

Clinical Study Protocol with Amendment 01

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients with Inadequate Response to Prior Preventive Treatments

Study Number TV48125-CNS-30068

NCT03308968

Protocol with Amendment 01 Approval Date: 23 October 2017

Clinical Study Protocol Amendment 01

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A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients with Inadequate Response to Prior Preventive Treatments

A Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Period on Efficacy and Safety of Fremanezumab in Adults with Migraine

A Study to Test if Fremanezumab is Effective in Preventing Migraine in Patients Who Did Not Respond to Prior Preventive Migraine Treatments

Efficacy and Safety Study (Phase 3)

IND number: 106,533; NDA number: Not applicable; BLA number: Not applicable;

EudraCT number: 2017-002441-30

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Protocol Approval Date: 27 July 2017

Protocol with Amendment 1 Approval Date: 23 October 2017

Sponsor

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

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

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).

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AMENDMENT HISTORY

The protocol for study TV48125-CNS-30068 (original protocol dated 27 July 2017) has been amended and reissued as follows:

Amendment 01	23 October 2017 0 patients randomized/enrolled to date
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The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section [16](#).

INVESTIGATOR AGREEMENT

Original Protocol Dated 27 July 2017

Clinical Study Protocol with Amendment 01

**IND number: 106,533; NDA number: Not applicable; BLA number: Not applicable;
EudraCT number: 2017-002441-30**

EMA Decision number of Pediatric Investigation Plan: not applicable

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**A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with
an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the
Prophylactic Treatment of Migraine in Patients with Inadequate Response to Prior
Preventive Treatments**

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

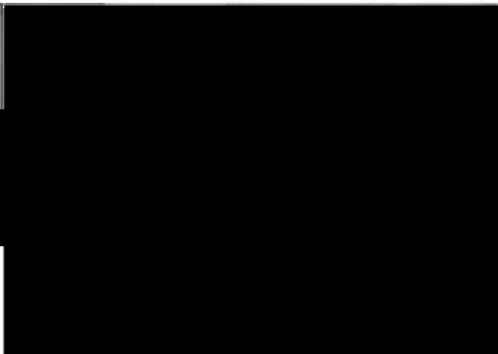

Tel: _____

I have read the protocol with Amendment 01 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

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

Principal Investigator	Signature	Date

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative		Date
		10.23.2017

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 27 July 20017

Clinical Study Protocol with Amendment 01

IND number: 106,533; NDA number: Not applicable; BLA number: Not applicable;
EudraCT number: 2017-002441-30

EMA Decision number of Pediatric Investigation Plan: not applicable

Article 45 or 46 of 1901/2006 does not apply

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients with Inadequate Response to Prior Preventive Treatments

I have read the protocol with Amendment 01 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]

The Netherlands

[Redacted]

Coordinating Investigator
[Redacted]

[Redacted]

Date
24/10/2017

CLINICAL STUDY PROTOCOL SYNOPSIS

with Amendment 01

Study TV48125-CNS-30068

Title of Study: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Study with an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients with Inadequate Response to Prior Preventive Treatments

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

Investigational New Drug (IND) Number: 106,533

New Drug Application (NDA) Number: Not Applicable

Biological License Application (BLA) Number: Not Applicable

EudraCT Number: 2017-002441-30

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

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

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

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

Indication: Fremanezumab is intended for migraine prophylaxis

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

Number of Investigational Centers Planned: The study is planned to be conducted in approximately 120 investigational centers.

Countries Planned: The study is planned to be conducted in approximately 15 countries.

Planned Study Period: 4Q 2017 to 4Q 2019

Number of Patients Planned (total): Approximately 804 patients (268 patients per treatment group)

Study Population: The study population will be composed of male and female patients, aged 18 to 70 years, inclusive, with a history of migraine (as defined by International Classification of Headache Disorders, 3rd revision [ICHD-3] criteria [[IHS 2013](#)]) for at least 12 months prior to screening and diagnosis of episodic migraine (EM) or chronic migraine (CM) prospectively documented via a review of headache data recorded daily in an electronic headache diary device during a 28-day run-in period.

At the time of screening, patients must have documented inadequate response to 2 to 4 classes of prior preventive migraine medications (as defined in [Appendix H](#)) within the past 10 years (in medical chart or by treating physician's confirmation, see [Appendix I](#) for acceptable documentation of previous treatment failure).

A subset of these patients (at least 120 patients) must have documented inadequate response to 2 to 3 classes of prior preventive medications (as defined in [Appendix H](#)) and in addition inadequate response to valproic acid. All inadequate responses must be within the past 10 years

(in medical chart or by treating physician’s confirmation; see [Appendix I](#) for acceptable documentation of previous treatment failure).

Inadequate response to prior preventive migraine medications (including valproic acid) is defined as (see also [Appendix H](#)): no clinically meaningful improvement per treating physician’s judgment, after at least 3 months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines, or when treatment has to be interrupted because of adverse events that made it intolerable by the patient, or the medication is contraindicated or not suitable for the prophylactic treatment of migraine for the patient. The 3-month period does not apply if the drug is intolerable or contraindicated or not suitable. If onabotulinumtoxinA is the previously failed preventive medication, at least 2 sets of injections and 3 months must have passed since the last set of injections prior to the screening visit.

Primary and Secondary Objectives and Endpoints

Primary and secondary objectives and endpoints are presented in the table below.

Objectives	Endpoints
<p>The primary objective of the study is to demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous (sc) injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo</p>	<p>The primary efficacy endpoint is the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab</p>
<p>The secondary objective of the study is to further evaluate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo</p>	<p>The secondary endpoints are as follows:</p> <ul style="list-style-type: none"> • proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab • proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute

Objectives	Endpoints
	<p>headache medications during the 12-week period after the 1st dose of fremanezumab</p> <ul style="list-style-type: none"> • mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of fremanezumab
<p>A secondary objective of the study is to evaluate the safety and tolerability of fremanezumab administered as monthly and quarterly sc injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo</p>	<p>Secondary safety/tolerability endpoints:</p> <ul style="list-style-type: none"> • occurrence of adverse events throughout the study • clinical laboratory (serum chemistry, hematology, coagulation and urinalysis) test results at specified time points • vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit. Note: In addition, oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity • 12-lead ECG findings at specified time points • use of concomitant medication for adverse events during the study • number (%) of patients who did not complete the study due to adverse events • clinically significant changes in physical examinations, including body weight • occurrence of severe hypersensitivity/anaphylaxis reactions • suicidal ideations and behaviors as measured by the eC-SSRS

ECG=electrocardiogram; eC-SSRS= electronic Columbia-Suicide Severity Rating Scale; sc=subcutaneous.

Exploratory Objectives and Endpoints

The exploratory objectives are as follows:

- to further evaluate the efficacy of fremanezumab in adult migraine patients with inadequate response to 2 to 4 classes of prior preventive treatments
- to evaluate immunogenicity and impact of antidrug antibody (ADA) on clinical outcome
- to explore the correlation between pharmacokinetic parameters and efficacy of fremanezumab

- to explore the relationship between genetic polymorphisms, migraine onset/severity and efficacy and safety of fremanezumab
- to explore the relationship between soluble exploratory biomarkers versus migraine response

The exploratory endpoints for the double-blind period are as follows:

- proportion of patients reaching at least 75% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of the study drug
- proportion of patients reaching at least 50% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed valproic acid for migraine in the past

- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past
- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the 6-item Headache Impact Test (HIT-6), at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in disability score, as measured by the Migraine Disability Assessment (MIDAS) questionnaire, at 4 weeks after the administration of the 3rd dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the Migraine-Specific Quality of Life (MSQOL) questionnaire, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EuroQol-5 Dimension (EQ-5D-5L) questionnaire at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the 2 item Patient Health Questionnaire (PHQ-2) and 9-item Patient Health Questionnaire (PHQ-9), at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) of patient satisfaction, as measured by the Patient Global Impression of Change (PGIC) scale, at 4 weeks after the 3rd dose of study drug

The exploratory endpoints for the open-label period are as follows:

- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of fremanezumab

- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of study drug
- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 4th dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 4th dose of the study drug
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed valproic acid for migraine in the past

- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the HIT-6, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after the administration of the 6th dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale, at 4 weeks after the last 6th dose of study drug

The exploratory endpoints for both the double-blind and open-label periods are as follows:

- to evaluate the immunogenicity response of fremanezumab and the impact of ADAs on clinical outcomes in patients exposed to sc fremanezumab.
- to explore the relationship between genetic polymorphisms (including those within the calcitonin gene-related peptide (CGRP) receptor-ligand complex, in migraine-associated susceptibility genes, and in as-yet undiscovered loci) versus migraine onset/severity, adverse events to medication and fremanezumab efficacy
- to explore the relationship between exploratory biofluid biomarkers versus fremanezumab concentrations, adverse events and fremanezumab efficacy

General Study Design:

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, study with an open-label period to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc fremanezumab compared with placebo in patients with CM and EM with inadequate response to prior preventive treatments.

The study will consist of a screening visit, a run-in period (28 days), a 12-week double-blind, placebo-controlled treatment period, a 12-week open-label period, and a follow-up visit 6.0 months after the last dose of fremanezumab for ADA blood sample collection.

At the end of the open-label treatment period (4 weeks after the last dose) an end of treatment study visit (visit 8) will be scheduled and patients should return to the care of their treating physicians. Patients should be treated with standard of care after withdrawal from or termination of the 24-week treatment period/study, as appropriate.

Double-blind period

At the baseline visit (visit 2), patients will be randomly assigned to a treatment group with fremanezumab (2 different dose regimens) or placebo in a 1:1:1 ratio as follows:

- For patients with CM:
 - sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
 - sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of matching placebo for 2 months or
 - 3 monthly doses of matching placebo
- For patients with EM:
 - sc administration of fremanezumab at 225 mg plus 2 matching placebo injections as first dose followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
 - sc administration of fremanezumab at 675 mg as first dose followed by monthly sc administration of matching placebo for 2 months or
 - 3 monthly doses of matching placebo

Open-label period

After visit 4, all patients completing the double-blind period will enter the open-label period. All patients (CM and EM) will receive sc 225 mg of fremanezumab monthly for 3 months. (visits 5, 6, and 7).

Randomization and treatment assignment for the double-blind period will be performed using electronic interactive response technology (IRT). The study will be stratified based on CM or EM, gender, country, and a special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in [Appendix H](#). The proportion of CM and EM patients in the study should be approximately 50:50 in each subgroup.

The open-label period will not be randomized as all patients will receive the same monthly dose (225 mg fremanezumab).

CM is defined as:

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

- Headache occurring on ≥ 15 days
- On ≥ 8 days, fulfilling any of the following:
 - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura ([Appendix U](#))
 - ICHD-3 criteria B and C for 1.2 Migraine with aura ([Appendix U](#))
 - Probable migraine (a migraine subtype where only 1 migraine criterion is missing)
 - The patient used a triptan or ergot derivative 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 run-in period:

- Headache occurring ≥ 6 days but < 15
- On ≥ 4 days, fulfilling any of the following:
 - 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)
 - The patient used a triptan or ergot derivative to treat an established headache

Blinded treatment will be administered sc once a month (approximately every 28 days) for a total of 3 doses (visits 2,3, and 4) and open-label treatment will administered for a total of 3 doses. (visits 5, 6, and 7). Final study assessments will be performed at visit 8 (end-of-treatment [EOT] visit), approximately 4 weeks after administration of last dose of fremanezumab. A follow-up visit will be scheduled 6.0 months (> 5 half-lives) after the last study drug administration for ADA blood sampling. Patients who discontinue early will have the follow-up visit 6.0 months after the last dose.

The total duration of patient participation in the study is planned to be 50 weeks including a run-in period lasting 28 days, a double-blind treatment period lasting 12 weeks, an open-label period lasting 12 weeks, and 1 follow-up visit at week 46.

Patients are expected to complete the entire duration of the study, including the open-label period and the follow-up visit.

The end of study is defined as the last visit of the last patient (follow-up visit, visit 9). However, an interim database lock will occur following the end of the double-blind treatment period of the last patient for analysis of that portion of the study data. Final database lock will occur following the end of the open-label period.

The total study duration, including the 6.0-month follow-up-period, will be approximately 2 years (from approximately 4Q 2017 to 4 Q 2019).

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

The purpose of this study is to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc doses of fremanezumab compared with sc doses of placebo in patients with CM or EM who have responded inadequately to 2 to 4 classes of prior preventive treatments. A subset of patients (at least 120) must have documented inadequate response to 2 to 3 classes of prior preventive medications and in addition inadequate response to valproic acid. All inadequate responses must be within the past 10 years (in medical chart or by treating physician’s confirmation).

The study will consist of a screening visit, a run-in period (28 days), a 12-week double-blind treatment period and a 12-week open-label treatment period, which includes a last study visit 4 weeks after the last dose administration. At the end of the study, patients will return to the care of their treating physicians. A follow-up visit will be scheduled 6.0 months after the last dose for ADA blood sample collection. The total duration of patient participation in the study is planned to be 50 weeks.

During the double-blind period, patients will be randomly assigned in a 1:1:1 ratio to receive 1 of 2 fremanezumab dose regimes or placebo as follows:

- For patients with CM:
 - sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
 - sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of matching placebo for 2 months or
 - 3 monthly doses of matching placebo
- For patients with EM:
 - sc administration of fremanezumab at 225 mg plus 2 matching placebo injections as first dose followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
 - sc administration of fremanezumab at 675 mg as first dose followed by monthly sc administration of matching placebo for 2 months or
 - 3 monthly doses of matching placebo

During the open-label period, all patients (CM and EM) will receive 3 monthly sc administrations of fremanezumab at 225 mg.

Efficacy will be evaluated using information entered daily by the patients in an electronic headache diary throughout the treatment period and administration of questionnaires to evaluate headache-related disability, change in quality of life, health status, and satisfaction with treatment.

Safety of fremanezumab will be evaluated through adverse event and concomitant medication inquiries, electrocardiograms (ECGs), vital sign measurements, clinical laboratory tests, physical

examinations, injection site reaction/pain assessments, assessments for anaphylaxis and hypersensitivity, and administration of the eC-SSRS. In addition, blood will be collected for pharmacokinetics, immunogenicity, biomarker, and pharmacogenomics analyses (unless not allowed per local regulation) and urine will be collected for biomarker analysis.

Method of Randomization and Blinding:

The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients will be blinded to treatment assignment during the double-blind period. A computer-generated master randomization list will be provided to drug packaging facilities. Packaging vendor(s) will package active drug and placebo into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance and contain 1 prefilled syringe with active drug or placebo. Adequate kit supply for upcoming study visits will be managed by IRT and kept (refrigerated at 2°C to 8°C) on site.

In this randomized study, the double-blind period will be stratified based on CM or EM, gender, country, and a special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in [Appendix H](#).

Each patient will undergo randomization in a 1:1:1 ratio within the stratum to which he or she belongs to receive 1 of the 2 fremanezumab dose regimens or placebo, as assigned by the IRT. The IRT will manage initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At the time of each study visit, the IRT will be queried, and site personnel will retrieve and administer a 1.5-mL volume from each syringe contained in the appropriately numbered kit(s).

The open-label period will not be randomized as all patients will receive the same monthly dose (225 mg fremanezumab).

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

The investigational medicinal products used in the study (double-blind and open-label periods) are described in the table below.

IMP name	Test IMP	Placebo IMP
Recombinant humanized IgG2a/kappa mAb	Fremanezumab	Placebo
Trade name and INN, if applicable, or company-assigned number	Fremanezumab Known also as: TEV-48125, LBR-101, PF-04427429, RN307	Placebo

IMP name Recombinant humanized IgG2a/kappa mAb	Test IMP Fremanezumab	Placebo IMP Placebo
Formulation	Prefilled syringes contain 1.5 mL solution for injection with 150 mg/mL (ie 225 mg total) of active ingredient fremanezumab Inactive ingredients include: L-histidine, sucrose, polysorbate-80, ethylenediaminetetraacetic acid (EDTA) and water for injection	Prefilled syringes contain 1.5 mL of the same vehicle and excipients as those for active injection. Inactive ingredients include: L-histidine, sucrose, polysorbate-80, ethylenediaminetetraacetic acid (EDTA) and water for injection
Unit dose strength(s)/Dosage level(s)	225 mg/1.5 mL	None
Route of administration	sc injection	sc injection
Dosing instructions/Dosing schedule/Titration periods/Treatment periods for the <u>double-blind period</u>	For CM patients: A dose of 675 mg fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 2 and 225 mg fremanezumab as 1 active injection (225 mg/1.5 mL) at visits 3 and 4. Or a dose of 675 mg fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 2	No placebo injections Single 1.5-mL placebo injection at visits 3 and 4
	For EM patients: 225 mg fremanezumab as 1 active injection (225 mg/1.5 mL) at visit 2, 3, and 4 Or a dose of 675 mg fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 2	Two 1.5-mL placebo injections at visit 2 Single 1.5-mL placebo injection at visits 3 and 4
	For both CM and EM patients who are on treatment placebo only: No active injections	Three 1.5-mL placebo injections at visit 2 and a single 1.5-mL placebo injection at visits 3 and 4
Dosing instructions/Dosing schedule/Titration periods/Treatment periods for the <u>open-label period</u>	For all CM and EM patients: 225 mg fremanezumab as 1 active injection (225 mg/1.5 mL) at visits 5, 6, and 7	No placebo injections
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

IMP name Recombinant humanized IgG2a/kappa mAb	Test IMP Fremanezumab	Placebo IMP Placebo
Manufacturer	<p>Drug Substance: Celltrion 23, Academy-ro Yeonsu-gu, Incheon, South Korea</p> <p>Drug Product: Vetter Pharma Fertigung GmbH & Co. KG Schuetzenstrasse 87, 99-101, Ravensburg, Baden-Wuerttemberg 88212 Germany</p> <p>Vetter Pharma Fertigung GmbH & Co. KG Mooswiesen 2, Ravensburg, Baden-Wuerttemberg 88214, Germany</p>	<p>Vetter Pharma Fertigung GmbH & Co. KG Schuetzenstrasse 87, 99-101, Ravensburg, Baden-Wuerttemberg 88212 Germany</p> <p>Vetter Pharma Fertigung GmbH & Co. KG Mooswiesen 2, Ravensburg, Baden-Wuerttemberg 88214, Germany</p>

CM=chronic migraine; EDTA= ethylene diamine tetra acetate; EM=episodic migraine; IMP=Investigational Medicinal Product; INN=international nonproprietary name; mAb=monoclonal antibody; sc=subcutaneous.

