-out rate, approximately 340 patients (approximately 170 patients per treatment group) will be randomized.	A sample size of 288 (144 per treatment group) evaluable patients completing the study will provide 90% power to detect a treatment difference of 2 days with a common standard deviation of 5.2 days in changes from the 28-day baseline period in monthly average migraine days between active and placebo groups at a 2-sided alpha level of 0.05. This sample size will provide approximately 80% power to detect a treatment difference of 2 points with a common standard deviation of 6 points in the change from randomization visit (day 1) in HAM-D 17 total score at a 2-sided alpha level of 0.05. Assuming a 15% drop-out rate, approximately 340 patients (approximately 170 patients per treatment group) will be randomized.	Clarification that the sample size was determined using a 2-sided alpha level of 0.05.
APPENDIX G. PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR 30% OF THE STUDY POPULATION AND ANTI-DEPRESSANT MEDICATIONS ALLOWED FOR THE WHOLE STUDY POPULATION FOR THE DURATION OF THE STUDY	**APPENDIX G. PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR 30% OF THE STUDY POPULATION AND ANTI-DEPRESSANT MEDICATIONS ALLOWED FOR THE WHOLE STUDY POPULATION FOR THE DURATION OF THE STUDY**	Clarification of the Appendix title to better reflect the information presented.
Antidepressant medications allowed for the	Antidepressant medications allowed for the	Clarification.

Original text with changes shown	New wording	Reason/ justification for change
whole study population for the duration of the study specifically include the following (if they were previously prescribed for depression or for another indication):	whole study population for the duration of the study specifically include the following (if they were previously prescribed for depression or for another indication):	

16.5. Letter of Clarification 01 Dated 26 August 2019

TEVA Pharmaceuticals

LETTER OF CLARIFICATION 01

Study number: TV48125-MH-40142

Clinical Study Protocol with Amendment 01

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, Dated 04 June 2019

IND number: 106533; BLA number: 761089; EudraCT number: 2019-001989-15

26 August 2019

Dear Investigator:

The purpose of this letter of clarification is to accomplish the following:

1. Update the estimated total blood volume (45 mL: approximately 12.5 mL at visit 1 and 6.5 mL at visits 2 through 6) to the actual total blood volume (64.2 mL: approximately 10.7 mL at visits 1 through 6) to be collected. This update applies to Section 5.11 Total Blood Volume and Appendix J of the study protocol.

Total Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Serum chemistry, hematology, coagulation, serum β-HCG test[a], and FSH[b]	10.7	1	10.7
Serum chemistry, hematology, and coagulation	10.7	5	53.5
Total		**6**	**64.2**

[a] A serum pregnancy test will be performed for women of child-bearing potential at the screening visit (visit 1).
[b] An FSH test will be performed only for women thought to be postmenopausal at the screening visit (visit 1).
β-HCG = beta-human chorionic gonadotropin; FSH = follicle stimulating hormone.

2. Correct a typographical error in the headache eDiary compliance calculation (eg, 75% of the 28-day baseline period is 21 days [not 24 days]). This correction applies to the Clinical Study Protocol Synopsis (inclusion criterion 'l') and Section 4.1 Patient Inclusion Criteria (inclusion criterion 'l').
3. Correct the name of the Sponsor's Authorized Representative listed in Appendix A from [redacted] to [redacted]

Teva Branded Pharmaceutical Products R&D, Inc 41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. [redacted]
www.tevapharm-na.com

Sponsor's Authorized Representative	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]

4. Correct the name of the Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study listed in Appendix A from [redacted] to [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]

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

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

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

Teva Branded Pharmaceutical Products R&D, Inc 41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. [redacted]
www.tevapharm-na.com

16.6. Amendment 01 Dated 04 June 2019

The primary reason for this amendment is to specify that the suicidality assessment to be used will be the eC-SSRS in conjunction with the clinical judgment of a qualified psychiatrist. This amendment is considered to be substantial (ie, requires approval by competent authority, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Table 4 (Study Procedures and Assessments) has been revised to reflect changes described below.

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	**Clinical Study Protocol with Amendment 01**	To update for Amendment 01
© ~~2018~~2019 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	© 2019 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	Correction
FOOTER PAGE 1 (Other sections affected by this change: all other footers)		
Protocol Approval Date 04 Jun 2019	Protocol Approval Date 04 Jun 2019	Formatting update
COORDINATING INVESTIGATOR AGREEMENT		
Signature *Signed page is retained in the sponsor's official repository.*	**Signature** *Signed page is retained in the sponsor's official repository.*	Clarification
2. STUDY OBJECTIVES AND ENDPOINTS		
2.2. Exploratory Objective and Endpoints (Other sections affected by this change: Section 6.1.9., Section 9.5.3. and Appendix B)		
[redacted]	[redacted]	[redacted]
3. **STUDY DESIGN**		
3.1. **General Study Design and Study Schematic Diagram**		
The patient fulfills the following criteria for EM in prospectively collected baseline information during the 28-day baseline	The patient fulfills the following criteria for EM in prospectively collected	Correction to align with screening criteria

