Clinical Study Protocol

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Proof of Concept Study of the Efficacy and Safety of Fremanezumab for Treatment of Patients with Fibromyalgia

Study Number TV48125-PN-20028

NCT03965091

Protocol with Amendment 05 Approval Date: 10 August 2021

Clinical Study Protocol with Amendment 05

Study Number TV48125-PN-20028

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Proof of Concept Study of the Efficacy and Safety of Fremanezumab for Treatment of Patients with Fibromyalgia
(Concealed version)

Proof of Concept Study (Phase 2)

IND number: 141519; BLA number: 761089

Protocol Approval Date: 06 December 2018

Protocol with Amendment 01 Approval Date: 08 February 2019

Protocol with Amendment 02 Approval Date: 16 April 2019

Protocol with Amendment 03 Approval Date: 22 July 2019

Protocol with Amendment 04 Approval Date: 16 June 2020

Protocol with Amendment 04 with Revision 01 Approval Date: 25 June 2020

Protocol with Amendment 05 Approval Date: 10 August 2021

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

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

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures

COVID-19 pandemic-related operational updates are provided in Appendix O.

Confidentiality Statement

AMENDMENT HISTORY

The protocol for Study TV48125-PN-20028 (original protocol dated 06 December 2018) has been amended and reissued as follows:

Amendment 05	10 August 2021 153 patients have been randomized/enrolled to date The following sections are affected: Preface Table 1 Study Procedures and Assessments Section 4.1 Patient Inclusion Criteria Section 4.2 Patient Exclusion Criteria Section 5.7.1 Permitted Concomitant Medication or Therapy Section 5.11 Total Blood Volume Section 7.4.2.2 Urine Drug Screen Section 9.6.4.2 Sensitivity Analysis Section 9.15 Planned Interim Analysis Appendix B Study Procedures and Assessments by Visit Appendix I. List of Prohibited Medications and Therapeutic Interventions Appendix J. Total Blood Volume Appendix O. Management of Study Activities During COVID-19

Amendment 04, Revision 01	25 June 2020 68 patients have been randomized/enrolled to date The protocol amendment 04 was approved on 16 June 2020. However, it was not distributed externally and was immediately followed by protocol amendment 4 revision 01, with the addition of an interim analysis. Protocol amendment 04 revision 01 was submitted to health authorities. The following sections are affected: Section 9.15 Planned Interim Analysis
Amendment 04	16 June 2020 68 patients have been randomized/enrolled to date The management of study activities during the COVID-19 pandemic are detailed in Appendix O. The following sections are affected: Section 3.1 General Study Design and Study Schematic Diagram Section 4.5 Rescreening Section 5.1.1.2 Dosing Visits and Dose Modification Appendix D. Quality Control and Quality Assurance Appendix E. Ethics
Amendment 03	22 July 2019 No patients have been randomized/enrolled to date
Amendment 02	16 April 2019 No patients have been randomized/enrolled to date
Amendment 01	08 February 2019 No patients have been randomized/enrolled to date

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

INVESTIGATOR AGREEMENT

Original Protocol Dated 06 December 2018

Clinical Study Protocol with Amendment 05

IND number: 141519; NDA number: Not Applicable; BLA number: 761089; EudraCT number: Not Applicable

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Proof of Concept Study of the Efficacy and Safety of Fremanezumab for Treatment of Patients with Fibromyalgia (Concealed version)

Principal Investigator: _____

Title: _____

_____

_____

_____

Tel: _____

I have read the protocol with Amendment 05 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, IMPs 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 the Trial Master File.

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]		

Executed signature pages are maintained within the Trial Master File.

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 06 December 2018

Clinical Study Protocol with Amendment 05

IND number: 141519; NDA number: Not Applicable; BLA number: 761089; EudraCT number: Not Applicable

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Proof of Concept Study of the Efficacy and Safety of Fremanezumab for Treatment of Patients with Fibromyalgia (Concealed version)

I have read the protocol with Amendment 05 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national and local legal and regulatory requirements and applicable regulations and guidelines.

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

Coordinating Investigator [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Tel: [redacted]

Coordinating Investigator	Signature	Date
[redacted]		

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

CLINICAL STUDY PROTOCOL SYNOPSIS

with Amendment 05

Study TV48125-PN-20028

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Proof of Concept Study of the Efficacy and Safety of Fremanezumab for Treatment of Patients with Fibromyalgia (Concealed version)

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

Investigational New Drug (IND) Number: 141519 New Drug Application Number: Not Applicable Biological License Application (BLA) Number: 761089 EudraCT Number: Not Applicable

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

Name of Test Investigational Medicinal Product (IMP) or Device: Fremanezumab, a recombinant humanized immunoglobulin G (IgG) 2Δa/kappa monoclonal antibody (mAb) against calcitonin gene-related peptide (CGRP)

EudraVigilance (EV) code for the IMP, if applicable: Not Applicable

Type of the Study: Proof of Concept Study

Indication: Fibromyalgia (FM)

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

Number of Investigational Centers Planned: The study is planned to be conducted at approximately 40 investigational centers.

