Clinical Study Protocol

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

Study Number TV48125-CNS-30088

NCT05458011

Protocol with Amendment 02 Approval Date: 08 March 2023

Clinical Study Protocol with Amendment 02 with Revision 01

Study Number TV48125-CNS-30088

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study with an Open-Label Treatment Period of Fremanezumab Administered Subcutaneously Monthly or Quarterly for the Preventive Treatment of Migraine in Adult Chinese Patients

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

A Study to Test if Fremanezumab is Effective in Relieving Migraine

Efficacy and Safety Study (Phase 3)

IND number: Not applicable; NDA number: Not applicable; BLA number: Not applicable; EudraCT number: Not applicable

EMA Decision number of Pediatric Investigation Plan: P/0411/2019

Article 45 or 46 of 1901/2006 does not apply

Protocol with Amendment 02 with Revision 01 Version Date: 08 March 2023

Sponsor

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

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

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation; current GCP as directed by China National Medical Products Administration and National Health Commission; United States Code of Federal Regulations and European Union Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures.

Confidentiality Statement

AMENDMENT HISTORY

The protocol for Study TV48125-CNS-30088 (original protocol dated 11 November 2020) has been amended and reissued as follows:

Amendment 02 with Revision 01	08 March 2023 22 patients randomized/enrolled to date
Amendment 02	14 February 2023 20 patients randomized/enrolled to date
Administrative Letter 01	26 July 2022
Amendment 01	15 September 2021 0 patients randomized/enrolled to date
Revision 01	01 April 2021 0 patients randomized/enrolled to date

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

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02 with Revision 01 Version Date: 08 March 2023

IND number: Not applicable; NDA number: Not applicable; BLA number: Not applicable; EudraCT number: Not applicable

EMA Decision number of Pediatric Investigation Plan: P/0411/2019

Article 45 or 46 of 1901/2006 does not apply

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study with an Open-Label Treatment Period of Fremanezumab Administered Subcutaneously Monthly or Quarterly for the Preventive Treatment of Migraine in Adult Chinese Patients

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

Tel: _____

I have read the protocol with amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

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

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

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

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]		

Executed signature pages are maintained within the Trial Master File.

CLINICAL STUDY PROTOCOL SYNOPSIS

with Amendment 02 with Revision 01

Study TV48125-CNS-30088

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study with an Open-Label Treatment Period of Fremanezumab Administered Subcutaneously Monthly or Quarterly for the Preventive Treatment of Migraine in Adult Chinese Patients

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

Investigational New Drug (IND) Number: Not applicable; **New Drug Application (NDA) Number:** Not applicable; **Biological License Application (BLA) Number:** Not applicable; **EudraCT Number:** Not applicable

EMA Decision number of Pediatric Investigation Plan: P/0411/2019; **Article 45 or 46 of 1901/2006 does not apply**

Name of Test Investigational Medicinal Product (IMP): Fremanezumab

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

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

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

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 30 investigational centers in China.

Countries Planned: The study is planned to be conducted in China.

Planned Study Period: approximately quarter 3 (Q3) 2022 to approximately quarter 2 (Q2) 2024

Number of Patients Planned (total): Approximately 372 patients (93 patients in each active treatment group and 186 patients in the placebo group) are planned to be enrolled in this study to have approximately 328 patients who complete the study (82 patients in each active treatment group and 164 patients in the placebo group); a 12% discontinuation rate is anticipated. The primary efficacy analysis will consider all fremanezumab-treated patients as 1 group.

Study Population: The study population will be composed of female and male patients, 18 to 70 years of age, inclusive, with a history of migraine (as defined by International Classification of Headache Disorders, 3rd revision [ICHD-3] criteria [IHS 2018, CMAPS 2016]) for at least 12 months prior to screening and a prospectively documented diagnosis of migraine confirmed via a review of headache data recorded daily in an electronic headache diary device during a 28-day baseline period. Guidelines consider preventive therapies as the standard for the treatment of migraine because of the frequency of headaches and high degree of disability. Accordingly, up to 30% of patients will be allowed to continue on a stable dose regimen of 1 migraine preventive medication listed in Appendix K for migraine or for other chronic conditions, which lists medications with reasonable efficacy for migraine prevention. Medications that may be used for migraine prevention that are not in this appendix are considered to have questionable efficacy and are therefore allowed for all patients but will not be counted toward the 30% limit. Patients must have been taking a stable dose of a medication for at

least 2 months of consecutive use prior to screening and do not expect to change dosing regimens or to change to another medication during the treatment phase of the study. Acute medications for breakthrough migraine are allowed. This study will include both patients with episodic migraine (EM) and patients with chronic migraine (CM), as in previous studies (eg, the global HALO studies and the pivotal studies for Japan [Dodick et al 2018b, Silberstein et al 2017, Sakai et al 2021a, 2021b]) that demonstrated similar effect size across efficacy and safety endpoints for both populations. Nevertheless, the enrollment minimum of either migraine type will be 30% to ensure a reasonable number of patients from migraine type. In addition, primary efficacy analysis will be stratified by EM and CM, and subgroup analysis for EM and CM will be conducted.

Primary and Secondary Objectives and Endpoints:

The primary and secondary study objectives and endpoints are presented in Table 1. Note that, for endpoints that are based on a monthly average, "baseline" refers to the monthly average value during the 28-day baseline period.

Table 1: Primary and Secondary Study Objectives and Endpoints

Objectives	Endpoints
The **primary objective** of the study is to demonstrate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine. The primary efficacy analysis will consider all fremanezumab-treated patients as 1 group.	The primary endpoint is the mean change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP.
The **secondary objective** of the study is to further demonstrate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine. The secondary efficacy analyses will consider all fremanezumab-treated patients as 1 group.	The secondary endpoints are as follows: • mean change from baseline in the number of migraine days during the 4-week period after the 1st dose of IMP • mean change from baseline in the monthly average number of days that any acute headache medications were used during the 12-week period after the 1st dose of IMP • 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 IMP • mean change from baseline in the monthly average number of days with headache of at least moderate severity during the 12-week period after the 1st dose of IMP
A **secondary objective** of the study is to evaluate the safety and tolerability of fremanezumab	The safety/tolerability endpoints are as follows: • occurrence of adverse events throughout the study

Objectives	Endpoints
administered as monthly and quarterly sc injections to adult Chinese patients with migraine.	• 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: 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 • assessment of the immunogenicity of fremanezumab and the impact of ADAs on clinical outcomes in patients exposed to sc fremanezumab • assessment of the ADA incidence and characteristics (eg, titer, kinetics, and neutralizing activities)

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

Pharmacokinetic and Other Objectives and Endpoints

Pharmacokinetic and other endpoints to address the objective to further characterize fremanezumab safety, efficacy, and pharmacokinetics are as follows:

- assessment of plasma concentration of fremanezumab during the 12-week period after the 1st dose of IMP and at the follow-up visit using a population pharmacokinetic modeling approach

[redacted]

[redacted]

General Study Design: This is a multicenter, randomized, double-blind, placebo-controlled study with an open-label treatment period to evaluate the efficacy, safety, and tolerability of monthly and quarterly subcutaneous (sc) fremanezumab for the preventive treatment of migraine in adults.

The study will consist of a screening visit, a baseline period (4 weeks), a 12-week double-blind treatment period, a 12-week open-label treatment period, and a follow-up period lasting approximately 3 months after the last dose of IMP (ie, 2 months after the end of treatment [EOT]/early termination [ET] visit).

Randomization using electronic interactive response technology (IRT) will be stratified based on preventive medication use and migraine type (EM or CM) to ensure balance.

Patients will be randomized to receive treatment with 1 of the following regimens:

- fremanezumab 225 mg sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; one 225-mg injection and 2 placebo injections at visit 2 and one 225-mg injection at visits 3 and 4
- fremanezumab 675 mg sc once a quarter (once at the beginning of the 12-week double-blind treatment period), for a total of 1 dose; three 225-mg injections at visit 2 and 1 placebo injection at visits 3 and 4 or
- placebo sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; 3 placebo injections at visit 2 and 1 placebo injection at visits 3 and 4

Patients must return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration. Additional details on these visits are provided in the protocol.

During the 12-week open-label treatment period, patients will receive fremanezumab 225 mg sc once a month (approximately every 4 weeks) for a total of 3 doses (one 225-mg injection at visits 5, 6, and 7).

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

Follow-up visits for ADA sample collection will occur approximately 1 month and 3 months after the last dose of study drug (visit 7), at the EOT/ET visit (visit 8) and at the end of study (EOS) visit (visit 9), respectively. The EOS is defined as the last visit of the last patient (follow-up visit, visit 9). Two interim analyses are planned. A first 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 (visit 5). A second interim database lock will occur following the end of the open-label period (visit 8). Final database lock will occur following the end of the follow-up period.

The schedule of study procedures and assessments is shown in Table 3.

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

The purpose of the study is to confirm the efficacy and safety of fremanezumab in adult Chinese patients with the diagnosis of migraine in China. Patients with migraine who successfully complete a 4-week baseline period and meet the eligibility criteria will be included in the study. At their 2nd visit, patients will be given either fremanezumab (the study drug) at 1 of 2 dosing regimens or placebo (looks like the study drug but has no medicine in it); they will also receive either fremanezumab or placebo at the 3rd and 4th study visits. At the 5th, 6th, and 7th visits, all patients in the study will receive the same dose of fremanezumab. Comparing fremanezumab and placebo will show if fremanezumab works or if it is the same as not having any treatment at all. The study staff will track patients' health and migraine symptoms during the treatment period. During the first 12-week treatment period (the 2nd, 3rd, and 4th visits), no one will know who got fremanezumab or placebo. This is called a "blind" and helps keep the results more accurate. During the second 12-week treatment period (the 5th, 6th, and 7th visits), the study staff and patients will know that all the patients got fremanezumab.

Following the treatment period, patients will go back to their regular physicians.

Method of Randomization and Blinding: This is a randomized, double-blind, placebo-controlled study with stratification based on preventive medication use and migraine type (CM vs EM). For treatment during the double-blind period, patients will be randomized in a 1:1:2 ratio within the appropriate stratum to receive fremanezumab monthly, fremanezumab quarterly, or placebo, respectively, as assigned by the IRT. Additionally, the IRT will manage initial drug supply, maintenance of adequate IMP supplies at each study center, and study randomization centrally. At the time of each study visit when the study drug is administered during the double-blind treatment period, the IRT will be queried, and the site personnel will retrieve and administer a 1.5 mL-volume from each syringe contained in the appropriately numbered kit(s).

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

IMPs: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate

The dosing regimens of fremanezumab to be evaluated in the double-blind treatment period of this study (225 mg once a month [approximately every 4 weeks, monthly] and 675 mg once every 3 months [approximately every 12 weeks, quarterly]) have been approved in the United States (US), the European Union, Japan, Korea, Australia, Canada, Israel, and many other countries and are commercially available in these countries. Inclusion of a placebo control group is consistent with guidelines for controlled studies of preventive treatment of migraine in adults (Silberstein et al 2008) and the Classification Committee of the International Headache Society guidelines for controlled trials of drugs in migraine, 3rd edition (Tfelt-Hansen et al 2012).

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

Adequate kit supply for upcoming study visits will be managed by the IRT and kept on-site.

Treatment (active or placebo) will be administered at visit 2, visit 3, and visit 4. Active treatment will be administered to all patients at visit 5, visit 6, and visit 7. Final treatment evaluation will be performed at visit 8 (EOT), approximately 4 weeks after administration of the last dose of study drug.

The IMP is defined as the test IMP (fremanezumab) and matching placebo IMP. Fremanezumab and placebo are characterized in Table 2.

Table 2: Investigational Medicinal Products Used in the Study

IMP name	**Fremanezumab, a fully humanized IgG2Δa/kappa mAb**	**Placebo**
Trade name and INN, if applicable, or company-assigned number	AJOVY Fremanezumab TEV-48125	Placebo
Formulation	Prefilled syringes containing 150 mg/mL of active ingredient: fremanezumab Inactive ingredients include L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate-80, disodium EDTA dihydrate, and water for injection	Prefilled syringes containing 1.5 mL of the same inactive vehicle and excipients that are in the active injections Inactive ingredients include L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate-80, disodium EDTA dihydrate, and water for injection
Unit dose strength(s)/ Dosage level(s)	225 mg	None
Route of administration	sc injection	sc injection
Dosing instructions	Quarterly: fremanezumab 675 mg as 3 injections (225 mg/1.5 mL) at visit 2; 1 placebo (1.5 mL) injection at visits 3 and 4 Monthly: fremanezumab 225 mg as 1 injection (225 mg/1.5 mL) and 2 placebo (1.5 mL) injections at visit 2; fremanezumab 225 mg as 1 injection (225 mg/1.5 mL) at visits 3 and 4	3 placebo (1.5 mL) injections at visit 2; 1 placebo (1.5 mL) injection at visits 3 and 4
Packaging	A uniquely numbered kit containing 1 prefilled syringe stored (refrigerated at 2°C to 8°C) on site	A uniquely numbered kit containing 1 prefilled syringe stored (refrigerated at 2°C to 8°C) on site
Manufacturer	**Drug substance:** [redacted] **Drug product:** [redacted]	[redacted]

EDTA=ethylenediaminetetraacetic acid; IgG2Δa=immunoglobulin G2Δa; IMP=investigational medicinal product; INN=international nonproprietary name; mAb=monoclonal antibody; sc=subcutaneous.

The recommended sc injection sites follow the Instructions for Use in the US-approved AJOVY Prescribing Information (2020). Appropriate injection sites are back of upper arms, stomach area (abdomen), and front of thighs. Fremanezumab should not be injected into an area that is tender, red, bruised, callused, tattooed, or hard; that has scars; or that has stretch marks.

Study drug should be removed from the refrigerator and allowed to equilibrate at room temperature for 30 minutes before administration of the study drug. The total number of sc injections and their injection site locations will be recorded on the case report form for each dosing visit (visits 2 through 7).

Test IMP: Fremanezumab

Reference IMP: Not applicable.

Placebo IMP: Matching placebo for fremanezumab

Duration of Patient Participation and Maximal Exposure to IMP: The total duration of patient participation in the study is planned to be approximately 9 months (including a screening visit, a 28-day baseline period, a 12-week double-blind treatment period, a 12-week open-label treatment period, and a follow-up period lasting approximately 3 months after the last dose of IMP (ie, 2 months after the EOT/ET visit).

The maximal exposure to IMP is 675 mg of fremanezumab, administered either once a month (ie, 1 dose of 225 mg approximately every 4 weeks) or once a quarter (ie, 3 doses of 225 mg during a single visit) during the 12-week double-blind treatment period. During the 12-week open-label treatment period, all patients will receive 1 dose of 225 mg approximately every 4 weeks.

Study Duration: Approximately 2 years and from approximately Q3 2022 to approximately Q2 2024

End of Study: EOS is defined as the last visit of the last patient.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: After the EOT visit (visit 8), patients will return to the care of their primary physician(s) for migraine management.

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

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

b. The patient is a man or woman 18 to 70 years of age, 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 evaluation, including medical and psychiatric history, physical examination, laboratory tests, and cardiac monitoring.

e. The patient has a body weight ≥45 kg and body mass index within the range 17.5 to 34.9 kg/m^2 (inclusive).

f. The patient has a history of migraine (according to the ICHD-3 criteria [IHS 2018, CMAPS 2016, Appendix J]), or clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥12 months prior to screening (visit 1).

g. The patient has a clinical history of migraine that is confirmed during a prospectively recorded 28-day baseline period with the following characteristics:

   – Patient has 4 or more migraine days consistent with the characteristics of migraine (Appendix J) or probable migraine (a migraine subtype where only 1 migraine criterion is missing) or used a triptan or ergot derivative to treat an ongoing headache.

   – Patient has 2 or more days per month that are completely free of migraine headache or associated migraine symptoms.

h. The patient agrees not to initiate any preventive migraine medications during the 28-day baseline and double-blind treatment period. Up to 30% of patients are allowed to continue on 1 migraine preventive medication listed in Appendix K. However, patients must have been taking a stable dose of these medications for at least 2 months of consecutive use prior to screening (visit 1) with no expectation to change dosing regimen or change to another migraine preventive medications during the treatment phase of the study.

i. [Revision 1] Other concomitant medications (including herbal medicine) and acupuncture for migraine or other conditions are allowed for all patients, provided that the patient has been on a stable dose regimen for at least 2 months of consecutive use prior to screening (visit 1) with no expectation to change dosing regimen or change to another medication during the treatment phase of the study.

j. The patient demonstrated compliance with the electronic headache diary device during the baseline period by entry of headache data on a minimum of 21 days during the baseline period and throughout the treatment period (approximately 75% diary compliance during each period).

k. Women may be included only if they have either a negative serum beta-human chorionic gonadotropin test at screening (visit 1), are sterile, or are postmenopausal. Definitions of sterile and postmenopausal are given in Appendix E.

l. Women of childbearing potential whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening [visit 1]) and for 6 months after discontinuation of the IMP. Further details are included in Appendix E.

m. Men must be sterile or, if they are potentially fertile/reproductively competent (not congenitally sterile) and their female partners are of childbearing potential, should use highly effective birth control for the duration of the study. Definitions of women of non-childbearing potential, sterile, and postmenopausal women; male contraception; and highly effective birth control methods, including examples, are given in Appendix E.

n. 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 further visits, as applicable, and 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. Uses medications containing opioids (including codeine), barbiturates (including butalbital), or any combination product containing opioids or barbiturates (including butalbital) on more than 4 days during the screening period for the treatment of migraine or for any other reason.

b. Has used an intervention/device (eg, scheduled nerve blocks or transcranial magnetic stimulation) for migraine, or in the head or neck area, during the 2 months prior to screening (visit 1).

c. Clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, ocular disease, or complications of an infection that, in the opinion of the investigator, could interfere with the normal completion of study activities.

d. 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, generalized anxiety disorder, any suicide attempt in the past, suicidal ideation with a specific plan in the past 2 years prior to screening (visit 1), or current suicidal ideation.

e. History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], or 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.

f. [Revision 1] Known current infection or any history of infection with human immunodeficiency virus, tuberculosis, or Lyme disease, or a known or suspected active infection of coronavirus disease 2019 (COVID-19).

g. Past or current history of cancer in the past 5 years, except for appropriately treated non-melanoma skin carcinoma.

h. Pregnant or nursing females or females who plan to become pregnant during the study.

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

j. Participation in a clinical study of a new chemical entity or a prescription medicine within 2 months before screening (visit 1) (or 3 months in the case of a biologic if the half-life of the biologic is unknown) or 5 half-lives, whichever is longer, or is currently participating in another study of an IMP or medical device.

k. Any prior exposure to a mAb targeting the calcitonin gene–related peptide pathway (erenumab, eptinezumab, galcanezumab, or fremanezumab) during the 6 months

before the screening visit (visit 1), or exposure to gepants for less than 5 half-lives before screening.

l. Any finding in the baseline 12-lead electrocardiogram (ECG) considered clinically significant in the judgment of the investigator.

m. Any finding that, in the judgment of the investigator, is a clinically significant abnormality, including physical examination findings, and serum chemistry, hematology, coagulation, and urinalysis test values (abnormal test results may be repeated for confirmation).

n. Hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) >2× the upper limit of normal (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law at screening (visit 1).

o. Serum creatinine >1.5× ULN, clinically significant proteinuria, or evidence of renal disease at screening (visit 1).

p. Any clinically significant uncontrolled medical condition (treated or untreated).

q. History of alcohol or drug abuse during the past 2 years or drug dependence during the past 5 years.

r. The patient cannot participate or successfully complete the study, in the opinion of his/her 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 that, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study

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

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

u. Vulnerable patients (eg, members of a group with a hierarchical structure [such as medical, pharmacy, dental, and nursing students], subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, persons kept in detention, patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent).

v. The patient has previously participated in this study or has been assigned previously to a study with the IMP.

w. [New Criterion] Known current infection or history of infection in the past 6 months with hepatitis B or C viruses.

Statistical Considerations

Sample Size Rationale: Using study data from 2 completed Phase 3 US pivotal studies in migraine, it is estimated that 163 completers per treatment group (ie, combined fremanezumab groups and placebo group) will provide at least 90% power to detect the assumed treatment difference at a significance level of 0.05. Assuming a 12% discontinuation rate, approximately 372 patients will be randomized in this study (93 patients in each fremanezumab treatment group and 186 patients in the placebo group). The primary efficacy analysis will consider all fremanezumab-treated patients including both patients with EM and with CM, both monthly and quarterly dosing, as 1 group, since similar effect size has been observed across these subgroups from previous studies (Sakai et al 2021a, 2021b, Dodick et al 2018b, Silberstein et al 2017).

[redacted]

Primary Efficacy Analysis: The primary comparison will be made between the combined fremanezumab groups versus the placebo group in the primary efficacy variable: mean change from baseline in the monthly average number of migraine days during the 12-week double-blind treatment period after the 1st dose of IMP. The primary efficacy analysis will consider all fremanezumab-treated patients as 1 group.

An estimand in general includes the following 4 interrelated attributes: population of interest, variable (endpoint) of interest, intercurrent events (ICEs) along with the strategy for handling ICEs, and population-level summary for the endpoint.

The estimand selected for the primary analysis will assess the 12-week monthly average number of migraine days as initially randomized in the modified intent-to-treat analysis set.