Original text with changes shown	New wording	Reason/justification for change
period: • headache occurring ≥~~4~~6 days but <15	baseline information during the 28-day baseline period: 1. headache occurring ≥4 days but <15	
3.5 Schedule of Study Procedures and Assessments		
[k] This is a required procedure for unscheduled visits. See further details in Appendix B.	[k] This is a required procedure for unscheduled visits. See further details in Appendix B.	Clarification
4. SELECTION AND WITHDRAWAL OF PATIENTS		
4.1. Patient Inclusion Criteria		
1. [Revision 1] The patient demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 24 days cumulative during the 28-day baseline period (~~85~~ 75% diary compliance).	[Revision 1] The patient demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 24 days cumulative during the 28-day baseline period (~75% diary compliance).	Adjusted compliance criteria for patient population needs
6. ASSESSMENT OF EFFICACY		
6.1. Assessments of Efficacy		
6.1.1. Electronic Headache Diary		
Approximately ~~85~~ 75% compliance is needed after the randomization period. Site personnel will monitor patient's compliance that approximately ~~85~~ 75% diary entry is met during the double-blind treatment phase and open-label extension phase.	Approximately 75% compliance is needed after the randomization period. Site personnel will monitor patient's compliance that approximately 75% diary entry is met during the double-blind treatment phase and open-label extension phase.	Adjusted compliance criteria for patient population needs
6.1.9. Work Productivity and Activity Impairment Questionnaire General Health V2.0 (Other sections affected by this change: Section 15.)		
~~Patients will complete the WPAI-MIGRAINE V2.0 at the time points detailed in Table 4. The WPAI-MIGRAINE questionnaire is used to assess the effect of headache on a patient's ability to work and perform regular activities.~~ The generic version of the WPAI questionnaire measures the overall effect of health on productivity at work and daily activities. The specific health problems version of the WPAI questionnaire allows investigators to	The generic version of the WPAI questionnaire measures the overall effect of health on productivity at work and daily activities. The specific health problems version of the WPAI questionnaire allows investigators to attribute productivity and activity impairment issues to specific health conditions. After the employment status of a respondent is identified, 3 open ended questions are asked	To select an equivalent tool with more available languages

Original text with changes shown	New wording	Reason/justification for change
attribute productivity and activity impairment issues to specific health conditions. After the employment status of a respondent is identified, 3 open ended questions are asked concerning (1) hours absent from work due to health problems (or specific condition), (2) hours absent from work due to other reasons, and (3) hours actually worked. Two additional questions are included that ask about the impact of health on productivity, 1 concerning productivity at work and the other concerning daily activities outside of work. The response format of each item of the WPAI questionnaire consists of an 11-point scale ranging from 0 (no impairment) to 10 (complete impairment) (Reilly, 1993). Patients will complete the WPAI questionnaire at the time points detailed in Table 4.	concerning (1) hours absent from work due to health problems (or specific condition), (2) hours absent from work due to other reasons, and (3) hours actually worked. Two additional questions are included that ask about the impact of health on productivity, 1 concerning productivity at work and the other concerning daily activities outside of work. The response format of each item of the WPAI questionnaire consists of an 11-point scale ranging from 0 (no impairment) to 10 (complete impairment) (Reilly, 1993). Patients will complete the WPAI questionnaire at the time points detailed in Table 4.	
7. ASSESSMENT OF SAFETY		
7.8. Electronic Columbia-Suicide Severity Rating Scale (Other sections affected by this change: Section 2.1., Section 9.7., Section 15., and Appendix B)		
7.8. Electronic Columbia-Suicide Severity Rating Scale~~Assessment of Suicidality~~	**7.8. Electronic Columbia-Suicide Severity Rating Scale**	To specify which tool to use in addition to clinical judgment of qualified psychiatrist
~~Suicidality will be assessed a~~As part of the overall safety evaluation~~, which will be assessed at the timepoints indicated in Table 4.~~ the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (Posner et al, 2011) will be used in conjunction with a qualified psychiatrist's clinical judgment to assess the patient's suicidal ideation (severity and intensity) and behavior. The eC-SSRS Lifetime version will be completed by the patient at visit 1, and the eC-SSRS Since Last Visit version will be completed by the patient at all other time points, as described in Table 4 Any positive findings on the eC-SSRS Since Last Visit version require evaluation by a qualified psychiatrist ~~A qualified psychiatrist will assess the patients. Any positive findings in the assessment require evaluation by a physician or doctoral level psychologist~~ for potential exclusion and/or discontinuation from the study.	As part of the overall safety evaluation the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (Posner et al, 2011) will be used in conjunction with a qualified psychiatrist's clinical judgment to assess the patient's suicidal ideation (severity and intensity) and behavior. The eC-SSRS Lifetime version will be completed by the patient at visit 1, and the eC-SSRS Since Last Visit version will be completed by the patient at all other time points, as described in Table 4. Any positive findings on the eC-SSRS Since Last Visit version require evaluation by a qualified psychiatrist for potential exclusion and/or discontinuation from the study.	To specify which tool to use in addition to clinical judgment of qualified psychiatrist