The suggested sites of injection are back of upper arms, lower abdomen/belly/waistline, and front of thighs. Each of the injections during an administration 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) responsible for administration of injections should inspect previous injection sites to ensure that they are free of bruising and tenderness and that proper rotation of sites is performed.

Study drug should be removed from the refrigerator and allowed to equilibrate at room temperature for 45-60 minutes before study drug administration. A 1.5-mL volume from each 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 for each dosing visit (visits 2, 3, 4, 5, 6, and 7).

Duration of Patient Participation and Maximal Exposure to IMP:

The total duration of patient participation in the study is planned to be 50 weeks including a run-in period lasting 28 days, a double-blind treatment period lasting 12 weeks, an open-label period lasting 12 weeks and 1 follow-up visit at week 46.

For the double-blind period, the starting dose for patients with CM will be 675 mg sc and the starting dose for patients with EM will be 225 mg sc or 675 mg sc. Further doses of 225 mg or placebo will be administered sc once monthly. The maximal dose administered sc per treatment will be 675 mg. For the open-label period, all patients will receive 225 mg fremanezumab monthly.

Study Duration: 2 years (from 4Q 2017 to 4Q 2019)

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

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

At the end of the 24-week treatment period, it is expected that patients should return to the care of their treating physicians.

Patients will return to the investigational center approximately 6.0 months following administration of the last dose of IMP for safety evaluation. No treatment is planned by the sponsor after completion of the 24-week treatment period and the study. Patients should be treated with standard of care after withdrawal from or termination of the 24-week treatment period, as appropriate.

Inclusion Criteria:

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

- a. The patient is capable of giving signed informed consent.
- b. Male or female patient aged 18 to 70 years, inclusive.
- c. The patient has a diagnosis of migraine with onset at ≤ 50 years of age.
- d. The patient is in good health in the opinion of the investigators as determined by medical history, physical examination, laboratory tests, and ECG.
- e. Body weight ≥ 45 kg and body mass index (BMI) within the range 17.5 to 34.9 kg/m² (inclusive).
- f. The patient has a history of migraine (according to ICHD-3 criteria [[IHS 2013](#)]) or clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥ 12 months prior to screening.
- g. The patient fulfills the following criteria for CM or EM in prospectively collected baseline information during the 28-day run-in period:

For patients with CM:

- Headache occurring on ≥ 15 days
- On ≥ 8 days, fulfilling any of the following:
 - 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)
 - The patient used a triptan or ergot derivative to treat an established headache

For patients with EM:

- Headache occurring on ≥ 6 days but < 15
- On ≥ 4 days, fulfilling any of the following:
 - 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)
 - The patient used a triptan or ergot derivative to treat an established headache
- h. At the time of screening, the patient must have documented inadequate response to 2 to 4 classes of prior preventive migraine medications (as defined in [Appendix H](#)) within the past 10 years (in medical chart or by treating physician’s confirmation; see [Appendix I](#) for acceptable documentation of previous treatment failure). Inadequate response to prior preventive migraine medications (including valproic acid) is defined as: no clinically meaningful improvement per treating physician’s judgment, after at least 3 months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines, or when treatment has to be interrupted because of adverse events that made it intolerable for the patient, or the medication (as defined in [Appendix H](#)) is contraindicated or unsuitable for the prophylactic treatment of migraine for the patient. The 3- month period does not apply if the drug is intolerable or contraindicated. If onabotulinumtoxinA is the previous preventive medication, at least 2 sets of injections and 3 months must have passed since the last set of injections prior to the screening visit.
- i. The patient agrees not to initiate any preventive migraine medications (as defined in [Appendix H](#)) during the run-in period double-blind treatment period and open-label period. At the screening visit, at least 5 half-lives of these medications must have passed since the patient has been on any migraine preventive medication as defined in [Appendix H](#).
- j. Other prescription medications not in [Appendix H](#) must have been on stable doses for at least 2 months at the screening visit with no expectation to change during the double-blind treatment period of the study.
- k. The patient demonstrated compliance with the electronic headache diary during the run-in period by entry of headache data on a minimum of 24 days cumulative during the run-in period (~85% diary compliance).
- l. Women may be included only if they have a negative serum beta-human chorionic gonadotropin (β -HCG) test at screening, are sterile, or postmenopausal. Definitions of sterile and postmenopausal are given in [Appendix E](#).
- m. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study and the follow-up period (ie, starting at screening) and for 6.0 months after discontinuation of IMP (for details of WOCBP, sterile, and postmenopausal women, see [Appendix E](#)).
- n. Men must be sterile, or if they are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must use, together with their female partners, acceptable birth control methods for the duration of the study and for 6.0 months after discontinuation of the IMP.

- o. The patient must be willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study period and to return to the clinic for the follow-up evaluations, as specified in this protocol.

Exclusion Criteria:

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

- a. At the time of screening visit, patient is receiving any preventive migraine medications, regardless of the medical indication (as defined in [Appendix H](#)) for more than 5 days and expects to continue with these medications.
- b. 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.
- c. 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 run-in period for the treatment of migraine or for any other reason.
- d. The patient has used an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening.
- e. The patient uses triptans/ergots as preventive therapies for migraine.
- f. Patient uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (eg, 81 mg) used for cardiovascular disease prevention is allowed.
- g. The patient suffers from unremitting headaches, 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.
- h. The patient has a clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.
- i. Evidence or medical history of 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 major depression, panic disorder, or generalized anxiety disorder, any suicide attempt in the past or suicidal ideation with a specific plan the past two years prior to screening or current suicidal ideation as measured by eC-SSRS.
- j. History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [e.g., 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.
- k. History of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection.
 - l. Past or current history of cancer, except for appropriately treated non-melanoma skin carcinoma in the last 5 years.
 - m. Pregnant or lactating female patients or female patients who plan to become pregnant during the study.
 - n. Participation in a clinical study of a new chemical entity or a prescription medicine within 2 months before screening (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. Any prior exposure to a monoclonal antibody targeting the CGRP pathway (such as AMG 334, ALD304, LY2951742, or fremanezumab).
 - p. Any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator.
 - q. 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. Hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) $>1.5 \times$ the upper limit of the normal (ULN) range after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law at screening.
 - s. Serum creatinine $>1.5 \times$ the ULN, clinically significant proteinuria, or evidence of renal disease at screening.
 - t. The patient has a history of alcohol abuse during the 2 years prior to screening.
 - u. The patient has a history of drug abuse during the past 2 years or drug dependence during the past 5 years.
 - 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 been previously screen failed for the study.

Statistical Considerations:

Sample Size Rationale: In the Phase 2b study for CM (Study LBR-101-021), the treatment difference between 675/225/225 mg and placebo in change from baseline in monthly average migraine days was 2.1 days (SD=5.2 days). In the phase 2b study for EM (Study LBR-101-022), the treatment difference between 225 mg monthly dose and placebo in change from baseline in monthly average migraine days was 2.7 days (SD=4.1 days). In the Phase 3 study for CM (Study TV48125-CNS-30049), the treatment differences to placebo in change from baseline in monthly average migraine days were 1.7 days and 1.8 days for the quarterly dose and the monthly dose, respectively (SD=5.4 days). In the Phase 3 study for EM (Study TV48125-CNS-30050), the treatment differences to placebo in change from baseline in monthly average migraine days were 1.3 days and 1.5 days for the quarterly dose and the monthly dose, respectively (SD=3.4 days). Combining the information above, a treatment difference of 1.8 days is used. Considering the patient population is different from the previous studies, a SD of 6 days is used to account for the complexity and uncertainty of this study.

A sample size of 705 (235 patients per treatment group) evaluable patients completing the study is needed for 90% power to show a 1.8 difference in migraine days (assuming a common standard deviation [SD] of 6 days) at an alpha level of 0.05. Assuming a 12% discontinuation rate for the double-blind period, 268 patients per treatment group will be randomized.

Analysis of Primary Endpoint: For the purpose of this study, a migraine day is endorsed when at least one of the following occurs:

- a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache, meeting criteria for migraine with or without aura (see [Appendix U](#))
- a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion is missing (see [Appendix U](#))
- a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine- specific acute medications (triptans and ergot compounds)

A headache day of at least moderate severity is endorsed when at least 1 of the following situations occurs:

- a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity
- a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine- specific acute medications (triptans and ergot compounds)

Analysis of Secondary Endpoints: The analysis of the secondary endpoints is specified in the statistical section of the protocol (Section [9.5.2](#)).

Primary Efficacy Analysis: The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) method. The model will include treatment, gender, region, special group

of treatment failure (Yes or No), migraine classification (ie, CM or EM), and treatment-by-migraine classification interaction as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using the estimate statement. Ninety-five percent confidence intervals will be constructed for the least squares means differences between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo.

Note: Special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in [Appendix H](#).

Sensitivity Analysis: Sensitivity analysis will be performed by imputing missing migraine days of months 1-3 using multiple imputation method. The average migraine days of months 1 to 3 from each imputed data set will be analyzed using the same ANCOVA model as the primary efficacy analysis. Ninety-five percent confidence intervals for the least square means differences between each fremaezumab treatment group (monthly dose and quarterly dose) and placebo will be constructed. The detailed SAS code for imputation and analysis procedure will be provided in the statistical analysis plan. This sensitivity analysis will be performed on the ITT analysis set.

Sensitivity analysis will also be performed using a mixed-effects repeated measures (MMRM) analysis model. If a patient is early terminated or has intermittent missing days and has fewer than 10 days of e-diary entries for a month, that month's value will be considered as missing. The MMRM model will include treatment, gender, region, special group of treatment failure (Yes or No), migraine classification (ie, CM or EM), month, treatment-by-migraine classification interaction, and treatment-by-month interaction as fixed effects, baseline value and years since onset of migraines as covariates, and patient in the repeated statement as a random effect. The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using the estimate statement. Ninety-five percent confidence intervals will be constructed for the least squares means differences between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo. This sensitivity analysis will be performed on the mITT analysis set.

Note: Special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in [Appendix H](#).

Secondary Efficacy Analysis: The continuous secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint. For the proportion of responders, defined as 50% or more reduction from baseline in the monthly average number of migraine days, a logistic regression model will be used with the following effects: treatment, gender, region, special group of treatment failure (Yes or No), and migraine classification (ie, CM or EM). The odds ratios, 95% confidence intervals, for odds ratios, and p-values will be presented for each fremanezumab treatment group (monthly dose and quarterly dose) comparing to placebo.

Multiple Comparisons and Multiplicity: The Hochberg’s method along with hierarchical testing procedure for multiple comparisons between treatment groups (2 comparisons: fremanezumab monthly dose compared with placebo and fremanezumab quarterly dose compared with placebo) for the primary and secondary endpoint analyses will be used to maintain the experiment-wise type I error of 5%.

In the primary analysis, according to the Hochberg’s method, if the null hypothesis is rejected for both the fremanezumab monthly and quarterly treatment groups at an alpha level of 5%, then no adjustment to the alpha level will be performed and both comparisons will be declared as statistically significant. The secondary variables will then be tested in the order as specified in Section 9.5.2 for both the fremanezumab monthly and quarterly treatment groups using the same procedure as the primary analysis. If the null hypothesis is not rejected for 1 of the doses at an alpha level of 5%, then the other dose will be tested using an alpha level of $5\%/2=2.5\%$, and the sequential testing will stop.

No multiplicity adjustments will be made for the exploratory efficacy analyses.

Analysis of Exploratory Endpoints: For the double-blind period, the continuous exploratory efficacy endpoints will be analyzed similarly as the primary efficacy endpoint. For the proportions of responders for the double-blind period, a logistic regression model will be used similarly as the secondary efficacy endpoint.

For the open-label period, the exploratory efficacy endpoints for the open-label period will be summarized using descriptive statistics.

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

Safety assessments and time points are provided in [Table 2](#).

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) 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) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

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

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

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

Tolerability Analysis: Local tolerability findings will be listed and summarized descriptively.

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

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

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

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

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

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

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

Planned Interim Analysis: An interim analysis is planned when the last patient has completed the double-blind period. A second interim lock is planned following the end of the open-label period.

The inferential analysis of efficacy variables for comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo will be done at the time of the first interim lock. The appropriate method for type 1 error control will be applied to the first interim analysis.

Efficacy analysis for the open-label portion of this study is considered exploratory and mainly descriptive. This analysis will be done at the time of the final database lock.

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LIST OF ABBREVIATIONS

Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ADA	antidrug antibody
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC _{last}	area under the plasma concentration-time curve from time 0 to the time of the last measurable IMP concentration
BLA	Biological License Application
BMI	body mass index
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CGRP	calcitonin gene-related peptide
CL/F	apparent total body clearance
CM	chronic migraine
C _{max}	maximum observed concentration
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
EC	Ethics Committee
ECG	electrocardiogram
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EM	episodic migraine
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D-5L	EuroQol-5 Dimension (5-level)
EudraCT	European Clinical Trials
EV	EudraVigilance
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Term
GGT	gamma glutamyl transpeptidase
HIT-6	6-item Headache Impact Test
ICDH	International Classification of Headache Disorders
ICF	informed consent form
ICH	The International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INN	international nonproprietary name
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	Intravenous
LSO	local safety officer
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSQOL	Migraine Specific Quality of Life questionnaire
n	Number
NDA	New Drug Application
NSAID	non-steroidal anti-inflammatory drug
PGIC	Patient Global Impression of Change scale
PHQ-2	2-item Patient Health Questionnaire
PHQ-9	9-item Patient Health Questionnaire
PP	per-protocol
RTSM	Randomization and Trial Supply Management
sc	subcutaneous
SD	standard deviation
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
ULN	upper limit of normal
V	Visit
VHP	Voluntary Harmonisation Procedure
V _z /F	apparent volume of distribution

Abbreviation	Term
W	Week
WOCBP	women of childbearing potential
WPAI	Work Productivity and Activity Impairment questionnaire
XML	Extensible Markup Language

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

1.1.1. Disease Overview

Migraine is a prevalent condition characterized by attacks of headache and associated symptoms (such as nausea, photophobia, or phonophobia). The 2 most common forms of migraine, migraine without aura and migraine with aura, occur on less than 15 days per month and are referred to as episodic forms of migraine (EM) (Lipton et al 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 et al 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, faces considerable disability (Bigal and Lipton 2008).

1.1.2. Rationale for Fremanezumab Development as a Preventive Treatment for Migraine

The goals of migraine treatment are to relieve pain, restore function, 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 two or higher, or where a patient's quality of life is severely impaired (Evers et al 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, compliance and adherence to these medications can be poor, and there is a need for preventive medications which are more effective and better tolerated than the current standard of care (Puledda et al 2017).

Calcitonin gene-related peptide (CGRP) is a well-studied neuropeptide found at the centers of the migraine processes, both centrally and peripherally (Eftekhari and Edvinsson 2010). Jugular levels of CGRP are increased during migraine attacks, and intravenous CGRP administration induces migraine-like headache in most individuals with migraine (Ashina et al 2000, Hansen et al 2010). CGRP is involved in the pathophysiology of migraine at all levels, peripherally (vasodilation, inflammation and protein extravasation), at the trigeminal ganglion, and inside the brain (Ho et al 2010). Studies have shown that inhibition of CGRP was efficacious in the treatment of EM (Hewitt et al 2011, Ho et al 2008, Olesen et al 2004) and CM (Bigal et al 2015b).

Fremanezumab (TEV-48125 [formerly LBR-101, PF-04427429, and RN307]) is a fully humanized IgG 2a/kappa monoclonal antibody, which is being developed for administration by the sc route for the preventive treatment of migraine. Fremanezumab is a potent, selective CGRP binder that blocks both CGRP isoforms (α - and β -CGRP) 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 et al 1999](#), [Zeller et al 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 (see the Investigator’s Brochure for more details). 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 fremanezumab at 900 mg or fremanezumab at 675 mg followed by monthly fremanezumab at 225 mg) in patients with CM and a randomized, double-blind, placebo-controlled Phase 2 study of 2 sc dosing regimens of fremanezumab (monthly fremanezumab at 675 or 225 mg) in patients with EM. Furthermore, the efficacy and tolerability profile have been confirmed in the Phase 3 development program.

The demonstrated efficacy, acceptable tolerability, long terminal elimination half-life ($t_{1/2}$, approximately 32-36 days), and ability to administer sc, make fremanezumab a potential therapeutic candidate for patients who failed prior preventive treatment for CM and EM.

1.1.3. Study Purpose

The purpose of the study is to determine whether fremanezumab is effective in the prophylactic treatment of migraine in patients with inadequate response to 2 to 4 classes of prior preventive treatments.

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.

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 $t_{1/2}$. 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 gender 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 ongoing 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 2884 subjects/patients (318 healthy subjects and 2566 patients with migraine) have participated across these clinical studies, and 1958 of these subjects/patients (256 healthy subjects and 1702 patients with migraine [929 patients with CM and 773 patients with EM]) have received at least 1 dose (iv or sc) of fremanezumab. One Phase 3 study (TV48125-CNS-30051) is 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) are ongoing and 1 Phase 3 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.

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 6 completed Phase 1 studies in doses ranging from 0.2 through 2000 mg. Studies included 2 single-ascending-dose pharmacokinetic and pharmacodynamic studies in healthy men (Studies B0141001 and B0141002); a 2-cohort, placebo-controlled crossover study to examine the acute effects of administration of fremanezumab on capsaicin flare response in healthy men (Study B0141006); a parallel-group, repeat-dose study of fremanezumab in healthy subjects (Study B0141007); a single-dose study evaluating the safety, tolerability, and pharmacokinetics of doses up to 2000 mg administered iv in healthy women (Study LBR-101-008 [formerly referred to as Study B0141008]); and a study assessing the safety, tolerability, absolute bioavailability, and pharmacokinetics of single iv or sc doses of fremanezumab in healthy subjects (Study LBR-101-011). These Phase 1 studies were analyzed using the original bioanalytical method that has been determined to be unreliable and underestimate measured plasma concentrations compared to the current validated assay.