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

Planned Study Period: The planned study period is from May 2019 until approximately July 2022.

Number of Patients Planned (total): Approximately 240 patients will be randomized.

Study Population: ≥18- to 75-year-old male and female patients with FM

Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
The **primary objective** of the study is to estimate the treatment effect of fremanezumab administered subcutaneously in reducing pain in adult patients with FM.	The primary efficacy endpoint is the change from baseline up to week 16 in the weekly average of the daily average Pain Intensity-Numerical Rating Scale (PI-NRS) score over the past 24 hours.
A **secondary objective** is to evaluate the effect of fremanezumab on other efficacy measures, including pain, quality of life, sleep, fatigue, improvement in health, physical functioning, and mood.	The secondary efficacy endpoints are as follows: • change from baseline up to week 16 in the individual components of the Fibromyalgia Impact Questionnaire Revised (FIQR): symptom subscore, impact subscore, and functional subscore score • responder rate of the Patient Global Impression of Change (PGIC) rating (percentage of patients much improved or very much improved) up to week 16 • the percentage of patients who experience a ≥30% reduction in the weekly average of the daily average PI-NRS score up to week 16 • the percentage of patients who experience a ≥50% reduction in the weekly average of the daily average PI-NRS score up to week 16 • change from baseline up to week 16 in the weekly average of the daily worst PI-NRS score over the past 24 hours • change from baseline up to week 16 in the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short Form (SF) 8a score • change from baseline up to week 16 in the PROMIS Physical Function SF12a score • change from baseline up to week 16 in the PROMIS Fatigue SF8a score • number (%) of patients who did not complete the treatment (Kaplan-Meier Survival Analysis) due to lack of efficacy

Objectives	Endpoints
A **secondary objective** of the study is to evaluate the safety and tolerability of fremanezumab administered subcutaneously in adult patients with FM.	The safety and tolerability endpoints are as follows: • occurrence of adverse events • change from randomization up to week 16 in the clinical laboratory tests (serum chemistry, hematology, and urinalysis) • change from baseline up to week 16 in vital signs (pulse, respiratory rate, systolic and diastolic blood pressure, and oral body temperature measurements at each visit) • clinically significant changes in physical examination, including body weight • abnormal standard 12-lead electrocardiogram (ECG) findings • tolerability at the injection site including but not limited to pain, erythema, induration, and ecchymosis • occurrence of hypersensitivity/anaphylaxis reactions using standardized criteria (Appendix C) • suicidal ideation and behavior as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) • number (%) of patients who did not complete the treatment (Kaplan-Meier Survival Analysis) due to adverse events

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Immunogenicity Objective and Endpoint:

Objectives	Endpoints
To evaluate the immunogenicity of fremanezumab and the impact of anti-drug antibodies (ADAs) on clinical outcomes	• incidence and characteristics of ADAs (eg, titers, kinetics, and neutralizing activities)

General Study Design: This is a 21-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fremanezumab in adult patients with FM. Fremanezumab 225 mg, fremanezumab 675 mg, or placebo will be administered subcutaneously (sc) for 4 total doses (1 dose [3 injections] administered each month). Patients will receive either placebo or 1 of 2 fremanezumab dose levels at Visits 3, 4, 5, and 6. All patients will receive either placebo or 1 of 2 fremanezumab dose levels for a total of 3 sc injections at each dosing visit. The study consists of the following:

- 17- to 35-day screening period (Visit 1, phone contact, and Baseline Assessment Period Start [BAPS] Visit [Visit 2])
- 16-week double-blind treatment period (Visits 3, 4, 5, 6, and 7)

Patients enrolled in the study will be male or female patients with FM. Patients will be required to washout all prohibited concomitant medication(s) prior to the start of the BAPS Visit (Visit 2).

No study assessments or procedures will be conducted until informed consent has been obtained. The screening period includes the following:

- Screening Visit (Visit 1) during which the informed consent will be reviewed and signed, and the screening procedures will occur.
- Phone contact no later than day -15 to inform the patient how to safely taper off prohibited concomitant medications and schedule the BAPS Visit (Visit 2).
- BAPS Visit (Visit 2) at which point patients will receive electronic diaries (e-diaries) to record their daily average pain intensity score and daily worst pain intensity score using the PI-NRS in the e-diary every evening at approximately the same time (between 1800 and 2200 hours). The PI-NRS score must also be recorded in the e-diary prior to taking rescue medication.

Training on tablet assessments and the e-diary will occur at the Screening Visit (Visit 1) and the BAPS Visit (Visit 2). As needed throughout the study, subsequent retraining on tablet assessments and the e-diary will be completed.