Original text with changes shown	New wording	Reason/justification for change
APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
(Other sections affected by this change: Section 2.1., 2.2., 3.1., 3.3., 4.1., 4.2., 5.7., 5.9., 7.1.2., 7.4.1., 9.5.1. to 9.5.3., 9.5.4.1, and 9.5.4.3.)		
1. Procedures for Screening (Visit 1, Days -28 to -1 ~~[+3 day window]~~)	**1. Procedures for Screening (Visit 1, Days -28 to -1)**	Correction
3. Procedures During Administration of Investigational Medicinal Product (Visit 3, Day 29 ~~+~~±3 days) (Double-Blind Treatment Phase)	**3. Procedures During Administration of Investigational Medicinal Product (Visit 3, Day 29 ±3 days) (Double-Blind Treatment Phase)**	Correction
4. Procedures During Administration of Investigational Medicinal Product (Visit 4, Day 57 ~~+~~±3 days) (Double-Blind Treatment Phase)	**4. Procedures During Administration of Investigational Medicinal Product (Visit 4, Day 57 ±3 days) (Double-Blind Treatment Phase)**	Correction
Open-Label Extension Phase (Visit 5, Day 85 ~~+~~±3 days)	**Open-Label Extension Phase (Visit 5, Day 85 ±3 days)**	Correction
Follow-up/End of Treatment/Early Termination (Visit 6, Day 169 ~~+~~±3 days)	**Follow-up/End of Treatment/Early Termination (Visit 6, Day 169 ±3 days)**	Correction

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Cell: [redacted]
Legal Representative of the Sponsor in the EU and Contact Person	[redacted] Merckle GmbH 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] and [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 Pharmaceutical Industries Ltd. Tel: [redacted] Cell: [redacted]
Contract Research Organization	Pharmaceutical Research Associates, Inc. 4130 Parklake Avenue Suite 400 Raleigh, North Carolina 27612 USA
Central Clinical Laboratory	PPD Global Central Laboratories 2 Tesseneer Drive Highland Heights, KY 41076

Central Electrocardiogram Evaluation	eResearchTechnology, Inc. 1818 Market Street Suite 1000 Philadelphia, PA 19103 USA
Bioanalytical Pharmacokinetics Evaluation	Not applicable
Bioanalytical Immunogenicity Evaluation	Not applicable
Pharmacogenomics/Biomarker Evaluation	Not applicable
Interactive response technology vendor	Parexel House, Castle Wharf, 4 Canal St. Nottingham NG1 7Eh

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

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

The screening visit (V1) 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 before any study-related procedures are performed
- review inclusion and exclusion criteria
- review medical and psychiatric history
- record demographic characteristics
- review prior medications and treatment history
- perform full physical examination (including height and weight)
- perform 12-lead electrocardiogram (ECG)
- perform vital signs measurements
- perform safety laboratory assessments
- perform serum beta-human chorionic gonadotropin (β-HCG) pregnancy test (for women of child-bearing potential and women thought to be postmenopausal) at the screening visit (V1) and follicle-stimulating hormone test (for women thought to be postmenopausal)
- inform patients of study restrictions and compliance requirements
- complete Mini Mental State Examination
- complete Patient Health Questionnaire-9 (PHQ-9)
- complete the eC-SSRS Lifetime version (used in conjunction with qualified clinician's clinical judgment to assess the patient's suicidal ideation [severity and intensity] and behavior)
- provide electronic headache diary
- complete electronic headache diary entries
- perform adverse events and health care resource utilization inquiry
- perform concomitant medication and therapy inquiry

2. **Procedures Before Administration of Investigational Medicinal Product(s) (Randomization [Visit 2, Day 1 +3 days]) (Double-Blind Treatment Phase)**

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

The following procedures will be performed at visit 2:

- review inclusion and exclusion criteria
- assign randomization/treatment numbers and enter in the electronic case report form (eCRF)
- perform physical examination
- perform 12-lead ECG
- perform vital signs measurement
- perform safety laboratory assessments
- perform urine β-HCG pregnancy test (for women of child-bearing potential)
- review study compliance
- complete the eC-SSRS Since Last Visit version (used in conjunction with qualified clinician's clinical judgment to assess the patient's suicidal ideation [severity and intensity] and behavior)
- complete Hamilton Depression Rating Scale-17 items (HAM-D 17) (qualified staff member to administer and record)
- complete Hamilton Anxiety Scale (HAM-A) (qualified staff member to administer and record)
- complete 6-item Headache Impact Test (HIT-6)
- complete Clinical Global Impression-Severity (CGI-S)
- complete Migraine-Specific Quality of Life (MSQoL)
- complete Work Productivity and Activity Impairment Questionnaire General Health (WPAI-GH)
- complete electronic headache diary
- review electronic headache diary
- perform adverse events and health care resource utilization inquiry
- dispense investigational medicinal product (IMP)
- patient self-administration of IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication and therapy inquiry

3. **Procedures During Administration of Investigational Medicinal Product (Visit 3, Day 29 ±3 days) (Double-Blind Treatment Phase)**

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

- perform physical examination
- perform 12-lead ECG
- perform vital signs measurement
- perform safety laboratory assessments
- perform urine β-HCG pregnancy test (for women of child-bearing potential)
- review study compliance
- complete PHQ-9
- complete the eC-SSRS Since Last Visit version (used in conjunction with qualified clinician's clinical judgment to assess the patient's suicidal ideation [severity and intensity] and behavior)
- complete HAM-D 17 (qualified staff member to administer and record)
- complete HAM-A (qualified staff member to administer and record)
- complete HIT-6
- complete CGI-S
- complete MSQoL
- complete WPAI-GH
- complete electronic headache diary
- review electronic headache diary
- perform adverse events and health care resource utilization inquiry
- dispense IMP
- patient self-administration of IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication and therapy inquiry