The ICEs that may affect the efficacy endpoint will include instances where a patient early terminates from the IMP, receives the wrong IMP due to medication errors, or receives a rescue medication due to worsening symptoms. If observations are collected after the occurrences of the ICEs, the observations will be included in the calculation of the primary endpoint for the primary analysis.

The population-level summaries would be the adjusted mean changes from baseline in monthly average number of migraine days for the treatment groups and corresponding 95% confidence intervals.

An analysis of covariance will be performed, including treatment and stratification factors of migraine type (CM vs EM) and preventive medication use as fixed factors, as well as baseline number of migraine days as a covariate in the model. A 95% confidence interval for the

treatment difference between the combined fremanezumab groups versus the placebo group will be derived through an appropriate contrast, and p-values for the comparison will be presented. Further details will be presented in the statistical analysis plan.

Sensitivity Analysis: A sensitivity analysis may be performed to assess the primary estimand using mixed-effects model for repeated measures (MMRM) as a different missing data handling approach. The MMRM model will include treatment and stratification factors of migraine type (CM vs EM) and preventive medication use as fixed factors, as well as treatment-by-month interaction effects, and baseline number of migraine days as a covariate with an unstructured covariance matrix. The 12-week monthly average number of migraine days will be estimated by the least squares means of the overall treatment effect over 3 months.

An additional sensitivity analysis may be conducted to assess a different estimand, ie, treatment effects due to initially randomized treatment as actually taken. For patients who early terminate from study drugs in the monthly dosing regimen group or start a rescue medication, observations collected more than 4 weeks after the last dose or after starting a rescue medication will be treated as missing and will not be used in the calculation of monthly average number of migraine days.

Finally, the primary analysis will be repeated in the intent-to-treat analysis set (in case there is a 10% difference in patient count in any treatment group) and per-protocol analysis set.

Secondary Efficacy Analysis: Comparisons of secondary endpoints will be made between the combined fremanezumab groups versus the placebo group. Analysis of the continuous secondary endpoints (monthly average number of days of efficacy endpoints) will be similar to the analysis of the primary efficacy endpoint. The responder endpoints will be analyzed using logistic regression, including treatment and stratification factors of migraine type (CM vs EM), preventive medication use as fixed factors, as well as baseline number of migraine days as a covariate in the model. The secondary efficacy analyses will consider all fremanezumab-treated patients as 1 group. Further details will be presented in the statistical analysis plan.

A fixed-sequence, hierarchical testing procedure will be implemented to control the type 1 error rate at 0.05 for formal hypothesis testing of the secondary endpoints. Upon the success of the primary analysis, the first secondary endpoint in the sequence will be tested at a significance level of 0.05, and a p-value $\leq$0.05 will be interpreted inferentially. The process will continue following the order of the sequence until a point when the test for the efficacy endpoint fails, ie, 2-sided p-value >0.05. Subsequently, no further test results will be interpreted inferentially. The sequence of testing will follow the order specified for secondary endpoints in Section 9.5.2.

Multiple Comparisons and Multiplicity: The type 1 error will be controlled at a significance level of 0.05 using the appropriate method for the analysis of the primary efficacy endpoint, which is conducted by pooling the fremanezumab patients in the 2 dosing regimens.

A fixed-sequence, hierarchical testing procedure will be implemented upon achieving the success of the primary analysis to control the type 1 error rate at 0.05 for formal hypothesis testing of the secondary endpoints. The sequence of testing will follow the order specified for secondary endpoints in Section 9.5.2.

Analysis of Other Efficacy Endpoints: [redacted]

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

Safety assessments and time points are provided in Table 3.

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

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

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with the IMP.

Safety data will be summarized descriptively by treatment group. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient discontinuations 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: Spontaneously reported 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.

The pharmacokinetic data from this study will be pooled with the data from other fremanezumab studies and assessed for comparability. Summary statistics of fremanezumab pharmacokinetic parameters model-based predictions of weight-adjusted exposures will be compared and will be reported separately.

Immunogenicity Analysis: Summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. This analysis will be reported separately.

Planned Interim Analysis: Two interim analyses are planned. The first interim analysis is planned when the last patient has completed the double-blind period (visit 5). A second interim analysis is planned following the end of the open-label period (visit 8).

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 second database lock.

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LIST OF ABBREVIATIONS

Abbreviation	Term
21CFR	Title 21 Code of Federal Regulations
β-HCG	beta-human chorionic gonadotropin
ADA	antidrug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-time curve
BA	bioavailability
CDE	Center for Drug Evaluation
CDMS	clinical data management system
CGRP	calcitonin gene–related peptide
CH	cluster headache
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
CM	chronic migraine
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiography/electrocardiogram
eCRF	electronic case report form
EM	episodic migraine
EOT	end of treatment (visit)
EOS	end of study
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FM	fibromyalgia
GCP	Good Clinical Practice

Abbreviation	Term
GLP	Good Laboratory Practice
GPSP	Global Patient Safety and Pharmacovigilance
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd revision
IEC	Independent Ethics Committee
IHS	International Headache Society
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intent-to-treat
iv	intravenous(ly)
IRT	interactive response technology
LS	least square
LSO	local safety officer
mAb	monoclonal antibody
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
NOAEL	no-observed-adverse-effect level
NSAIDs	non-steroidal anti-inflammatory drugs
PEF	peak expiratory flow
PGIC	Patient Global Impression of Change
PP	per-protocol
PPK	population pharmacokinetic
PRN	taken as needed
PTH	posttraumatic headache
Q2	quarter 2
Q3	quarter 3
RBC	red blood cell
RSI	reference safety information
sc	subcutaneous(ly)
SD	standard deviation
SOP	standard operating procedure

Abbreviation	Term
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
ULN	upper limit of normal
US	United States
XML	extensible markup language

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

Migraine is a prevalent disease characterized by attacks of headache and associated symptoms (such as nausea, vomiting, photophobia, or phonophobia). The most common form of migraine occurs on less than 15 days per month and is referred to as episodic migraine (EM) (Lipton et al 2007). However, 3% to 6% of individuals with EM evolve, in any given year, to a significantly more disabling form of the disease 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, face considerable disability (Bigal and Lipton 2008).

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

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

Calcitonin gene–related peptide (CGRP) is a well-studied neuropeptide that is implicated in both central and peripheral processes underlying the pathophysiology of migraine (Eftekhari and Edvinsson 2010). Jugular levels of CGRP are increased during migraine attacks, and intravenous (iv) CGRP administration induces migraine-like headache in most individuals with migraine (Ashina et al 2000, Hansen et al 2010). CGRP is thought to be involved in the pathophysiology of migraine at all levels, peripherally (eg, neuronal sensitization, 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 (Bigal et al 2015a, Dodick et al 2018a, Dodick et al 2018b, Reuter et al 2018) and CM (Bigal et al 2015b, Silberstein et al 2017).

Fremanezumab (TEV-48125 [formerly LBR-101, PF-04427429, and RN-307]) is a fully humanized immunoglobulin G 2(delta)a/kappa monoclonal antibody (mAb), which has been developed for administration by the subcutaneous (sc) route in monthly or quarterly doses for the preventive treatment of migraine. Fremanezumab was approved for use in adults in the United States (US) on 14 September 2018 and was approved by the European Medicines Agency (EMA) in March 2019, and marketing authorization applications have been submitted and approved in several countries worldwide, including Canada, Australia, Korea, and Japan. Pivotal studies leading to these approvals have been published (Sakai et al 2021a, 2021b, Dodick et al 2018b, Silberstein et al 2017). Fremanezumab potently and selectively binds to both CGRP isoforms (α- and β-CGRP) to prevent them from binding to the CGRP receptor. Fremanezumab is specific for CGRP and does not bind to other closely related neuropeptides (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 efficacy and tolerability profiles of fremanezumab have been confirmed in the Phase 3 development program (HALO studies; monthly sc doses of 225 mg and quarterly sc doses of 675 mg).

In addition to migraine prevention from fremanezumab, more than half of total patients who had participated in the fremanezumab HALO long-term study who were surveyed about their treatment response reported that the treatment satisfactorily reduced related migraine-associated symptoms (55%), pain intensity (55%), migraine-associated disability (60%), and attack duration (69%; Lipton et al 2019). Pain intensity and migraine symptoms are 2 of the strongly correlated factors in disability due to migraine (Park et al 2008).

The purpose of the study is to confirm the efficacy and safety of fremanezumab in adult Chinese patients with the diagnosis of migraine in China. The epidemiology and treatment guidelines in China are similar to those in the US and the European Union (EU) and are summarized here. The 1-year prevalence of migraine in China was estimated to range from 9.3% to 10.5%, with incidences of 1.5% and 1.1%, respectively (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). In China, there are a large number of acute medications used for the treatment of migraine, although there is a lack of preventive treatment and excessive use of analgesic drugs (Liu et al 2013). Migraine treatment guidelines in China recommend the use of preventive treatment when the patient's quality of life, work, and study are seriously impaired, the migraine frequency is more than 2 times per month, acute treatment is ineffective or not tolerable, the patient experiences prolonged or extremely uncomfortable aura, acute treatment is used more than 6 to 8 times a month (continuously for at least 2 months), or the migraine attacks last for more than 72 hours. Treatment recommendations from the Chinese guidelines include nonsteroidal anti-inflammatory drugs (naproxen or aspirin), magnesium, riboflavin, or coenzyme Q10. Other medication recommendations include antiepileptics (topiramate and valproic acid), beta blockers (propranolol and metoprolol), and antidepressants (amitriptyline and venlafaxine) (CMAPS 2016). Of note, none of these molecules were developed for migraine based on attempts to target the biological dysfunction underlying the disease. They are all registered for another primary indication; efficacy of these drugs in migraine prevention was detected by serendipity and not by pathophysiological considerations. Furthermore, these drugs require titration, daily use, or multiple uses per day and are often associated with notable adverse events that reduce compliance with long-term use and prompt many patients to discontinue treatment (D'Amico and Tepper 2008, Tfelt-Hansen and Olesen 2012). Thus, there remains a significant need for safe and effective preventive migraine medications that are mechanism-based.

Refer to the locally approved prescribing information (for countries where fremanezumab is approved for the preventive treatment of migraine) or the current Investigator's Brochure (IB) (for countries where fremanezumab is not yet approved) for detailed information on the background, pharmaceutical particulars, nonclinical experience, and clinical experience with fremanezumab.

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 IB.

1.2.1. Nonclinical Studies

In vivo pharmacology studies of fremanezumab in animal models demonstrated 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 capsaicin-induced skin flare response in cynomolgus monkeys. In addition, efficacy was demonstrated in 2 rat models relevant for visceral/chronic pain.

Safety pharmacology parameters of fremanezumab were assessed in the pivotal toxicology studies in cynomolgus monkeys and a separate cardiovascular safety pharmacology study in male cynomolgus monkeys. There were no treatment-related changes in electrocardiograms (ECGs) or heart rates in the 1- and 3-month toxicity studies, and a single iv dose of fremanezumab 100 mg/kg did not result in changes in cardiovascular parameters or body temperature in monkeys. Moreover, no concern for fremanezumab to cause any biologically significant changes in the respiratory system and central nervous system of rats was identified in safety pharmacology studies after administration of sc doses of fremanezumab up to 300 mg/kg.

In the general toxicology studies conducted in rats and monkeys, no target organ toxicity was identified. In the chronic repeat-dose studies, the no-observed-adverse-effect level (NOAEL) ranged from 100 to 300 mg/kg/week administered either iv or sc (the highest doses tested in the studies). 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 considered to be the result of an incidental immune-mediated reaction and of doubtful relevance. No similar finding was noted in the 1- or 6-month studies in monkeys after administration of fremanezumab up to 300 mg/kg/week iv or sc and after high exposures.

Fremanezumab was administered to rats and monkeys by the iv or sc route for up to 3 months in duration and was found to be well tolerated. In addition, weekly sc administration of fremanezumab was well tolerated in a 6-month chronic toxicology study in monkeys.

In the pivotal 6-month chronic toxicity study in monkeys, no fremanezumab-related abnormalities were noted. No target organs were identified after microscopic evaluation, and no apparent adverse injection site reactions were recorded. The NOAEL of this study was considered to be at least the highest dose tested (ie, 300 mg/kg/week). At this dose, the calculated safety margins (based on area under the plasma drug concentration-time curve [AUC]) were at least 158-fold higher than the expected clinical exposure for the migraine indication, where the clinical dose was 225 mg sc once monthly.

Additionally, pivotal reproductive and developmental toxicity studies in animals with fremanezumab were completed. 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. In addition, a pre-and postnatal development study in rats was completed, and no treatment-related effects were noted.

Good Laboratory Practice (GLP) juvenile toxicity studies in rats and a non-GLP dose range-finding study in juvenile rats were conducted. No toxicological findings were noted following weekly sc administration of fremanezumab (starting from postnatal day 28) at dose levels up to 450 mg/kg/week.

In a standalone local tolerance study in rabbits, no injection site reactions were observed after administration of fremanezumab at 150 mg/mL when compared to vehicle control via 5 alternate routes of administration (iv, sc, intramuscular, paravenous, and intra-arterial).

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

After sc administration, mean systemic exposure values (calculated using AUC from time 0 to 168 hours after study drug administration) were 65% to 67% and 81% to 92% of the equivalent iv doses for rats (300 mg/kg dose) and monkey (100 and 300 mg/kg dose levels), respectively, demonstrating reasonably high sc bioavailability (BA). After multiple dosing in the 2 species, both iv and sc administration showed accumulation due to the long $t_{½}$ of the drug (longer than the period between dosing intervals).

Further details may be found in the current IB.

1.2.2. Clinical Studies

As of 30 August 2019, fremanezumab has been studied in a total of 24 completed, terminated, or ongoing clinical studies (9 in healthy subjects, 9 in adult patients with migraine, 1 in pediatric patients with migraine, 3 in patients with cluster headache [CH], 1 in patients with posttraumatic headache [PTH], and 1 in patients with fibromyalgia [FM]). As of 30 August 2019, a cumulative total of 5804 subjects and patients (536 healthy subjects, 4741 adult patients with migraine, 15 pediatric patients with migraine, 428 patients with CH, 77 patients with PTH, and 7 patients with FM) have been enrolled in the fremanezumab clinical studies. Of the enrolled subjects and patients, approximately 4972 patients (474 healthy subjects, 4062 adult patients with migraine, 15 pediatric patients with migraine, 380 patients with CH, 37 patients with PTH, and an estimated 4 patients with FM) have received at least 1 dose of fremanezumab.

A brief summary of clinical pharmacology and clinical safety and efficacy studies of fremanezumab follows. Further details may be found in the current IB.

1.2.2.1. Pharmacokinetics

Absorption

After single sc administrations of 225 and 675 mg of fremanezumab, the median time to maximum observed concentration in healthy subjects was 5 to 7 days. The estimated absolute BA of fremanezumab after sc administrations of 225 and 900 mg in healthy subjects was 55% to 66%, respectively. Dose proportionality, based on population pharmacokinetics, was observed between 225 and 900 mg. Steady state was approached by 3 months of dosing and was expected to be achieved by approximately 168 days (about 6 months) following 225-mg monthly and

675-mg quarterly dosing regimens. The median accumulation ratio, based on once-monthly and once-quarterly dosing regimens, was approximately 2.4 and 1.2, respectively. The pharmacokinetics of fremanezumab demonstrated bioequivalence when delivered sc via a prefilled syringe versus via an AI.

Distribution

Assuming the model-derived estimated BA of 66%, the volume of distribution for a typical patient was 3.6 L (35.1% coefficient of variation [CV]) following sc administrations of 225, 675, and 900 mg of fremanezumab.

Biotransformation

Similar to other mAbs, fremanezumab is expected to be degraded by enzymatic proteolysis into small peptides and amino acids.

Elimination

Assuming the model-derived estimated BA of 66%, the central CL for a typical patient was 0.09 L/day (23.4% CV) following sc administrations of 225, 675, and 900 mg of fremanezumab. Fremanezumab has an estimated terminal elimination half-life of 30 days.

Drug Interactions

No formal clinical drug interaction studies have been performed with fremanezumab. No pharmacokinetic drug interactions are expected based on the characteristics of fremanezumab. Furthermore, concomitant use of acute migraine treatments (specifically analgesics, ergots, and triptans) and preventive migraine medicinal products during the clinical studies did not affect the pharmacokinetics of fremanezumab.

Special Populations

A population pharmacokinetic analysis looking at age, race, sex, and weight was conducted on data from 2546 subjects. Approximately twice as much exposure is expected in the lowest body weight quartile (43.5 to 60.5 kg) compared to the highest body weight quartile (84.4 to 131.8 kg). However, body weight did not have an observed effect on the clinical efficacy based on the exposure-response analyses in patients with EM and CM. No dose adjustments are required for fremanezumab for migraine.

Renal or Hepatic Impairment

As mAbs are not known to be eliminated via renal pathways or to be metabolized in the liver, renal and hepatic impairments are not expected to impact the pharmacokinetics of fremanezumab. Patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2) have not been studied. A population pharmacokinetic analysis of integrated data from the fremanezumab clinical studies did not reveal a difference in the pharmacokinetics of fremanezumab in patients with mild to moderate renal impairment or hepatic impairment relative to those with normal renal or hepatic function.

1.2.2.2. Clinical Safety and Efficacy Studies

Fremanezumab was well tolerated with a favorable safety profile across the 8 completed Phase 1 studies in healthy subjects and the 2 completed Phase 2b studies and 2 completed Phase 3 studies in patients with migraine. The treatment-emergent adverse events reported in the Phase 1, Phase 2b, and Phase 3 studies were predominantly mild to moderate in severity. A specific "pattern of adverse events" that could be associated with a dose or a dose range of fremanezumab has not been identified, nor has a maximally tolerated dose been identified. Overall, the nature and occurrence of the reported treatment-related adverse events across the clinical program have not raised any specific safety concerns.

Two pivotal Phase 3 studies in CM and EM patients (Studies TV48125-CNS-30049 and TV48125-CNS-30050, respectively) confirmed the efficacy findings in Phase 2.
Study TV48125-CNS-30049 (Silberstein et al 2017) 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 675 mg fremanezumab [675 mg/placebo/placebo; N=379] and a starting dose of 675 mg fremanezumab followed by monthly 225 mg fremanezumab [675/225/225 mg; N=376]) and placebo (N=375) in adults (18 through 70 years of age) with CM. Patients who were on monotherapy (79%) and patients on stable doses of preventive medications (21%) were included in the study. The study consisted of a screening visit (visit 1), a baseline period lasting approximately 4 weeks (~28 days), and a treatment period lasting approximately 12 weeks.

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

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

Fremanezumab at the doses tested was generally safe and well tolerated for 3 months in patients with CM. Serious adverse events and adverse events leading to discontinuation from the study occurred infrequently and with similar incidence across the treatment groups. Most adverse

events were mild to moderate. Injection site–related adverse events were the most frequent treatment-related adverse events and were overall comparable across all treatment groups.

Study TV48125-CNS-30050 (Dodick et al 2018b) was a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy, safety, and tolerability of 2 dose regimens of sc fremanezumab (quarterly dose of 675 mg fremanezumab [675 mg/placebo/placebo; N=291] and monthly doses of 225 mg fremanezumab [225/225/225 mg; N=290]) and placebo (N=294) in adults (18 through 70 years of age) with EM. Patients who were on monotherapy (79%) and patients on stable doses of preventive medications (21%) were included in the study. The study consisted of a screening visit (visit 1), a baseline period lasting approximately 4 weeks (~28 days), and a treatment period lasting approximately 12 weeks.

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

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

Three Otsuka-sponsored studies in Japanese and Korean patients with EM and CM to evaluate the efficacy and safety of fremanezumab have been completed. These studies are 2 Phase 2b/3 double-blind, placebo-controlled studies in approximately 900 patients (406-102-00001 and 406-102-00002; Sakai et al 2021a, 2021b) and 1 long-term study in 50 patients (406-102-00003; manuscript accepted by Drug Safety as of 31 August 2021). The study designs of the Otsuka studies are the same as those of the HALO studies. Efficacy results demonstrated that treatment with fremanezumab monthly and quarterly was associated with statistically significant and clinically meaningful improvements on all primary and secondary efficacy measures. The safety profile observed in these studies was found to be consistent with that seen in the global pivotal efficacy studies; no safety signals were identified. These studies, together with the global HALO studies, led to marketing authorization in Japan and Korea in 2021.

Fremanezumab at the doses tested was generally safe and well tolerated for 3 months in patients with migraine. Serious adverse events and adverse events leading to discontinuation from the study occurred infrequently and with similar frequency across the treatment groups. Injection

site–related adverse events were the most frequent treatment-related adverse events and were comparable across all treatment groups.

One Phase 3 study (Study TV48125-CNS-30051) was conducted to further evaluate the long-term efficacy, safety, and tolerability of various dose regimens of fremanezumab in the preventive treatment of migraine (CM and EM). For the placebo rollover and the new patients, the efficacy profile during the first 3 months was similar to what was seen in Studies TV48125-CNS-30049 and TV48125-CNS-30050 for patients treated with fremanezumab. For all patients, efficacy was sustained for over 12 months in the long-term treatment period when patients received fremanezumab without interruption.