A recently completed pharmacokinetic, safety, and tolerability study in healthy Japanese and Caucasian subjects (TV48125-PK-10078) dosed fremanezumab as a single sc dose of 225, 675 or 900 mg. Plasma concentration-time profile was measured using the current validated bioanalytical method and the pharmacokinetic results are described below. The pharmacokinetics (non-compartmental analysis) of fremanezumab demonstrated an increase in C_{max} and AUCs values slightly greater than dose proportionality over sc dose range of 225 to 900 mg. Median time to maximum observed concentration (t_{max}) values generally occurred 5 to 7 days post sc doses. Mean values for apparent volume of distribution (V_z/F) after a single sc dose ranged from 5.7 to 6.4 L at 225 mg to 900 mg sc doses. The mean apparent total body clearance (CL/F) ranged from 0.0777 to 0.0895 mL/min at this dose range. The mean $t_{1/2}$ ranged from 32.2 to 36.2 days. Fremanezumab exposure parameters and overall pharmacokinetic profile was 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 et al 2015a](#), [Bigal et al 2015b](#)). The results of both studies showed fremanezumab to be superior to placebo for primary and secondary endpoints (benefit at 3 months of therapy).

Fremanezumab was well tolerated with favorable safety profile across the 6 completed Phase 1, 2 completed Phase 2b studies, and 2 completed Phase 3 studies. 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 EM and CM patients confirmed efficacy findings in phase 2 (Studies TV48125-CNS-30049 and TV48125-CNS-30050). 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 (quarterly dosing with fremanezumab at 675 mg [675/225/225-mg; N=376] and a loading dose of fremanezumab at 675 mg followed by monthly doses of fremanezumab at 225 mg [675 mg/placebo/placebo; N=379]) 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 run-in 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) vs. -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 vs. placebo, respectively. The least square (LS) mean difference with 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), and a treatment effect in favor of the fremanezumab treatment groups was also evident in months 2 and 3 (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 ($\geq 50\%$ 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 they 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 event 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 dosing with fremanezumab at 675 mg [675-mg/placebo/placebo; N=291] and monthly doses of fremanezumab at 225 mg [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 run-in 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) vs. -2.7 days (mean reduction 2.6 days) for the 675 mg/placebo/placebo and 225/225/225 mg treatment groups vs. placebo, respectively. The LS mean difference with placebo of 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), and a treatment effect in favor of the fremanezumab treatment groups was also evident in months 2 and 3 (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 ($\geq 50\%$ reduction in the number of migraine days), had significantly fewer days with use of acute headache medication, and they 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.

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 Fremanezumab

Additional information regarding benefits and risks to patients may be found in the Investigator's Brochure.

1.3.1.1. Identified Risks

1.3.1.1.1. General Disorders and Administrative Site Conditions

Reports of transient administration site disorders/reactions, including injection site bruising, injection site swelling, administration site pain, injection site pain, injection site pruritus, injection site induration, injection site erythema, injection site inflammation, injection site warmth, injection site extravasation, injection site dermatitis, injection site rash, injection site edema, injection site discomfort, injection site hemorrhage, injection site irritation, injection site mass, and injection site hematoma, have occurred with sc administration. In addition, mild and transient infusion site pain and swelling after iv administration were reported. Among these events, the following have been identified as adverse drug reactions (identified risks): injection site erythema, administration site pain, injection site pain, injection site pruritus, and injection site dermatitis. None of 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, 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 been identified as adverse drug reactions. To date, 1 subject [REDACTED] in Study LBR-101-008 has had an infusion-related reaction considered related to the study drug, and 1 subject [REDACTED] in Study LBR-101-021 has had drug hypersensitivity considered related to the study drug.

- [REDACTED] with no relevant medical history, had a non-serious infusion-related reaction assessed as moderate in severity and related to the study drug. The event, which started 11 minutes after starting the iv dose of fremanezumab at 2000 mg, resulted in discontinuation of study drug administration after 380 mg. The subject was treated with diphenhydramine and methylprednisolone sodium succinate injection (125 mg), and the event resolved. Oxygen saturation was monitored during the infusion per protocol and was normal throughout. No reports of hypotension or tachycardia were made by the investigator. The first protocol scheduled vital signs assessment was performed approximately 1 hour and 40 minutes after event onset and was normal. At the 4-hour post-dose adverse event assessment, the event was reported as resolved. No delayed hypersensitivity-type reactions have been observed in clinical studies.
- [REDACTED] (monthly sc fremanezumab 900-mg treatment group), a [REDACTED] with a medical history of hypersensitivity and drug hypersensitivity to sulfa drugs, had a treatment-emergent adverse event of drug hypersensitivity assessed as moderate in severity and related to the study drug. The event led to permanent discontinuation of the study drug. The patient received diphenhydramine hydrochloride and methylprednisolone for the event that started 1 day after the patient received [REDACTED] second dose of study drug, and the event was reported as resolved after 23 days. No reports of hypotension or tachycardia were made by the investigator.

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, the following 4 major cardiovascular effects are of potential concern with CGRP inhibition, a priori: medication-induced hypertension, counterbalancing the effect of anti-hypertensive drugs that have vasodilatory properties, inhibition of stress- (or ischemia-) induced vasodilation, and impairment of cardioprotective mechanisms. Extensive research conducted with the CGRP receptor antagonists has not identified relevant safety cardiovascular concerns in humans. Dedicated studies conducted in monkey and in 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/risk assessment for fremanezumab is favorable following review of all available efficacy and safety data.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are presented in [Table 1](#):

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
<p>The primary objective of the study is to demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous (sc) injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo</p>	<p>The primary efficacy endpoint is the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab</p>
<p>The secondary objective of the study is to further evaluate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo</p>	<p>The secondary endpoints are as follows:</p> <ul style="list-style-type: none"> • proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab • proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of fremanezumab

Objectives	Endpoints
<p>A secondary objective of the study is to evaluate the safety and tolerability of fremanezumab administered as monthly and quarterly sc injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo</p>	<p>Secondary safety/tolerability endpoints:</p> <ul style="list-style-type: none"> ● occurrence of adverse events throughout the study ● clinical laboratory (serum chemistry, hematology, coagulation and urinalysis) test results at specified time points ● vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit. Note: In addition, oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity ● 12-lead ECG findings at specified time points ● use of concomitant medication for adverse events during the study ● number (%) of patients who did not complete the study due to adverse events ● clinically significant changes in physical examinations, including body weight ● occurrence of severe hypersensitivity/anaphylaxis reactions ● suicidal ideations and behaviors as measured by the eC-SSRS

ECG=electrocardiogram; eC-SSRS= electronic Columbia-Suicide Severity Rating Scale; Test; sc=subcutaneous.

2.1.1. Justification of Primary Endpoint

The primary endpoint was chosen based on the 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 et al 2008](#)).

2.2. Exploratory Efficacy Objectives and Endpoints

The exploratory objectives are as follows:

- to further evaluate the efficacy of fremanezumab in adult migraine patients with inadequate response to 2 to 4 classes of prior preventive treatments
- to evaluate immunogenicity and impact of antidrug antibody (ADA) on clinical outcome
- to explore the correlation between pharmacokinetic parameters and efficacy of fremanezumab

- to explore the relationship between genetic polymorphisms, migraine onset/severity and efficacy and safety of fremanezumab
- to explore the relationship between soluble exploratory biomarkers versus migraine response

The exploratory endpoints for the double-blind period are as follows:

- proportion of patients reaching at least 75% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of the study drug
- proportion of patients reaching at least 50% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed valproic acid for migraine in the past

- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past
- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the 6-item Headache Impact Test (HIT-6), at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in disability score, as measured by the Migraine Disability Assessment (MIDAS) questionnaire, at 4 weeks after the administration of the 3rd dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the Migraine-Specific Quality of Life (MSQOL) questionnaire, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EuroQol-5 Dimension (EQ-5D-5L) questionnaire at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the 2 item Patient Health Questionnaire (PHQ-2) and 9-item Patient Health Questionnaire (PHQ-9), at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) of patient satisfaction, as measured by the Patient Global Impression of Change (PGIC) scale, at 4 weeks after the 3rd dose of study drug

The exploratory endpoints for the open-label period are as follows:

- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 4th dose of fremanezumab

- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of study drug
- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 4th dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 4th dose of the study drug
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed valproic acid for migraine in the past

- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the HIT-6, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after the administration of the 6th dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale, at 4 weeks after the last 6th dose of study drug

The exploratory endpoints for both the double-blind and open-label periods are as follows:

- to evaluate the immunogenicity response of fremanezumab and the impact of ADAs on clinical outcomes in patients exposed to sc fremanezumab.
- to explore the relationship between genetic polymorphisms (including those within the calcitonin gene-related peptide (CGRP) receptor-ligand complex, in migraine-associated susceptibility genes, and in as-yet undiscovered loci) versus migraine onset/severity, adverse events to medication and fremanezumab efficacy
- to explore the relationship between exploratory biofluid biomarkers versus fremanezumab concentrations, adverse events and fremanezumab efficacy

3. GENERAL STUDY DESIGN AND STUDY SCHEMATIC DIAGRAM

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study with an open-label period to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc fremanezumab compared with placebo in patients with CM and EM with inadequate response to prior preventive treatments.

The study will consist of a screening visit, a run-in period (28 days), a 12-week double-blind, placebo-controlled treatment period, a 12-week open-label period, and a follow-up visit 6.0 months after the last dose of fremanezumab for ADA blood sample collection.

At the end of the open-label treatment period (4 weeks after the last dose) an end of treatment study visit (visit 8) will be scheduled and patients should return to the care of their treating physicians. Patients should be treated with standard of care after withdrawal from or termination of the 24-week treatment period/study, as appropriate.

Double-blind period

At the baseline visit (visit 2), patients will be randomly assigned to a treatment group with fremanezumab (2 different dose regimens) or placebo in a 1:1:1 ratio as follows:

- For patients with CM:
 - sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
 - sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of matching placebo for 2 months or
 - 3 monthly doses of matching placebo
- For patients with EM:
 - sc administration of fremanezumab at 225 mg plus 2 matching placebo injections as first dose followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
 - sc administration of fremanezumab at 675 mg as first dose followed by monthly sc administration of matching placebo for 2 months or
 - 3 monthly doses of matching placebo

Randomization and treatment assignment for the double-blind period will be performed using electronic interactive response technology (IRT). The study will be stratified based on CM or EM, gender, country, and a special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in [Appendix H](#).

The proportion of CM and EM patients in the study should be approximately 50:50 in each subgroup.

CM is defined as:

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

- Headache occurring on ≥ 15 days
- On ≥ 8 days, fulfilling any of the following:
 - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura ([Appendix U](#))
 - ICHD-3 criteria B and C for 1.2 Migraine with aura ([Appendix U](#))
 - Probable migraine (a migraine subtype where only 1 migraine criterion is missing)
 - The patient used a triptan or ergot derivative 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 run-in period:

- Headache occurring ≥ 6 days but < 15
- On ≥ 4 days, fulfilling any of the following:
 - 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)
 - The patient used a triptan or ergot derivative to treat an established headache

Blinded treatment will be administered sc once a month (approximately every 28 days) for a total of 3 doses (visits 2,3, and 4)

Open-label period

After visit 4, all patients completing the double-blind period will enter the open-label period. All patients (CM and EM) will receive sc 225 mg of fremanezumab monthly for 3 months (visits 5, 6, and 7).

The open-label period will not be randomized as all patients will receive the same monthly dose (225 mg fremanezumab).

Open-label treatment will administered for a total of 3 doses (visits 5, 6, and 7). Final study assessments will be performed at visit 8 (end-of-treatment [EOT] visit), approximately 4 weeks after administration of last dose of fremanezumab.

Follow up period

A follow-up visit will be scheduled 6.0 months (> 5 half-lives) after the last study drug administration for ADA blood sampling. Patients who discontinue early will have the follow-up visit 6.0 months after the last dose.

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The total duration of patient participation in the study is planned to be 50 weeks including a run-in period lasting 28 days, a double-blind treatment period lasting 12 weeks, an open-label period lasting 12 weeks, and 1 follow-up visit at week 46.

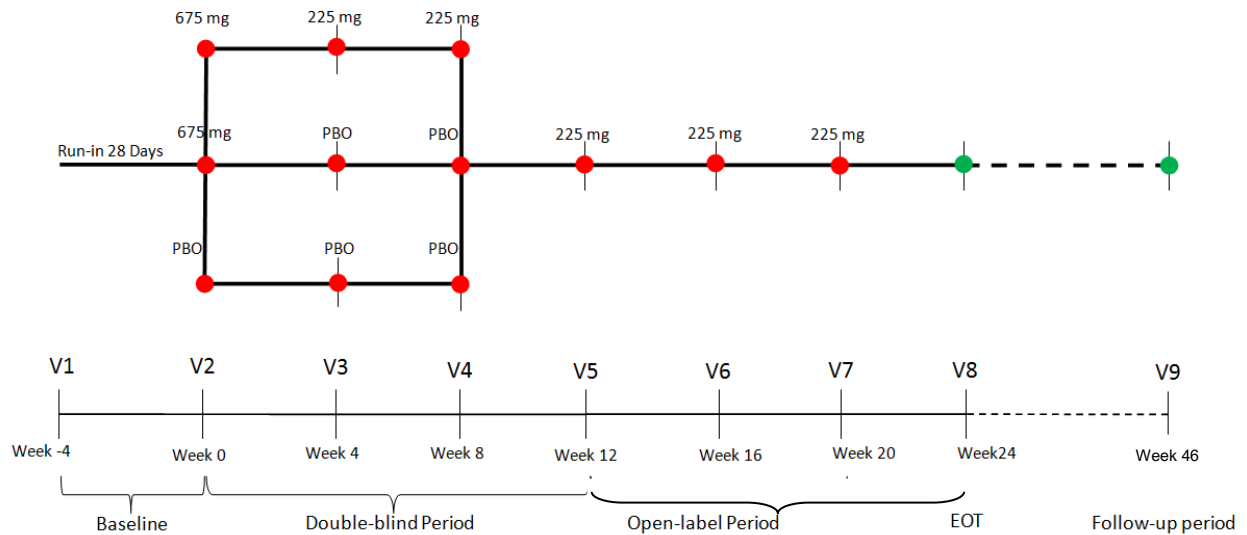
Patients are expected to complete the entire duration of the study, including the open-label period and the follow-up visit.

The end of study is defined as the last visit of the last patient (follow-up visit, visit 9). However, an interim database lock will occur following the end of the double-blind treatment period of the last patient for analysis of that portion of the study data. A second interim lock will occur following the end of the open-label period.

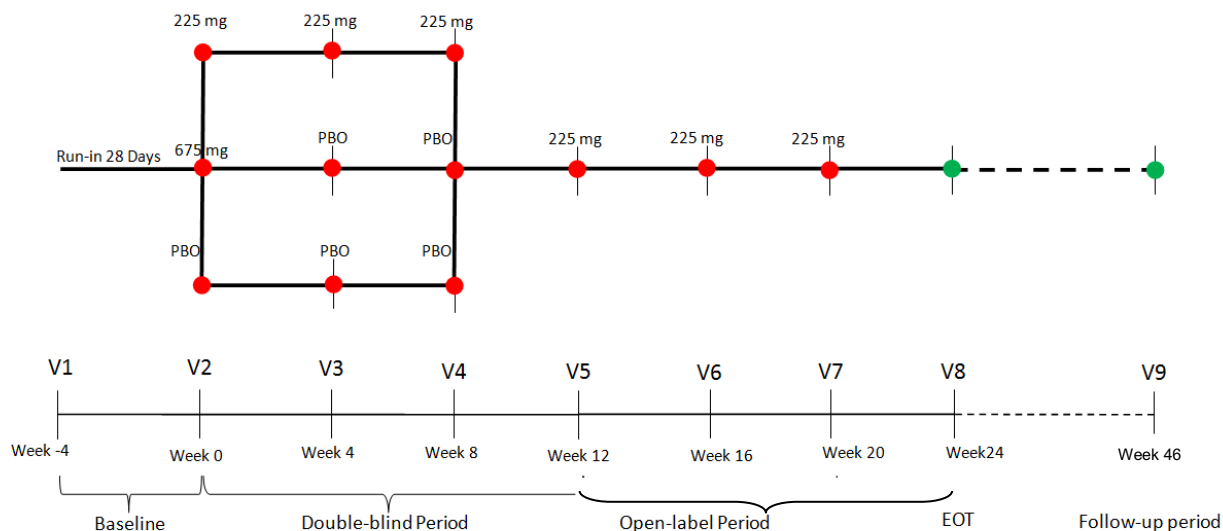
The total study duration, including the 6.0-month follow-up-period, will be approximately 2 years (from approximately 4Q 2017 to 4 Q 2019).

The study schematic diagram for patients with CM is presented in [Figure 1](#) and for patients with EM in [Figure 2](#).

Figure 1: Overall Study Schematic Diagram for Patients with Chronic Migraine



EOT=end of treatment; PBO=placebo; V=visit.

Figure 2: Overall Study Schematic Diagram for Patients with Episodic Migraine

EOT=end of treatment; PBO=placebo; V=visit.

3.1. Planned Number of Patients and Countries

Approximately 804 patients (268 patients per treatment group) are planned to be enrolled in this study to have approximately 705 completers (235 completers per treatment group). A 12% drop-out rate is anticipated.

The study is planned to be conducted in approximately 15 countries in approximately 120 investigational centers.

3.2. 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 history of migraine (as defined by International Classification of Headache Disorders, 3rd revision [ICHD-3] criteria [IHS 2013]) for at least 12 months prior to screening and diagnosis of EM and CM prospectively documented via a review of headache data recorded daily in an electronic headache diary device during a 28-day run-in period. In addition, patients need to have documented history of inadequate response to 2 to 4 classes of prior preventive medication treatments for migraine and a subset of patients (at least 120) will have documented inadequate response to 2 to 3 classes of prior preventive medications and in addition inadequate response to valproic acid. All inadequate responses must be within the past 10 years (in medical chart or by treating physician's confirmation, see [Appendix I](#)). Fremanezumab is expected to be a later line treatment in the EU. This study is intended to generate data for that specific population defined within EM and CM.