4. **Procedures During Administration of Investigational Medicinal Product (Visit 4, Day 57 ±3 days) (Double-Blind Treatment Phase)**

The following procedures/assessments will be performed at visit 4:

- perform physical examination
- perform 12-lead ECG
- perform vital signs measurement

- perform safety laboratory assessments
- perform urine β-HCG pregnancy test (for women of child-bearing potential)
- review study compliance
- complete PHQ-9
- complete the eC-SSRS Since Last Visit version (used in conjunction with qualified clinician's clinical judgment to assess the patient's suicidal ideation [severity and intensity] and behavior)
- complete HAM-D 17 (qualified staff member to administer and record)
- complete HAM-A (qualified staff member to administer and record)
- complete HIT-6
- complete CGI-S
- complete MSQoL
- complete WPAI-GH
- complete electronic headache diary
- review electronic headache diary
- perform adverse events and health care resource utilization inquiry
- dispense IMP
- patient self-administration of IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication and therapy inquiry

5. **Open-Label Extension Phase (Visit 5, Day 85 ±3 days)**

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

- perform physical examination
- perform 12-lead electrocardiogram
- perform vital signs measurement
- perform safety laboratory assessments
- perform urine β-HCG pregnancy test (for women of child-bearing potential)
- review study compliance
- complete PHQ-9
- complete the eC-SSRS Since Last Visit version (used in conjunction with qualified clinician's clinical judgment to assess the patient's suicidal ideation [severity and intensity] and behavior)

- complete HAM-D 17 (qualified staff member to administer and record)
- complete HAM-A (qualified staff member to administer and record)
- complete HIT-6
- complete CGI-S
- complete MSQoL
- complete WPAI-GH
- complete electronic headache diary
- review electronic headache diary
- perform adverse events and health care resource utilization inquiry
- dispense of IMP
- patient self-administration of IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication and therapy inquiry

6. **Follow-up/End of Treatment/Early Termination (Visit 6, Day 169 ±3 days)**

The following procedures and assessments will be performed at the follow-up visit 6 or during the early termination visit:

- perform physical examination
- perform 12-lead electrocardiogram
- perform vital signs measurement
- perform safety laboratory assessments
- perform urine β-HCG pregnancy test (for women of child-bearing potential)
- review study compliance
- complete PHQ-9
- complete the eC-SSRS Since Last Visit version (used in conjunction with qualified clinician's clinical judgment to assess the patient's suicidal ideation [severity and intensity] and behavior)
- complete HAM-D 17 (qualified staff member to administer and record)
- complete HAM-A (qualified staff member to administer and record)
- complete HIT-6
- complete CGI-S
- complete MSQoL

- complete WPAI-GH
- complete electronic headache diary
- review electronic headache diary
- return headache diary device
- perform adverse events and health care resource utilization inquiry
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication and therapy inquiry

In the case of early termination, site personnel should perform a follow-up phone call to ensure the patient does not report suicidal ideation or behavior. Phone calls should be performed once weekly for 2 weeks. If signs of suicidality are identified during the follow-up phone call, the site personnel should provide direction to the patient for further psychiatric evaluation at the site or at a community psychiatrist referenced by the site. Relevant emergency psychiatric care services should be notified in the event that the patient is deemed to be a threat to themself.

7. **Unscheduled Visits**

An unscheduled visit may be performed at any time during the study (ie, pre-treatment, double-blind treatment phase, open-label extension, and follow-up period) at the patient's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the eCRF as well as any other data obtained from procedures and assessments.

Procedures performed during unscheduled visits include the following:

- review study compliance
- review electronic headache diary
- perform adverse event and health care resource utilization inquiry
- perform concomitant medication and therapy inquiry

Other procedures and assessments may be performed at the discretion of the investigator and should be documented in the eCRF.

APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

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

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 IMP administration; and use of prohibited medications. Important protocol deviations will be identified and recorded by investigational center personnel on the electronic case report form (eCRF). All important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important protocol deviation is reported, the sponsor will determine whether to 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 investigational center personnel learn that a patient who did not meet the 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 procedures, 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 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 will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (case report forms and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

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

Audit and Inspection

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

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

APPENDIX D. ETHICS

Informed Consent

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

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

For COVID-19 updates, see Appendix P.

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

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

Confidentiality Regarding Study Patients

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

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

Registration of the Clinical Study

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

APPENDIX E. BIRTH CONTROL METHODS AND PREGNANCY TESTING

Contraception recommendations and pregnancy testing should encompass all IMPs as well as non-investigational medicinal products, eg, background therapy, and the measures to be followed should be based on the medicinal product with highest risk.

Assessment of likelihood of possible interaction between investigational medicinal product (IMP) or concomitant medications and hormonal contraception should be conducted. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method, eg, cytochrome P450 (CYP) 4A inducers.