One additional placebo-controlled study followed by an open-label and follow-up period Phase 3b study (Study TV48125-CNS-30068 [Ferrari et al 2019]) was conducted to evaluate the efficacy, safety, and tolerability of monthly and quarterly fremanezumab compared with placebo in patients with CM and EM with documented inadequate response to 2 to 4 prior preventive migraine medications. The results of this study demonstrate that sc administration of fremanezumab via quarterly or monthly dosing over 3 months was effective and well tolerated in patients with CM and EM with documented prior failure of 2 to 4 classes of preventive migraine medications. Improvements were sustained throughout the 3-month duration of the double-blind portion of the study.

No clinically relevant changes in clinical laboratory values, vital signs measurements, or ECG findings have been observed in any of the studies to date.

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

One Phase 4 study (Study TV48125-MH-40142) was conducted (last patient last visit: 31 August 2021) to evaluate the efficacy and safety of fremanezumab in adult patients with migraine and comorbid major depressive disorder. The main objective of this study was to determine whether fremanezumab is effective in the preventive treatment of migraine in patients who also have major depressive disorder given the significant number of people afflicted by both diseases.

1.3. Known and Potential Benefits and Risks to Patients

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

Additional information regarding benefits and risks to patients may be found in the IB or approved Product Information or Summary of Product Characteristics applicable.

1.3.1.1. Identified Risks

1.3.1.1.1. General Disorders and Administrative Conditions

Reports of transient administration site reactions, including injection site bruising, injection site swelling, injection site pain, injection site pruritus, injection site induration, injection site erythema, injection site inflammation, injection site warmth, injection site dermatitis, injection

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

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

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

Type III hypersensitivity reactions occur as a consequence of an antibody response to the injected protein resulting in immune complex formation. Such immune complex formation and subsequent deposition in tissues may result in symptoms, including rash, urticaria, polyarthritis, myalgias, polysynovitis, fever, neuritis, and angioedema, and, if untreated and severe, can progress to glomerulonephritis. Type III hypersensitivity reactions were not observed in clinical trials with fremanezumab.

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

While no severe hypersensitivity or anaphylactic reactions related to fremanezumab administration occurred in the clinical development program for migraine, a small number of severe hypersensitivity reactions, including anaphylaxis, have been reported in the postmarketing period. One patient, who was taking multiple concomitant medications including lamotrigine and treated with fremanezumab, was reported to have Stevens-Johnson Syndrome. This reaction has also been rarely reported to occur in patients taking other mAbs targeting the CGRP pathway, along with concomitant medications including lamotrigine.

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 mAb rather than a pharmacologic toxicity and are not likely to be relevant in a clinical setting. Moreover, a confirmatory 6-month study could not repeat the findings.

1.3.1.2.2. Consequences of Calcitonin Gene–Related Peptide Inhibition

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

heart rate, blood pressure, or other cardiovascular parameters. No cardiovascular safety signals have been detected in the completed studies or in the postmarketing period.

1.3.2. Overall Benefit and Risk Assessment for This Study

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

Note that, for endpoints that are based on a monthly average, "baseline" refers to the monthly average value during the 28-day baseline period.

The primary endpoint was chosen based on the International Headache Society (IHS) guidelines for studies 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).

The primary and secondary study objectives and endpoints are the following:

Objectives	Endpoints
The **primary objective** of the study is to demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous (sc) injections to adult Chinese patients with migraine. The primary efficacy analysis will consider all fremanezumab-treated patients as 1 group.	The primary endpoint is the mean change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of investigational medicinal product (IMP).
The **secondary objective** of the study is to further demonstrate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine. The secondary efficacy analyses will consider all fremanezumab-treated patients as 1 group.	The secondary endpoints are as follows: • mean change from baseline in the number of migraine days during the 4-week period after the 1st dose of IMP • mean change from baseline in the monthly average number of days that any acute headache medications were used during the 12-week period after the 1st dose of IMP • 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 IMP • mean change from baseline in the monthly average number of days with headache of at least moderate severity during the 12-week period after the 1st dose of IMP
A **secondary objective** of the study is to evaluate the safety and tolerability of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine.	The safety/tolerability endpoints are as follows: • occurrence of adverse events throughout the study

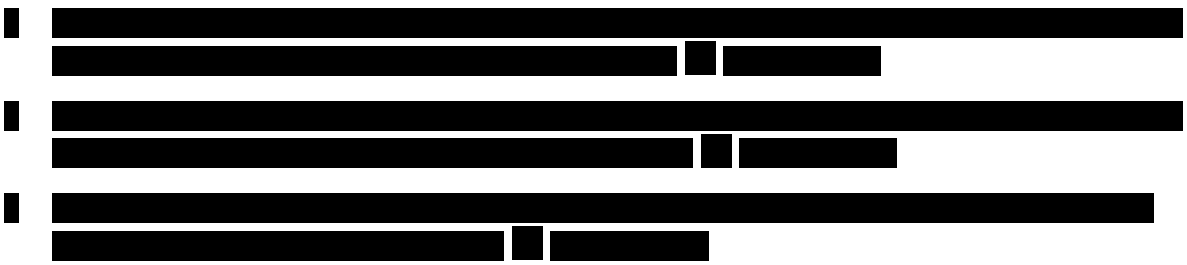
Objectives	Endpoints
	• clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results at specified time points • vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit (Note: Oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity.) • 12-lead electrocardiogram (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 • assessment of the immunogenicity of fremanezumab and the impact of antidrug antibodies (ADAs) on clinical outcomes in patients exposed to sc fremanezumab • assessment of the ADA incidence and characteristics (eg, titer, kinetics, and neutralizing activities)

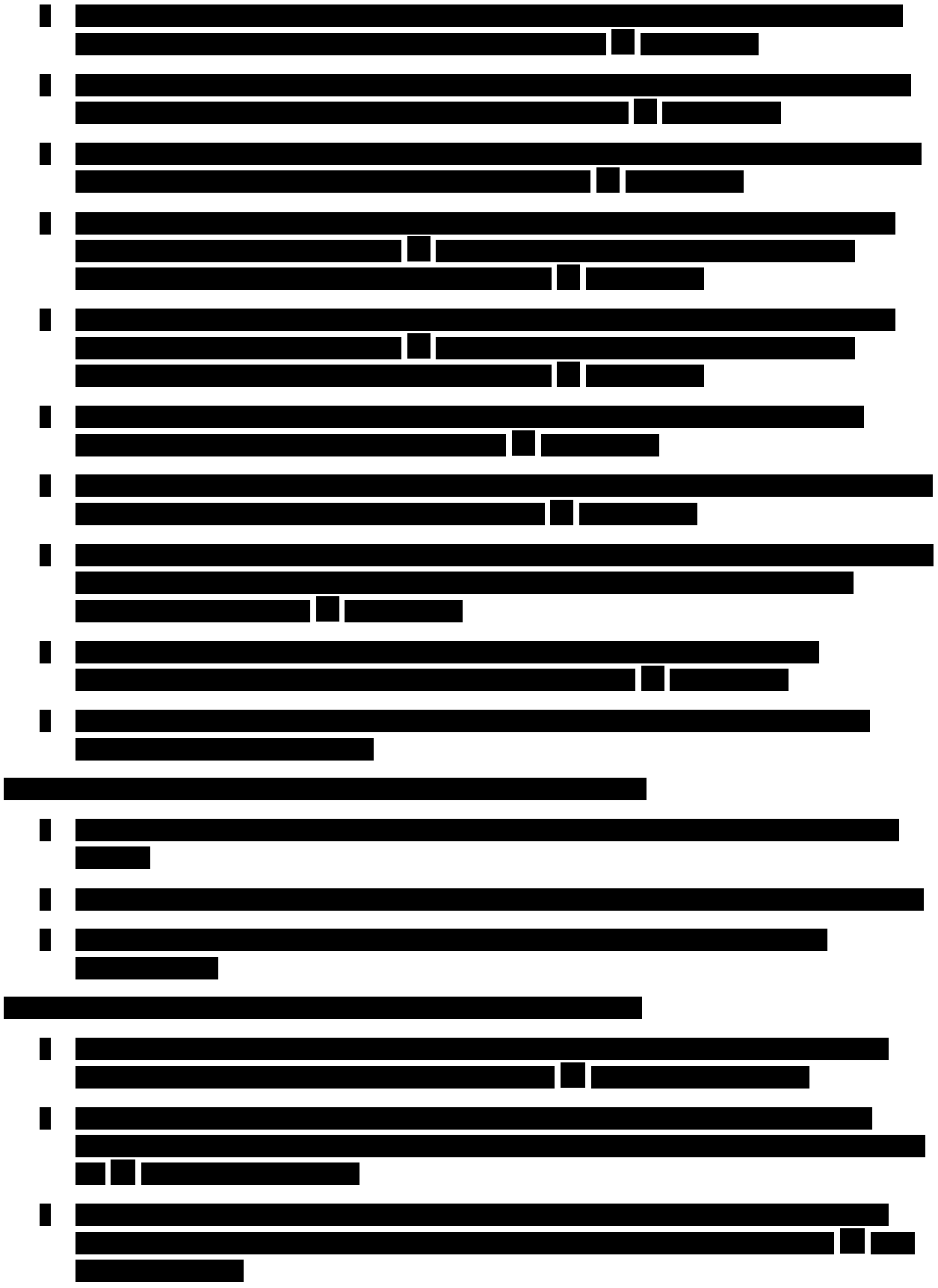
ADA=antidrug antibody; ECG=electrocardiogram; IMP=investigational medicinal product; sc=subcutaneous.

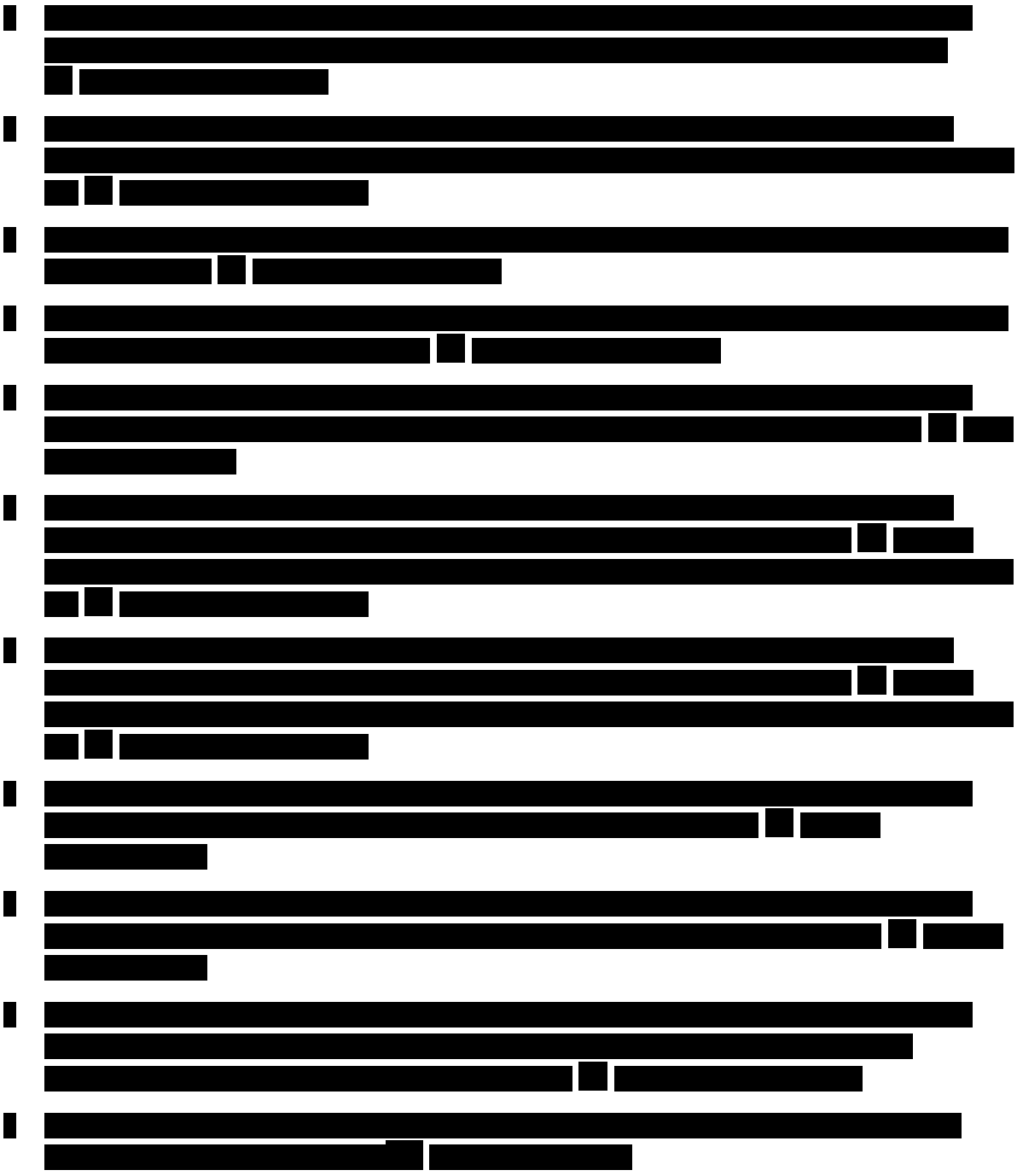
2.2. Pharmacokinetic and Other Objectives and Endpoints

Pharmacokinetic and other endpoints for the double-blind treatment period to address the objective to further characterize fremanezumab safety, efficacy, and pharmacokinetics are as follows:

- assessment of plasma concentration of fremanezumab during the 12-week period after the 1st dose of investigational medicinal product (IMP) and at the follow-up visit using a population pharmacokinetic modeling approach







3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a multicenter, randomized, double-blind, placebo-controlled study with an open-label treatment period to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc fremanezumab for the preventive treatment of migraine in adults. The study will consist of a screening visit, a baseline period (4 weeks), a 12-week double-blind treatment period, a 12-week open-label treatment period, and a follow-up period lasting approximately 3 months after the last dose of IMP (ie, 2 months after the end of treatment [EOT]/early termination [ET] visit). A follow-up visit 3 months after the last dose of fremanezumab will occur for ADA blood sample collection.

The total duration of patient participation in the study is planned to be approximately 9 months.

This study will include female and male patients, aged 18 to 70 years, inclusive, with a history of migraine (as defined by the International Classification of Headache Disorders, 3rd revision [ICHD-3] criteria [IHS 2018, CMAPS 2016]) for at least 12 months prior to screening and a prospectively documented diagnosis of migraine confirmed via a review of headache data recorded daily in an electronic headache diary device during a 28-day baseline period.

Up to 30% of patients will be allowed to continue on a stable dose of 1 preventive migraine medication listed in Appendix K for migraine prevention or for other chronic conditions that they were using before screening (patients must have been taking a stable dose of these medications for at least 2 months of consecutive use prior to screening and do not expect to change dosing regimens or to change to another medication during the treatment phase of the study). Patients will be allowed to use acute medications to treat breakthrough migraines as needed, with the exception of medications containing opioids and barbiturates, which cannot be used on more than 4 days during the screening period for the treatment of migraine or for any other reason. Traditional Chinese therapy (including herbal medicine) and acupuncture are allowed if the patient is on a stable dose/regimen for at least 2 months (consecutive) before screening.

After completing the informed consent process (screening visit [visit 1]), patients will be screened for eligibility. Eligible patients will enter a 28-day baseline period. Headache information will be captured daily during the screening/baseline period and treatment period using an electronic headache diary device.

After completing the baseline period, patients will be asked to return to the study center on day 1 (visit 2). Patients who have confirmed migraine and meet all other eligibility criteria (including electronic headache diary device compliance criteria during the 28-day baseline period) will be randomly assigned in a 1:1:2 ratio to 1 of 3 treatment groups:

- fremanezumab 225 mg sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; one 225-mg injection and 2 placebo injections at visit 2 and one 225-mg injection at visits 3 and 4
- fremanezumab 675 mg sc once a quarter (once at the beginning of the 12-week double-blind treatment period), for a total of 1 dose; three 225-mg injections at visit 2 and 1 placebo injection at visits 3 and 4 or

- placebo sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; 3 placebo injections at visit 2 and 1 placebo injection at visits 3 and 4

Patients must return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration. Additional details on these visits are provided in Section 8.1.

During the 12-week open-label treatment period, patients will receive fremanezumab 225 mg sc once a month (approximately every 4 weeks) for a total of 3 doses (one 225-mg injection at visits 5, 6, and 7).

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

Randomization using electronic interactive response technology (IRT) will be stratified based on migraine type (CM vs EM) and preventive medication use to ensure balance. Blinded treatment will be administered sc once monthly (ie, approximately every 4 weeks), for a total of 3 doses. First treatment administration will occur at visit 2 (day 1), and additional doses will be administered at visits 3 and 4.

The Patient Global Impression of Change (PGIC) scale, safety evaluations, and blood draws for pharmacokinetic and immunogenicity analysis will be performed throughout the study according to the schedule of study procedures and assessments (Table 3).

Patients will have treatment evaluations performed at visit 8 (EOT visit), approximately 4 weeks after administration of the final dose of study drug.

Follow-up visits for ADA sample collection will occur approximately 1 month and 3 months after the last dose of study drug (visit 7), at the EOT/ET visit (visit 8) and at the end of study (EOS) visit (visit 9), respectively.

Patients who discontinue treatment prematurely should be encouraged to continue to attend the regular scheduled visits and complete the prescribed safety and efficacy evaluations through the EOT/ET visit and the follow-up visit, if at all possible.

Patients who both discontinue treatment and also withdraw from the study should have EOT/ET visit procedures/assessments (Table 3) performed on the last day that the patient receives the IMP or as soon as possible thereafter. The patient should also return for the follow-up visit approximately 3 months after the last dose IMP if at all possible.

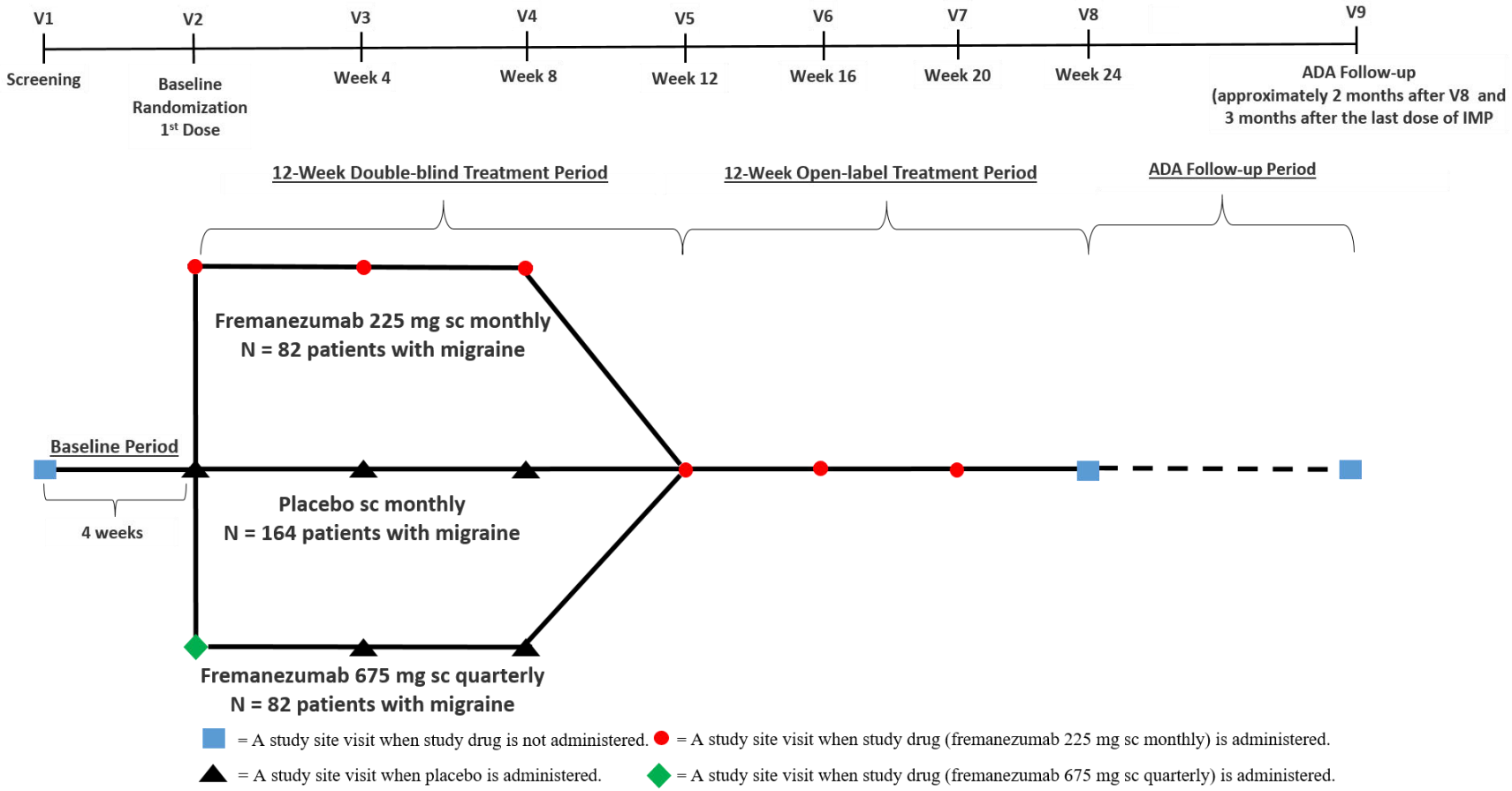
The EOS is defined as the last visit of the last patient (follow-up visit, visit 9). Two interim analyses are planned. The first interim database lock will occur following the end of the double-blind treatment period of the last patient for analysis of that portion of the study data (visit 5). A second interim database lock will occur following the end of the open-label period (visit 8). Final database lock will occur following the end of the follow-up period.