The same dosing regimens used in the phase 3 studies will be investigated in the double-blind period. One of the dosing regimens from the phase 3 studies expected to be efficacious for this study population will be used in the open-label period.

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 et al 2012).

3.3. Stopping Rules for the Study

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

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

- new toxicological or pharmacological findings or safety issues invalidating the earlier positive benefit-risk assessment
- development of the IMP being discontinued

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, protocol deviation as defined in Appendix C, noncompliance, or adverse event). In addition, patients with positive eC-SSRS findings or abnormal hepatic laboratory values (eg, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyl transpeptidase [GGT], bilirubin [total, direct, or indirect], or international normalized ratio [INR]) may meet criteria for discontinuation from the IMP as summarized in Appendix R.

3.4. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 2.

Note that blood samples for plasma drug concentration determination will be collected prior to dosing (where applicable) at visits 2, 3, 4, 5, 6, and 8.

Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 2: Study Procedures and Assessments

Study period	Pretreatment (incl. screening visit and run-in period)	Double-blind treatment period			Open-label period				Follow up period
		V1	V2 ^a	V3	V4	V5	V6		
Day and allowed time windows	Screening (Days -28 to -1)	Month 0 (Day 0+3 days)	Month 1 (Day 28±3 days)	Month 2 (Day 56±3 days)	Month 3 (Day 84±3 days)	Month 4 (Day 112±5 days)	Month 5 (Day 140±5 days)	End of Treatment/ Early termination (Day 168±5 days)	6.0 months after the last dose of IMP (Day 320±15 days)
Procedures and assessments	Screening Week -4	Baseline Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 46
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 ^b	X								
Clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis)	X	X	X		X	X		X	
Physical examination, including height and weight ^c	X	X			X			X	
12-Lead ECG ^d	X	X			X			X	
Vital signs measurement ^{e, f}	X	X	X	X	X	X	X	X	X

Study period	Pretreatment (incl. screening visit and run-in period)	Double-blind treatment period			Open-label period				Follow up period
		V1	V2 ^a	V3	V4	V5	V6		
Day and allowed time windows	Screening (Days -28 to -1)	Month 0 (Day 0±3 days)	Month 1 (Day 28±3 days)	Month 2 (Day 56±3 days)	Month 3 (Day 84±3 days)	Month 4 (Day 112±5 days)	Month 5 (Day 140±5 days)	End of Treatment/ Early termination (Day 168±5 days)	6.0 months after the last dose of IMP (Day 320±15 days)
Procedures and assessments	Screening Week -4	Baseline Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 46
Serum β-HCG test ^g	X							X	
Urine pregnancy test ^g		X	X	X	X	X	X	X	
FSH ^h	X								
Inform patients of study restrictions and compliance requirements	X								
Review study compliance ^f		X	X	X	X	X	X	X	
Provide electronic headache diary ⁱ	X								
Complete electronic headache diary entries ^j	X							X	
Review electronic headache diary ^f		X	X	X	X	X	X	X	
Return headache diary device								X	
Blood samples for plasma concentration of IMP ^k		X	X	X	X	X		X	
Blood samples for serum ADA assessment ^l		X	X		X	X		X	X

Study period	Pretreatment (incl. screening visit and run-in period)	Double-blind treatment period			Open-label period				Follow up period
		V1	V2 ^a	V3	V4	V5	V6		
Day and allowed time windows	Screening (Days -28 to -1)	Month 0 (Day 0±3 days)	Month 1 (Day 28±3 days)	Month 2 (Day 56±3 days)	Month 3 (Day 84±3 days)	Month 4 (Day 112±5 days)	Month 5 (Day 140±5 days)	End of Treatment/ Early termination (Day 168±5 days)	6.0 months after the last dose of IMP (Day 320±15 days)
Procedures and assessments	Screening Week -4	Baseline Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 46
Blood collection for serum, plasma, and RNA biomarker analysis		X	X		X	X		X	
Urine collection for biomarker analysis		X	X		X	X		X	
Saliva sample for biomarker analysis		X	X		X	X		X	
Blood samples for pharmacogenetics ^m		X							
HIT-6		X	X		X			X	
MIDAS		X	X		X			X	
PHQ-2/PHQ-9 ⁿ		X			X			X	
MSQOL questionnaire		X	X		X			X	
EQ-5D-5L questionnaire		X			X			X	
PGIC scale			X		X			X	
WPAI questionnaire		X			X			X	
eC-SSRS ^{o, f}	X		X	X	X	X	X	X	
Adverse events ^{g, p} and health care resource utilization inquiry		X	X	X	X	X	X	X	X
Administration of IMP		X	X	X	X	X	X		

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Study period	Pretreatment (incl. screening visit and run-in period)	Double-blind treatment period			Open-label period				Follow up period
		V1	V2 ^a	V3	V4	V5	V6		
Day and allowed time windows	Screening (Days -28 to -1)	Month 0 (Day 0±3 days)	Month 1 (Day 28±3 days)	Month 2 (Day 56±3 days)	Month 3 (Day 84±3 days)	Month 4 (Day 112±5 days)	Month 5 (Day 140±5 days)	End of Treatment/ Early termination (Day 168±5 days)	6.0 months after the last dose of IMP (Day 320±15 days)
Procedures and assessments	Screening Week -4	Baseline Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 46
Hypersensitivity/ Anaphylaxis ^g		X	X	X	X	X	X	X	
Concomitant medication inquiry ^f		X	X	X	X	X	X	X	X

^a All visit 2/baseline procedures must be performed before study drug administration and health care resource utilization inquiry. Inquiries about adverse events will be made before and after study drug administration. Post-dose inquiries will be made before the patient leaves the study center.

^b Collection of prior medications is limited to those medications administered within 6 months before study drug administration (visit 2) and preventive medications taken within 10 years.

^c Height will be measured only at the screening visit.

^d Electrocardiograms will be performed in triplicate. Procedure will be performed before other assessments (eg, blood draws and administration of questionnaires). The ECGs should be performed after the patient has been supine for at least 5 minutes.

^e 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.

^f Procedures for unscheduled visits.

^g Women of child bearing potential only.

^h Postmenopausal women only.

ⁱ Eligible patients will be given an electronic headache diary device and will be trained in its use and compliance requirements on the day of screening.

^j Patients will complete electronic headache diary entries about the previous day daily beginning on day -27 through the EOT/ early termination visit.

^k Blood samples for plasma drug concentration determination will be collected prior to dosing (as applicable) at visits 2, 3, 4, 5, 6, and 8.

^l Blood samples for serum ADA assessment will be collected prior to dosing (as applicable) at visits 2, 3, 5, 6, 8, and 9 and will also be collected upon observation of any severe hypersensitivity reaction i.e., severe hypersensitivity reaction and anaphylaxis.

^m A single blood sample for pharmacogenomic analysis will be collected at visit 2, before study drug administration from patients who consent to this procedure. A separate informed consent form for pharmacogenomic sampling must be signed by the patient.

ⁿ Patients will respond first to the PHQ-2. They will respond to questions 3 through 9 (unique questions) of the PHQ-9 only if PHQ-2 is positive.

^o The eC-SSRS Baseline/Screening version will be completed at visit 1 and the eC-SSRS Since Last Visit version will be completed at all other visits.

^p Inquiries about adverse events will be made before and after study drug administration. Post-dose inquiries will be made before the patient leaves the study center.

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⁹ 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 S](#).

ADA=anti-drug antibodies; β -HCG=beta human chorionic gonadotropin; ECG=electrocardiogram; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; EOT=end of treatment; EQ-5D-5L=EuroQol-5 Dimension, 5 response level version; FSH=follicle-stimulating hormone; HIT-6=6-item Headache Impact Test; IMP=investigational medicinal product; MIDAS=Migraine Disability Assessment; MSQOL=Migraine-Specific Quality of Life; PGIC=Patient Global Impression of Change; PHQ-2=2-item Patient Health Questionnaire; PHQ-9=9-item Patient Health Questionnaire; V=visit;; WPAI=Work Performance and Activity Impairment.

4. SELECTION AND WITHDRAWAL OF PATIENTS

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

4.1. Patient Inclusion Criteria

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

- a. The patient is capable of giving signed informed consent.
- b. Male or female patient aged 18 to 70 years, inclusive.
- c. The patient has a diagnosis of migraine with onset at ≤ 50 years of age.
- d. The patient is in good health in the opinion of the investigators as determined by medical history, physical examination, laboratory tests, and ECG.
- e. Body weight ≥ 45 kg and body mass index (BMI) within the range 17.5 to 34.9 kg/m² (inclusive).
- f. The patient has a history of migraine (according to ICHD-3 criteria [[IHS 2013](#)]) or clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥ 12 months prior to screening.
- g. The patient fulfills the following criteria for CM or EM in prospectively collected baseline information during the 28-day run-in period:

For patients with CM:

- Headache occurring on ≥ 15 days
- On ≥ 8 days, fulfilling any of the following:
 - 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)
 - The patient used a triptan or ergot derivative to treat an established headache

For patients with EM:

- Headache occurring on ≥ 6 days but < 15
- On ≥ 4 days, fulfilling any of the following:
 - 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)

- The patient used a triptan or ergot derivative to treat an established headache
- h. At the time of screening, the patient must have documented inadequate response to 2 to 4 classes of prior preventive migraine medications (as defined in [Appendix H](#)) within the past 10 years (in medical chart or by treating physician’s confirmation; see [Appendix I](#) for acceptable documentation of previous treatment failure). Inadequate response to prior preventive migraine medications (including valproic acid) is defined as: no clinically meaningful improvement per treating physician’s judgment, after at least 3 months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines, or when treatment has to be interrupted because of adverse events that made it intolerable for the patient, or the medication (as defined in [Appendix H](#)) is contraindicated or unsuitable for the prophylactic treatment of migraine for the patient. The 3- month period does not apply if the drug is intolerable or contraindicated. If onabotulinumtoxinA is the previous preventive medication, at least 2 sets of injections and 3 months must have passed since the last set of injections prior to the screening visit.
- i. The patient agrees not to initiate any preventive migraine medications (as defined in [Appendix H](#)) during the run-in period, double-blind treatment period, and open-label period. At the screening visit, at least 5 half-lives of these medications must have passed since the patient has been on any migraine preventive medication as defined in [Appendix H](#).
- j. Other prescription medications not in [Appendix H](#) must have been on stable doses for at least 2 months at the screening visit with no expectation to change during the double-blind treatment period of the study.
- k. The patient demonstrated compliance with the electronic headache diary during the run-in period by entry of headache data on a minimum of 24 days cumulative during the run-in period (~85% diary compliance).
- l. Women may be included only if they have a negative serum beta-human chorionic gonadotropin (β -HCG) test at screening, are sterile, or postmenopausal. Definitions of sterile and postmenopausal are given in [Appendix E](#).
- m. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study and the follow-up period (ie, starting at screening) and for 6.0 months after discontinuation of IMP (for details of WOCBP, sterile, and postmenopausal women, see [Appendix E](#)).
- n. Men must be sterile, or if they are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must use, together with their female partners, acceptable birth control methods for the duration of the study and for 6.0 months after discontinuation of the IMP.

- o. The patient must be willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study period and to return to the clinic for the follow-up evaluations, as specified in this protocol.

4.2. Patient Exclusion Criteria

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

- a. At the time of screening visit, patient is receiving any preventive migraine medications, regardless of the medical indication (as defined in [Appendix H](#)) for more than 5 days and expects to continue with these medications.
- b. 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.
- c. 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 run-in period for the treatment of migraine or for any other reason.
- d. The patient has used an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening.
- e. The patient uses triptans/ergots as preventive therapies for migraine.
- f. Patient uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (eg, 81 mg) used for cardiovascular disease prevention is allowed.
- g. The patient suffers from unremitting headaches, 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.
- h. The patient has a clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.
- i. Evidence or medical history of 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 major depression, panic disorder, or generalized anxiety disorder, any suicide attempt in the past or suicidal ideation with a specific plan the past two years prior to screening or current suicidal ideation as measured by eC-SSRS.

- j. History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [e.g., 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.
- k. History of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection.
- l. Past or current history of cancer, except for appropriately treated non-melanoma skin carcinoma in the last 5 years.
- m. Pregnant or lactating female patients or female patients who plan to become pregnant during the study.
- n. Participation in a clinical study of a new chemical entity or a prescription medicine within 2 months before screening (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. Any prior exposure to a monoclonal antibody targeting the CGRP pathway (such as AMG 334, ALD304, LY2951742, or fremanezumab).
- p. Any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator.
- q. 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. Hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) $>1.5 \times$ the upper limit of the normal (ULN) range after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law at screening.
- s. Serum creatinine $>1.5 \times$ the ULN, clinically significant proteinuria, or evidence of renal disease at screening.
- t. The patient has a history of alcohol abuse during the 2 years prior to screening.
- u. The patient has a history of drug abuse during the past 2 years or drug dependence during the past 5 years.
- 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 been previously screen failed for the study.

4.3. Withdrawal Criteria and Procedures for the Patient

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

1. Patient withdraws consent or requests discontinuation from the IMP 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 as defined in this protocol.
5. A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.
6. The sponsor requests withdrawal of the patient.
7. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient.

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

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

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

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 both on the source documentation and in the CRF; both the adverse events page and the relevant page of the CRF will be completed at that time.

The investigator must inform the Sponsor or delegate 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 include also adverse events, the relevant page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be “need to take a prohibited medication”, not the adverse event.

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

All protocol-specified procedures/assessments should be performed at the EOT/ early withdrawal visit (see [Table 2](#)). Patients who withdraw from the study will be instructed to come back to the site for blood sample collection for the purpose of evaluating ADA 6.0 months (180 days [the approximate equivalent of 5 half-lives]) after their last dose of study drug. A patient should only be designated as lost to follow up if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

4.4. Replacement of Patients

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

4.5. Rescreening

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

4.6. Screening Failure

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

5. TREATMENTS

5.1. Investigational Medicinal Products Used in the Study

Investigational medicinal products are defined as the test IMP (fremanezumab) and matching placebo IMP. A summary of IMPs used in the study is presented in [Table 3](#). Additional details may be found in the Investigator’s Brochure for fremanezumab.

Table 3: Investigational Medicinal Products Used in the Study

IMP name Recombinant humanized IgG2a/kappa mAb	Test IMP Fremanezumab	Placebo IMP Placebo
Trade name and INN, if applicable, or company-assigned number	Fremanezumab Known also as: TEV-48125, LBR-101, PF-04427429, RN307	Placebo
Formulation	Prefilled syringes contain 1.5 mL solution for injection with 150 mg/mL (ie 225 mg total) of active ingredient fremanezumab Inactive ingredients include: L-histidine, sucrose, polysorbate-80, ethylenediaminetetraacetic acid (EDTA) and water for injection	Prefilled syringes contain 1.5 mL of the same vehicle and excipients as those for active injection. Inactive ingredients include: L-histidine, sucrose, polysorbate-80, ethylenediaminetetraacetic acid (EDTA) and water for injection
Unit dose strength(s)/Dosage level(s)	225 mg/1.5 mL	None
Route of administration	sc injection	sc injection
Dosing instructions/Dosing schedule/Titration periods/Treatment periods for the <u>double-blind period</u>	For CM patients: A dose of 675 mg fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 2 and 225 mg fremanezumab as 1 active injection (225 mg/1.5 mL) at visits 3 and 4. Or a dose of 675 mg fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 2	No placebo injections Single 1.5-mL placebo injection at visits 3 and 4
	For EM patients: 225 mg fremanezumab as 1 active injection (225 mg/1.5 mL) at visit 2, 3, and 4 Or a dose of 675 mg fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 2	Two 1.5-mL placebo injections at visit 2 Single 1.5-mL placebo injection at visits 3 and 4
	For both CM and EM patients who are on treatment placebo only: No active injections	Three 1.5-mL placebo injections at visit 2 and a single 1.5-mL placebo injection at visits 3 and 4

IMP name Recombinant humanized IgG2a/kappa mAb	Test IMP Fremanezumab	Placebo IMP Placebo
Dosing instructions/Dosing schedule/Titration periods/Treatment periods for the <u>open-label period</u>	For all CM and EM patients: 225 mg fremanezumab as 1 active injection (225 mg/1.5 mL) at visits 5, 6, and 7	No placebo injections
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
Manufacturer	Drug Substance: Celltrion 23, Academy-ro Yeonsu-gu, Incheon, South Korea Drug Product: Vetter Pharma Fertigung GmbH & Co. KG Schuetzenstrasse 87, 99-101, Ravensburg, Baden-Wuerttemberg 88212 Germany Vetter Pharma Fertigung GmbH & Co. KG Mooswiesen 2, Ravensburg, Baden-Wuerttemberg 88214, Germany	Vetter Pharma Fertigung GmbH & Co. KG Schuetzenstrasse 87, 99-101, Ravensburg, Baden-Wuerttemberg 88212 Germany Vetter Pharma Fertigung GmbH & Co. KG Mooswiesen 2, Ravensburg, Baden-Wuerttemberg 88214, Germany

CM=chronic migraine; EDTA=ethylene diamine tetra acetate; EM=episodic migraine; IMP=Investigational Medicinal Product; INN=international nonproprietary name; mAb=monoclonal antibody; sc=subcutaneous.

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

At the time of each study visit, the IRT will be queried, and site personnel will retrieve and administer 1.5 mL from each 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 V](#)).

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) responsible for administration of injections should inspect previous injection sites to ensure that they are free of bruising and tenderness and that proper rotation of sites is performed.

Study drug should be removed from the refrigerator and allowed to equilibrate at room temperature for 45-60 minutes before study drug administration. A 1.5-mL volume from each 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 CRF for each dosing visit (visits 2, 3, 4, 5, 6, and 7).

5.1.1. Test Investigational Medicinal Product (Fremanezumab)

5.1.1.1. Starting Dose and Dose Levels

For the double-blind period, the starting dose for patients with CM will be 675 mg sc and the starting dose for patients with EM will be 225 mg sc or 675 mg sc. Further doses of 225 mg or placebo will be administered sc once monthly. The maximal dose administered sc per treatment will be 675 mg.

For the open-label period, all patients will receive 225 mg fremanezumab monthly.