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

In addition, fremanezumab is not expected to indirectly influence the CYP enzymes. In general, protein products that are cytokine modulators have been reported to affect the metabolism or disposition of co-administered medication by altering CYP enzymes/transporters. Fremanezumab is an immunoglobulin G2 isotype that is directed against a non-immunologic and soluble (not cell bound) target. Thus, the risk of cytokine release is considered to be low in the clinical setting. Furthermore, fremanezumab was tested for stimulation of pro-inflammatory cytokine release in human whole blood (Study 111320). Fremanezumab did not elicit significant cytokine release (tumor necrosis factor-α, interleukin-6, interferon-γ, or interleukin-1β) in any donor including at concentrations up to 100 µg/mL. As such, there is no reason to suspect that fremanezumab may influence CYP activity.

Women of non-child-bearing potential are defined as:

- Surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- Postmenopausal

Postmenopausal women:

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

Description of different birth control methods

Highly effective birth control methods:

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

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP
- Progestogen-only hormonal contraception (oral, injectable, or implantable) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP
- Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before the screening visit (V1).
- Bilateral tubal occlusion
- 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, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

Male contraception

Male patients must always use a condom including vasectomized men if their partners are of child-bearing potential.

Vasectomy:

Use of contraceptive methods also applies to vasectomized men.

Pregnant female partners of male study participants:

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

APPENDIX F. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and 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 documented attempts via 2 different methods [telephone, text, email, certified letter, etc]). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of "lost to follow-up."

APPENDIX G. PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR 30% OF THE STUDY POPULATION AND ANTI-DEPRESSANT MEDICATIONS ALLOWED FOR THE WHOLE STUDY POPULATION FOR THE DURATION OF THE STUDY

The use of up to 1 preventive migraine medication is allowed for the duration of the study for up to 30% of the total population of patients (see Section 5.7).

Preventive migraine medications allowed for the duration of the study specifically include the following (if they were previously prescribed for migraine or for another indication):

- beta-blockers: atenolol, propranolol, metoprolol, nadolol, and timolol
- calcium channel blockers/benzocycloheptenes: flunarizine and pizotifen
- antidepressants: amitriptyline, venlafaxine, nortriptyline, and duloxetine
- anti-epileptic medications: topiramate, valproate, and divalproate

Patients are not permitted to use onabotulinumtoxinA for any indication for the duration of the study.

Antidepressant medications allowed for the whole study population for the duration of the study specifically include the following (if they were previously prescribed for depression or for another indication):

- selective serotonin reuptake inhibitors
  - fluoxetine
  - paroxetine
  - sertraline
  - citalopram
  - fluvoxamine
  - escitalopram
- serotonin and norepinephrine reuptake inhibitors
  - venlafaxine
  - duloxetine
  - desvenlafaxine
  - milnacipran
  - levomilnacipran
- tricyclic antidepressants
  - amitriptyline

  - desipramine
  - amoxapine
  - clomipramine
  - nortriptyline
  - imipramine
  - protriptyline
  - trimipramine
  - doxepin
- atypical antidepressants
  - bupropion
  - mirtazapine
  - trazodone
  - vortioxetine
  - vilazodone
  - fluoxetine and olanzapine

Mayo Clinic. Antidepressants: Selecting one that's right for you. Available at: https://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20046273. Updated November 17, 2017. Accessed February 22, 2019.

APPENDIX H. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

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

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

1. acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b. reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
    a. involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    c. reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
    d. persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. reduced blood pressure after exposure to *known allergen for that patient* (minutes to several hours):
    a. adults: systolic blood pressure of <90 mm Hg or >30% decrease from that person's baseline

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

APPENDIX I. ICHD-3 DIAGNOSTIC CRITERIA

For further details, refer to IHS, 2013.

Migraine without Aura

a. at least 5 attacks fulfilling criteria B through D
b. headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)
c. headache has at least 2 of the following 4 characteristics:
   - unilateral location
   - pulsating quality
   - moderate or severe pain intensity
   - aggravation by, or causing avoidance of, routine physical activity (eg, walking or climbing stairs)
d. during headache, at least one of the following:
   - nausea and/or vomiting
   - photophobia and phonophobia
e. not better accounted for by another International Classification of Headache Disorders, 3rd revision (ICHD-3) criteria diagnosis

Migraine with Aura

a. at least 2 attacks fulfilling criteria B and C
b. one or more of the following fully reversible aura symptoms:
   - visual
   - sensory
   - speech and/or language
   - motor
   - brainstem
   - retinal
c. at least 2 of the following 4 characteristics:
   - at least 1 aura symptom spreads gradually over ≥5 minutes, and/or 2 or more symptoms occur in succession
   - each individual aura symptom lasts 5 to 60 minutes
   - at least 1 aura symptom is unilateral
   - the aura is accompanied, or followed within 60 minutes, by headache not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

APPENDIX J. TOTAL BLOOD VOLUME

Total blood volume to be collected for each patient in this study is approximately 64.2 mL.

Total Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Serum chemistry, hematology, coagulation, serum β-HCG test[a] and FSH[b]	10.7	1	10.7
Serum chemistry, hematology, and coagulation	10.7	5	53.5
Total		**6**	**64.2**

[a] A serum pregnancy test will be performed for women of child-bearing potential and women thought to be postmenopausal at the screening visit (V1).
[b] An FSH test will be performed only for women thought to be postmenopausal at the screening visit (V1).
β-HCG = beta-human chorionic gonadotropin; FSH = follicle stimulating hormone.