The study duration will be approximately 2 years, from approximately quarter 3 (Q3) 2022 to approximately quarter 2 (Q2) 2024.

The study schematic diagram is presented in Figure 1.

In the event of an emergency situation (eg, pandemic or potential pandemic), the investigational center will inform the patient of the safeguards being taken and will discuss their willingness or feasibility to come to the site for upcoming visits. If an ongoing patient cannot go to the site, the Medical Monitor will be notified to discuss further plans for that patient.

Figure 1: Overall Study Schematic Diagram



ADA=antidrug antibody; IMP=investigational medicinal product; N=planned number of patients in the study population; sc=subcutaneous; V=visit.
Note: Blood samples for plasma drug concentration will be collected at visits 2, 3, and 4. Patients will be asked to return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration (one being 3 to 10 days after either visit 2, visit 3, or visit 4 and the other being 15 to 20 days after either visit 2, visit 3, or visit 4). If 2 additional visits are not possible for the patient, then the patient must return for only 1 additional pharmacokinetic blood sampling at either of the aforementioned time points. When patients return to the study center for additional blood sampling, then inquiries about adverse events and concomitant medications will be performed.

3.2. Planned Number of Patients and Countries

Approximately 372 patients (93 patients in each active treatment group and 186 patients in the placebo group) are planned to be enrolled in this study to have approximately 328 patients who complete the study (82 patients in each active treatment group and 164 patients in the placebo group); a 12% discontinuation rate is anticipated.

The study is planned to be conducted in China in approximately 30 investigational centers. The study is expected to start in approximately Q3 2022 and last until approximately Q2 2024.

3.3. Justification for Study Design and Selection of Population

Efficacy has been demonstrated in patients in North America, Europe, Japan, and Korea in the fremanezumab pivotal studies, the HALO studies, which led to its approval in the US, the EU, Australia, Canada, Taiwan, Hong Kong, Brazil, Mexico, Israel, and several other countries. (Section 1.2.2). Additional double-blind, placebo-controlled studies have been completed in Japan and South Korea and have demonstrated consistent efficacy and safety profiles. Those studies, together with the HALO studies, led to approval in Japan and Korea (Dodick et al 2018b, Silberstein et al 2017, Sakai et al 2021a, 2021b). The pharmacokinetic and safety/tolerability profiles of fremanezumab are consistent among non-Japanese and Japanese patients (as well as Korean patients), as demonstrated in the pharmacokinetic bridging study in western and Japanese populations, and as observed in an independently executed and completed study by Otsuka. In the population pharmacokinetic analysis, race was not found to be a significant covariate. No ethnic differences are expected or observed in the safety or efficacy of fremanezumab used for the preventive treatment of migraine.

This study is intended to confirm the efficacy and safety of fremanezumab in adult Chinese patients with the diagnosis of migraine in China. Study design elements, including treatment duration; dosing regimen; inclusion/exclusion criteria; and efficacy, safety, and pharmacokinetic assessments, are consistent with the global pivotal HALO studies and studies for Japanese and Korean patients with migraine. The sample size calculation is based on the observed effect size from these completed global efficacy studies. More specifically, all patients with migraine meeting the Chinese preventive migraine treatment guidelines will be eligible for screening and will, in general, be allowed to continue their current acute migraine management regimen. Up to 30% of patients will also be allowed to continue their current preventive migraine regimen. Patients in the study will be randomized to double-blind treatment in a 1:1:2 ratio to receive 225 mg fremanezumab once a month (approximately every 4 weeks, monthly), 675 mg fremanezumab once every 3 months (approximately every 12 weeks, quarterly), or placebo monthly for 3 months, respectively. After 12 weeks of double-blind treatment, all patients will receive fremanezumab 225 mg sc once a month (approximately every 4 weeks, monthly). Both fremanezumab dosing regimens are approved in the US, the EU, Japan, Korea, Australia, Canada, Israel, and several additional countries.

Study design elements, including the duration of the double-blind and open-label treatment periods; dosing regimen; inclusion/exclusion criteria; and efficacy, safety and pharmacokinetic assessments are consistent with the pivotal HALO studies and all fremanezumab migraine efficacy studies completed so far.

Throughout the global fremanezumab clinical program, patients with the full range of clinical severities, from the episodic to chronic subtypes of migraine, both separately and combined, have consistently demonstrated similar efficacy and safety with fremanezumab treatment by the same measures. Therefore, in this study, the primary analysis will consider patients representing the entire disease spectrum of migraine as a single study population stratified by EM and CM. Moreover, this study population is fully consistent with the currently approved indication for migraine in the US, Canada, EU, and other countries, and fully reflects the intended population for use in Chinese patients. In order to provide added granularity to the migraine subtypes, data for patients with EM and CM will be provided as subgroup analyses. Pharmacokinetic samples will be collected during the treatment and follow-up periods and analyzed using a population pharmacokinetic (PPK) modeling approach. Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point by treatment group. The pharmacokinetic data from this study will be compared with the general migraine population data in order to demonstrate comparability. Anti-drug antibody samples will be collected and analyzed during and after the treatment period.

Primary efficacy will be measured by the change from baseline in the monthly average number of migraine days during the 12 weeks after the 1st dose of IMP. This primary efficacy endpoint is widely accepted by the US Food and Drug Administration (FDA) and the EMA for preventive migraine medication studies. This endpoint was used in the Phase 3 HALO studies that were pivotal for FDA and EMA approval. It was also used in the Otsuka-sponsored Phase 3 fremanezumab studies in Japanese patients that were deemed pivotal for approval by the Pharmaceuticals and Medical Devices Agency in Japan. All aforementioned Phase 3 fremanezumab studies have demonstrated similar efficacy and safety profiles across regions, races, sexes, and ages. In addition, PGIC will be recorded. Pharmacokinetic samples will be collected during the double-blind treatment period and the follow-up period and will be analyzed using a population pharmacokinetic approach. ADAs will be evaluated according to established validated methods during the double-blind treatment period and approximately 3 months (3 half-lives) after the last dose of study drug.

3.4. Stopping Rules for the Study

There are no formal rules for ET of this study. During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns.

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

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

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, or adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, protocol deviation as defined in Appendix C, noncompliance, or adverse event).

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 3. 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 immunogenicity assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 3: Study Procedures and Assessments

Study period	**Pretreatment (screening visit and baseline period)**	**Double-blind treatment period**			**Open-label treatment period**			**Follow-up period**	
Visit number	**V1**	**V2[a]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[b]**
Time point	**Week -4**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Approximately 3 months after the last dose of IMP (2 months after V8)**
Day and allowed time windows[c]	**Day -28 to -1**	**Day 1 +3 days**	**Day 29 ±3 days**	**Day 57 ±3 days**	**Day 85 ±5 days**	**Day 113 ±5 days**	**Day 141 ±5 days**	**Day 169 ±5 days**	**Day 225 ±15 days**
Procedures and assessments	**Screening**	**Baseline**						**EOT/ET**	**EOS**
Informed consent	X								
Inclusion and exclusion criteria	X	X							
Assign randomization/treatment number		X							
Medical and psychiatric history	X								
Record demographic characteristics	X								
Prior medication and treatment history[d]	X								
Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis)[e]	X	X		X	X			X	X[f]
Blood samples for plasma concentration of the IMP[g]		X	X	X				X	
Blood samples for serum ADA assessment[h]		X		X				X	X
Physical examination, including height and weight[i]	X	X	X	X	X			X	X
12-Lead ECG[j]	X	X		X				X	X[f]

Study period	**Pretreatment (screening visit and baseline period)**	**Double-blind treatment period**			**Open-label treatment period**			**Follow-up period**	
Visit number	**V1**	**V2[a]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[b]**
Time point	**Week -4**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Approximately 3 months after the last dose of IMP (2 months after V8)**
Day and allowed time windows[c]	**Day -28 to -1**	**Day 1 +3 days**	**Day 29 ±3 days**	**Day 57 ±3 days**	**Day 85 ±5 days**	**Day 113 ±5 days**	**Day 141 ±5 days**	**Day 169 ±5 days**	**Day 225 ±15 days**
Procedures and assessments	**Screening**	**Baseline**						**EOT/ET**	**EOS**
Vital signs measurement[k,l]	X	X	X	X	X	X	X	X	X
Serum β-HCG test[m]	X							X	
Urine pregnancy test[m]		X	X	X	X	X	X	X	
FSH[n]	X								
Inform patients of study restrictions and compliance requirements	X								
Review study compliance[l]		X	X	X	X	X	X	X	
Provide the electronic headache diary device[o]	X								
Complete electronic headache diary entries[p]	X ←							→ X	
Review the electronic headache diary[l]		X	X	X	X	X	X	X	
Return the electronic headache diary device								X	
PGIC scale					X			X	
Adverse events[l q]		X	X	X	X	X	X	X	X
Administration of IMP		X	X	X	X	X	X		

Study period	**Pretreatment (screening visit and baseline period)**	**Double-blind treatment period**			**Open-label treatment period**			**Follow-up period**	
Visit number	**V1**	**V2[a]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[b]**
Time point	**Week -4**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Approximately 3 months after the last dose of IMP (2 months after V8)**
Day and allowed time windows[c]	**Day -28 to -1**	**Day 1 +3 days**	**Day 29 ±3 days**	**Day 57 ±3 days**	**Day 85 ±5 days**	**Day 113 ±5 days**	**Day 141 ±5 days**	**Day 169 ±5 days**	**Day 225 ±15 days**
Procedures and assessments	**Screening**	**Baseline**						**EOT/ET**	**EOS**
Hypersensitivity/anaphylaxis[r]		X	X	X	X	X	X	X	
Concomitant medication inquiry[l]		X	X	X	X	X	X	X	X

[a] All visit 2/baseline procedures must be performed before IMP administration. Inquiries about adverse events will be made before and after IMP administration. Postdose inquiries will be made before the patient leaves the study center.

[b] The EOS is defined as the last visit of the last patient. Each patient attends his/her follow-up visit approximately 3 months after the last dose of IMP (approximately 2 months after the EOT/ET visit [visit 8]).

[c] In case of an emergency situation (eg, pandemic or potential pandemic), visit windows for post baseline visits may be extended to 14 calendar days, except for visit 2. The window for visit 2 may only be extended to 7 calendar days in case of an emergency situation (eg, pandemic or potential pandemic). In case of an out-of-window visit, the date of the next visit will be calculated based on the actual date of the last administration of study drug.

[d] Collection of prior medications is limited to those medications administered within 6 months before IMP administration (visit 2) and preventive medications taken within 10 years.

[e] At visits where IMP is administered, clinical laboratory tests should be performed predose.

[f] To be performed at visit 9 (follow-up) if assessment at visit 8 (EOT/ET) shows abnormality.

[g] Blood samples for plasma drug concentration determination will be collected prior to dosing (as appropriate). Patients will be asked to return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration (one being 3 to 10 days after either visit 2, visit 3, or visit 4 and the other being 15 to 20 days after either visit 2, visit 3, or visit 4). If 2 additional visits are not possible for the patient, then the patient must return for only 1 additional pharmacokinetic blood sampling at either of the aforementioned time points. When patients return to the study center for additional blood sampling, then inquiries about adverse events and concomitant medications will be performed.

[h] Blood samples for serum ADA assessment will be collected prior to dosing (as appropriate).

i Height will be measured only at the screening visit.

j A single ECG will be performed predose. The ECG should be performed after the patient has been supine for at least 5 minutes. If results are abnormal, the ECG will be repeated 1 time.

[k] 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.
[l] Procedures for unscheduled visits.
[m] Women of childbearing potential only. At visits where IMP is administered, serum/urine β-HCG tests should be performed predose (see Appendix E).
[n] Postmenopausal women only (see Appendix E).
[o] Eligible patients will be given an electronic headache diary device and will be trained in its use and compliance requirements on the day of screening.
[p] Patients will complete electronic headache diary entries about the previous day daily beginning on day -27 through the EOT/ET visit.
[q] Inquiries about adverse events will be made before and after IMP administration. Postdose inquiries will be made before the patient leaves the study center.
[r] Patients will be assessed for severe hypersensitivity/anaphylaxis reaction during and after administration of the IMP. Oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity.

β-HCG=beta human chorionic gonadotropin; ADA=antidrug antibody; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; IMP=investigational medicinal product; PGIC=Patient Global Impression of Change; V=visit.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from the 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 randomized/enrolled in this study only if they meet all of the following criteria:

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

b. The patient is a man or woman 18 to 70 years of age, 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 evaluation, including medical and psychiatric history, physical examination, laboratory tests, and cardiac monitoring.

e. The patient has a body weight ≥45 kg and body mass index within the range 17.5 to 34.9 kg/m^2 (inclusive).

f. The patient has a history of migraine (according to the ICHD-3 criteria [IHS 2018, CMAPS 2016, Appendix J]), or clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥12 months prior to screening (visit 1).

g. [Revision 1] The patient has a clinical history of migraine that is confirmed during a prospectively recorded 28-day baseline period with the following characteristics:

   – Patient has 4 or more migraine days consistent with the characteristics of migraine (Appendix J) or probable migraine (a migraine subtype where only 1 migraine criterion is missing) or used a triptan or ergot derivative to treat an ongoing headache.

   – Patient has 2 or more days per month that are completely free of migraine headache or associated migraine symptoms.

h. The patient agrees not to initiate any preventive migraine medications during the 28-day baseline and double-blind treatment period. Up to 30% of patients are allowed to continue on 1 migraine preventive medication listed in Appendix K. However, patients must have been taking a stable dose of these medications for at least 2 months of consecutive use prior to screening (visit 1) with no expectation to change dosing regimen or change to another migraine preventive medications during the treatment phase of the study.

i. [Revision 1] Other concomitant medications (including herbal medicine) and acupuncture for migraine or other conditions are allowed for all patients, provided that the patient has been on a stable dose regimen for at least 2 months of consecutive

use prior to screening (visit 1) with no expectation to change dosing regimen or change to another medication during the treatment phase of the study.

j. The patient demonstrated compliance with the electronic headache diary device during the baseline period by entry of headache data on a minimum of 21 days during the baseline period and throughout the treatment period (approximately 75% diary compliance during each period).

k. Women may be included only if they have either a negative serum beta-human chorionic gonadotropin (β-HCG) test at screening (visit 1), are sterile, or are postmenopausal. Definitions of sterile and postmenopausal are given in Appendix E.

l. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening [visit 1]) and for 6 months after discontinuation of the IMP. Further details are included in Appendix E.

m. Men must be sterile or, if they are potentially fertile/reproductively competent (not congenitally sterile) and their female partners are of childbearing potential, should use highly effective birth control for the duration of the study. Definitions of women of non-childbearing potential, sterile, and postmenopausal women; male contraception; and highly effective birth control methods, including examples, are given in Appendix E.

n. 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 further visits, as applicable, and the follow-up evaluations, as specified in this protocol.

4.2. Patient Exclusion Criteria

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

a. Uses medications containing opioids (including codeine), barbiturates (including butalbital), or any combination product containing opioids or barbiturates (including butalbital) on more than 4 days during the screening period for the treatment of migraine or for any other reason.

b. Has used an intervention/device (eg, scheduled nerve blocks or transcranial magnetic stimulation) for migraine, or in the head or neck area, during the 2 months prior to screening (visit 1).

c. Clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, ocular disease, or complications of an infection that, in the opinion of the investigator, could interfere with the normal completion of study activities.

d. 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, generalized anxiety disorder, any suicide attempt in the past, suicidal ideation with a

specific plan in the past 2 years prior to screening (visit 1), or current suicidal ideation.

e. History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], or 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.

f. [Revision 1] Known current infection or any history of infection with human immunodeficiency virus, tuberculosis, or Lyme disease, or a known or suspected active infection of coronavirus disease 2019 (COVID-19).

g. Past or current history of cancer in the past 5 years, except for appropriately treated non-melanoma skin carcinoma.

h. Pregnant or nursing females or females who plan to become pregnant during the study.

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

j. Participation in a clinical study of a new chemical entity or a prescription medicine within 2 months before screening (visit 1) (or 3 months in the case of a biologic if the half-life of the biologic is unknown) or 5 half-lives, whichever is longer, or is currently participating in another study of an IMP or medical device.

k. Any prior exposure to a mAb targeting the CGRP pathway (erenumab, eptinezumab, galcanezumab, or fremanezumab) during the 6 months before the screening visit (visit 1), or exposure to gepants for less than 5 half-lives before screening.

l. Any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator.

m. Any finding that, in the judgment of the investigator, is a clinically significant abnormality, including physical examination findings, and serum chemistry, hematology, coagulation, and urinalysis test values (abnormal test results may be repeated for confirmation).

n. Hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]) >2× the upper limit of normal (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law at screening (visit 1).

o. Serum creatinine >1.5× ULN, clinically significant proteinuria, or evidence of renal disease at screening (visit 1).

p. Any clinically significant uncontrolled medical condition (treated or untreated).

q. History of alcohol or drug abuse during the past 2 years or drug dependence during the past 5 years.

r. The patient cannot participate or successfully complete the study, in the opinion of his/her 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 that, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study

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

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

u. Vulnerable patients (eg, members of a group with a hierarchical structure [such as medical, pharmacy, dental, and nursing students], subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, persons kept in detention, patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent).

v. The patient has previously participated in this study or has been assigned previously to a study with the IMP.

w. [New criterion] Known current infection or history of infection in the past 6 months with hepatitis B or C viruses.

4.3. Withdrawal Criteria and Procedures for the Patient

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

1. Patient withdraws consent or requests discontinuation from the IMP or withdrawal from the study for any reason.
2. Patient develops an illness that would interfere with his/her continued participation.
3. Patient is noncompliant with the study procedures and assessments or administration of IMPs in the opinion of the investigator.
4. Patient takes prohibited concomitant medications 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 that indicates to the investigator that continued participation is not in the best interest of the patient.

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

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

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

If the reason for withdrawal from the study or discontinuation from the 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 or until the patient is referred to the care of a health care professional). The specific event or test result (including repeated test results, as applicable) must be recorded on the source documents and in the CRF as applicable.

If a patient is withdrawn from the study or discontinues IMP for multiple reasons that also include adverse events, the relevant page of the CRF should indicate that the withdrawal/discontinuation 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 "Other," specifying the details as "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.

4.4. Replacement of Patients

Generally, a patient who is randomized but does not complete the treatment period will not be replaced.

ET rate and screen failures due to an emergency situation (eg, pandemic or potential pandemic) will be monitored during the study. In order to maintain study power, an excess loss of patients will be replaced (eg, if there are >5% patients lost due to an emergency situation [eg, pandemic or potential pandemic], additional patients may be recruited).

4.5. Rescreening

A patient who is screened but not randomized (eg, because study eligibility criteria were not met [inclusion criteria not met or exclusion criteria met]) due to any of the following reasons: technical issues (eg, diary malfunction), out of visit 2 window due to an emergency situation (eg, pandemic or potential pandemic), a change in the patient's medical background, a modification of study inclusion and exclusion criteria, or upon the sponsor's discretion on a case-by-case basis, may be considered for rescreening 1 time.

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

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

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. 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

Treatment (active or placebo) will be administered at visit 2, visit 3, and visit 4. Active treatment will be administered to all patients at visit 5, visit 6, and visit 7. Final treatment evaluation will be performed at visit 8 (EOT), approximately 4 weeks after administration of the last dose of study drug.

IMP is defined as the test IMP (fremanezumab) and matching placebo IMP. A summary of IMPs is presented in Table 4. Additional details may be found in the IB for fremanezumab.

Table 4: Investigational Medicinal Products Used in the Study

IMP name	**Fremanezumab, a fully humanized IgG2Δa/kappa mAb**	**Placebo**
Trade name and INN, if applicable, or company- assigned number	AJOVY Fremanezumab TEV-48125	Placebo
Formulation	Prefilled syringes containing 150 mg/mL of active ingredient: fremanezumab Inactive ingredients include L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate-80, disodium EDTA dihydrate, and water for injection	Prefilled syringes containing 1.5 mL of the same inactive vehicle and excipients that are in the active injections Inactive ingredients include L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate-80, disodium EDTA dihydrate, and water for injection
Unit dose strength(s)/ Dosage level(s)	225 mg	None
Route of administration	sc injection	sc injection
Dosing instructions	Quarterly: fremanezumab 675 mg as 3 injections (225 mg/1.5 mL) at visit 2; 1 placebo (1.5 mL) injection at visits 3 and 4 Monthly: fremanezumab 225 mg as 1 injection (225 mg/1.5 mL) and 2 placebo (1.5 mL) injections at visit 2; fremanezumab 225 mg as 1 injection (225 mg/1.5 mL) at visits 3 and 4	3 placebo (1.5 mL) injections at visit 2; 1 placebo (1.5 mL) injection at visits 3 and 4
Packaging	A uniquely numbered kit containing 1 prefilled syringe stored (refrigerated at 2°C to 8°C) on site	A uniquely numbered kit containing 1 prefilled syringe stored (refrigerated at 2°C to 8°C) on site
Manufacturer	**Drug substance:** [redacted] **Drug product:** [redacted]	[redacted]

EDTA=ethylenediaminetetraacetic acid; IgG2Δa=immunoglobulin G2Δa; IMP=investigational medicinal product; INN=international nonproprietary name; mAb=monoclonal antibody; sc=subcutaneous.