5.1.1.2. Dose Modification and Dose Stratification

No dose modifications were allowed.

This is a randomized study with stratification based on CM or EM (in the double-blind period), gender, country, and a special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in [Appendix H](#).

The proportion of CM and EM patients in the study should be approximately 50:50 in each subgroup.

The open-label period will not be randomized as all patients will receive the same monthly dose (225 mg fremanezumab).

5.1.2. Placebo Investigational Medicinal Product

Placebo (matching the test IMP fremanezumab) will be provided and administered as described in [Table 3](#).

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

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

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

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

During the Phase 2b studies, four dose regimens (ie, EM: monthly 225 mg or 675 mg, and CM: monthly 675 mg followed by 225 mg or monthly 900 mg of fremanezumab sc) were tested and shown to be effective, safe and well tolerated at the 3 month treatment period. As it is considered best practice to select the lower dose for administration from two doses that show

equivalence in efficacy (to avoid higher dose than necessary) the 2 monthly dose regimens of 225 mg monthly with 675 mg loading dose (CM) or without loading dose (EM) were used as one active arm in each of the Phase 3 studies. A second active arm included in both EM and CM studies was 675 mg fremanezumab sc 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.

Thus, two dose regimens are included in this study: 225 mg monthly (with 675 mg loading dose at the start of the CM dose regimen) and 675 mg quarterly to provide patients and physicians convenience and flexibility on their treatment options for the preventive treatment of EM and CM.

The 225 mg monthly dosing regimen selected for the open-label period is one of the phase 3 dosing regimen that was efficacious and well tolerated. The open-label period is intended to provide the placebo-treated patients the opportunity to receive potential benefit from therapeutic doses. It also provides an opportunity to explore efficacy and tolerability beyond 3 months.

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 et al 2008](#)) and the Classification Committee of the IHS guidelines for controlled trials of drugs in migraine, 3rd edition ([Tfelt-Hansen et al 2012](#)).

5.4. Treatment after the End of the Study

At the end of the 24-week treatment period, it is expected that patients should return to the care of their treating physicians.

Patients will return to the investigational center approximately 6.0 months following administration of the last dose of IMP for safety evaluation. No treatment is planned by the sponsor after completion of the 24-week treatment period and the study. Patients should be treated with standard of care after withdrawal from or termination of the 24-week treatment period, as appropriate.

5.5. Restrictions

Patients will be required to comply with the following restrictions:

5.5.1. Activity

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

5.5.2. Blood Donation

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

5.5.3. 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](#).

5.6. Prior and Concomitant Medication or Therapy

Patients must not be on any migraine prophylactic medications (as defined in [Appendix H](#)) at the time of screening. At least 5 half-lives must have passed prior to the screening visit. No migraine prophylactic medications (as defined in [Appendix H](#)) are allowed to be initiated during the run-in and double-blind treatment period. Medications listed in [Appendix H](#) taken for other reason than migraine/headache are also disallowed during the run-in and double-blind period.

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

Any prior or concomitant therapy, medication, or procedure that a patient has had within 6 months before study drug administration and up to the end of the study period will be recorded on the CRF. In addition, migraine preventive medication listed in [Appendix H](#) that a patient took within 10 years before study drug administration will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. In addition, medical record or treating physician's affidavit (see [Appendix I](#)) or signed notes from the principal investigator (if he/she is not the treating physician) after interviewing the treating physician, will be required as source documents to corroborate patient's report of inadequate response to 2 to 4 classes of prior migraine preventive medications. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary.

No IMPs other than the ones used in this study or vaccine will be allowed during the study including follow-up period. A list of prohibited medications is given in [Appendix H](#). Prescription or over the counter drugs to treat adverse events are allowed.

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

5.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn. The IEC/IRB should be notified.

5.8. Randomization and Blinding

The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients will be blinded to treatment assignment during the double-blind period. A computer-generated master randomization list will be provided to drug packaging facilities. Packaging vendor(s) will package active drug and placebo into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance and contain 1 prefilled syringe with active drug or placebo. Adequate kit supply for upcoming study visits will be managed by IRT and kept (refrigerated at 2°C to 8°C) on site.

In this randomized study, the double-blind period will be stratified based on CM or EM, gender, country, and a special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in [Appendix H](#).

Each patient will undergo randomization in a 1:1:1 ratio within the stratum to which he or she belongs to receive 1 of the 2 fremanezumab dose regimens or placebo, as assigned by the IRT. The IRT will manage initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At the time of each study visit, the IRT will be queried, and site personnel will retrieve and administer a 1.5-mL volume from each syringe contained in the appropriately numbered kit(s).

5.9. Maintenance of Randomization and Blinding

5.9.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of the final 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).

5.9.2. Blinding and Unblinding

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

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

In case of a serious adverse event or pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient's drug assignment as deemed necessary, mainly in emergency situations. Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) at the study center via the IRT, both via telephone and internet. If possible, the sponsor should be notified of the event prior to breaking of the code. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's drug code assignment should not be revealed. Breaking of the treatment code (in emergency cases) can always be performed by the site without prior approval by the sponsor.

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

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

In this study, for adverse events that are defined as: suspected, unexpected, serious, adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance may independently request that the treatment code be revealed (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, analysis, and reporting of the data.

5.9.3. Data Monitoring Committee

There will be no Data Monitoring Committee in this study.

5.10. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 180.5 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 CRF. However, in the event that such data are collected, these data will not be analyzed.

A detailed description of assessments and procedures are presented in [Appendix B](#).

6.1. Assessments of Efficacy

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. At least 75% compliance is needed after the randomization period. Site personnel will monitor patient's compliance that at least 75% diary entry is met during the double-blind and open-label periods.

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 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 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.

6.1.1. Six-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 et al 2011](#)).

Patients will complete the HIT-6 at the time points detailed in [Table 2](#).

6.1.2. Migraine Disability Assessment

The MIDAS questionnaire is a 5-item instrument developed to assess headache-related disability based on lost days of activity in 3 domains (work, household work, and nonwork) over the previous 3 months. The total of the scores of the first 5 questions is used for grading of disability, with scores of 0 to 5, 6 to 10, 11 to 20, and ≥ 21 interpreted as disability grades 1 (little or no disability), 2 (mild disability), 3 (moderate disability), and 4 (severe disability), respectively. It has been shown to be reliable and valid for migraine, with substantially higher scores in migraine cases than non-migraine cases ([Stewart et al 1999a](#), [Stewart et al 1999b](#)).

Patients will complete the MIDAS questionnaire at time points detailed in [Table 2](#).

6.1.3. Two-Item Patient Health Questionnaire/9-Item Patient Health Questionnaire

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 major depressive disorder. 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 et al 1999](#)). The PHQ-2 was developed from the PHQ-9 to rapidly screen for depression and consists of the first 2 questions from the PHQ-9. The PHQ-2 and the PHQ-9 are validated measures for detecting and monitoring depression, anxiety, and somatization ([Kroenke et al 2010](#)).

Patients will complete the PHQ-2 at the time points detailed in [Table 2](#). If the PHQ-2 is positive (ie, a score of ≥ 3), patients will complete questions 3 through 9 (unique questions) of the PHQ-9.

6.1.4. Migraine-Specific Quality of Life Questionnaire

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 et al 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 2](#).

6.1.5. EuroQol-5 Dimension Questionnaire

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

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

6.1.6. Patient Global Impression of Change Scale

The PGIC scale is a validated generic tool for assessment of overall change in the severity of illness following treatment. Patients will rate how they describe the change (if any) that their migraine/headaches have had in their general quality of life and health status since beginning the treatment in this study on a 7-point scale where 1=no change (or condition got worse); 2=almost the same, hardly any change at all; 3=a little better, but no noticeable change; 4=somewhat better, but the change has not made any real difference; 5=moderately better, and a slight but noticeable change; 6=better, and a definite improvement that has made a real and worthwhile difference; and 7=a great deal better, and a considerable improvement that has made all the difference.

Patients will complete the PGIC scale at the time points detailed in [Table 2](#).

6.1.7. Work Productivity and Activity Impairment Questionnaire

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

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

7. ASSESSMENT OF SAFETY

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

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

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

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

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

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

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

- all events of possible drug-induced liver injury with hyperbilirubinemia (defined as AST or ALT ≥ 3 times the ULN, plus either total bilirubin ≥ 2 times the ULN or INR > 1.5) or Hy's Law events require immediate study treatment cessation and reporting

as a serious adverse event. Refer to [Appendix R](#) for guidance regarding monitoring patients with elevated liver function tests.

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.

Medical occurrences that begin before signing ICF will be recorded on the medical history/current medical conditions section of the CRF

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period is defined for each patient as the time period from signature of the informed consent form to the end of the follow-up period. The follow-up period of recording of adverse events is defined as 6.0 months 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.

All adverse events that occur during the defined study period must be recorded on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events, and protocol defined adverse events of special interest (see Section 7.1.7) the serious and protocol defined adverse event report form must be completed and the serious adverse event or protocol defined adverse event of special interest must be reported immediately (Section 7.1.5.3). The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events and adverse events of special interest occurring in a patient after the defined study period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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

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

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

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

Further details are given in the Safety Monitoring Plan.

7.1.3. Severity of an Adverse Event

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

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

For severity grading of local tolerability (injection site erythema, induration, ecchymosis, and pain), refer to Section [7.9](#).

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 described in [Table 4](#).

Table 4: 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 Investigational Medicinal Product (IMP).	The relationship of an adverse event may be considered “no reasonable possibility” if it is clearly due to extraneous causes or if at least 2 of the following apply: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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 informed consent form 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 informed consent form will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient’s participation in this study.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one’s ability to conduct normal life functions)
 - is a congenital anomaly/birth defect
 - an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

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

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

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3x the upper limit of normal (ULN)
- total bilirubin increase of >2x ULN
- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])
- no other explanation for the observed abnormalities

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

7.1.5.2. Expectedness

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

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

For the purpose of SUSAR reporting, the version of the Investigator’s Brochure 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 Global Patient Safety and Pharmacovigilance 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 gender 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 Global Patient Safety and Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences form/extensible markup language (XML) file to the LSO and/or CRO for submission to the regulatory authorities, IEC/IRBs, and investigators, according to regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Blinding will be maintained for people who are involved directly in the study. Therefore, in case of a SUSAR, only the LSO or CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

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

7.1.5.3.2. Sponsor Responsibility

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

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

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

7.1.6. Protocol-Defined Adverse Events not for Expedited Reporting

Not applicable.

7.1.7. Protocol-Defined Adverse Events of Special Interest

For purposes of this protocol, the following treatment emergent events are considered protocol-defined adverse events of special interest to be sent to the sponsor's Global Patient Safety and Pharmacovigilance Department for evaluation:

- ophthalmic related adverse events of at least moderate severity,
- events of possible drug-induced liver injury (AST or ALT $\geq 3 \times$ the ULN, total bilirubin $\geq 2 \times$ the ULN, or INR > 1.5), Hy's Law events, or
- events of anaphylaxis and severe hypersensitivity reactions.

For guidance regarding monitoring of patients with elevated liver function tests, refer to [Appendix R](#). Anaphylaxis and severe hypersensitivity will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis ([Sampson et al 2006](#)) (also see [Appendix S](#)). In the event of suspected anaphylaxis and severe hypersensitivity, vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator. As a precaution, each site should have a resuscitation cart nearby.

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

7.1.8. Protocol Deviations Because of an Adverse Event

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

7.2. Pregnancy

Any female subject becoming pregnant during the study will discontinue IMP. All pregnancies of women participating in the study and female partners of men participating in the study, that occur during the study, or within 6.0 months after administration of the last dose of the IMP, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section [7.1.5.3](#)). The investigator is not required to report female subjects who are found to be pregnant between screening and baseline, provided no protocol-related procedures were applied.

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

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

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

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

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

Any administration of IMP that is not in accordance with the study protocol should be reported as an important deviation, if it meets the important deviation criteria specified in the protocol ([Appendix C](#)), it or as a deviation, in the patient's source documents, regardless of whether or not an adverse event occurs as a result. When meeting important protocol deviation criteria, all instances of incorrect IMP administration should be categorized in clinical trial management system.

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 or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. When the identification of the IMP is required, the investigator must follow the procedures for unblinding outlined in [Section 5.9.2](#).
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.

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

7.4. Clinical Laboratory Tests

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

- abnormal and not clinically significant
- abnormal and clinically significant

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

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

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 2. Clinical laboratory tests will be performed using the central laboratory. However, in case of abnormal coagulation during screening (run-in 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 T.

7.4.1. Other Clinical Laboratory Tests

7.4.1.1. Human Chorionic Gonadotropin Test

Serum β -HCG tests and urine β -HCG tests will be performed for all women of childbearing potential at time points described in Table 2. Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.4.1.2. Follicle-Stimulating Hormone Test

Postmenopausal women will have a follicle-stimulating hormone (FSH) test at screening (see Table 2).

7.4.1.3. Saliva Collection

Saliva samples (~ 1 mL) will be collected using a standardized protocol available in the laboratory manual at time points described in Table 2. Care should be taken to freeze at -70°C (or at/below -20°C if no -70°C freezer available) the properly collected saliva samples as soon as possible (3-5 minutes) after collection from the patient. For additional details see Appendix M.

7.5. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit only) and weight, will be performed at the time points detailed in [Table 2](#). A complete physical examination will include the following organ systems: general appearance; head, eyes, ears, nose, and throat; chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Any physical examination finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered an adverse event, recorded on the CRF, and monitored as described in [Section 7.1.2](#).

7.6. Vital Signs

Vital signs (pulse, systolic and diastolic blood pressure, oral temperature, and respiratory rate) will be measured at the time points detailed in [Table 2](#). All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

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

7.7. Electrocardiography

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

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

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

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

clinically significant should be recorded in the relevant CRF modules (eg, adverse event, medical history).

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

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

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

- abnormal and not clinically significant
- abnormal and clinically significant

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

7.8. Immunogenicity

Blood samples for serum ADA assessment will be collected at the time points detailed in [Table 2](#). Only the samples from fremanezumab-treated patients will be analyzed for ADAs. Blood samples for ADA assessment will also be collected upon observation of any severe hypersensitivity reaction and anaphylaxis. Bioanalytical personnel should be made aware of anaphylaxis occurrence as soon as possible in case an anti-fremanezumab IgE assay is needed.

Clinical criteria for diagnosing anaphylaxis are detailed in [Appendix S](#).

7.9. Assessment of Local Tolerability and Pain

Spontaneous reports of injection site reactions will be recorded as AEs according to the following severity assessment criteria

- Spontaneous reports of injection-site erythema, induration, and ecchymosis will be recorded according to measurements: 5 to ≤ 50 mm (mild), >50 to ≤ 100 mm (moderate), and >100 mm (severe).
- Spontaneous report of local pain after the injection will be recorded as mild, moderate or severe according to patient's self-report.
- Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.

7.10. Assessment of Suicidality

The study population being administered fremanezumab should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing fremanezumab in participants who experience signs of suicidal ideation or behavior without relevant medical history.

Families and caregivers of participants being treated with fremanezumab should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence

of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

The eC-SSRS will be used to assess the patient's suicidal ideation (severity and intensity) and behavior (Posner et al 2011). The time points when the eC-SSRS Baseline/Screening version and the eC-SSRS Since Last Visit version will be completed are detailed in Table 2. Any positive findings on the eC-SSRS Since Last Visit version requires evaluation by a physician or doctoral-level psychologist.

A positive finding will be defined as a current suicide ideation with some intent to act and no plan. The investigator, based on his/her medical judgment, will determine if the patient should be seen by a mental health specialist and if he/she should continue participating in the study. If a patient reports current suicide ideation with specific plan and intent, then the patient should be immediately discontinued from the study and seen by a mental health specialist.

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

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

7.11. Concomitant Therapy or Medication

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

8. ASSESSMENT OF PHARMACOKINETICS/BIOMARKERS/ PHARMACOGENOMICS/IMMUNOGENICITY

8.1. Pharmacokinetic Assessment

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

Blood samples (approximately 4 mL) for plasma concentration measurements of fremanezumab will be collected via venipuncture/indwelling catheter at time points detailed in [Table 2](#). Samples from patients who receive active IMP will be analyzed for concentration of fremanezumab using a validated method. Samples from patients who were randomized to receive placebo will not be analyzed (at the double-blind period only). Details on sample handling, storage, shipment, and analysis are given in [Appendix K](#).

8.2. Pharmacodynamics Assessment

Pharmacodynamic parameters are not evaluated in this study.

8.3. Immunogenicity Testing

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

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

Details on sample handling, storage, shipment, and analysis are provided in [Appendix L](#).

8.4. Assessment of Exploratory Biomarkers

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

Based on the known biology of CGRP's mechanism of action, biomarker assessment will potentially include measurement of CGRP and other potential mediators involved in migraine, as well as markers of bone remodeling, inflammation, and angiogenesis. Exploratory multiplex immunoassay panels will be applied to measure baseline levels and changes in proteins in various biofluids which may include urine, serum, plasma, and/or saliva. Whole blood RNA (via Paxgene tubes) will also be collected for future analysis.

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

8.5. Pharmacogenetics

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

9. STATISTICS

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, study with an open-label period to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc fremanezumab compared with placebo in patients with CM and EM with inadequate response to prior preventive treatments. Eligible patients will be randomized in a 1:1:1 ratio to receive a monthly dose of TEV-48125, quarterly dose of TEV-48125 at 675 mg followed by monthly placebo, or monthly placebo. Randomization will be stratified by gender, country, migraine classification (CM or EM), and special group of treatment failure (yes, no).

9.1. Sample Size and Power Considerations

In the Phase 2b study for CM (study LBR-101-021), the treatment difference between 675/225/225 mg and placebo in change from baseline in monthly average migraine days was 2.1 days (SD=5.2 days). In the phase 2b study for EM (study LBR-101-022), the treatment difference between 225 mg monthly dose and placebo in change from baseline in monthly average migraine days was 2.7 days (SD=4.1 days). In the Phase 3 study for CM (Study TV48125-CNS-30049), the treatment differences to placebo in change from baseline in monthly average migraine days were 1.7 days and 1.8 days for the quarterly dose and the monthly dose, respectively (SD=5.4 days). In the Phase 3 study for EM (Study TV48125-CNS-30050), the treatment differences to placebo in change from baseline in monthly average migraine days were 1.3 days and 1.5 days for the quarterly dose and the monthly dose, respectively (SD=3.4 days). Combining the information above, a treatment difference of 1.8 days is used. Considering the patient population is different from the previous studies, a SD of 6 days is used to account for the complexity and uncertainty of this study.