APPENDIX K. PRODUCT COMPLAINTS

Clinical Product Complaints

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

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

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

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

1. Product Complaint Information Needed from the Investigational Center

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

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

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

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

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

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

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

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

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

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

4. **Documenting a Product Complaint**

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

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

APPENDIX 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 electronic case report form (eCRF). Data may not be recorded directly on the eCRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the eCRF.

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 eCRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, Independent Ethics Committee/Institutional Review Board (IEC/IRB), and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, 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 case report forms (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 (United States of America) 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 eCRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, electronic patient-reported outcome tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the eCRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the eCRF. Data may not be recorded directly on the eCRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the eCRF.

For patients who enter a study but do not meet the 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 eCRF.

Data Quality Control

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

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

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

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

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

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

Investigator Responsibilities

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

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

- reports of receipt, use, and disposal 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 the sponsor has not provided written notification of destruction, then the investigator may submit a written request to the sponsor at least 60 days before any planned disposal of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposal, 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:

- 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. CLINICAL LABORATORY TESTS

Table 7 provides the clinical laboratory assessments to be performed in the study.

Table 7: Clinical Laboratory Tests

Serum Chemistry	Hematology and Coagulation	Urinalysis
Calcium	Hemoglobin	Protein
Phosphate	Hematocrit	Glucose
Sodium	Erythrocytes	Ketones
Potassium	Platelets	Hemoglobin
Chloride	Leucocytes	pH
Creatinine	– Neutrophils	Specific gravity
Glucose	– Lymphocytes	Microscopic tests
BUN	– Eosinophils	– Bacteria
LDL	– Monocytes	– Erythrocytes
HDL	– Basophils	– Leucocytes
Triglycerides	Lymphocytes atypical	– Crystals
Urate	Prothrombin INR	– Casts
ALT		
AST		
LDH		
GGT		
Alkaline phosphatase		
Bicarbonate		
Carbon dioxide		
Protein		
Albumin		
Bilirubin		
Direct bilirubin		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyl transpeptidase; HDL = high density lipoprotein; INR = International Normalized Ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein.

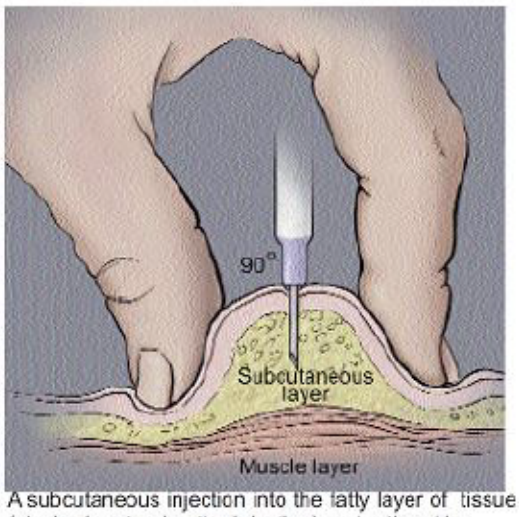
APPENDIX O. INJECTION INSTRUCTIONS

Patient Education Clinical Center NATIONAL INSTITUTES OF HEALTH

Giving a subcutaneous injection

What is a subcutaneous injection?

A subcutaneous injection is given in the fatty layer of tissue just under the skin.



A subcutaneous injection into the fatty layer of tissue (pinched up to give the injection) under the skin.

Why are subcutaneous injections given?

These injections are given because there is little blood flow to fatty tissue, and the injected medication is generally absorbed more slowly, sometimes over 24 hours. Some medications that can be injected subcutaneously are growth hormone, insulin, epinephrine, and other substances.

Preparing to give medication

Subcutaneous injections are not given if the skin is burned, hardened,inflamed, swollen, or damaged by a previous injection.

1. Wash your hands thoroughly. This is the best way to prevent infection.
2. Assemble your equipment:

Medication

- May be a multidose vial of liquid or may be a vial with powder that requires "reconstitution." Follow the manufacturer's instructions as to what and how much diluent to use. The diluent is usually saline (a mixture of salt water) or sterile water.

Syringe or pen and needle

Depending on the amount of medication to be given and the size of the child or adult:

- 0.5 cc,1.0 cc, or 2 cc with 27-gauge needle (5/8 of an inch long)
- 3-cc luer lock syringe—used when solution is more than 1 cc
- 25-gauge needle (5/8 of an inch long or 27-gauge needle (5/8 of an inch long)
- 0.3 mL insulin syringes with 31-gauge needles (3/16 to 5/16 inches long) are available for those who are visually impaired or for those who need very small doses of medication.
- medication log
- container for syringe disposal
- sterile 2 x 2-inch gauze pad
- alcohol pads

Drawing up medication

1. Check the label for correct medication.
2. Remove the soft metal or plastic cap protecting the rubber stopper of the vial.
3. If the medication vial or pen can be used for more than one dose, record the date and time on the label.