Three individual, uniquely numbered visit kits each containing 1 prefilled syringe will be provided.

At the time of each dosing visit, the IRT will be queried, and site staff will retrieve and administer 1.5 mL from each prefilled syringe contained in the appropriately numbered kits.

The recommended sc injection sites follow the Instructions for Use in the US-approved AJOVY Prescribing Information (2020). Appropriate injection sites are back of upper arms, stomach area (abdomen), and front of thighs. Fremanezumab should not be injected into an area that is tender, red, bruised, callused, tattooed, or hard; that has scars; or that has stretch marks.

Study drug should be removed from the refrigerator and allowed to equilibrate at room temperature for 30 minutes before administration of the study drug. The total number of sc injections and their injection site locations will be recorded on the CRF for each dosing visit.

5.1.1. Test Investigational Medicinal Product

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

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

Adequate kit supply for upcoming study visits will be managed by the IRT and kept on-site.

5.1.1.1. Starting Dose and Dose Levels

The starting dose of fremanezumab will be either 675 mg or 225 mg at visit 2 (day 1), depending on the treatment group. 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 double-blind period and 225 mg for the open-label treatment period.

5.1.1.2. Dose Modification

No dose modifications are allowed.

5.1.2. Placebo Investigational Medicinal Product

Placebo (matching the test IMP fremanezumab) will be provided and administered as described in Table 4.

5.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products

5.2.1. Storage and Security

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

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

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

5.2.2. Labeling

Supplies of IMPs will be labeled according to the current China National Medical Products Administration (NMPA) and National Health Commission (NHC) guidelines on Good Clinical Practice (China GCP), International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice, and will include any locally required statements. Labels will be translated into the local language.

5.2.3. Accountability

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

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the national and local regulations and used in accordance with this protocol.

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

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

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Prefilled syringes should never be used partially. Empty syringes should be destroyed at the investigational center after reconciliation is performed. If the investigational center does not have the capability to destroy the empty syringes, they should be sent back to the sponsor. Unused prefilled syringes of the IMP will be returned to the sponsor or designee.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The 2 dosing regimens for this study have been approved in the US, the EU, Japan, Korea, and in all other countries in which AJOVY received approval. Three dose regimens of fremanezumab administered sc were tested during two Phase 3 pivotal studies in the CM and EM patient populations (Studies TV48125-CNS-30049 and TV48125-CNS-30050, respectively). CM dosing regimens were 675-mg starting dose/monthly 225 mg or quarterly 675 mg, and EM dosing regimens were monthly 225 mg or quarterly 675 mg. Post hoc analysis demonstrated that the starting dose of 675 mg is not necessary, which led to the 2 approved dosing regimen for both EM and CM patients.

During the Phase 2b studies, 4 dose regimens of fremanezumab (ie, EM: monthly 225 mg or 675 mg; CM: monthly 675 mg, followed by 225 mg or monthly 900 mg sc) were tested and shown to be effective, safe, and well tolerated during the 3-month treatment period. Because it is considered best practice to select the lower dose for administration from 2 doses that show equivalence in efficacy (to avoid higher dose than necessary), the 2 monthly dose regimens of 225 mg with the 675-mg starting dose (CM) or without starting dose (EM) were used as 1 active arm in each of the global Phase 3 studies and Otsuka Japanese and Korean studies. A 2nd active arm included in both the EM and CM studies was 675 mg sc fremanezumab administration once every 3 months. Hence, each study retained the lowest effective dose from Phase 2 while exploring different intervals of administration. Furthermore, the addition of the quarterly dose regimen 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 different 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 migraine in adults. In addition, all active dose regimens showed no significant difference in efficacy and safety parameters.

The quarterly 675-mg and monthly 225-mg sc doses of fremanezumab were selected for this study. These 2 dosing regimen have been approved for migraine prevention in all countries Teva received approval, including US, EU, Japan, Korea, Canada, Australia, Israel, and many other countries.

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 studies of preventive 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). In addition, acute (rescue) medications are allowed for breakthrough migraine episodes.

5.4. Treatment after the End of the Study

After the EOT visit (visit 8), patients will return to the care of their primary physician(s) for migraine management.

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 30 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 months) after the last dose of the IMP.

5.6. Prior and Concomitant Medication or Therapy

Any prior or concomitant therapy, medication, or procedure (ie, procedures for the treatment of migraine [eg, nerve blocks]) 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 (preventive medications taken within 10 years will be recorded). Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization Drug Dictionary.

Details regarding excluded prior medications, including preventive migraine treatments, are described in the exclusion criteria (Section 4.2).

Up to 30% of patients will be allowed to remain on stable doses of no more than 1 preventive migraine medication presented in Appendix K (in addition to other medications not listed in Appendix K) for the duration of the study. Patients on preventive medication must be on a stable dose for at least 2 months of consecutive use prior to screening with no expectation to change dosing regimen or change to another migraine preventive medications during the treatment phase of the study.

Patients will be allowed to use acute medication to treat breakthrough migraines as needed, with the exception of medications containing opioids and barbiturates, which cannot be used on more than 4 days during the screening period. Traditional Chinese therapy (including herbal medicine) and acupuncture are allowed if the patient is on a stable dosing regimen for at least 2 months (consecutive) before screening.

Use of concomitant therapies for indications other than migraine prevention is allowed throughout the course of the study, provided patients have been on a stable dose for at least 2 consecutive months prior to screening and do not expect to change dosing regimen or to change to another medication during the treatment phase of the study.

All concomitant medications or treatments taken during the study, including over-the-counter medications, vitamins, nutritional supplements, or acupuncture, must be recorded with the

indication, daily dose, and start and stop dates of administration. All patients will be asked about concomitant medication use at each visit.

After the EOT visit (visit 8), patients will return to the care of their primary physician(s) for migraine management.

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 Independent Ethics Committee/Institutional Review Board (IEC/IRB) should be notified.

5.8. Randomization and Blinding

After the 28-day baseline period, the next 12 weeks of the study will be double blind. Patients and investigators will remain blinded to IMP assignment during this double-blind period.

A computer-generated master randomization list will be provided to drug packaging facilities. The packaging vendor(s) will package the active IMP and placebo each into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance, and each will contain 1 prefilled syringe with either active IMP or placebo. Kits will be administered at each dosing visit according to Table 3.

Patients will be stratified based on migraine type (CM vs EM) and preventive medication use. Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list using electronic IRT. This system is used to ensure a balance across treatment groups. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

At visit 2 (day 1), patients will be randomized in a 1:1:2 ratio within the appropriate stratum to 1 of 3 treatment groups, as assigned by the IRT:

- fremanezumab 225 mg sc once a month (approximately every 4 weeks), for a total of 3 doses; one 225-mg injection and 2 placebo injections at visit 2 and one 225 mg injection at visits 3 and 4
- fremanezumab 675 mg sc once a quarter (once at the beginning of the 12-week double-blind treatment period), for a total of 1 dose; three 225-mg injections at visit 2 and 1 placebo injection at visits 3 and 4 or
- placebo sc once a month (approximately every 4 weeks), for a total of 3 doses; 3 placebo injections at visit 2 and 1 placebo injection at visits 3 and 4

The placebo will contain the same vehicle and excipients as those for the active injection.

The IRT will manage the initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At the time of each study visit when the study drug is administered, the IRT will be queried, and the site personnel will retrieve the study drug from refrigerated storage and will administer a 1.5-mL volume from each syringe contained in the appropriately numbered kit(s).

The sponsor's clinical personnel (and delegates) involved in the study will be blinded to the identity of the IMPs until the database is locked for analysis and the IMP assignment is known.

In the event of an emergency, it will be possible to determine to which treatment group the patient has been allocated by accessing the IRT system. All investigational centers will be provided with details on how to access the system for code breaking at the start of the study. The medical monitor or equivalent should be notified following unblinding. Any unblinding of the IMP performed by the investigator must be recorded in the source documents.

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

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 first interim analysis, after receiving the unblinding request from the Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant standard operating procedure.

5.9.2. Blinding and Unblinding

Blinded pharmacokinetic data may be assessed during the study. For patients who have pharmacokinetic sample bioanalysis or data analysis conducted, the individuals responsible for sample bioanalysis and other responsible personnel will know who received the test IMP and who received the placebo IMP during the study (of those patients only). Personnel responsible for bioanalysis will be provided with the randomization code to facilitate the analysis. However, the personnel responsible for bioanalysis and pharmacokinetic data analysis will not have access to clinical safety and efficacy data and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to the concentration data of an individual patient).

In case of a serious adverse event or a pregnancy or when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations, through specialized access in the IRT system. Breaking of the treatment code can always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified that the code was broken, but the patient treatment assignment should not be revealed to the sponsor.

When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded on the 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 documents. Assignment of IMP should not be recorded in any study documents or source documents.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the blind code be broken (on a

case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study and the analysis and reporting of the data.

5.9.3. Data Monitoring Committee

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

5.10. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 110 mL.

Details are provided in the Laboratory Manual.

6. ASSESSMENT OF EFFICACY

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

6.1. Assessments of Efficacy

6.1.1. Electronic Headache Diary Device

The primary efficacy endpoint (and secondary and other efficacy endpoints) will be derived from headache variables collected daily using an electronic headache diary device (Table 3). 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 headache diary. Approximately 75% compliance is needed during the baseline (ie, entry of headache data on a minimum of 21 days) and treatment 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 device training manual.

If a patient fails to complete the diary for the preceding day, the patient will be prompted to enter the missed day's information the next time he/she accesses the electronic headache diary, provided no more than 48 hours has elapsed since completion of that day. If more than 48 hours has 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 the duration of headache for each day will be completed in the electronic headache 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 acute migraine medications (the name of the drug, the number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day. These acute medications are opioids, barbiturates, triptans, ergots, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and their combination products.

6.1.2. Patient Global Impression of Change

The PGIC scale is a validated generic tool for the assessment of overall change in the severity of illness following treatment. Patients will rate how they 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 3.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including height and weight measurements), use of concomitant medication, local tolerability and pain, immunogenicity, and occurrence of severe hypersensitivity/anaphylactic reactions.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

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

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to 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

  Note: A condition recorded as pre-existing that is intermittently symptomatic (eg, headache) and that occurs during this study should be recorded as an adverse event.

- drug interactions
- events occurring during diagnostic procedures or during any follow-up period 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.

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 the 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 the recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the follow-up period. The follow-up period of the recording of adverse events is defined as 3 months after the last dose of IMP. The period for reporting treatment-emergent adverse events is defined as the period after the 1st dose of IMP is administered and until the end of the follow-up period.

All adverse events that occur during the defined study period must be recorded both on the source documents and the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events, the serious adverse event form must be completed, and the serious adverse event must be reported immediately (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period. Serious adverse events and adverse events of special interest (Section 7.1.6) occurring after the defined study period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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

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

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

The relationship of each adverse event to the 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 one of the following:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

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

The relationship of an adverse event to the IMP is characterized per Table 5.

Table 5: The Relationship of an Adverse Event to the Investigational Medicinal Product

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

IMP=investigational medicinal product.

7.1.5. Serious Adverse Events

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

7.1.5.1. Definition of a Serious Adverse Event

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

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

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

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

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

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

All Hy's law events (ie, all 3 of the criteria above) require immediate discontinuation of IMP.

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

7.1.5.2. Expectedness

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

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

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

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

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

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

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

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

Additional information includes:

- age and sex of patient
- date of 1st dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history

- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

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

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

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

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

7.1.5.3.2. Sponsor Responsibility

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

In addition to notifying the investigators and competent authorities (and the 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 of Special Interest

For purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to the sponsor's GPSP for evaluation: severe hypersensitivity and anaphylaxis, as well as ophthalmic events of at least moderate severity. Hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al 2006). The clinical criteria for

diagnosing anaphylaxis are provided in Appendix L. In the event of suspected anaphylaxis, vital signs (including oxygen saturation and respiration rate) will be measured.

The process for reporting a protocol-defined adverse event of special interest is the same as that for reporting a serious adverse event (Section 7.1.5.3). Protocol-defined adverse events of special interest to be reported to GPSP can be either serious or nonserious, according to the criteria outlined in Section 7.1.5.1.

7.1.7. Protocol Deviations Because of an Adverse Event

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

7.2. Pregnancy

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

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

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

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

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

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

Any administration of IMP that is not in accordance with the study protocol should be reported in the patient's source documents, regardless of whether or not an adverse event occurs as a result.

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the 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.
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 nonprofessional 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 (Table 6) outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documents and the CRF as an adverse event and will be 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 the 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 the 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. However, in case of

abnormal coagulation during screening (baseline period), a local retest can be authorized by the sponsor on a case-by-case basis.

Table 6: Clinical Laboratory Tests

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

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma glutamyl transpeptidase; HDL=high-density lipoprotein; INR=international normalized ratio; LDH=lactate dehydrogenase; LDL=low-density lipoprotein.

7.4.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis) will be performed at the time points detailed in Table 3. At visits where IMP is administered, clinical laboratory tests should be performed predose. Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided in Table 6. Note, reflex tests (eg, red blood cell [RBC] shapes, RBC morphology, and other microscopic findings) may be triggered automatically.

7.4.2. Other Clinical Laboratory Tests

7.4.2.1. Human Chorionic Gonadotropin Tests

Human chorionic gonadotropin tests in serum or urine will be performed for all WOCBP at the time points detailed in Table 3. At visits where IMP is administered, β-HCG tests should be performed predose. Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.4.2.2. Follicle-Stimulating Hormone Tests

Postmenopausal women will have a follicle-stimulating hormone test at screening (visit 1); see Table 3.

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 3. 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 abnormal 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 (blood pressure [systolic/diastolic], respiratory rate, body temperature, and pulse) will be measured at the time points detailed in Table 3. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

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

7.7. Electrocardiography

A single 12-lead ECG will be performed at the time points detailed in Table 3. This procedure will be performed predose.

A qualified physician at a central diagnostic center will provide an interpretation of the ECG. ECGs should be performed and transmitted according to the central ECG reading instructions provided in the ECG user manual. ECG equipment will be provided to all clinical sites. Although the ECG interpretation will be provided centrally, the clinical evaluation of the ECG remains the investigator's responsibility.

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

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

- abnormal and not clinically significant
- abnormal and clinically significant

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

The ECG will be evaluated by the investigator at the time of recording (signed and dated), and the printout should be kept in the source document 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 document file. The investigator's interpretation will be recorded on the CRF regardless of the central reading interpretation. Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit [visit 1]) will be considered an adverse event, recorded on the source documents and the CRF, and monitored as described in Section 7.1.2.

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

7.8. Immunogenicity

Blood samples for serum ADA assessment will be collected at the time points detailed in Table 3. Only the samples from fremanezumab-treated patients will be analyzed for ADAs.

7.9. Assessment of Local Tolerability and Pain

Spontaneous reports of injection site reactions will be recorded as adverse events 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

Any suicide attempt in the past, suicidal ideation with a specific plan in the past 2 years prior to screening (visit 1), or current suicidal ideation will result in patient exclusion.

Investigators will inquire about and evaluate suicidal ideation, plan, and behavior based on their clinical judgement and refer patients to psychiatric care as appropriate.

8. ASSESSMENT OF PHARMACOKINETICS/IMMUNOGENICITY

8.1. Pharmacokinetic Assessment

Sampling for pharmacokinetics will be sparse. The fremanezumab pharmacokinetic concentrations will be analyzed using a population pharmacokinetic model and will be reported separately from the clinical study report (CSR); individual pharmacokinetic concentration data will be summarized and listed in the CSR.

Patients will be asked to return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration (one being 3 to 10 days after either visit 2, visit 3, or visit 4 and the other being 15 to 20 days after either visit 2, visit 3, or visit 4). If 2 additional visits are not possible for the patient, then the patient must return for only 1 additional pharmacokinetic blood sampling at either of the aforementioned time points. When patients return to the study center for additional blood sampling, then inquiries about adverse events and concomitant medications will be performed.

Blood samples (8 mL for the predose sample at visit 2; 4 mL for all other samples) will be collected via venipuncture or indwelling catheter (for details, see the Laboratory Manual) at the time points detailed in Table 3 for plasma concentration measurements of fremanezumab. The dates and times of IMP administration and the date and time of each pharmacokinetic sample collection will be recorded in the source documents and entered into the CRF.

Samples from patients who received the active IMP will be analyzed for the concentration of fremanezumab using a validated method. Samples from patients who were randomized to receive placebo will not be analyzed.

Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

8.2. Pharmacodynamic Assessment

Pharmacodynamic parameters are not evaluated in this study.

8.3. Immunogenicity Testing

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

Blood samples (10 mL for the predose sample at visit 2; 6 mL for all other samples) will be collected via venipuncture or indwelling catheter (for details, see the Laboratory Manual) at the time points detailed in Table 3 for immunogenicity testing. The dates and times of IMP administration and the date and time of each ADA sample collection will be recorded in the source documents and entered into the CRF.

Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

8.4. Assessment of Exploratory Biomarkers

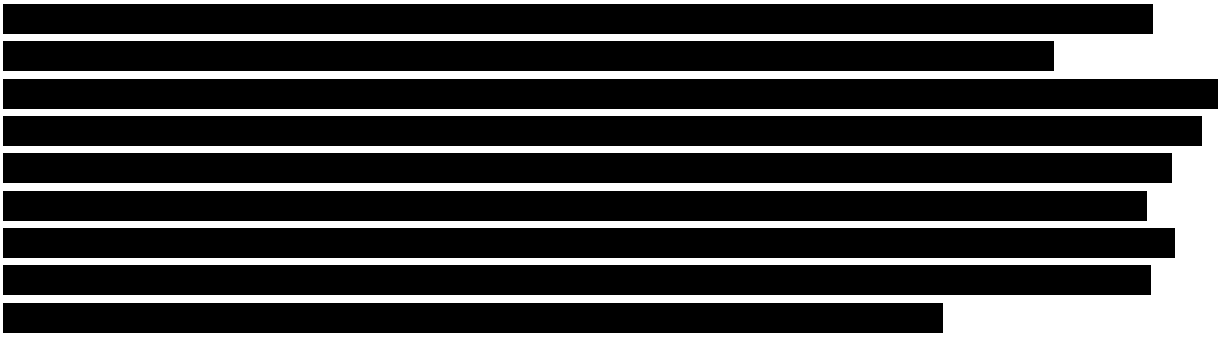
Biomarkers are not evaluated in this study.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the CSR.

9.1. Sample Size and Power Considerations

Using study data from 2 completed Phase 3 US pivotal studies in migraine, it is estimated that 163 completers per treatment group (ie, combined fremanezumab groups and placebo group) will provide at least 90% power to detect the assumed treatment difference at a significance level of 0.05. Assuming a 12% discontinuation rate, approximately 372 patients will be randomized in this study (93 patients in each fremanezumab treatment group and 186 patients in the placebo group). The primary efficacy analysis will consider all fremanezumab-treated patients as 1 group.



To ensure adequate representation of patients with both migraine types (EM and CM), the enrollment minimum of either migraine type is 30%. In addition, primary efficacy analysis will be stratified by EM and CM, and subgroup analysis for EM and CM will be conducted.

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 IMP and have at least 10 days of diary entries after baseline.

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

9.2.3. Safety Analysis Set

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

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

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 treatment without any important deviations such as important inclusion/exclusion criteria deviations or any important deviations or omissions of the IMP administration.

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

9.3. Data Handling Conventions

9.3.1. Handling Withdrawals and Missing Data

For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified. Detailed data imputation rules 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. In addition, the primary and secondary efficacy endpoints will also be analyzed using the per-protocol analysis set.

9.4.1. Patient Disposition

Data from patients screened; patients screened but not randomized and reason for not being randomized; patients randomized; patients randomized but not treated; patients in the ITT, safety, and PP analysis sets; patients who complete the IMP; and patients who discontinue the IMP will be summarized using descriptive statistics. Data from patients who discontinue the IMP 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 examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, SD, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.5. Efficacy Analysis

For the purpose of this study, a migraine day is endorsed when at least 1 of the following situations occurs:

- A calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of a headache meeting the criteria for migraine with or without aura
- A calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of a headache meeting the criteria for probable migraine, a migraine subtype where only 1 migraine criterion is missing
- A calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds)

Migraine classification definitions are presented below.

CM is defined as:

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

- Headache occurring on ≥15 days
- On ≥8 days, fulfilling any of the following:
  - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix J)
  - ICHD-3 criteria B and C for 1.2 Migraine with aura (Appendix J)
  - 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.

EM is defined as:

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

- Headache occurring ≥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 (Appendix J)
  - ICHD-3 criteria B and C for 1.2 Migraine with aura (Appendix J)
  - 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.