A sample size of 705 (235 patients per treatment group) evaluable patients completing the study is needed for 90% power to show a 1.8 difference in migraine days (assuming a common standard deviation [SD] of 6 days) at an alpha level of 0.05. Assuming a 12% discontinuation rate, 268 patients per treatment group will be randomized in the study.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

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

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

9.2.2. 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 study drug and have at least 10 days of post baseline efficacy assessment on the primary endpoint.

9.2.3. Safety Analysis Set

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

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

9.2.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the mITT analysis set including only patients who complete the study without important protocol deviations or any deviations/omissions of the study drug 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 diary entries completed for the entire study period will be imputed. The monthly average number of headache days/hours will be calculated based on the observed data prorated to a 28-day rate for those patients who had at least 10 days of post-baseline diary data. It is believed that at least 10 days of diary data should provide a reasonable estimate of patient's disease status in the study while only excluding limited number of patients from efficacy analysis (those who had less than 10 days of diary data) to minimize potential bias. In calculation of a patient's monthly number of days/hours of efficacy variables during the 4-week period after each dose of study drug for months 1, 2, and 3, the following method will be used to handle the missing data:

- If a patient had ≥ 10 days of e-diary data for a month, the monthly number of days/hours of efficacy variables will be prorated to 28 days for that month.
- If a patient had < 10 days of e-diary data for a month, the monthly number of days/hours of efficacy variables will be considered as missing.

Detailed missing data imputation rules for the headache diary data will be described in the statistical analysis plan.

9.4. Study Population

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

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

9.5. Efficacy Analysis

For the purpose of this study, a migraine day is endorsed when at least one of the following occurs:

- a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache, meeting criteria for migraine with or without aura (see [Appendix U](#))
- a calendar day (0:00 to 23:59) demonstrating least 4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion is missing (see [Appendix U](#))
- a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine- specific acute medications (triptans and ergot compounds)

A headache day of at least moderate severity is endorsed when at least 1 of the following situations occurs:

- a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity
- a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine- specific acute medications (triptans and ergot compounds)

9.5.1. Primary Endpoint

The primary efficacy endpoint is the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab.

9.5.2. Secondary Endpoints

The secondary endpoints to further demonstrate efficacy are as follows:

- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab
- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of fremanezumab
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of fremanezumab

9.5.3. Exploratory Endpoints

The exploratory objectives are as follows:

- to further evaluate the efficacy of fremanezumab in adult migraine patients with inadequate response to 2 to 4 classes of prior preventive treatments
- to evaluate immunogenicity and impact of ADA on clinical outcome
- to explore the correlation between pharmacokinetic parameters and efficacy of fremanezumab
- to explore the relationship between genetic polymorphisms, migraine onset/severity and efficacy and safety of fremanezumab
- to explore the relationship between soluble exploratory biomarkers versus migraine response

The exploratory endpoints for the double-blind period are as follows:

- proportion of patients reaching at least 75% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of the study drug

- proportion of patients reaching at least 50% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed valproic acid for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past
- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the HIT-6, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after the administration of the 3rd dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at 4 weeks after administration of the 3rd dose of study drug

- mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale, at 4 weeks after the 3rd dose of study drug

The exploratory endpoints for the open-label period are as follows:

- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 4th dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of study drug
- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 4th dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 4th dose of the study drug
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of

study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug

- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed valproic acid for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the HIT-6, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after the administration of the 6th dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the 6th dose of study drug

- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale, at 4 weeks after the last 6th dose of study drug

The exploratory endpoints for both the double-blind and open-label periods are as follows:

- to evaluate the immunogenicity response of fremanezumab and the impact of ADAs on clinical outcomes in patients exposed to sc fremanezumab.
- to explore the relationship between genetic polymorphisms (including those within the calcitonin gene-related peptide (CGRP) receptor-ligand complex, in migraine-associated susceptibility genes, and in as-yet undiscovered loci) versus migraine onset/severity, adverse events to medication and fremanezumab efficacy
- to explore the relationship between exploratory biofluid biomarkers versus fremanezumab concentrations, adverse events and fremanezumab efficacy

9.5.4. Planned Method of Analysis

The mITT analysis set (Section 9.2.2) 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 will be analyzed using an analysis of covariance (ANCOVA) method. The model will include treatment, gender, region, special group of treatment failure (Yes or No), migraine classification (ie, CM or EM), and treatment-by-migraine classification interaction as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using the estimate statement. Ninety-five percent confidence intervals will be constructed for the least squares means differences between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo.

Note: Special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in [Appendix H](#).

9.5.4.2. Sensitivity Analysis

Sensitivity analysis will be performed by imputing missing migraine days of months 1-3 using multiple imputation method. The average migraine days of months 1-3 from each imputed data set will be analyzed using the same ANCOVA model as the primary efficacy analysis. Ninety-five percent confidence intervals for the least squares means differences between each fremanezumab treatment groups (monthly dose and quarterly dose) and placebo will be

constructed. The detailed SAS code for imputation and analysis procedure will be provided in the statistical analysis plan. This sensitivity analysis will be performed on the ITT analysis set.

Sensitivity analysis will also be performed using a mixed-effects repeated measures (MMRM) analysis model. If a patient is early terminated or has intermittent missing days and has fewer than 10 days of e-diary entries for a month, that month's value will be considered as missing. The MMRM model will include treatment, gender, region, special group of treatment failure (Yes or No), migraine classification (ie, CM or EM), month, treatment-by-migraine classification interaction, and treatment-by-month interaction as fixed effects, baseline value and years since onset of migraines as covariates, and patient in the repeated statement as a random effect. The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using the estimate statement. Ninety-five percent confidence intervals will be constructed for the least squares means differences between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo. This sensitivity analysis will be performed on the mITT analysis set.

Note: Special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in [Appendix H](#).

9.5.4.3. Secondary Efficacy Analysis

The continuous secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint. For the proportion of responders, defined as 50% or more reduction from baseline in the monthly average number of migraine days, a logistic regression model will be used with the following effects: treatment, gender, region, special group of treatment failure (Yes or No), and migraine classification (ie, CM or EM). The odds ratios, 95% confidence intervals for odds ratios, and p-values will be presented for each fremanezumab treatment group (monthly dose and quarterly dose).

9.5.4.4. Exploratory Efficacy Analysis

For the double-blind period, the continuous exploratory efficacy endpoints period will be analyzed similarly as the primary efficacy endpoint. For the proportions of responders for the double-blind period, a logistic regression model will be used similarly as the secondary efficacy endpoint.

For the open-label period, the exploratory efficacy endpoints will be summarized using descriptive statistics.

9.5.4.5. Subgroup Analysis

The ANCOVA analysis defined in Section [9.5.4.1](#) and MMRM analysis defined in Section [9.5.4.2](#) will also be applied for the following subgroups for the primary endpoint.

- age group (18-45 years, >45 years)
- sex (male, female)

- region (North America, Europe)
- migraine classification (CM, EM)

An exploratory analysis for the primary endpoint will also be performed by adding the treatment-by-region interaction to the primary analysis model to test whether treatment effects are homogenous across regions.

9.6. Multiple Comparisons and Multiplicity

The Hochberg's method along with hierarchical testing procedure for multiple comparisons between treatment groups (2 comparisons: fremanezumab monthly dose compared with placebo and fremanezumab quarterly dose compared with placebo) for the primary and secondary endpoint analyses will be used to maintain the experiment-wise type I error of 5%.

In the primary analysis, according to the Hochberg's method, if the null hypothesis is rejected for both the fremanezumab monthly and quarterly treatment groups at an alpha level of 5%, then no adjustment to the alpha level will be performed and both comparisons will be declared as statistically significant. The secondary variables will then be tested in the order as specified in Section 9.5.2 for both the fremanezumab monthly and quarterly treatment groups using the same procedure as the primary analysis. If the null hypothesis is not rejected for 1 of the doses at an alpha level of 5%, then the other dose will be tested using an alpha level of $5\%/2=2.5\%$, and the sequential testing will stop.

No multiplicity adjustments will be made for exploratory efficacy analyses.

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 2.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) 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 (i.e., reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

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

Safety data will be summarized descriptively overall and by treatment group. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. The denominator for categorical variables will exclude missing observations. Descriptive summaries of serious adverse events,

patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided as well.

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

9.8. Tolerability Analysis

Local tolerability findings will be listed and summarized descriptively.

9.9. Pharmacokinetic Analysis

Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point by treatment group and indication.

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

9.10. Pharmacokinetic/Pharmacodynamic Analysis

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

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

9.11. Exploratory Biomarker Analysis

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

9.12. Pharmacogenomic Analysis

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

9.13. Immunogenicity Analysis

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

9.14. Planned Interim Analysis

An interim analysis is planned when the last patient has completed the double-blind period. Final database lock will occur following the end of the open-label period.

The inferential analysis of efficacy variables for comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo will be done at the time of the first interim lock. The appropriate method for type 1 error control will be applied to the first interim analysis.

Efficacy analysis for the open-label portion of this study is considered exploratory and mainly descriptive. This analysis will be done at the time of the final database lock.

9.15. Reporting Deviations from the Statistical Plan

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

For the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint refer to [Appendix O](#).

11. COMPLIANCE STATEMENT

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

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

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the Investigator's Brochure 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 Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with competent authorities.

For the ethics expectations of informed consent competent authorities and independent ethics committee and institutional review board, confidentiality regarding study patients, and requirements for registration of the clinical study, see [Appendix D](#).

12. DATA MANAGEMENT AND RECORD KEEPING

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

13. FINANCING AND INSURANCE

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

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are 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 (FDA) 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. PUBLICATION POLICY

For information regarding the publication policy see [Appendix Q](#).

15. REFERENCES

- Anttila V, Winsvold BS, Gormley P, Kurth T, Bettella F, McMahon G, et al. Genome-wide meta-analysis identifies new susceptibility loci for migraine. *Nat Genet* 2013;45(8):912-7.
- Armour KL, Clark MR, Hadley AG, Williamson LM. Recombinant human IgG molecules lacking Fcγ receptor I binding and monocyte triggering activities. *Eur J Immunol* 1999;29(8):2613–24.
- Ashina M, Bendtsen L, Jensen R, Schifter S, Jansen-Olesen I, Olesen J. Plasma levels of calcitonin gene-related peptide in chronic tension-type headache. *Neurology* 2000;55(9):1335–40.
- Bagley CL, Rendas-Baum R, Maglente GA, Yan M, Varon SF, Lee J, et al. Validating Migraine-specific Quality of Life questionnaire v 2.1 in episodic and chronic migraine. *Headache* 2012;52(3):409-21.
- Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet Neurol* 2015a;14:1081-90.
- Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings ELH, Diener H, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet Neurol* 2015b;14:1091-100.
- Bigal ME, Lipton RB. Clinical course in migraine: conceptualizing migraine transformation. *Neurology* 2008;71(11):848-55.
- Eftekhari S, Edvinsson L. Possible sites of action of the new calcitonin gene-related peptide receptor antagonists. *Ther Adv Neurol Disord* 2010;3(6):369–78.
- Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. *Europ J Neurol* 2009;16:968-81.
- Food and Drug Administration (FDA). Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. 2012. Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf>.
- Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. *Cephalalgia* 2010;30(10):1179–86.
- Hewitt DJ, Aurora SK, Dodick DW, Goadsby PJ, Ge YJ, Bachman R, et al. Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. *Cephalalgia* 2011;31(6):712–22.
- Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat Rev Neurol* 2010;6(10):573–82.

Ho TW, Ferrari MD, Dodick DW, Galet V, Kost J, Fan X, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. *Lancet* 2008;372(9656):2115–23.

International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013;33(9):629-808.

Kosinski M, Bayliss MS, Bjorner JB, Ware JE Jr, Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res* 2003;12(8)963-74.

Kroenke K, Spitzer RL, Williams JB, Löwe B. The Patient Health Questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatry* 2010;32(4):345-59.

Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007;68(5):343–9.

Martelletti P, Katsarava Z, Lampl C, Magis D, Bendtsen L, Negro A, et al. Refractory chronic migraine: a Consensus Statement on clinical definition from the European Headache Federation. *J Headache Pain* 2014,15(47): 1-6.

Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, et al. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. *N Engl J Med* 2004;350(11):1104–10.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011;168(12):1266-77.

Puledda F, Messina R, and Goadsby PJ. An update on migraine: current understanding and future directions. *J Neurol* 2017 Mar 20. doi: 10.1007/s00415-017-8434-y. [Epub ahead of print]

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics* 1993; 4(5):353-65.

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

Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain* 2003;106(1-2):81–9.

Silberstein S, Tfelt-Hansen P, Dodick DQ, Limmroth V, Lipton RB, Pascual J, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. *Cephalalgia* 2008;28:484-95.

Spitzer RL, Kroenke K, Williams JBW. Validation and utility of self-report version of PRIME-MD: the PHQ primary care study. *JAMA* 1999;282(18):1737-44.

Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia* 1999a Mar;19(2):74,107-14.

Stewart WF, Lipton RB, Whyte J, Dowson A, Kolodner K, Liberman JN, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology* 1999b;53(5):988-94.

Tfelt-Hansen P, Pascual J, Ramadan N, Dahlöf C, Domenico D, Diener H-C, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. *Cephalalgia* 2012;32(1):6-38.

Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6™) across episodic and chronic migraine. *Cephalalgia* 2011;31(3):357-67.

Zeller J, Poulsen KT, Sutton JE, Abdiche YN, Collier S, Chopra R, et al. CGRP function-blocking antibodies inhibit neurogenic vasodilatation without affecting heart rate or arterial blood pressure in the rat. *Br J Pharmacol* 2008;155(7):1093–103.

16. SUMMARY OF CHANGES TO PROTOCOL**16.1. Amendment 01 Dated 23 October 2017**

The primary reason for this amendment is to fulfill all conditions raised during Voluntary Harmonisation Procedure (VHP)-procedure VHP1154 (VHP2017110) in association with the conditional approval received on October 17th, 2017. This amendment is primarily in the statistical section in response to VHP request. Clarification language about emergency unblinding was also added in response to VHP request. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). There is no change in inclusion or exclusion criteria. These changes will not 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
In the footer of every page, including the title page		
	Protocol Version 2 with Amendment 01, 23 October 2017	This addition was added for clarification as requested by VHP
Section 2.2 Exploratory Efficacy Objectives and Endpoints Other sections affected by this change: Section 9.5.3 Exploratory Endpoints, synopsis		
12-week period after the 4 th <u>1st</u> dose of study drug	12-week period after the 1 st dose of study drug	Typo
Section 4.3 Withdrawal Criteria and Procedures for the Patient		
ADA 6.0 months (180 225 days)	ADA 6.0 months (180 days)	Typo; correction to reflect the number of days in 6 months
Section 5.9.2 Blinding and Unblinding		
	In the event that the IRT system is not functioning for emergency unblinding, the next course of action is to contact via phone the IRT on-call customer support helpline for manual emergency unblinding. Additional contact details can be found in the pharmacy manual.	Text added per VHP request on emergency unblinding
Section 7.6 Vital Signs		
blood pressure, body <u>oral</u> temperature	blood pressure, oral temperature	Typo; correction to align with secondary safety/tolerability endpoints
Section 9.1 Sample Size and Power Considerations Other sections affected by this change: synopsis		
	In the Phase 2b study for CM (Study LBR-101-021), the treatment difference between 675/225/225 mg and placebo in	Text added per VHP request on statistics