4. Clean the exposed rubber stopper using an alcohol swab.
5. Remove the syringe from the plastic or paper cover. If necessary, attach the needle securely.
6. Pull back and forth on the plunger by grasping the plunger handle. Grasping the handle end will prevent contamination of the plunger shaft (which is sterile).
7. With the needle capped, pull back the plunger, filling the syringe with air equal to the amount of medication to be administered.
8. Remove the cap covering the needle and set it on its side to prevent contamination. Be careful not to touch the needle. The inside of the cap and needle is sterile, and the needle will be covered again with this cap.
9. With the vial in an up-right position, push the needle through the cleansed rubber stopper on the vial. Push the needle in at a 90 degree angle, being careful not to bend the needle.
10. Inject the air in the syringe into the vial. Air is injected into a multi-dose vial to prevent a vacuum from forming. If too little or no air is injected, withdrawing the medication may be difficult. If too much air is injected, the plunger may be forced out of the barrel causing the medication to spill.
11. Turn the vial upside down, with the needle remaining in the vial. The needle will be pointing upward.
12. Make sure that the tip of the needle is completely covered by the medication. This will make it easier to withdraw the solution (and not air).
13. Pull back on the plunger to fill the syringe with the correct dose of medication.
14. Keep the vial upside down, with the needle in the vial pointed upward. Tap the syringe, or "flick" it with your fingertips. This helps move bubbles to the top of the syringe.
15. Once the bubbles are at the top of the syringe, gently push on the plunger to force the bubbles out of the syringe and back into the vial.

    Or, you may push all the medication solution back into the vial, withdraw again slowly, and repeat steps 14 and 15.

    Note: It is important to eliminate large air bubbles because they take up space needed for the medication, and they may cause pain or discomfort when injected.
16. After removing the bubbles, check the dose of medication in the syringe to be sure you have drawn up the correct amount.

If using a pen, skip steps 5 to 16. Do the following:

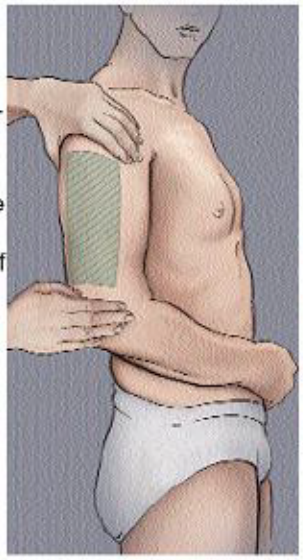
a. Attach needle to pen by cleaning the top with alcohol and screwing on the needle.
b. Dial in your prime volume (usually 0.02 mL) using the manufacturer's directions.
c. With pen needle pointed up, push the injection button completely. You should see a drop or stream of liquid. If you do not, repeat priming steps until this occurs.
d. Dial in prescribed dose of medication.

17. After the medication is correctly drawn up, carefully replace the needle cap to prevent contamination.

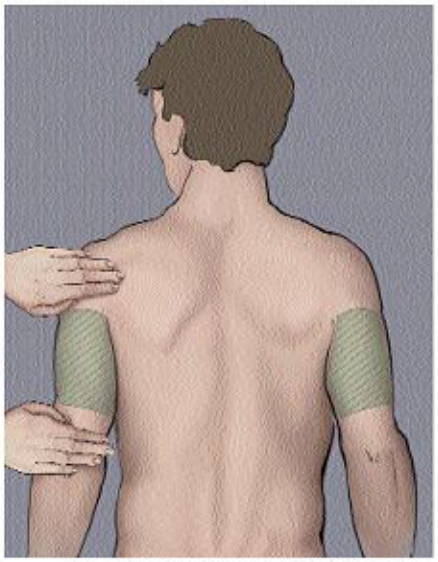
Locating injection sites

Subcutaneous injections can be given in the arms, legs, or abdomen. Your nurse or doctor will help you select the best sites to administer your medication.

1. To locate injection sites on the arms, fold one arm across the chest. Place your hand on the shoulder and draw an imaginary line below your hand. Place another hand on the elbow..Draw an imaginary line down the outer side of the arm and down the center front of the arm, starting at the elbow. The area inside these imaginary lines is where injections are given. (If you are injecting imagine the hand placement.)

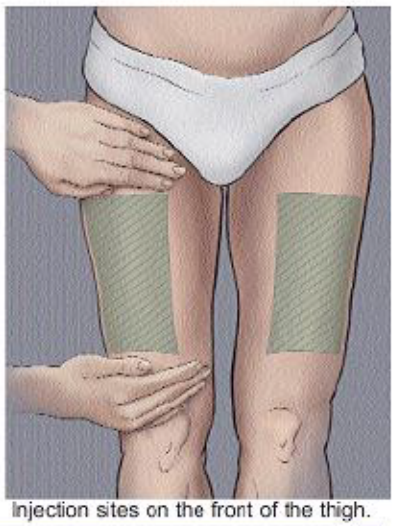


Injection sites on the side of the arm.



Injection sites on the back of the arm.

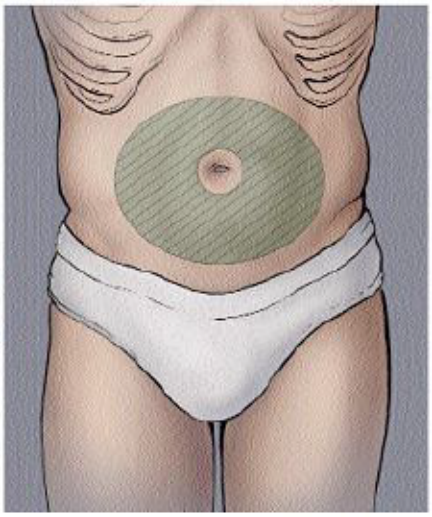
2. To locate injection sites on the thighs, sit down, place your hand above the knee, and draw an imaginary line above it. Place your hand at the uppermost part of the thigh and draw an imaginary line below your hand. Draw an imaginary line down the outer side of the leg and down the center front of the leg. The area within these imaginary lines is where injections may be given.
3. To locate injection sites on the abdomen, place your hands on the lower ribs and draw an imaginary line them. Use this area below your hands for injections, as far around as you can pinch up fatty tissue. use a 1-inch area around the navel.