Missing data or visits due to the COVID-19 pandemic will be evaluated for the primary and secondary endpoints. COVID-19 may have an impact on patients' migraine symptoms, with headache reported to be a common complication as a result of contracting the disease. All COVID-19 cases will be included in the primary analysis; however, observations following COVID-19 diagnosis will be discarded from the calculation of the monthly average endpoint. The data handling strategy will be detailed in the statistical analysis plan.

9.5.1. Primary Endpoint

The primary efficacy endpoint is the mean change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP.

The monthly average number of migraine days during the 12-week period after the 1st dose of study drug will be derived and normalized to 28 days equivalent using the following formula.

$$\frac{\sum Days\ of\ migraine\ over\ the\ 12\ week\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 12\ week\ period} \times 28 \quad (1)$$

9.5.2. Secondary Endpoints

The secondary efficacy endpoints are as follows:

- mean change from baseline in the number of migraine days during the 4-week period after the 1st dose of IMP
- mean change from baseline in the monthly average number of days that any acute headache medications were used during the 12-week period after the 1st dose of IMP
- 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 IMP
- mean change from baseline in the monthly average number of days with headache of at least moderate severity during the 12-week period after the 1st dose of IMP

Similar to the primary endpoint, the monthly average number of days of efficacy variables (eg, days of headache of at least moderate severity and days of acute headache medication use) during the 12-week period after the 1st dose of study drug will be derived and normalized to 28 days equivalent using the following formula.

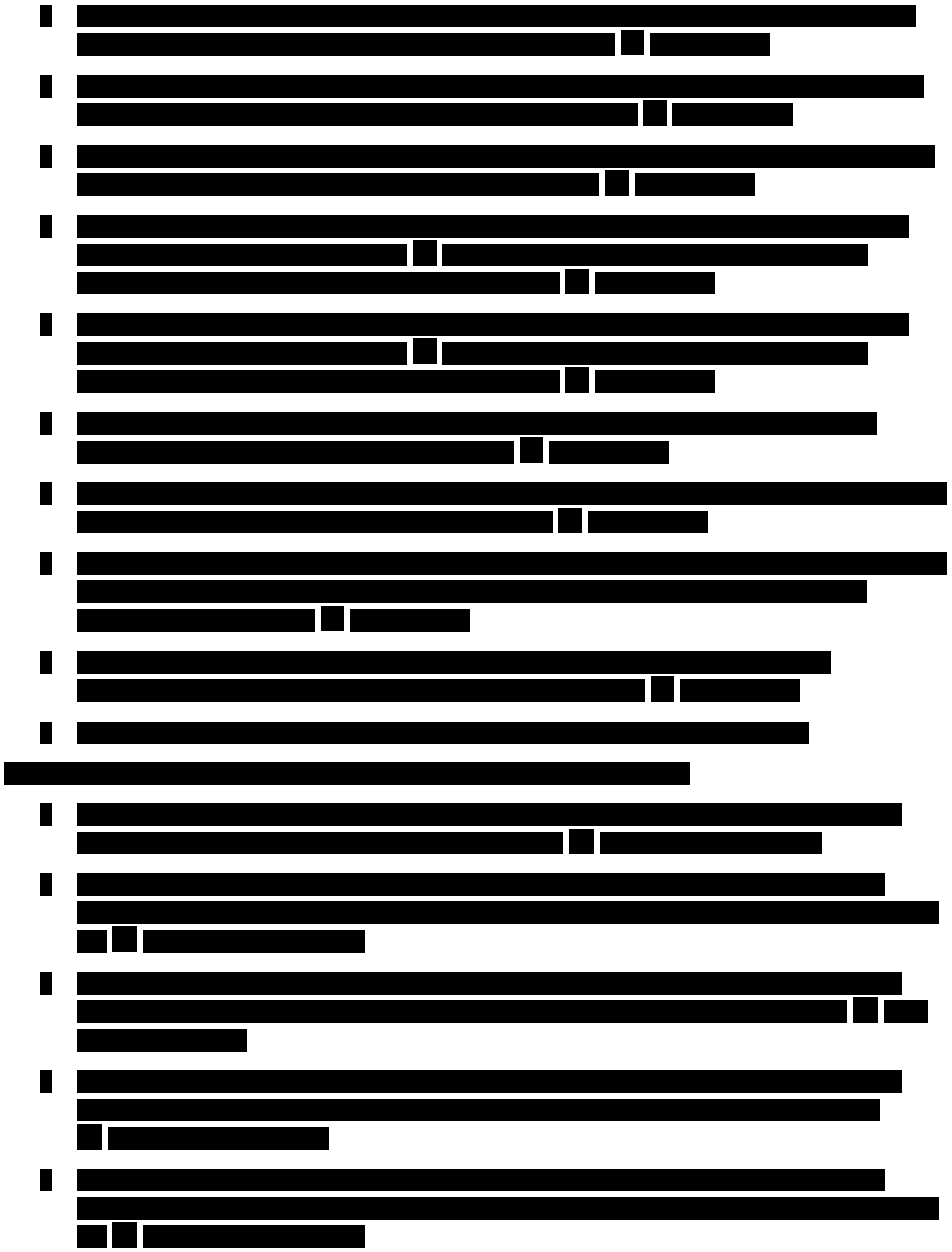
$$\frac{\sum Days\ or\ hours\ of\ efficacy\ variable\ over\ the\ 12\ week\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 12\ week\ period} \times 28 \quad (2)$$

The monthly average number of migraine days during a 4-week period after each dose will be derived and normalized to 28 days equivalent using the following formula, where monthly data separated by each visit of study drug dosing:

$$\frac{\sum Days\ or\ hours\ of\ efficacy\ variable\ during\ the\ 4\ week\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 4\ week\ period} \times 28 \quad (3)$$

9.5.3. Other Efficacy Endpoints

[redacted]



[redacted]

9.5.4. Planned Method of Analysis

The mITT analysis set (Sections 9.2.1, 9.2.2, and 9.2.4) will be used for all efficacy analyses. Summaries will be presented by treatment group. In addition, the primary and secondary efficacy endpoints will also be analyzed using the per-protocol analysis set.

9.5.4.1. Primary Efficacy Analysis

The primary comparison will be made between the combined fremanezumab groups versus the placebo group in the primary efficacy variable: mean change from baseline in the monthly average number of migraine days during the 12-week double-blind treatment period after the 1st dose of IMP. The primary efficacy analysis will consider all fremanezumab-treated patients as 1 group (ie, regardless of dosing regimen or migraine type).

An estimand in general includes the following 4 interrelated attributes: population of interest, variable (endpoint) of interest, intercurrent events (ICEs) along with the strategy for handling ICEs, and population-level summary for the endpoint.

The estimand selected for the primary analysis will assess the 12-week monthly average number of migraine days as initially randomized in the mITT analysis set.

The ICEs that may affect the efficacy endpoint will include instances where a patient early terminates from the IMP, receives the wrong IMP due to medication errors, or receives a rescue medication due to worsening symptoms. If observations are collected after the occurrences of the ICEs, the observations will be included in the calculation of the primary endpoint for the primary analysis.

The population-level summaries would be the adjusted mean changes from baseline in monthly average number of migraine days for the treatment groups and corresponding 95% confidence intervals.

An analysis of covariance (ANCOVA) will be performed, including treatment and stratification factors of migraine type (CM vs EM) and preventive medication use as fixed factors, as well as baseline number of migraine days as a covariate in the model. A 95% confidence interval for the treatment difference between the combined fremanezumab groups versus the placebo group will be derived through an appropriate contrast, and p-values for the comparison will be presented. Further details will be presented in the statistical analysis plan.

9.5.4.2. Sensitivity Analysis

A sensitivity analysis may be performed to assess the primary estimand using mixed-effects model for repeated measures (MMRM) as a different missing data handling approach. The MMRM model will include treatment and stratification factors of migraine type (CM vs EM) and preventive medication use as fixed factors, as well as treatment-by-month interaction effects, and baseline number of migraine days as a covariate with an unstructured covariance matrix. The 12-week monthly average number of migraine days will be estimated by the LS means of the overall treatment effect over 3 months.

An additional sensitivity analysis may be conducted to assess a different estimand, ie, treatment effects due to initially randomized treatment as actually taken. For patients who early terminate from study drugs in the monthly dosing regimen group or start a rescue medication, observations collected more than 4 weeks after the last dose or after starting a rescue medication will be treated as missing and will not be used in the calculation of monthly average number of migraine days.

Finally, the primary analysis will be repeated in the ITT analysis set (in case there is a 10% difference in patient count in any treatment group) and PP analysis set.

9.5.4.3. Secondary Efficacy Analysis

Comparisons of secondary endpoints will be made between the combined fremanezumab groups versus the placebo group. Analysis of the continuous secondary endpoints (monthly average number of days of efficacy endpoints) will be similar to the analysis of the primary efficacy endpoint. The responder endpoints will be analyzed using logistic regression, including treatment and stratification factors of migraine type (CM vs EM) and preventive medication use as fixed factors, as well as baseline number of migraine days as a covariate in the model. The secondary efficacy analyses will consider all fremanezumab-treated patients as 1 group. Further details will be presented in the statistical analysis plan.

A fixed-sequence, hierarchical testing procedure will be implemented to control the type 1 error rate at 0.05 for formal hypothesis testing of the secondary endpoints. Upon the success of the primary analysis, the first secondary endpoint in the sequence will be tested at a significance level of 0.05, and a p-value ≤0.05 will be interpreted inferentially. The process will continue following the order of the sequence until a point when the test for the efficacy endpoint fails, ie, 2-sided p-value >0.05. Subsequently, no further test results will be interpreted inferentially. The sequence of testing will follow the order specified for secondary endpoints in Section 9.5.2.

9.5.4.4. Other Efficacy Analysis

[redacted]

9.6. Multiple Comparisons and Multiplicity

The type 1 error will be controlled at a significance level of 0.05 using the appropriate method for the analysis of the primary efficacy endpoint, which is conducted by pooling the fremanezumab patients in the 2 dosing regimens.

A fixed-sequence, hierarchical testing procedure will be implemented upon achieving the success of the primary analysis to control the type 1 error rate at 0.05 for formal hypothesis testing of the secondary endpoints. The sequence of testing will follow the order specified for secondary endpoints in Section 9.5.2.

9.7. Safety Analysis

Safety analyses will be performed on the safety analysis set.

Safety assessments and time points are provided in Table 3.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity),

adverse events determined by the investigator to be related to the test IMP (ie, reasonable possibility; defined as related or with missing relationship [overall and by severity]), serious adverse events, and adverse events leading to discontinuation from the study. Summaries will be presented by treatment group. Patient listings of serious adverse events and adverse events leading to discontinuation will be presented.

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

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with the IMP.

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

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

9.8. Tolerability Analysis

Spontaneously reported local tolerability findings will be listed and summarized descriptively.

9.9. Pharmacokinetic Analysis

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

The pharmacokinetic data from this study will be pooled with the data from other fremanezumab studies and assessed for comparability. Summary statistics of fremanezumab pharmacokinetic parameters model-based predictions of weight-adjusted exposures will be compared and will be reported separately.

9.10. Immunogenicity Analysis

Summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. This analysis will be reported separately.

9.11. Planned Interim Analysis

Two interim analyses are planned. The first interim analysis is planned when the last patient has completed the double-blind period. A second interim analysis 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 second database lock.

9.12. Reporting Deviations from the Statistical Plan

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

Refer to Appendix G for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with current China GCP, 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 GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

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

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

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

See Appendix D for the ethics expectations of informed consent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix H for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

13. FINANCING AND INSURANCE

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

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

14. PUBLICATION POLICY

See Appendix I for information regarding the publication policy.

15. REFERENCES

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 02 with Revision 01 Dated 08 March 2023

The primary reason for this revision of protocol amendment 02 was to clarify which medications should be recorded in the eDiary and that automatically triggered reflex tests applies to hematology tests. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (eg, typos and punctuation) have been made to the protocol (and protocol synopsis, as appropriate).

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Section 6.1.1. Electronic Headache Diary Device		
…will record any acute migraine medications (the name of the drug, the number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day. These acute medications are opioids, barbiturates, triptans, ergots, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and their combination products.	…will record any acute migraine medications (the name of the drug, the number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day. These acute medications are opioids, barbiturates, triptans, ergots, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and their combination products.	Clarification on which medications should be recorded in the eDiary.
Section 7.4.1Serum Chemistry, Hematology, and Urinalysis		
Note, reflex tests (~~ie, microanalysis tests like squamous epithelial cells and mucous threads~~eg, red blood cell [RBC] shapes, RBC morphology, and other microscopic findings) ~~test~~ may be triggered automatically.	Note, reflex tests (eg, red blood cell [RBC] shapes, RBC morphology, and other microscopic findings) may be triggered automatically.	Reflex tests should entail hematology and not urine tests.

16.2. Amendment 02 Dated 14 February 2023

The primary reason for this amendment is to include planned interim analyses, to modify the inclusion/exclusion criteria to assist with recruitment rates, to specify that the secondary efficacy endpoints will also be analyzed using the per-protocol analysis set, and to extend specific site visit windows for local public health emergencies. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Table 3 (Study Procedures and Assessments) and Table 6 (Clinical Laboratory Tests) have been revised to reflect changes described below. Minor editorial changes (eg, typos and punctuation) have been made to the protocol (and protocol synopsis, as appropriate).

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Section 1.2.2.2 Clinical Safety and Efficacy Studies		
One Phase 4 study (Study TV48125-MH-40142) ~~is~~ was ~~currently being~~ conducted (last patient last visit: 31 August 2021) to evaluate…	One Phase 4 study (Study TV48125-MH-40142) was conducted (last patient last visit: 31 August 2021) to evaluate…	Update study status
Section 3.1 General Study Design and Study Schematic Diagram		
Traditional Chinese therapy (including~~other than~~ herbal medicine) and acupuncture are allowed if the patient is on a stable dose/regimen for at least 2 months (consecutive) before screening.	Traditional Chinese therapy (including herbal medicine) and acupuncture are allowed if the patient is on a stable dose/regimen for at least 2 months (consecutive) before screening.	Alignment of text with updated relaxation of inclusion criteria to aid with recruitment
• fremanezumab 225 mg sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; one 225-mg injection and 2 placebo injections at visit 2 and one 225-mg injection at visits 3 and 4… • placebo sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; 3 placebo injections at visit 2 and 1 placebo injection at visits 3 and 4… ~~(Note: For this study, monthly dosing refers to dosing approximately every 4 weeks [28 days].)~~	fremanezumab 225 mg sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; one 225-mg injection and 2 placebo injections at visit 2 and one 225-mg injection at visits 3 and 4… • placebo sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; 3 placebo injections at visit 2 and 1 placebo injection at visits 3 and 4	Combined text statement with information in bullet points
Follow~~A follow~~-up visits for ADA sample collection will occur approximately 1 month and 3 months after the last dose of study drug (visit 7), at the EOT/ET visit (visit 8)	Follow-up visits for ADA sample collection will occur approximately 1 months and 3 months after the last dose of study drug (visit 7), at the EOT/ET visit (visit 8) and at the end of study (EOS) visit (visit 9), respectively.	Clarification of ADA sample collection during follow-up visits

Original text with changes shown	New wording	Reason/Justification for change
and ~~approximately 2 months after visit 8~~ at the end of study (EOS) visit (visit 9), respectively.		
The EOS~~end of study~~ is defined as the last visit of the last patient (follow-up visit, visit 9). Two interim analyses are planned. The first 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 (visit 5). A second interim database lock will occur following the end of the open-label period (visit 8). Final database lock will occur following the end of the follow-up period. The study duration will be approximately 2 years, from approximately ~~Q1/Q2~~Q3 2022 to approximately ~~Q1~~Q2 2024.	The EOS is defined as the last visit of the last patient (follow-up visit, visit 9). Two interim analyses are planned. The first 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 (visit 5). A second interim database lock will occur following the end of the open-label period (visit 8). Final database lock will occur following the end of the follow-up period. The study duration will be approximately 2 years, from approximately Q3 2022 to approximately Q2 2024.	Added interim analyses and updated study period due to experienced delays
In the event of an ~~public health~~ emergency situation (eg, pandemic or potential pandemic), the investigational center will inform the patient of the safeguards being taken…	In the event of an emergency situation (eg, pandemic or potential pandemic), the investigational center will inform the patient of the safeguards being taken…	Revised language to be aligned within the protocol
Section 3.2 Planned Number of Patients and Countries		
The study is expected to start in approximately Q3~~Q1/Q2~~ 2022 and last until approximately Q2~~Q1~~ 2024	The study is expected to start in approximately Q3 2022 and last until approximately Q2 2024.	Updated study period due to experienced delays
Section 3.5 Schedule of Study Procedures and Assessments		
Table 3 Study Procedures and Assessments [c] In case of an~~a public health~~ emergency situation (eg, pandemic or potential pandemic), visit windows for post baseline visits may be extended to 14 calendar days, except for visit 2. The window for visit 2 may only be extended to 7 calendar days in case of an emergency situation (eg, pandemic or potential pandemic). In case of an out-of-window visit, the date of the next visit will be calculated based on the actual date of the last administration of study drug.	**Table 3 Study Procedures and Assessments** [c] In case of an emergency situation (eg, pandemic or potential pandemic), visit windows for post baseline visits may be extended to 14 calendar days, except for visit 2. The window for visit 2 may only be extended to 7 calendar days in case of an emergency situation (eg, pandemic or potential pandemic). In case of an out-of-window visit, the date of the next visit will be calculated based on the actual date of the last administration of study drug.	Amended visit window to mitigate impact from an emergency situation (eg, pandemic or possible pandemic)
Section 4.1 Patient Inclusion Criteria "g"		

Original text with changes shown	New wording	Reason/Justification for change
[Revision 1] The patient has a clinical history of migraine that is confirmed during a prospectively recorded 28-day baseline period with the following characteristics: - Patient has 4 or more migraine days consistent with the characteristics of migraine (Appendix J) or probable migraine (a migraine subtype where only 1 migraine criterion is missing) or used a triptan or ergot derivative to treat an ongoing headache. - Patient has 42 or more days per month that are completely free of migraine headache or associated migraine symptoms.	[Revision 1] The patient has a clinical history of migraine that is confirmed during a prospectively recorded 28-day baseline period with the following characteristics: - Patient has 4 or more migraine days consistent with the characteristics of migraine (Appendix J) or probable migraine (a migraine subtype where only 1 migraine criterion is missing) or used a triptan or ergot derivative to treat an ongoing headache. - Patient has 2 or more days per month that are completely free of migraine headache or associated migraine symptoms.	Relaxation of inclusion criteria to aid with recruitment
Section 4.1 Patient Inclusion Criteria "i"		
[Revision 1] Other concomitant medications (excluding including herbal medicine) and acupuncture for migraine or other conditions are allowed for all patients, provided that the patient has been on a stable dose regimen for at least 2 months of consecutive use prior to screening (visit 1) with no expectation to change dosing regimen or change to another medication during the treatment phase of the study.	[Revision 1] Other concomitant medications (including herbal medicine) and acupuncture for migraine or other conditions are allowed for all patients, provided that the patient has been on a stable dose regimen for at least 2 months of consecutive use prior to screening (visit 1) with no expectation to change dosing regimen or change to another medication during the treatment phase of the study.	Relaxation of inclusion criteria to aid with recruitment
Section 4.2 Patient Exclusion Criteria "f"		
Known current infection or any history of infection with human immunodeficiency virus, tuberculosis, or Lyme disease, or hepatitis B or C virus, or a known or suspected active infection of coronavirus disease 2019 (COVID-19).	Known current infection or any history of infection with human immunodeficiency virus, tuberculosis, or Lyme disease, or a known or suspected active infection of coronavirus disease 2019 (COVID-19).	Update and relaxation of exclusion criteria to aid with recruitment
Section 4.2 Patient Exclusion Criteria "w"		
[New Criterion] Known current infection or history of infection in the past 6 months with hepatitis B or C viruses.	[New criterion] Known current infection or history of infection in the past 6 months with hepatitis B or C viruses.	Update and relaxation of exclusion criteria to aid with recruitment
Section 4.4 Replacement of Patients		
Early termination rate and screen failures due to ana public health emergency situation (eg, pandemic or	Early termination rate and screen failures due to an emergency situation (eg, pandemic or potential pandemic)	Clarification

Original text with changes shown	New wording	Reason/Justification for change
potential pandemic) will be monitored during the study. In order to maintain study power, an excess loss of patients will be replaced (eg, if there are >5% of patients lost to ana ~~public health~~ emergency situation [eg, pandemic or potential pandemic], additional patients may be recruited).	will be monitored during the study. In order to maintain study power, an excess loss of patients will be replaced (eg, if there are >5% of patients lost to an emergency situation [eg, pandemic or potential pandemic], additional patients may be recruited).	
Section 5.6 Prior and Concomitant Medication or Therapy		
…Traditional Chinese therapy (including~~other than~~ herbal medicine) and acupuncture are allowed if the patient is on a stable dosing regimen for at least 2 months (consecutive) before screening.	Traditional Chinese therapy (including herbal medicine) and acupuncture are allowed if the patient is on a stable dosing regimen for at least 2 months (consecutive) before screening.	Alignment of text with updated relaxation of inclusion criteria to aid with recruitment
Section 5.9.1 Maintenance of Randomization		
At the time of the first interim analysis ~~(after the end of study)~~, after receiving the unblinding request from the Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant standard operating procedure.	At the time of the first interim analysis, after receiving the unblinding request from the Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant standard operating procedure.	Updated according to included interim analyses
Section 7.1.2 Recording and Reporting of Adverse Events		
For the recording of adverse events, the study period is defined for each patient as the time period from ~~the beginning of study treatment~~ signature of the ICF to the end of the follow-up period. The follow-up period of the recording of adverse events is defined as 3~~6~~ months after the last dose of IMP.	For the recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the follow-up period. The follow-up period of the recording of adverse events is defined as 3 months after the last dose of IMP.	Correction for inconsistencies within the protocol. Adverse event reporting starts with each subject signing the informed consent form. The follow-up period is 3 months.
Section 7.1.5 Serious Adverse Events		
For the recording of serious adverse events, the study period is defined for each patient as the time period from ~~the beginning of study treatment~~ signature of the ICF to the end of the follow-up period.	For the recording of serious adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the follow-up period.	Correction for inconsistencies within the protocol. Adverse event reporting starts with each subject signing the informed consent form.
Section 7.4 Clinical Laboratory Test		
Not Applicable	**Table 6 Clinical Laboratory Test**	Clarification that total cholesterol is being tested