Original text with changes shown	New wording	Reason/Justification for change
	<p>change from baseline in monthly average migraine days was 2.1 days (SD=5.2 days). In the phase 2b study for EM (Study LBR-101-022), the treatment difference between 225 mg monthly dose and placebo in change from baseline in monthly average migraine days was 2.7 days (SD=4.1 days). In the Phase 3 study for CM (Study TV48125-CNS-30049), the treatment differences to placebo in change from baseline in monthly average migraine days were 1.7 days and 1.8 days for the quarterly dose and the monthly dose, respectively (SD=5.4 days). In the Phase 3 study for EM (Study TV48125-CNS-30050), the treatment differences to placebo in change from baseline in monthly average migraine days were 1.3 days and 1.5 days for the quarterly dose and the monthly dose, respectively (SD=3.4 days). Combining the information above, a treatment difference of 1.8 days is used. Considering the patient population is different from the previous studies, a SD of 6 days is used to account for the complexity and uncertainty of this study.</p>	
Section 9.2.2 Modified Intent-to-Treat Analysis		
at least ± <u>10 days of</u> post baseline	at least 10 days of post baseline	Typo
Section 9.3 Data Handling Conventions		
<p>Efficacy variables from patients who do not have diary entries completed for the entire study period will be imputed. <u>The monthly average number of headache days/hours will be calculated based on the observed data prorated to a 28-day rate for those patients who had at least 10 days of post-baseline diary data. It is believed that at least 10 days of diary data should provide a reasonable estimate of patient’s disease status in the study while only excluding limited number of patients from efficacy analysis</u></p>	<p>Efficacy variables from patients who do not have diary entries completed for the entire study period will be imputed. The monthly average number of headache days/hours will be calculated based on the observed data prorated to a 28-day rate for those patients who had at least 10 days of post-baseline diary data. It is believed that at least 10 days of diary data should provide a reasonable estimate of patient’s</p>	<p>Text added per VHP request on statistics</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><u>(those who had less than 10 days of diary data) to minimize potential bias. In calculation of a patient’s monthly number of days/hours of efficacy variables during the 4-week period after each dose of study drug for months 1, 2, and 3, the following method will be used to handle the missing data:</u></p> <ul style="list-style-type: none"> • <u>If a patient had ≥10 days of e-diary data for a month, the monthly number of days/hours of efficacy variables will be prorated to 28 days for that month.</u> • <u>If a patient had <10 days of e-diary data for a month, the monthly number of days/hours of efficacy variables will be considered as missing.</u> <p>Detailed data imputation rules will be described in the statistical analysis plan.</p> <p>For all variables, the observed data from the patients will be used in the by visit summaries.</p>	<p>disease status in the study while only excluding limited number of patients from efficacy analysis (those who had less than 10 days of diary data) to minimize potential bias. In calculation of a patient’s monthly number of days/hours of efficacy variables during the 4-week period after each dose of study drug for months 1, 2, and 3, the following method will be used to handle the missing data:</p> <ul style="list-style-type: none"> • If a patient had ≥10 days of e-diary data for a month, the monthly number of days/hours of efficacy variables will be prorated to 28 days for that month. <p>If a patient had <10 days of e-diary data for a month, the monthly number of days/hours of efficacy variables will be considered as missing.</p>	
<p>Section 9.5.4.1 Primary Efficacy Analysis Other section affected by this change: synopsis</p>		
<p>(Yes or No), and migraine classification (ie, CM or EM), <u>and treatment-by-migraine classification interaction</u> as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. <u>The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using the estimate statement.</u> Ninety-five percent confidence intervals will be constructed for the least squares means differences between each fremanezumab treatment group (monthly dose and quarterly dose) <u>and placebo.</u></p>	<p>(Yes or No), and migraine classification (ie, CM or EM), and treatment-by-migraine classification interaction as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using the estimate statement. Ninety-five percent confidence intervals will be constructed for the least squares means differences between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo.</p>	<p>Text changed per VHP request on statistics</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>Section 9.5.4.2 Sensitivity Analysis Other section affected by this change: synopsis</p>		
<p>Sensitivity analysis will<u>may</u> be performed by imputing missing migraine days of months 1-3 using multiple imputation method. The average migraine days of months 1 to 3 from each imputed data set will be analyzed using the same ANCOVA- model as the primary efficacy analysis. <u>Ninety-five percent confidence intervals for the least square means differences between each fremaezumab treatment group (monthly dose and quarterly dose) and placebo will be constructed. The detailed SAS code for imputation and analysis procedure will be provided in the statistical analysis plan. This sensitivity analysis will be performed on the ITT analysis set.</u> Sensitivity analysis will<u>may</u> also</p>	<p>Sensitivity analysis will be performed by imputing missing migraine days of months 1-3 using multiple imputation method. The average migraine days of months 1 to 3 from each imputed data set will be analyzed using the same ANCOVA model as the primary efficacy analysis. Ninety-five percent confidence intervals for the least square means differences between each fremaezumab treatment group (monthly dose and quarterly dose) and placebo will be constructed. The detailed SAS code for imputation and analysis procedure will be provided in the statistical analysis plan. This sensitivity analysis will be performed on the ITT analysis set. Sensitivity analysis will also</p>	<p>Text added per VHP request on statistics</p>
<p>The MMRM model will include, treatment, gender, region, special group of treatment failure (Yes or No), migraine classification (ie, CM or EM), month, treatment-by-migraine classification interaction, and treatment-by-month interaction as fixed effects, baseline value and years since onset of migraines as covariates, and patient in the repeated statement as a random effect. The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using contrast the estimate statement. <u>Ninety-five percent confidence intervals will be constructed for the least squares means differences</u></p>	<p>The MMRM model will include treatment, gender, region, special group of treatment failure (Yes or No), migraine classification (ie, CM or EM), month, treatment-by-migraine classification interaction, and treatment-by-month interaction as fixed effects, baseline value and years since onset of migraines as covariates, and patient in the repeated statement as a random effect. The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using the estimate statement. Ninety-five percent confidence intervals will be constructed for the least squares means differences between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo. This</p>	<p>Text added per VHP request on statistics</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><u>between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo. This sensitivity analysis will be performed on the mITT analysis set.</u> Sensitivity analysis will be performed using the ITT analysis set.</p>	<p>sensitivity analysis will be performed on the mITT analysis set.</p>	
<p>Section 9.5.4.3 Secondary Efficacy Analysis Other section affected by this change: synopsis</p>		
<p><u>a logistic regression model will be used with the following effects: treatment, gender, region, special group of treatment failure (Yes or No), and migraine classification (ie, CM or EM). The odds ratios, 95% confidence intervals for odds ratios, and p-values will be presented for each fremanezumab treatment group (monthly dose and quarterly dose). Cochran-Mantel-Haenszel test will be used as appropriate.</u></p>	<p>a logistic regression model will be used with the following effects: treatment, gender, region, special group of treatment failure (Yes or No), and migraine classification (ie, CM or EM). The odds ratios, 95% confidence intervals for odds ratios, and p-values will be presented for each fremanezumab treatment group (monthly dose and quarterly dose).</p>	<p>Text changed per VHP request on statistics</p>
<p>Section 9.5.4.4 Exploratory Efficacy Analysis Other section affected by this change: synopsis</p>		
<p>double-blind period, the Cochran-Mantel-Haenszel test <u>a logistic regression model</u> will be used <u>similarly as the secondary efficacy endpoint.</u></p>	<p>double-blind period, a logistic regression model will be used similarly as the secondary efficacy endpoint.</p>	<p>Text changed per VHP request on statistics</p>
<p>Section 9.5.4.5 Subgroup Analysis</p>		
	<p><u>9.5.4.5 Subgroup Analysis</u> <u>The ANCOVA analysis defined in Section 9.5.4.1 and MMRM analysis defined in Section 9.5.4.2 will also be applied for the following subgroups for the primary endpoint.</u></p> <ul style="list-style-type: none"> • <u>age group (18-45 years, >45 years)</u> • <u>sex (male, female)</u> • <u>region (North America, Europe)</u> • <u>migraine classification (CM, EM)</u> <p><u>An exploratory analysis for the</u></p>	<p>Subsection added per VHP request on statistics</p>

Original text with changes shown	New wording	Reason/Justification for change
	<p><u>primary endpoint will also be performed by adding the treatment-by-region interaction to the primary analysis model to test whether treatment effects are homogenous across regions.</u></p>	
<p>Section 9.14 Planned Interim Analysis Other section affected by this change: synopsis</p>		
<p>A second interim <u>Final database lock will occur following the end of the open-label period.</u></p> <p><u>The inferential analysis of efficacy variables for comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo will be done at the time of the first interim lock. The appropriate method for type 1 error control will be applied to the first interim analysis.</u></p> <p><u>Efficacy analysis for the open-label portion of this study is considered exploratory and mainly descriptive. This analysis will be done at the time of the final database lock.</u></p>	<p>Final database lock will occur following the end of the open-label period.</p> <p>The inferential analysis of efficacy variables for comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo will be done at the time of the first interim lock. The appropriate method for type 1 error control will be applied to the first interim analysis.</p> <p>Efficacy analysis for the open-label portion of this study is considered exploratory and mainly descriptive. This analysis will be done at the time of the final database lock.</p>	<p>Text changed per VHP request on statistics</p>
<p>Appendix J Total Blood Volume</p>		
<p>^a A serum pregnancy test will be performed for women of childbearing potential at screening and at visit 8<u>only</u>.</p>	<p>^a A serum pregnancy test will be performed for women of childbearing potential at screening and at visit 8.</p>	<p>Typo; correction to be consistent with associated Table 2 (Study Procedures and Assessments)</p>

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

Sponsor's Authorized Representative	<p>[REDACTED]</p> <p>Teva Branded Pharmaceutical Products R&D, Inc.</p> <p>[REDACTED]</p>
Legal Representative of the Sponsor in the EU	<p>[REDACTED]</p> <p>Teva GmbH</p> <p>[REDACTED]</p>
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study	<p>[REDACTED]</p> <p>PRA Health Sciences</p> <p>[REDACTED]</p>
<p>Sponsor's Representative of Global Patient Safety and Pharmacovigilance</p> <p>For serious adverse events:</p> <p>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.</p>	<p>[REDACTED]</p> <p>Ratiopharm GmbH</p> <p>[REDACTED]</p>
Contract Research Organization	<p>Pharmaceutical Research Associates, Inc. 4130 Parklake Avenue Suite 400 Raleigh, North Carolina 27612 USA</p>
Central Clinical Laboratory	<p>Q SQUARED SOLUTIONS LLC 1600 Terrell Mill Road Suite 100 Marietta, GA 30067 USA</p>
Electronic Clinical Outcome Assessment	<p>eResearchTechnology, Inc. 1818 Market Street Philadelphia, PA 19103 USA</p>

<p>Central Electrocardiogram Evaluation</p>	<p>eResearchTechnology, Inc.1818 Market Street Suite 1000 Philadelphia, PA 19103 USA</p>
<p>Bioanalytical Pharmacokinetics Evaluation</p>	<p>[REDACTED] Teva Branded Pharmaceuticals R&D, Inc. [REDACTED] 145 Brandywine Parkway West Chester, PA 19380, USA [REDACTED] Teva Branded Pharmaceuticals R&D, Inc.</p>
<p>Bioanalytical Immunogenicity Evaluation</p>	<p>[REDACTED] Teva Branded Pharmaceuticals R&D [REDACTED] [REDACTED] 145 Brandywine Parkway West Chester, PA19380 USA</p>
<p>Pharmacogenomics/Biomarker Evaluation</p>	<p>Storage of samples: BioStorage Technologies, GmbH Receiving Department Im Leuschnerpark 1b 64347 Griesheim Germany [REDACTED] BioStorage Technologies, Inc. Receiving Department 2910 Fortune Circle West, Suite E Indianapolis, IN 46241, USA [REDACTED]</p>
<p>Randomization and Trial Supply Management (RTSM) vendor</p>	<p>Medidata Solutions 350 Hudson Street 9th Floor New York, NY 10014 USA</p>

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT**1. Procedures for Screening/Run-in Period (Visit 1, Days -28 to -1 Before Visit 2)**

The screening visit (visit 1) will take place during a run-in period not more than -28 days before the baseline 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 medication and treatment history
- perform clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis)
- perform physical examination, including height and weight
- perform 12-lead ECGs in triplicate
- perform vital signs measurement
- perform beta human chorionic gonadotropin (β -HCG) serum pregnancy test (for women of child-bearing potential)
- perform FSH for postmenopausal women only
- inform patients of study restrictions and compliance requirements
- complete eC-SSRS

Patients who meet all inclusion and none of the exclusion criteria will be given an electronic headache diary device and will be trained in its use and compliance requirements on the day of screening. Patients will complete electronic headache diary entries about the previous day daily beginning on day -27 (visit 1) through the EOT/early withdrawal visit (visit 8).

2. Procedures Before Administration of Investigational Medicinal Products (Baseline Visit 2, Day 0+3 Days)

Patients who meet all inclusion and none of the exclusion criteria at visit 1 will continue to visit 2 (week 0), when baseline assessments will be conducted.

The following procedures will be performed at visit 2:

- review inclusion and exclusion criteria
- assign randomization/treatment numbers and enter in CRF
- perform clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis)

- perform physical examination, including weight
- perform 12-lead ECGs in triplicate
- perform vital signs measurements
- perform urine pregnancy test (women of child bearing potential only)
- review study compliance
- review electronic headache diary
- obtain blood samples for plasma concentration of IMP prior to dosing
- obtain a blood sample for serum ADA assay prior to dosing
- obtain blood collection for serum, plasma, and RNA biomarker analysis
- obtain urine sample for biomarker analysis
- collect a saliva sample for biomarker analysis
- obtain blood samples for pharmacogenetics before study drug administration from patients who consent to this procedure
- complete HIT-6
- complete the MIDAS
- complete the PHQ-2/ PHQ-9. Patients will respond first to the PHQ-2. Patients will respond to questions 3 through 9 (unique questions) of the PHQ-9 only if PHQ-2 is positive.
- complete the MSQOL questionnaire
- complete the EQ-5D-5L questionnaire
- complete the WPAI questionnaire
- inquire about adverse events and health care resource utilization
- inquire about concomitant medication

3. Procedures During Administration of Investigational Medicinal Product (Double-Blind Period and Open-Label Period, Visits 2 Through 8, Days 0+3 Through 168±5 Days)

Patients will complete electronic headache diary entries about the previous day daily beginning on day -27 (visit 1) through the EOT/early withdrawal visit (visit 8).

Visit 2 (baseline, day 0+3 days)

After completion of pre-dose assessments, patients will be treated with IMP (for additional details regarding IMP administration, refer to Section 5.1).

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

- assess hypersensitivity and anaphylaxis
- inquire about post-dose adverse events before the patient leaves the study center

Visit 3 (week 4, day 28±3 days)

The following pre-dose procedures and assessments will be performed at visit 3:

- perform clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis)
- perform vital signs measurements
- perform urine pregnancy test (women of child bearing potential only)
- review study compliance
- review electronic headache diary
- obtain blood samples for plasma concentration of IMP prior to dosing
- obtain a blood sample for serum ADA assay prior to dosing
- obtain blood collection for serum, plasma, and RNA biomarker analysis
- obtain urine sample for biomarker analysis
- collect a saliva sample for biomarker analysis
- complete HIT-6
- complete MIDAS
- complete MSQOL questionnaire
- complete PGIC scale
- complete eC-SSRS
- inquire about adverse events and health care resource utilization inquire about concomitant medication

After completing pre-dose assessments, patients will be treated with IMP (for additional details regarding IMP administration, refer to Section 5.1).

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

- assessment of hypersensitivity and anaphylaxis
- inquire about post-dose adverse events before the patient leaves the study center

Visit 4 (week 8, day 56±3 days)

The following pre-dose procedures and assessments will be performed at visit 4:

- perform vital signs measurements
- perform urine pregnancy test (women of child bearing potential only)
- review study compliance

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- review electronic headache diary
- obtain blood samples for plasma concentration of IMP prior to dosing
- complete eC-SSRS
- inquire about adverse events and health care resource utilization
- inquire about concomitant medication

After completing pre-dose assessments, patients will be treated with IMP (for additional details regarding IMP administration, refer to Section 5.1).

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

- assess hypersensitivity and anaphylaxis
- inquire about post-dose adverse events before the patient leaves the study center

Visit 5 (week 12, day 84±3 days)

The following pre-dose procedures and assessments will be performed at visit 5:

- assign randomization/treatment numbers and enter in CRF
- perform clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis)
- perform physical examination, including weight
- perform 12-lead ECGs in triplicate
- perform vital signs measurements
- perform urine pregnancy test (women of child bearing potential only)
- review study compliance
- review electronic headache diary
- obtain blood samples for plasma concentration of IMP prior to dosing
- obtain a blood sample for serum ADA assay prior to dosing
- obtain blood collection for serum, plasma, and RNA biomarker analysis
- obtain urine sample for biomarker analysis
- collect a saliva sample for biomarker analysis
- complete HIT-6
- complete MIDAS
- complete PHQ-2/ PHQ-9. Patients will respond first to the PHQ-2. Patients will respond to questions 3 through 9 (unique questions) of the PHQ-9 only if PHQ-2 is positive.
- complete the MSQOL questionnaire

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- complete the EQ-5D-5L questionnaire
- complete PGIC scale
- complete WPAI questionnaire
- complete eC-SSRS
- inquire about adverse events and health care resource utilization
- inquire about concomitant medication

After completing pre-dose assessments, patients will be treated with IMP (for additional details regarding IMP administration, refer to Section 5.1).

The following procedures and assessments will be performed at visit 5 (week 12) after dosing:

- assess hypersensitivity and anaphylaxis
- inquire about post-dose adverse events before the patient leaves the study center

Visit 6 (week 16, day 112±5 days)

The following pre-dose procedures and assessments will be performed at visit 6:

- perform clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis)
- perform vital signs measurements
- perform urine pregnancy test (women of child bearing potential only)
- review study compliance
- review electronic headache diary
- obtain blood samples for plasma concentration of IMP prior to dosing
- obtain a blood sample for serum ADA assay prior to dosing
- obtain blood collection for serum, plasma, and RNA biomarker analysis
- obtain urine sample for biomarker analysis
- collect a saliva sample for biomarker analysis
- complete eC-SSRS
- inquire about adverse events and health care resource utilization
- inquire about concomitant medication

After completing pre-dose assessments, patients will be treated with IMP (for additional details regarding IMP administration, refer to Section 5.1).

The following procedures and assessments will be performed at visit 6 (week16) after dosing:

- assess hypersensitivity and anaphylaxis
- inquire about post-dose adverse events before the patient leaves the study center

Visit 7 (week 20, day 140±5 days)

The following pre-dose procedures and assessments will be performed at visit 7:

- perform vital signs measurements
- perform urine pregnancy test (women of child bearing potential only)
- review study compliance
- review electronic headache diary
- complete eC-SSRS
- inquire about adverse events and health care resource utilization
- inquire about concomitant medication

After completing pre-dose assessments, patients will be treated with IMP (for additional details regarding IMP administration, refer to Section 5.1).

The following procedures and assessments will be performed at visit 7 (week 20) after dosing:

- assess hypersensitivity and anaphylaxis
- inquire about post-dose adverse events before the patient leaves the study center

4. Procedures for End-of-Treatment/Early Termination (Week 24, Visit 8, Day 168±5 Days)

The following procedures and assessments will be performed at the EOT visit (visit 8)/early withdrawal visit:

- perform clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis)
- perform physical examination, including weight
- perform 12-lead ECGs in triplicate
- perform vital signs measurements
- perform β -HCG serum pregnancy test (for women of child-bearing potential)
- perform urine pregnancy test (women of child bearing potential only)
- review study compliance
- review electronic headache diary and return diary device
- obtain blood samples for plasma concentration of IMP
- obtain a blood sample for serum ADA assay

- obtain blood collection for serum, plasma, and RNA biomarker analysis
- obtain urine collection for biomarker analysis
- collect a saliva sample for biomarker analysis
- complete HIT-6
- complete MIDAS
- complete PHQ-2/ PHQ-9. Patients will respond first to the PHQ-2. Patients will respond to questions 3 through 9 (unique questions) of the PHQ-9 only if PHQ-2 is positive.
- complete MSQOL questionnaire
- complete EQ-5D-5L questionnaire
- complete PGIC scale
- complete WPAI questionnaire
- complete eC-SSRS
- inquire about adverse events and health care resource utilization
- inquire about concomitant medication
- assess hypersensitivity and anaphylaxis

5. Procedures for Follow up Period (Week 46, Visit 9, Day 320±15 Days)

The following procedures and assessments will be performed at the follow up visit (visit 9):

- Perform vital signs measurements
- obtain a blood sample for serum ADA assay
- inquire about adverse events and health care resource utilization
- inquire about concomitant medication

6. Procedures for Unscheduled Visits

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

Procedures performed during unscheduled visits include:

- review electronic diary data
- review study compliance
- perform vital signs measurements
- inquire about adverse events and health care resource utilization

- inquire about/review concomitant medications
- complete the eC-SSRS Since Last Visit version

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

APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

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

Important Deviations

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

When a 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.