Injection sites on the front of the thigh.

Rotating injection sites

It is extremely important to rotate sites to keep the skin healthy. Repeated injections in the same spot can cause scarring and hardening of fatty tissue that will interfere with absorption of medication. Each injection should be about 1 inch apart. Each injection site can be measured with a small dot Band-Aid, providing the patient is not sensitive to the adhesive. Start injections at the highest point of the area and continue down toward the point farthest away from the body (for example, upper arm down toward elbow). It is preferable to use all sites available on one body part (arm or leg) before moving on to another. However, some parents find that children are more accepting of injections if they are rotated from one body part to another (arm, leg, arm, leg). Avoid giving injections in areas that are burned, reddened, inflamed, swollen, or damaged by prior injections.



Injection sites on the abdomen

Preparing the skin

Since the skin is the body's first defense against infection, it must be cleansed thoroughly before a needle is inserted.

Cleanse the skin with a back-and-forth motion using an alcohol swab. This motion moves bacteria away from the injection site. Allow the alcohol to dry completely by air.

Giving the injection

1. Take the cover off the needle. Be careful not to contaminate the needle. Place the cover on its side.
2. Hold the syringe in one hand like pencil or a dart.
3. Grasp the skin between the thumb and index finger with your other hand and pinch up.
4. Quickly thrust the needle all the way into the skin. Do not "push" the needle into the skin slowly or thrust the needle into the skin with great force.

Do not press down on the top of the plunger while piercing the skin.

5. Insert the needle at a 90-degree (right) angle. This angle is important to ensure that the medications will be injected into the fatty tissue. However, for small children, and persons with little subcutaneous fat on thin skin, you may be taught to use a 45-degree angle.

   If using a pen, insert the pen needle at a 90-degree angle.

6. After the needle is completely inserted into the skin, release the skin that you are grasping.

   Press down on the plunger to release medication into the subcutaneous layer in a slow, steady pace.

   If using a pen, press the injection button completely (or until it clicks). Count 10 seconds before removing the needle from the skin.

7. As the needle is pulled out of the skin, gently press a 2 x 2 gauze onto the needle insertion site. Pressure over the site while removing the needle prevents skin from pulling back, which may be uncomfortable. The gauze also helps seal the punctured tissue and prevents leakage.

8. If instructed to do so, press or rub the site for a few seconds.

9. It is not serious if you notice blood at the site after the needle is removed. You may have nicked a surface blood vessel when you injected, and blood is following the needle track out to the surface. Simply press the site with a 2 x 2 gauze pad. Also, a small amount of clear fluid may appear at the site. This may be medication that is following the needle track to the surface. Again, apply pressure using a 2 x 2 gauze pad.

   If using a pen:
   Untwist needle on the pen and safely dispose the needle. Replace pen cap and store as instructed.

Safe needle disposal

Please refer to the Clinical Center pamphlet "Handling Sharp Objects Safely at Home."

- Place the syringe or needle in a hard plastic or metal container with a tightly secured lid.
- Do not re-cap needles after use. Keep the container out of the reach of children or pets.
- When the container is three-quarters full, take it to a health care facility (hospital or doctor's office) for proper disposal. If you live within driving distance of NIH, you can bring your container to NIH for proper disposal.

Medication
Dose
Schedule
Primary Nurse Phone
Physician Phone

This information is prepared specifically for persons taking part in clinical research at the National Institutes of Health Clinical Center and may not apply to patients elsewhere. If you have questions about the information presented here, talk to a member of your health care team.

Products/resources named serve as examples and do not imply endorsement by NIH. The fact that a certain product/resource is not named does not imply that such product/resource is unsatisfactory.

National Institutes of Health Clinical Center
Bethesda, MD 20892

Questions about the Clinical Center?
http://www.cc.nih.gov/comments.shtml

6/2012

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APPENDIX P. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19

This appendix is to address the modifications in study conduct during the Coronavirus disease 2019 (COVID-19) pandemic.

The changes specified in this appendix will be effective for the duration of the COVID-19 pandemic. Once the pandemic resolves and centers/countries are able to resume normal functioning, this appendix will become void.

The following sections are affected:

Section 3.5 Schedule of Study Procedures and Assessments (Table 4)

Home visits are permitted for patients who are not able to go to the investigational center for their visit(s) or if the investigational center staff are not able to see patients at the investigational center due to the COVID-19 pandemic. Home visits must be completed by the principal investigator or a subinvestigator and may also include trained study staff (ie, a medically qualified person designated by the investigator or a home care service provider for certain assessments), as required, to complete all visit assessments/procedures.

Visits should be conducted in accordance with the timelines specified in the protocol (see Table 4).

Appendix D. Ethics

For home visits, a verbal consent process will be applied for each patient prior to the home visit and will follow written informed consent as per local regulations before any study procedures or assessments are performed.