Original text with changes shown	New wording	Reason/Justification for change
	Added "Total Cholesterol" to the column with serum chemistry tests	
Section 7.4.1 Serum Chemistry, Hematology, and Urinalysis		
Specific laboratory tests to be performed are provided in Table 6. Note, reflex (ie, microanalysis tests like squamous epithelial cells and mucous threads) tests may be triggered automatically.	Specific laboratory tests to be performed are provided in Table 6. Note, reflex (ie, microanalysis tests like squamous epithelial cells and mucous threads) test may be triggered automatically.	Clarification that reflex tests may be triggered automatically but are not required by the protocol
Section 9.2.4 Per-Protocol Analysis Set		
…only patients who complete treatment without any important deviations such as important inclusion/exclusion criteria deviations or any important ~~violations~~deviations or omissions of the IMP administration.	…only patients who complete treatment without any important deviations such as important inclusion/exclusion criteria deviations or any important deviations or omissions of the IMP administration.	Correction of criteria for per-protocol analysis subset
Section 9.4 Study Population		
Summaries will be presented by treatment group and for all patients. In addition, the primary and secondary efficacy endpoints will also be analyzed using the per-protocol analysis set.	Summaries will be presented by treatment group and for all patients. In addition, the primary and secondary efficacy endpoints will also be analyzed using the per-protocol analysis set.	Clarification that the primary and secondary endpoints will also be analyzed using the per-protocol analysis set
Section 9.5.4 Planned Method of Analysis		
Summaries will be presented by treatment group. In addition, the primary and secondary efficacy endpoints will also be analyzed using the per-protocol analysis set.	In addition, the primary and secondary efficacy endpoints will also be analyzed using the per-protocol analysis set.	Clarification that the primary and secondary endpoints will also be analyzed using the per-protocol analysis set
Section 9.11 Planned Interim Analysis		
~~There will be no formal interim analysis.~~ Two interim analyses are planned. The first interim analysis is planned when the last patient has completed the double-blind period. A second interim analysis 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	Two interim analyses are planned. The first interim analysis is planned when the last patient has completed the double-blind period. A second interim analysis 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	Added interim analyses

Original text with changes shown	New wording	Reason/Justification for change
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 second database lock.	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 second database lock.	
Appendix A Clinical Laboratories and other Departments and Institutions		
Sponsor's Representative of Global Patient Safety and Pharmacovigilance **For serious adverse events:** Send by email to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	~~Teva Branded Pharmaceutical Products R&D, Inc.~~ ~~Tel:~~ [redacted] ~~Cell:~~ [redacted] Teva Pharmaceuticals, Cell: [redacted]	**Sponsor's Representative of Global Patient Safety and Pharmacovigilance** **For serious adverse events:** Send by email to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	Teva Pharmaceuticals, Cell: [redacted]	Updated contact information
Appendix C Quality Control and Quality Assurance		
Deviations from the study conduct due to emergency situations (eg, pandemic or potential~~the COVID-19~~ pandemic), including…	Deviations from the study conduct due to emergency situations (eg, pandemic or potential pandemic), including…	Revised language to be aligned within the protocol
In case of an emergency situation (eg, pandemic or potential~~the COVID-19~~ pandemic), where study monitors…	In case of an emergency situation (eg, pandemic or potential pandemic), where study monitors…	

Original text with changes shown	New wording	Reason/Justification for change
In case of an emergency situation (eg, pandemic or potential~~the COVID-19~~ pandemic), where auditors…	In case of an emergency situation (eg, pandemic or potential pandemic), where auditors…	
Appendix H Data Management and Record Keeping		
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 (visit 8).	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 (visit 8).	Added interim analyses

16.3. Administrative Letter 01 Dated 26 July 2022

ADMINISTRATIVE LETTER 01

Study number: TV48125-CNS-30088

Clinical Study Protocol with Amendment 01

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study with an Open-Label Treatment Period of Fremanezumab Administered Subcutaneously Monthly or Quarterly for the Preventive Treatment of Migraine in Adult Chinese Patients,

Approval date 15 September 2021

26 July 2022

Dear Investigator:

The purpose of this letter is to correct for inconsistencies in the study protocol related to the commencement of the collection of adverse events (AE). The Sponsor would like to clarify that AE reporting starts with informed consent form (ICF) signing by each subject, as indicated in Section 7.1.1 ("*Medical occurrences that begin before signing the ICF will be recorded on the medical history/current medical conditions section of the CRF.*") and Appendix H ("*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.*") of the protocol. This approach is standard clinical study practice and in line with Good Clinical Practice principles.

Table 1 below summarizes the relevant sections and page numbers to be revised, the existing protocol text, the new wording, and the reason for the change. The acual changes to the text are shown (revisions and additions are shown in bold and underlined; deletions are shown in strikethrough).

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

Please feel free to contact the study [redacted] (at [redacted] or [redacted]) if you have any questions or concerns regarding this letter.

Sincerely,

DocuSigned by:

[redacted]

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

Table 1: Revisions and Clarifications to the TV48125-CNS-30088 Clinical Study Protocol - Administrative Letter 01

Item number	Item	Section	Current wording	New wording	Reason for change
1	Adverse events recording	Section 7.1.2, Page 71	For the recording of adverse events, the study period is defined for each patient as the time period from ~~the beginning of study treatment~~ **signature of the informed consent form** to the end of the follow-up period.	For the 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.	Correction for inconsistencies within the protocol. Adverse events reporting starts with informed consent form signing by each subject
2	Adverse events recording	Section 7.1.5, Page 72	For the recording of serious adverse events, the study period is defined for each patient as the time period from ~~the beginning of study treatment~~ **signature of the informed consent form** to the end of the follow- up period.	For the recording of serious 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.	Correction for inconsistencies within the protocol. Adverse events reporting starts with informed consent form signing by each subject

16.4. Amendment 01 Dated 15 September 2021

The primary reason for this amendment is to add an open-label treatment period at the request of the China National Medicinal Products Administration's Center for Drug Evaluation and the ethics committee. Associated objectives and endpoints were added, and the randomization stratification factors were modified to include stratification by EM and CM migraine types. Furthermore, it was clarified that additional visits for pharmacokinetic assessment are required for the double-blind treatment period.

All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Changes to the Protocol

Original text with changes shown	New wording	Reason/justification for change
Title Page (Other sections affected by this change: Amendment History and Investigator Agreement)		
Clinical Study Protocol with ~~Revision~~ Amendment 01 … A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study with an Open-Label Treatment Period of Fremanezumab Administered Subcutaneously Monthly or Quarterly for the Preventive Treatment of Migraine in Adult Chinese Patients A Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Period on Efficacy and Safety of Fremanezumab in Chinese Adults with Migraine ... **Protocol with Amendment 01 Approval Date: 15 September 2021**	Clinical Study Protocol with Amendment 01 … A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study with an Open-Label Treatment Period of Fremanezumab Administered Subcutaneously Monthly or Quarterly for the Preventive Treatment of Migraine in Adult Chinese Patients A Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Period on Efficacy and Safety of Fremanezumab in Chinese Adults with Migraine ... **Protocol with Amendment 01 Approval Date: 15 September 2021**	Updated version and revised the title of the protocol
Section 1.1 Introduction (Other sections affected by this change: Sections 3.3 and 5.3.1)		
Fremanezumab was approved for use in adults in the United States (US) on 14 September 2018 and was approved by the European Medicines Agency (EMA) in March 2019, and marketing authorization applications have been submitted and approved in several countries worldwide, including	Fremanezumab was approved for use in adults in the United States (US) on 14 September 2018 and was approved by the European Medicines Agency (EMA) in March 2019, and marketing authorization applications have been submitted and approved in several countries worldwide, including Canada,	Noted completion and publication of pivotal studies supporting approval

Original text with changes shown	New wording	Reason/justification for change
Canada, Australia, Korea, and Japan. Pivotal studies leading to these approvals have been published.	Australia, Korea, and Japan. Pivotal studies leading to these approvals have been published.	
Section 1.1 Introduction (Other sections affected by this change: Sections 3.2 and 3.3)		
The purpose of the study is to confirm the efficacy and safety of fremanezumab in adult Chinese patients with the diagnosis of migraine in ~~mainland~~ China ~~and Hong Kong~~.	The purpose of the study is to confirm the efficacy and safety of fremanezumab in adult Chinese patients with the diagnosis of migraine in China.	Clarified location of study conduct
Section 1.2.2.2 Clinical Safety and Efficacy Studies (Other sections affected by this change: Section 3.3)		
Three Otsuka-sponsored studies in Japanese and Korean patients with EM and CM to evaluate the efficacy and safety of fremanezumab have been completed. These studies are 2 Phase 2b/3 double-blind, placebo-controlled studies in approximately 900 patients (406-102-00001 and 406-102-00002; Sakai et al 2021a, 2021b) and 1 long-term study in 50 patients (406-102-00003; manuscript accepted by Drug Safety as of 31 August 2021). The study designs of the Otsuka studies are the same as those of the HALO studies. Efficacy results demonstrated that treatment with fremanezumab monthly and quarterly was associated with statistically significant and clinically meaningful improvements on all primary and secondary efficacy measures. The safety profile observed in these studies was found to be consistent with that seen in the global pivotal efficacy studies; no safety signals were identified. These studies, together with the global HALO studies, led to marketing authorization in Japan and Korea in 2021. Fremanezumab at the doses tested was generally safe and well tolerated for 3 months in patients with ~~EM~~ migraine. 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.	Three Otsuka-sponsored studies in Japanese and Korean patients with EM and CM to evaluate the efficacy and safety of fremanezumab have been completed. These studies are 2 Phase 2b/3 double-blind, placebo-controlled studies in approximately 900 patients (406-102-00001 and 406-102-00002; Sakai et al 2021a, 2021b) and 1 long-term study in 50 patients (406-102-00003; manuscript accepted by Drug Safety as of 31 August 2021). The study designs of the Otsuka studies are the same as those of the HALO studies. Efficacy results demonstrated that treatment with fremanezumab monthly and quarterly was associated with statistically significant and clinically meaningful improvements on all primary and secondary efficacy measures. The safety profile observed in these studies was found to be consistent with that seen in the global pivotal efficacy studies; no safety signals were identified. These studies, together with the global HALO studies, led to marketing authorization in Japan and Korea in 2021. Fremanezumab at the doses tested was generally safe and well tolerated for 3 months in patients with migraine. 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.	Added efficacy and safety results from Otsuka-sponsored studies in Japanese and Korean patients Clarified the indication in patients treated with fremanezumab for 3 months

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/justification for change</th></tr>
<tr><td colspan="3">Section 2.1 Primary and Secondary Study Objectives and Endpoints</td></tr>
<tr><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>The primary objective of the study is to demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous (sc) injections to adult Chinese patients with migraine. The primary efficacy analysis will consider all fremanezumab treated patients as 1 group.</td><td>The primary endpoint is the mean change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of investigational medicinal product (IMP).</td></tr>
<tr><td>The secondary objective of the study is to further demonstrate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine. The secondary efficacy analyses will consider all fremanezumab treated patients as 1 group.</td><td>The secondary endpoints are as follows:
• mean change from baseline in the number of migraine days during the 4 week period after the 1st dose of IMP
• mean change from baseline in the monthly average number of days that any acute headache medications were used during the 12-week period after the 1st dose of IMP
• 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 IMP
• mean change from baseline in the monthly average number of days with headache of at least moderate severity during</td></tr>
</table>
</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>The primary objective of the study is to demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous (sc) injections to adult Chinese patients with migraine. The primary efficacy analysis will consider all fremanezumab treated patients as 1 group.</td><td>The primary endpoint is the mean change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of investigational medicinal product (IMP).</td></tr>
<tr><td>The secondary objective of the study is to further demonstrate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine. The secondary efficacy analyses will consider all fremanezumab treated patients as 1 group.</td><td>The secondary endpoints are as follows:
• mean change from baseline in the number of migraine days during the 4 week period after the 1st dose of IMP
• mean change from baseline in the monthly average number of days that any acute headache medications were used during the 12-week period after the 1st dose of IMP
• 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 IMP
• mean change from baseline in the monthly average number of days</td></tr>
</table>
</td><td>Clarified the make-up of the study population</td></tr>
</table>

Original text with changes shown	New wording	Reason/justification for change
<table><tr><td></td><td>the 12-week period after the 1st dose of IMP</td></tr><tr><td>A secondary objective of the study is to evaluate the safety and tolerability of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine.</td><td>The safety/tolerability endpoints are as follows: • occurrence of adverse events throughout the study • clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results at specified time points</td></tr></table> ADA=antidrug antibody; ECG=electrocardiogram; IMP=investigational medicinal product; sc=subcutaneous.	<table><tr><td></td><td>with headache of at least moderate severity during the 12-week period after the 1st dose of IMP</td></tr><tr><td>A secondary objective of the study is to evaluate the safety and tolerability of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine.</td><td>The safety/tolerability endpoints are as follows: • occurrence of adverse events throughout the study • clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results at specified time points</td></tr></table> ADA=antidrug antibody; ECG=electrocardiogram; IMP=investigational medicinal product; sc=subcutaneous.	
Section 2.2 Pharmacokinetic and Other Objectives and Endpoints (Other sections affected by this change: Sections 9.5.3 and 9.5.4.4)		
Pharmacokinetic and other endpoints for the double-blind treatment period to address the objective to further characterize fremanezumab safety, efficacy, and pharmacokinetics are as follows: … [redacted]	Pharmacokinetic and other endpoints for the double-blind treatment period to address the objective to further characterize fremanezumab safety, efficacy, and pharmacokinetics are as follows: … [redacted]	Defined the new objectives and endpoints relevant to the added open-label treatment period

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

Original text with changes shown	New wording	Reason/justification for change
[redacted]	[redacted]	
Section 3.1 General Study Design and Study Schematic Diagram (Other sections affected by this change: Sections 2.2, 3.3, 3.5, 5.1, 5.4, 5.6, 8.1, 9.5.4.1, 9.5.4.4, and Appendix B)		
This is a multicenter, randomized, double-blind, placebo-controlled study with an open-label treatment period to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc fremanezumab for the preventive treatment of migraine in adults. The study will consist of a screening visit, a baseline period (4 weeks), a 12-week double-blind treatment period, a 12-week open-label treatment period, and a follow-up period lasting approximately 3 months after the last dose of IMP (ie, 2 months after the end of treatment [EOT]/early termination [ET] visit). The total duration of patient participation in the study is planned to be approximately ~~6~~9 months.	This is a multicenter, randomized, double-blind, placebo-controlled study with an open-label treatment period to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc fremanezumab for the preventive treatment of migraine in adults. The study will consist of a screening visit, a baseline period (4 weeks), a 12-week double-blind treatment period, a 12-week open-label treatment period, and a follow-up period lasting approximately 3 months after the last dose of IMP (ie, 2 months after the end of treatment [EOT]/early termination [ET] visit).	Added open-label treatment period

Original text with changes shown	New wording	Reason/justification for change
… Patients must return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration. Additional details on these visits are provided in Section 8.1. Following 12 weeks of randomized treatment, patients enter the 12-week open-label treatment period to receive fremanezumab 225 mg sc once a month (approximately every 4 weeks) for a total of 3 doses (one 225-mg injection at visits 5, 6, and 7). 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 3 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 EOT study visit (visit 8) will be scheduled. Patients should return to the care of their treating physicians after visit 8. Patients should be treated with standard of care after withdrawal from or termination of the 24-week treatment period/study, as appropriate. (Note: For this study, monthly dosing refers to dosing approximately every 4 weeks [28 days].) … Patients will have treatment evaluations performed at visit 8 (EOT visit), approximately 4 weeks after administration of the final dose of study drug. A follow-up visit for ~~anti-drug antibody (~~ADA~~)~~ sample collection will occur approximately ~~2~~3 months after the last dose of study drug at the EOT/ET visit (visit ~~5~~8) and approximately 2 months after visit 8 at the end of study visit (visit 9). … The study duration will be approximately 2 years from ~~Q3 2021~~ approximately Q1/Q2 2022 to approximately Q1 2024~~Q2 2023~~.	The total duration of patient participation in the study is planned to be approximately 9 months. … Patients must return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration. Additional details on these visits are provided in Section 8.1. Following 12 weeks of randomized treatment, patients enter the 12-week open-label treatment period to receive fremanezumab 225 mg sc once a month (approximately every 4 weeks) for a total of 3 doses (one 225-mg injection at visits 5, 6, and 7). 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 3 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 EOT study visit (visit 8) will be scheduled. Patients should return to the care of their treating physicians after visit 8. Patients should be treated with standard of care after withdrawal from or termination of the 24-week treatment period/study, as appropriate. (Note: For this study, monthly dosing refers to dosing approximately every 4 weeks [28 days].) … Patients will have treatment evaluations performed at visit 8 (EOT visit), approximately 4 weeks after administration of the final dose of study drug. A follow-up visit for ADA sample collection will occur approximately 3 months after the last dose of study drug at the EOT/ET visit (visit 8) and approximately 2 months after visit 8 at the end of study visit (visit 9).	

Original text with changes shown	New wording	Reason/justification for change
	… The study duration will be approximately 2 years from approximately Q1/Q2 2022 to approximately Q1 2024.	
Note: Blood samples for plasma drug concentration will be collected at visits 2, 3, ~~4, 5,~~ and ~~6~~4. Patients will be asked to return to the study center after visit 2, visit 3, or visit 4 for ~~up to~~ 2 additional ~~visits after any dose of IMP for~~ blood sampling ~~for~~ visits to measure plasma fremanezumab concentration ~~determination and~~(one being 3 to 10 days after either visit 2, visit 3, or visit 4 and the other being 15 to 20 days after either visit 2, visit 3, or visit 4). If 2 additional visits are not possible for the patient, then the patient must return for only 1 additional pharmacokinetic blood sampling at either of the aforementioned time points. When patients return to the study center for additional blood sampling, then inquiries about adverse events and concomitant medications. ~~These visits should occur during the following time periods relative to any dose of IMP: 3 to 10 days and/or 15 to 20 days after IMP administration~~ will be performed.	Note: Blood samples for plasma drug concentration will be collected at visits 2, 3, and 4. Patients will be asked to return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration (one being 3 to 10 days after either visit 2, visit 3, or visit 4 and the other being 15 to 20 days after either visit 2, visit 3, or visit 4). If 2 additional visits are not possible for the patient, then the patient must return for only 1 additional pharmacokinetic blood sampling at either of the aforementioned time points. When patients return to the study center for additional blood sampling, then inquiries about adverse events and concomitant medications will be performed.	Clarified that additional visits for pharmacokinetic assessment are required for the double-blind treatment period
Section 3.1 General Study Design and Study Schematic Diagram (Other sections affected by this change: Sections 3.3, 5.8, 9.5.4.1, 9.5.4.2, and 9.5.4.3)		
Randomization using electronic interactive response technology (IRT) will be stratified based on ~~sex,~~ migraine type (CM vs EM) and preventive medication use~~, and region~~ to ensure balance.	Randomization using electronic interactive response technology (IRT) will be stratified based on migraine type (CM vs EM) and preventive medication use to ensure balance.	Changed randomization stratification
Section 3.3 Justification for Study Design and Selection of Population		
...No ethnic differences are expected or observed in the safety or efficacy of fremanezumab used for the preventive treatment of migraine. …Both fremanezumab dosing regimens are approved in the US, the EU, Australia, Israel, and several additional countries. Study design elements, including the duration of the double-blind and open-label treatment periods; dosing regimen; inclusion/exclusion criteria; and efficacy, safety, and	...No ethnic differences are expected or observed in the safety or efficacy of fremanezumab used for the preventive treatment of migraine. …Both fremanezumab dosing regimens are approved in the US, the EU, Australia, Israel, and several additional countries. Study design elements, including the duration of the double-blind and open-label treatment periods; dosing regimen; inclusion/exclusion criteria; and efficacy,	Added rational for combining patients with CM and patients with EM for primary analysis.