Waivers in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol deviation. If such patient has already completed the study or has withdrawn early, no action will be taken but the deviation will be recorded.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member's responsibilities. This list must be updated throughout the study, as necessary.

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

Study Monitoring

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

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

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

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

Audit and Inspection

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

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

APPENDIX D. ETHICS

Informed Consent

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

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

Adult patients with a legally acceptable representative should provide informed consent according to national and local requirements.

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 have given written approval or a favorable opinion.

Confidentiality Regarding Study Patients

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

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

Registration of the Clinical Study

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

APPENDIX E. BIRTH CONTROL METHODS AND PREGNANCY TESTING

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

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

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

Women of non-childbearing potential are defined as:

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

Highly effective birth control methods:

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

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, or transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before 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 (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2 months before screening.
- Bilateral tubal occlusion
- vasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process.
- Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency).

Acceptable birth control methods:

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

Unacceptable birth control methods:

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

Male contraception:

Male subjects must always use a condom.

Vasectomy:

Use of contraceptive methods applies also to vasectomized men.

Pregnant female partners of male study participants:

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

APPENDIX F. LOST TO FOLLOW-UP

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

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

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

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

Storage and Security

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

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

Fremanezumab and placebo supplies must be kept in a secure area (eg, locked refrigerator) with access limited to the investigator and authorized staff at the investigational center.

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.

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.

Accountability

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

Each investigator is responsible for ensuring that deliveries of study drug and other study materials from Teva are correctly received, recorded, handled, stored, accounted for, and used in accordance with this protocol. In addition, each investigator is responsible for ensuring that study drug and other materials from Teva are correctly, safely, and properly disposed of in accordance with local regulations.

A record of study drug accountability (ie, study drug and other 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.

APPENDIX H. MEDICATIONS TO EVALUATE PATIENT QUALIFICATION FOR INADEQUATE RESPONSE TO PRIOR TREATMENT AND DISALLOWED DURING THE RUN-IN TREATMENT PERIOD, AND FOLLOW-UP PERIOD

(Martelletti et al 2014)

The use of the medications listed below on a daily basis for other indications is disallowed for the duration of the study.

- beta-blockers: propranolol, metoprolol, atenolol, and bisopropol
- anticonvulsants: topiramate
- tricyclics: amitriptyline
- calcium channel blocker: flunarizine
- angiotensin II receptor antagonist: candesartan
- onabotulinumtoxinA
- valproic acid

Any of the listed medications are allowed if given as topical or eye drops.

Other medications in the same classes but not included in this list are allowed.

Definition of Inadequate Response to Prior Treatment

- Patients must have documented inadequate response (in medical chart or by treating physician's confirmation) to 2 to 4 classes of prior preventive medications from the list above regardless of which class the medication belongs to.
- Inadequate response is defined as: no clinically meaningful improvement per treating physician's judgment, after at least 3 months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines, or when treatment has to be interrupted because of adverse events that made it intolerable by the patient or the drug is contraindicated or not suitable for the patient. The 3 month period does not apply if the drug is intolerable or contraindicated or not suitable for the patient.
- If onabotulinumtoxinA is a previous preventive medication, at least 2 sets of injections and 3 months must have passed since the last set of injections prior to the screening visit

**APPENDIX I. ACCEPTABLE DOCUMENTATION OF PREVIOUS
TREATMENT FAILURES**

Medical record with medication's name (from [Appendix H](#)), treatment duration, dose level and reasons for discontinuation

OR

If the principal investigator is also the treating physician, the principal investigator can provide a dated and signed written note with the above information

OR

If the principal investigator is not the treating physician, the principal investigator can interview the treating physician to confirm the above information and document the interview with date and his/her signature

APPENDIX J. TOTAL BLOOD VOLUME

Total blood volume to be collected for each patient in this study is approximately 180.5 mL.

Total Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Serum chemistry, hematology, and coagulation	6.5	6	39
Serum β -HCG test ^a	3	2	6
FSH ^b	3	1	3
Pharmacokinetics	4	6	24
ADA	5	6	30
Biomarker	14.5 ^c	5	72.5
Pharmacogenomic ^d	6	1	6
Total	--	26	180.5

^a A serum pregnancy test will be performed for women of childbearing potential at screening and at visit 8.

^b Postmenopausal women only.

^c For each 14.5 mL sample, individual volumes will be 6 mL each for serum and plasma and 2.5 mL for RNA.

^d For patients who consent to pharmacogenomics testing.

ADA=antidrug antibody; β -HCG=beta-human chorionic gonadotropin; FSH=follicle-stimulating hormone; RNA=ribonucleic acid.

Appendix K. PHARMACOKINETICS SAMPLES

Specimen Sampling and Handling

For plasma collection, samples will be collected in K2EDTA anticoagulant tubes, inverted slowly 6 to 8 times to mix the contents, and placed on water/ice (approximately 4°C). Blood samples will be centrifuged (1500g, approximately 10 minutes, at 2 to 8°C) between 5 minutes and 1 hour after sampling. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Other measures should be taken as appropriate to prevent samples from heating significantly during centrifugation. Separated plasma will be transferred in approximately equal portions in the 2 provided labeled 2-mL polypropylene tubes (Sets A and B).

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

Shipment and Analysis of Samples

Plasma samples set A for all patients will be shipped from the investigational center to the central laboratory, where they will be stored until shipped to the sponsor or designee for analysis. Plasma samples set B for all patients will be shipped from the investigational center to the central laboratory once the set A samples are received at the central laboratory. Samples will be stored in an upright position at -70°C (or at/below -20°C if no -70°C freezer available) until shipment to bioanalytical laboratory. The bioanalytical laboratory will be notified before the shipment of the samples and will be sent the shipping information including the sample manifest when the samples are shipped. An electronic file containing the sample manifest will be emailed to the bioanalytical laboratory and the sponsor's representatives from bioanalytical departments for each shipment.

Set A samples will be transported with a temperature data logger and frozen with dry ice sufficient for 4 days, by next-day courier to the central laboratory or bioanalytical laboratory.

Set B samples will be shipped with a temperature data logger to the central laboratory and kept there until the end of the study unless requested by the sponsor. Instructions as to the disposition of the Set B samples will be provided by the sponsor.

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

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

Appendix L. IMMUNOGENICITY SAMPLES

Blood Sampling and Handling

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

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

Shipment and Analysis of Samples

Serum samples for set A all patients will be shipped from the investigational center to the central laboratory, where they will be stored until shipped to the sponsor or designee for analysis. Plasma samples set B for all patients will be shipped from the investigational center to the central laboratory once the set A samples are received at the central laboratory. Samples will be stored in an upright position at -70°C (or at/below -20°C if no -70°C freezer available) until shipment to bioanalytical laboratory. The bioanalytical laboratory will be notified before the shipment of the samples and will be sent the shipping information including the sample manifest when the samples are shipped. An electronic file containing the sample manifest will be emailed to the bioanalytical laboratory and the sponsor's representatives from bioanalytical departments for each shipment.

Set A samples will be transported frozen, with a temperature data logger and with dry ice sufficient for 4 days, by next-day courier to the central laboratory.

Set B samples will be shipped with a temperature data logger to the central laboratory and kept there until the end of the study unless requested by the sponsor. Instructions as to the disposition of the Set B samples will be provided by the sponsor.

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

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

Appendix M. EXPLORATORY BIOMARKERS SAMPLES

Blood and Urine Samples

Blood samples (total of 14.5 mL; 6 mL each for plasma and serum and 2.5 mL for RNA [PAXgene]) will be collected via venipuncture or indwelling catheter at the time points detailed in [Table 2](#) for serum, plasma, and RNA biomarker measures. Urine will be collected in parallel with blood collection. In addition, a 6-mL whole blood sample will be collected at baseline (or a later visit) for DNA. Blood samples for serum and plasma should be processed within 3-5 minutes of collection. Details for processing and handling of each type of biomarker sample will be outlined in the laboratory manual.

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

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

Shipment and Analysis of Blood and Urine Samples

Biomarker samples for serum, plasma, RNA, and urine will be stored within 3-5 minutes of processing at -70°C (or at/below -20°C if no -70°C freezer available) and sent to the central laboratory on dry ice, per instructions in the laboratory manual. Sample labels should include study number, patient randomization number, visit code, collection date and time, and indication that they are biomarker samples. Shipments should be made as specified in the laboratory manual. An electronic file containing sample demographics will be emailed to the respective biomarker laboratory and the sponsor's biomarker representative for each shipment.

Following DNA extractions of whole blood, the samples will be stored at -70°C (or at/below -20°C if no -70°C freezer available) and labeled with a new code (ie, double coding), so that genomic data will not be recorded with a patient number. Data will be kept confidential and stored separately.

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

Saliva Samples

Saliva samples should be collected using standard procedures as described in the Saliva Collection Handbook (SalivaBio). Briefly, saliva samples should be collected into high quality polypropylene tubes. Because saliva is subject to blood contamination, patients should not have blood in their mouth and should not have had dental procedures within 24 hours or brushed their teeth within the last hour prior to collection. They also should not have eaten a meal within the last hour prior to collection, and they should rinse their mouths with water 10 minutes before giving the saliva sample.

The most optimal method for collecting is via a method known as "passive drool." Patients should allow saliva to pool in their mouths for 1-2 minutes, then bring collection tube to their

mouth and allow the pooled saliva to spill into the collection tube. This should be repeated until sufficient volume is collected. It is important to leave approximately 15 to 20% of open air space in the tube to allow for expansion of saliva after freezing. Once the proper volume has been collected, the tube should be capped and frozen within 3-5 minutes at -70°C (or at/below -20°C if no -70°C freezer available) and stored at -70°C (or at/below -20°C if no -70°C freezer available) until it is shipped to the sample repository.

APPENDIX N. PHARMACOGENETIC ASSESSMENTS

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

Pharmacogenetic assessment will be performed based on study results. Samples will be used only for investigations related to headache or response to fremanezumab or related investigational medicinal products.

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

APPENDIX O. PRODUCT COMPLAINTS

Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical 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 P. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

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

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

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

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11 (USA) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

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

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

Data Quality Control

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

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

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

An interim database lock will occur following the end-of-double-blind treatment visit (visit 5) of the last patient. A second interim lock will occur following the end of the open-label period. At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

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

Investigator Responsibilities

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

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

- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

APPENDIX Q. PUBLICATION POLICY

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results: “Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements:

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

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

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

APPENDIX R. GUIDANCE ON SAFETY MONITORING

Guidance on Monitoring Patients with Elevated Liver Function Tests

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

In any case of elevated ALT or AST to a level exceeding $\geq 2 \times$ the ULN (including patients whose baseline ALT or AST levels are $\geq 2 \times$ and $\leq 3 \times$ the ULN, who may be enrolled in the study), a thorough medical history and physical examination with a focus on liver disease should be undertaken.¹ In addition, the patient should be instructed to refrain from alcoholic beverages.

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

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

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

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

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

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

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

- the baseline value was above the ULN and ALT or AST is $\geq 2 \times$ the baseline value

Additional Tests/Evaluations:

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

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

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

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

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

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

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

- Alanine aminotransferase, AST, GGT, ALP, total bilirubin, direct bilirubin, indirect bilirubin, CBC and differential count (to assess for eosinophilia), and INR should be monitored twice a week.

- At least for every other measurement, the tests should be sent to the central laboratory. The rest of the tests may be sent to a local laboratory. The INR should always be sent to a local laboratory.

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

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

- The IMP should be discontinued immediately, and the early withdrawal visit should be performed.
- For follow-up guidance, please see below section “Follow-Up of Liver Enzymes After Stopping Rules Are Met.”

Stopping Rules

In the following circumstances, the IMP will be discontinued immediately:

- any increase in ALT or AST to $\geq 3 \times$ the ULN, combined with INR $>1.5 \times$ the ULN or total bilirubin $>2 \times$ the ULN
- any increase in ALT or AST to $\geq 3 \times$ the ULN, which is accompanied by symptoms clearly associated with impaired liver function (eg, vomiting, nausea, fever, rash, and eosinophilia) and not deemed related to other diseases (eg, vomiting or nausea triggered by cluster headache)
- any increase in ALT or AST to levels ≥ 5 but $<8 \times$ the ULN, which is persistent for ≥ 2 weeks of repeated measurements
- any increase in ALT or AST to levels $\geq 8 \times$ the ULN
- in any case where monitoring of liver enzymes cannot be performed according to the protocol guidance

Follow-Up of Liver Enzymes After Stopping Rules Are Met

- A patient who meets the above criteria for discontinuation of the IMP should be invited to the investigational site to return the IMP. Early withdrawal visit activities should be performed as soon as possible.
- Liver enzymes should be monitored until normalization or stabilization of the abnormality, according to the discretion of the investigator.
- In any case, following the early withdrawal visit, the minimal follow-up period will be 30 days and will include measurement of liver enzymes at least once weekly (may be performed in local laboratory, with at least 1 test being sent to the central laboratory).

Every effort should be made to complete the additional tests/evaluations, as described above.

APPENDIX S. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

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

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

5. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least 1 of the following:
 - a. respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
 - b. reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
6. Two or more of the following that occur rapidly after exposure to a *likely allergen for that patient* (minutes to several hours):
 - a. involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
7. Reduced blood pressure after exposure to a *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 T. CLINICAL LABORATORY TESTS**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
Blood urea nitrogen (BUN)	– Eosinophils	– Bacteria
Low density lipoprotein (LDL)	– Monocytes	– Erythrocytes
High density lipoprotein (HDL)	– Basophils	– Leucocytes
Triglycerides	Lymphocytes atypical	– Crystals
Urate	Prothrombin International Normalized Ratio (INR)	– Casts
Alanine aminotransferase (ALT)		
Aspartate aminotransferase (AST)		
Lactate dehydrogenase (LDH)		
Gamma-glutamyl transpeptidase (GGT)		
Alkaline phosphatase		
Bicarbonate		
Carbon dioxide		
Protein		
Albumin		
Bilirubin		
Direct bilirubin		

APPENDIX U. 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 1 of the following:
 - nausea and/or vomiting
 - photophobia and phonophobia
- e. e. not better accounted for by another ICHD-3 diagnosis

Migraine with Aura

- a. at least 2 attacks fulfilling criteria B and C
- b. 1 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
- d. not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

APPENDIX V. INJECTION INSTRUCTIONS

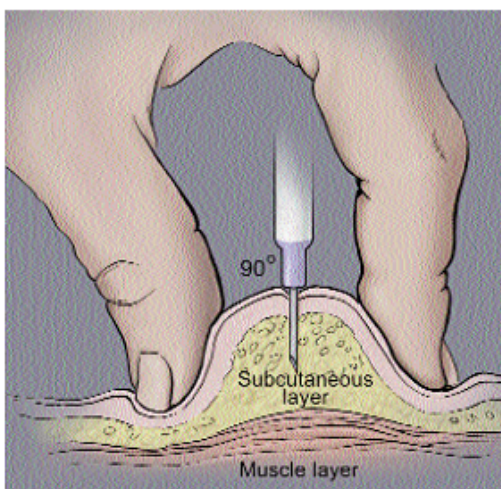
Patient Education

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

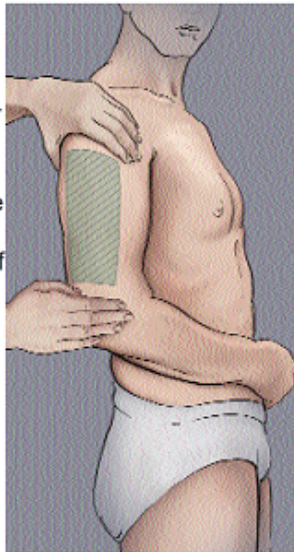
1. Check the label for correct medication.
2. Remove the soft metal or plastic cap protecting the rubber stopper of the vial.
3. If the medication vial or pen can be used for more than one dose, record the date and time on the label.

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.

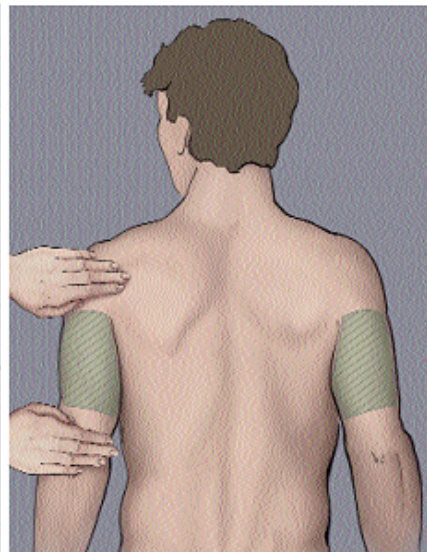
Locating injection sites

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.

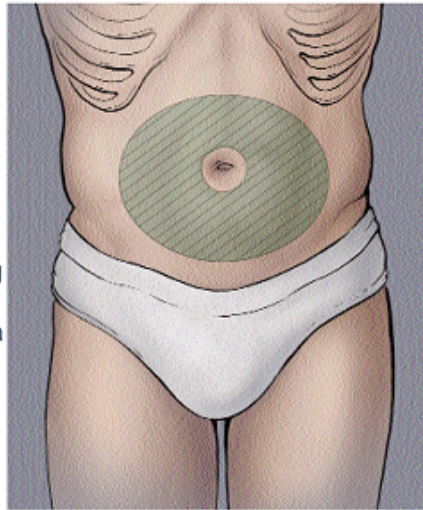


Injection sites on the front of the thigh.

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."

- o Place the syringe or needle in a hard plastic or metal container with a tightly secured lid.
- o Do not re-cap needles after use. Keep the container out of the reach of children or pets.
- o 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

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Bethesda, MD 20892

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

6/2012



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