Original text with changes shown	New wording	Reason/justification for change
pharmacokinetic assessments are completely consistent with the pivotal HALO studies and all fremanezumab migraine efficacy studies completed so far. Throughout the global fremanezumab clinical program, patients with the full range of clinical severities, from the episodic to chronic subtypes of migraine, both separately and combined, have consistently demonstrated similar efficacy and safety with fremanezumab treatment by the same measures. Therefore, in this study, the primary analysis will consider patients representing the entire disease spectrum of migraine as a single study population stratified by EM and CM. Moreover, this study population is fully consistent with the currently approved indication for migraine in the US, Canada, EU, and other countries, and fully reflects the intended population for use in Chinese patients. In order to provide added granularity to the migraine subtypes, data for patients with EM and CM will be provided as subgroup analyses. Pharmacokinetic samples will be collected during the treatment and follow-up periods and analyzed using a population pharmacokinetic (PPK) modeling approach. Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point by treatment group. The pharmacokinetic data from this study will be compared with the general migraine population data in order to demonstrate comparability. Anti-drug antibody samples will be collected and analyzed during and after the treatment period. Primary efficacy will be measured by the change from baseline in the monthly average number…	safety, and pharmacokinetic assessments are completely consistent with the pivotal HALO studies and all fremanezumab migraine efficacy studies completed so far. Throughout the global fremanezumab clinical program, patients with the full range of clinical severities, from the episodic to chronic subtypes of migraine, both separately and combined, have consistently demonstrated similar efficacy and safety with fremanezumab treatment by the same measures. Therefore, in this study, the primary analysis will consider patients representing the entire disease spectrum of migraine as a single study population stratified by EM and CM. Moreover, this study population is fully consistent with the currently approved indication for migraine in the US, Canada, EU, and other countries, and fully reflects the intended population for use in Chinese patients. In order to provide added granularity to the migraine subtypes, data for patients with EM and CM will be provided as subgroup analyses. Pharmacokinetic samples will be collected during the treatment and follow-up periods and analyzed using a population pharmacokinetic (PPK) modeling approach. Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point by treatment group. The pharmacokinetic data from this study will be compared with the general migraine population data in order to demonstrate comparability. Anti-drug antibody samples will be collected and analyzed during and after the treatment period. Primary efficacy will be measured by the change from baseline in the monthly average number…	

Original text with changes shown	New wording	Reason/justification for change
Section 3.5 Schedule of Study Procedures and Assessments		
Table 3 Study Procedures and Assessments c In case of a public health emergency, visit windows may be extended to 7 calendar days. In case of an out-of-window visit, the date of the next visit will be calculated based on the actual date of the last administration of study drug.	**Table 3 Study Procedures and Assessments** c In case of a public health emergency, visit windows may be extended to 7 calendar days. In case of an out-of-window visit, the date of the next visit will be calculated based on the actual date of the last administration of study drug.	Added the method of calculating the next visit for cases of out-of-window visits
Section 4.1 Patient Inclusion Criteria		
g. The patient has a clinical history of migraine that is confirmed during a prospectively recorded 28-day baseline period with the following characteristics: – Patient has 4 or more ~~headache~~ migraine days consistent with the characteristics of migraine (Appendix J) or probable migraine (a migraine subtype where only 1 migraine criterion is missing) or used a triptan or ergot derivative to treat an ongoing headache. – Patient has 4 or more days per month that are completely free of migraine headache or associated migraine symptoms.	g. The patient has a clinical history of migraine that is confirmed during a prospectively recorded 28-day baseline period with the following characteristics: – Patient has 4 or more migraine days consistent with the characteristics of migraine (Appendix J) or probable migraine (a migraine subtype where only 1 migraine criterion is missing) or used a triptan or ergot derivative to treat an ongoing headache. – Patient has 4 or more days per month that are completely free of migraine headache or associated migraine symptoms.	Clarified the clinical history of migraine in patients
Section 4.2 Patient Exclusion Criteria		
b. Has used an intervention/device (eg, scheduled nerve blocks or transcranial magnetic stimulation) for migraine, or in the head or neck area, during the 2 months prior to screening (visit 1).	b. Has used an intervention/device (eg, scheduled nerve blocks or transcranial magnetic stimulation) for migraine, or in the head or neck area, during the 2 months prior to screening (visit 1).	Clarified the use of interventional/device by the patient prior to screening
Section 5.1.1.1 Starting Dose and Dose Levels		
The starting dose of fremanezumab will be either 675 mg or 225 mg at visit 2 (day 1), depending on the treatment group. 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 double-blind period and 225 mg for the open-label treatment period.	The starting dose of fremanezumab will be either 675 mg or 225 mg at visit 2 (day 1), depending on the treatment group. 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 double-blind period and 225 mg for the open-label treatment period.	Clarified the maximal dose administered for the double-blind and open-label periods

Original text with changes shown	New wording	Reason/justification for change
Section 7.10 Assessment of Suicidality		
Any ~~patient should be excluded if any suicidal behaviors are reported~~ suicide attempt in the past, suicidal ideation with a specific plan in the past 2 years prior to screening (visit 1), or current suicidal ideation will result in patient exclusion. ~~Any patient with lifetime suicidal behaviors (actual, interrupted, and aborted attempts and preparatory actions) and current suicidal ideation should be excluded and/or discontinued from study treatment.~~ Investigators will inquire about and evaluate suicidal ideation, plan, and behavior based on their clinical judgement and refer patients to psychiatric care as appropriate.	Any suicide attempt in the past, suicidal ideation with a specific plan in the past 2 years prior to screening (visit 1), or current suicidal ideation will result in patient exclusion. Investigators will inquire about and evaluate suicidal ideation, plan, and behavior based on their clinical judgement and refer patients to psychiatric care as appropriate.	Clarified the assessment of suicidality that will result in patient exclusion
Section 9.1 Sample Size and Power Considerations		
Therefore, the sample size and power estimation were conducted, assuming that the treatment difference between fremanezumab and placebo is 1.6 days (common SD 4.45 days). To ensure adequate representation of patients with both migraine types (EM and CM), the enrollment minimum of either migraine type is 30%. In addition, primary efficacy analysis will be stratified by EM and CM and subgroup analysis for EM and CM will be conducted.	Therefore, the sample size and power estimation were conducted, assuming that the treatment difference between fremanezumab and placebo is 1.6 days (common SD 4.45 days). To ensure adequate representation of patients with both migraine types (EM and CM), the enrollment minimum of either migraine type is 30%. In addition, primary efficacy analysis will be stratified by EM and CM and subgroup analysis for EM and CM will be conducted.	Clarified enrollment minimums for each migraine type
Appendix A CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Bioanalytical Pharmacokinetics Evaluation Accurant Biotechnology Co, Ltd Room 505, Floor 5 No.8 Jiafeng Road Free Trade Zone, Shanghai 200131 China	**Bioanalytical Pharmacokinetics Evaluation** Accurant Biotechnology Co, Ltd Room 505, Floor 5 No.8 Jiafeng Road Free Trade Zone, Shanghai 200131 China	Clarified the address
Bioanalytical Immunogenicity Evaluation Accurant Biotechnology Co, Ltd Room 505, Floor 5 No.8 Jiafeng Road	**Bioanalytical Immunogenicity Evaluation** Accurant Biotechnology Co, Ltd Room 505, Floor 5 No.8 Jiafeng Road	

Original text with changes shown	New wording	Reason/justification for change
Free Trade Zone, Shanghai 200131 China	Free Trade Zone, Shanghai 200131 China	
Appendix K PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR 30% OF THE STUDY POPULATION FOR THE DURATION OF THE STUDY		
~~The use of up to 1 preventive migraine medication is allowed for the duration of the study for up to 30% of the total population of patients (see Section .)5.6~~ ~~Preventive migraine medications allowed for the duration of the study specifically include the following (if they were previously prescribed for migraine or for another indication):~~ The chronic use of up to 1 of the following concomitant medications is allowed in up to 30% of patients and should be entered in the electronic case report form (eCRF) pages specific for migraine preventive medication. Patients using up to 1 of the following migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication. Patients must have been on a stable, well-tolerated dose regimen of this medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 70% of patients, the chronic use of the following medications are not allowed for migraine or for any other indications. PRN (ie, taken as needed) use of the following medications are allowed during the course of the study. PRN use of these medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the prescribing information or local treatment guidelines. Patients will be allowed to use acute medications to treat acute migraine attacks as needed, with the exception of medications containing opioids and barbiturates.	The chronic use of up to 1 of the following concomitant medications is allowed in up to 30% of patients and should be entered in the electronic case report form (eCRF) pages specific for migraine preventive medication. Patients using up to 1 of the following migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication. Patients must have been on a stable, well-tolerated dose regimen of this medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 70% of patients, the chronic use of the following medications are not allowed for migraine or for any other indications. PRN (ie, taken as needed) use of the following medications are allowed during the course of the study. PRN use of these medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the prescribing information or local treatment guidelines. Patients will be allowed to use acute medications to treat acute migraine attacks as needed, with the exception of medications containing opioids and barbiturates. • beta-blockers: atenolol, propranolol, metoprolol, nadolol, and timolol • calcium channel blockers/benzocycloheptenes: flunarizine and pizotifen	Revised the use of preventative migraine medications allowed for 30% of the study population for the duration of the study

Original text with changes shown	New wording	Reason/justification for change
• beta-blockers: atenolol, propranolol, metoprolol, nadolol, and timolol • calcium channel blockers/benzocycloheptenes: flunarizine and pizotifen • antidepressants: amitriptyline, venlafaxine, nortriptyline, and duloxetine • anti-epileptic medications: topiramate, valproate, and divalproate • onabotulinumtoxinA Other agents that are not on this list but used for migraine prevention that may be used per local guidelines or clinical practice preference are considered to have questionable efficacy for migraine prevention and are therefore treated the same as other concomitant medications (ie, recorded as concomitant medications on the case report form) and DO NOT need to be captured in eCRF pages specific for migraine preventive medications.	• antidepressants: amitriptyline, venlafaxine, nortriptyline, and duloxetine • anti-epileptic medications: topiramate, valproate, and divalproate • onabotulinumtoxinA Other agents that are not on this list but used for migraine prevention that may be used per local guidelines or clinical practice preference are considered to have questionable efficacy for migraine prevention and are therefore treated the same as other concomitant medications (ie, recorded as concomitant medications on the case report form) and DO NOT need to be captured in eCRF pages specific for migraine preventive medications.	

16.5. Revision 01 Dated 01 April 2021

The primary reason for this revision of the original protocol is to revise the contract research organization listed in Appendix A of the protocol. In addition, the other endpoint of "assessment of ADA during and after the treatment period" was removed, as ADAs will be evaluated as part of the secondary safety analysis. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study	[redacted] [redacted] [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]
Sponsor's Representative of Global Patient Safety and Pharmacovigilance **For serious adverse events:** Send by email to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	[redacted] [redacted] Teva Pharmaceuticals, [redacted] [redacted] Cell: [redacted] [redacted]
Contract Research Organization	Pharmaceutical Research Associates, Inc. 4130 Parklake Avenue Suite 400 Raleigh, North Carolina 27612 USA
Coordinating Clinical Laboratory	Contracting entity ICON Laboratory Services, Inc. – Ireland South County Business Park, Leopardstown, Dublin 18, Ireland ICON Laboratory Services, Inc. – China Floor 1-3, No 3 Building, Hongda Industrial Park, No. 8 Hongda North Road, Yizhhuang Development Zone, Daxing District, Beijing, 100176, China
Bioanalytical Pharmacokinetics Evaluation	Accurant Biotechnology Co, Ltd Room 505, Floor 5 No.8 Jiafeng Road Free Trade Zone, Shanghai 200131 China
Bioanalytical Immunogenicity Evaluation	Accurant Biotechnology Co, Ltd Room 505, Floor 5 No.8 Jiafeng Road Free Trade Zone, Shanghai 200131 China

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

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

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

- obtain written informed consent before any study-related procedures are performed
- review inclusion and exclusion criteria
- review medical and psychiatric history
- record demographic characteristics
- review prior medications and treatment history
- perform clinical laboratory tests
- perform physical examination (including height and weight)
- perform 12-lead electrocardiogram (ECG)
- perform vital signs measurements
- perform serum beta-human chorionic gonadotropin (β-HCG) pregnancy test (for women of childbearing potential [WOCBP]) and follicle-stimulating hormone test (for postmenopausal women)
- inform patients of study restrictions and compliance requirements
- provide the electronic headache diary device
- complete electronic headache diary entries

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

Patients who meet the inclusion and exclusion criteria at visit 1 will enter a 28-day baseline period (when headache information will be captured daily in an electronic headache diary device) and then will continue to visit 2, when additional baseline assessments will be conducted.

The following procedures will be performed at visit 2:

- review inclusion and exclusion criteria
- assign randomization/treatment number
- perform clinical laboratory tests
- collect blood samples for plasma concentration of the investigational medicinal product (IMP)
    - Patients will be asked to return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration (one being 3 to 10 days after either visit 2, visit 3, or visit 4 and the other being 15 to 20 days after either visit 2, visit 3, or visit 4). If 2 additional

visits are not possible for the patient, then the patient must return for only 1 additional pharmacokinetic blood sampling at either of the aforementioned time points. When patients return to the study center for additional blood sampling, then inquiries about adverse events and concomitant medications will be performed.

- collect blood samples for serum antidrug antibody (ADA) assessment
- perform physical examination (including weight)
- perform 12-lead ECG
- perform vital signs measurements
- perform urine pregnancy test (for WOCBP)
- review study compliance
- complete electronic headache diary entries
- review the electronic headache diary
- perform adverse event inquiry
- administer the IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication inquiry

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

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

- collect blood samples for plasma concentration of the IMP
  - Patients will be asked to return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration (one being 3 to 10 days after either visit 2, visit 3, or visit 4 and the other being 15 to 20 days after either visit 2, visit 3, or visit 4). If 2 additional visits are not possible for the patient, then the patient must return for only 1 additional pharmacokinetic blood sampling at either of the aforementioned time points. When patients return to the study center for additional blood sampling, then inquiries about adverse events and concomitant medications will be performed.
- perform physical examination (including weight)
- perform vital signs measurements
- perform urine pregnancy test (for WOCBP)
- review study compliance
- complete electronic headache diary entries

- review the electronic headache diary
- perform adverse events inquiry
- administer the IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication inquiry

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

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

- perform clinical laboratory tests
- collect blood samples for plasma concentration of the IMP
  - Patients will be asked to return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration (one being 3 to 10 days after either visit 2, visit 3, or visit 4 and the other being 15 to 20 days after either visit 2, visit 3, or visit 4). If 2 additional visits are not possible for the patient, then the patient must return for only 1 additional pharmacokinetic blood sampling at either of the aforementioned time points. When patients return to the study center for additional blood sampling, then inquiries about adverse events and concomitant medications will be performed.
- collect blood samples for serum ADA assessment
- perform physical examination (including weight)
- perform 12-lead ECG
- perform vital signs measurements
- perform urine pregnancy test (for WOCBP)
- review study compliance
- complete electronic headache diary entries
- review the electronic headache diary
- perform adverse events inquiry
- administer the IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication inquiry

5. **Procedures During Administration of Investigational Medicinal Product(s) (Visit 5, Day 85 ±5 days) (Open-Label Treatment Period)**

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

- perform clinical laboratory tests
- perform physical examination (including weight)
- perform vital signs measurements
- perform urine pregnancy test (for WOCBP)
- review study compliance
- complete electronic headache diary entries
- review the electronic headache diary
- complete the Patient Global Impression of Change (PGIC) scale
- perform adverse events inquiry
- administer the IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication inquiry

6. **Procedures During Administration of Investigational Medicinal Product(s) (Visit 6, Day 113 ±5 days) (Open-Label Treatment Period)**

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

- perform vital signs measurements
- perform urine pregnancy test (for WOCBP)
- review study compliance
- complete electronic headache diary entries
- review the electronic headache diary
- perform adverse events inquiry
- administer the IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication inquiry

7. **Procedures During Administration of Investigational Medicinal Product(s) (Visit 7, Day 141 ±5 days) (Open-Label Treatment Period)**

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

- perform vital signs measurements
- perform urine pregnancy test (for WOCBP)

- review study compliance
- complete electronic headache diary entries
- review the electronic headache diary
- perform adverse events inquiry
- administer the IMP
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication inquiry

8. **Procedures During End of Treatment/Early Termination Visit (Visit 8, Day 169 ±5 days)**

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

- perform clinical laboratory tests
- collect blood samples for plasma concentration of the IMP
- collect blood samples for serum ADA assessment
- perform physical examination (including weight)
- perform 12-lead ECG
- perform vital signs measurements
- perform serum β-HCG pregnancy test (for WOCBP)
- perform urine pregnancy test (for WOCBP)
- review study compliance
- complete electronic headache diary entries
- review the electronic headache diary
- return the electronic headache diary device
- complete the PGIC scale
- perform adverse events inquiry
- assess for hypersensitivity/anaphylaxis
- perform concomitant medication inquiry

9. **Procedures During Follow-up (Visit 9, Day 225 ±15 days)**

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

- collect blood samples for serum ADA assessment
- perform physical examination (including weight)
- perform vital signs measurements
- perform adverse events inquiry

- perform concomitant medication inquiry

In addition, if the clinical laboratory tests, physical examination, or 12-lead ECG performed at visit 8 (EOT/ET) showed an abnormality, the assessment should be repeated during the follow-up visit.

10. **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 the following:

- perform vital signs measurements
- review study compliance
- review the electronic headache diary
- perform adverse events inquiry
- perform concomitant medication inquiry

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

APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

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

Important Protocol Deviations

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

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

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

Deviations from the study conduct due to emergency situations (eg, pandemic or potential pandemic), including implemented contingency measures and their impact (eg, patient discontinuation from treatment with IMP and/or study, alternative procedures used to collect critical safety and/or efficacy data, etc), will be described in the appropriate sections of the clinical study report, as applicable.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center

authorization form, which includes a clear description of each personnel member's responsibilities. This list must be updated throughout the study, as necessary.

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

Study Monitoring

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

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitors 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 monitors will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (case report forms and other pertinent source data records, including specific electronic source documents 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.

In case of an emergency situation (eg, pandemic or potential pandemic), where study monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with local regulations.

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.

In case of an emergency situation (eg, pandemic or potential pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be audited remotely, where allowed, and in accordance with local regulations.

APPENDIX D. ETHICS

Informed Consent

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

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

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

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

Confidentiality Regarding Study Patients

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

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

Registration of the Clinical Study

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

APPENDIX E. BIRTH CONTROL METHODS AND PREGNANCY TESTING

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

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

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

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

Women of non-childbearing potential are defined as:

- surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- postmenopausal

Postmenopausal women:

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

Description of different birth control methods

Highly effective birth control methods:

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include 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 1st 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 1st dose of IMP
- Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before the screening visit (visit 1)
- Bilateral tubal occlusion
- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient

Unacceptable birth control methods:

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

Male contraception

Male patients that are not sterile and have female partners of childbearing potential should use highly effective birth control.

Appendix F. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she 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, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 documented attempts via 2 different methods [telephone, text, email, certified letter, etc]). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of "lost to follow-up."

APPENDIX G. PRODUCT COMPLAINTS

Clinical Product Complaints

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

- suspected contamination
- questionable stability (eg, color change, flaking, or crumbling)
- defective components
- missing or extra units (eg, the 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, odor, or both
- device not working correctly or appears defective in some manner

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

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

1. **Product Complaint Information Needed from the Investigational Center**

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

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return (Yes/No)
- product 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 IMPs, 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 a 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 documents 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 H. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documents 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, Independent Ethics Committee/Institutional Review Board (IEC/IRB), and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, or 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 for the unambiguous identification of each patient.

Data Collection

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

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

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, or 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 documents in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly in the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

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

Data Quality Control

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

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

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

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 (visit 8). 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 contract research organization or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

APPENDIX I. 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 J. INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS, 3RD REVISION, DIAGNOSTIC CRITERIA

For further details, refer to (IHS 2018) and/or CMAPS 2016.

1.1 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, presence of at least one of the following:

- nausea and/or vomiting
- photophobia and phonophobia

e. not better accounted for by another International Classification of Headache Disorders, 3rd revision [ICHD-3] diagnosis

1.2 Migraine with aura

a. at least 2 attacks fulfilling criteria b and c

b. one or more of the following fully reversible aura symptoms:

- visual
- sensory
- speech and/or language
- motor
- brainstem
- retinal

c. at least 2 of the following 4 characteristics:

- at least 1 aura symptom spreads gradually over ≥5 minutes and/or 2 or more symptoms occur in succession
- each individual aura symptom lasts 5 to 60 minutes
- at least 1 aura symptom is unilateral
- the aura is accompanied, or followed within 60 minutes, by headache

d. not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

APPENDIX K. PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR 30% OF THE STUDY POPULATION FOR THE DURATION OF THE STUDY

The chronic use of up to 1 of the following concomitant medications is allowed in up to 30% of patients and should be entered in the electronic case report form (eCRF) pages specific for migraine preventive medication. Patients using up to 1 of the following migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication. Patients must have been on a stable, well-tolerated dose regimen of this medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 70% of patients, the chronic use of the following medications are not allowed for migraine or for any other indications. PRN (ie, taken as needed) use of the following medications are allowed during the course of the study. PRN use of these medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the prescribing information or local treatment guidelines. Patients will be allowed to use acute medications to treat acute migraine attacks as needed, with the exception of medications containing opioids and barbiturates.

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

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

Appendix L. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

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

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

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

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