The duration of the washout period will be 7 to 19 days; suggested washout periods for commonly used analgesics are listed in Table 4. The baseline assessment period is 14 days (from Visit 2 to Visit 3) during which patients must complete at least 12 of 14 days of e-diary entries. The average of the daily average pain score using the PI-NRS during the baseline assessment period (ie, from day -14 to day -1) will be used to qualify the patient for randomization.

Patients meeting study eligibility requirements will be randomly assigned to 1 of 3 treatments in a 1:1:1 ratio. For the purposes of reducing bias, improving scientific integrity, and increasing assay sensitivity, a Concealed Protocol approach will be used. The Concealed Protocol will not specify eligibility criteria for randomization, treatment randomization, nor the timing of the primary endpoint. Investigators, site personnel, and study staff (ie, contract research organization [CRO]) will work from the Concealed Protocol.

Study procedures, assessments, and administration of the first dose of IMP will occur at Visit 3 (day 1). Patients will return to the study center approximately every 4 weeks (Visits 4, 5, and 6) for blinded administration of the IMP, and for vital signs, efficacy, safety, and blood samples for pharmacokinetic analysis, immunogenicity, and biomarkers at various time points.

Before the Randomization Visit (Visit 3) and during the 16-week double-blind treatment period, patients will record their daily average pain intensity score and daily worst pain intensity score using the PI-NRS in the e-diary every evening between 1800 and 2200 hours. During the 16-week double-blind treatment period, each week, patients will record their sleep score using the PROMIS Sleep Disturbance SF8a once weekly (in the morning) in the e-diary. Patients will be permitted to take acetaminophen as rescue medication (as needed) and record their pain intensity score before taking rescue medication in the e-diary. At least 75% compliance with e-diary recordings on a weekly basis is expected after the randomization visit. Site personnel will monitor patients' compliance that e-diary entry is at least 75% every week during the double-blind treatment period.

At monthly visits during the double-blind treatment period, end-of-treatment (EOT), and at the time points described in Table 1, the IMD, FIQR, EQ-5D-5L, PGIC, PROMIS Physical Function SF12a, PROMIS Fatigue SF8a, HADS, and C-SSRS questionnaires will be completed at study sites. The PROMIS Sleep Disturbance SF8a will be completed weekly by the patient in the morning in the e-diary. Patients who both discontinue treatment and terminate early from the study before completing the 16-week double-blind treatment period will have the EOT/end-of-study (EOS) or early termination (ET) Visit (Visit 7) procedures and assessments performed as soon as possible thereafter. The e-diaries will be collected at the week 16 visit (Visit 7).

The procedures and assessments will include collection of adverse events, concomitant medication information, vital signs, C-SSRS, and samples for pharmacokinetic analysis, biomarker analysis, and immunogenicity analysis at the time points included in Table 1.

Patients who complete all scheduled visits will have final procedures and assessments performed at the EOT/EOS or ET Visit (Visit 7), approximately 4 weeks after administration of the final dose of the IMP (Visit 6).

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

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

This is a 21-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fremanezumab 225 mg sc or 675 mg sc against placebo sc administered monthly for 4 doses in adult patients with FM. The study will consist of a 17- to 35-day screening period (Visit 1, phone contact, and BAPS Visit [Visit 2]) and a 16-week double-blind treatment period (Visits 3, 4, 5, 6, and 7. Patients enrolled in the study will be male or female patients with FM. Patients will be required to wash out of all prohibited concomitant medication(s) prior to the BAPS Visit (Visit 2).

Method of Randomization and Blinding: The sponsor, investigators, study staff (ie, CRO; except for staff involved in bioanalytical analyses), and patients will be blinded to treatment assignment throughout the study. A computer-generated master randomization list will be provided to drug packaging facilities. Packaging vendor(s) will package active drug and placebo according to Good Manufacturing Practice procedures. Kits will be identical in appearance. Adequate kit supply for upcoming study visits will be managed by the Randomization and Trial Supply Management (RTSM) system. The IMP will be kept refrigerated at 2°C to 8°C on site.

Patients will be randomized in a 1:1:1 ratio to either of 2 dose regimens (225 mg sc or 675 mg sc) or placebo sc by the RTSM system. Patients will be stratified by sex (male/female) and age at FM onset (<40 years old and ≥40 years old). The RTSM system will manage initial drug supply, maintenance of adequate IMP supplies on site, and study randomization centrally.

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

The prespecified treatments with fremanezumab or placebo will be administered by qualified study personnel as sc injection approximately every 4 weeks (28 days) for a total of 4 doses, on days 1, 29, 57, and 85.

Test IMP: Fremanezumab; recombinant humanized IgG2Δa/kappa mAb against CGRP

Reference IMP: None

Placebo IMP: Fremanezumab placebo. This is the same vehicle as the test IMP formulation but does not contain active fremanezumab.

Duration of Patient Participation and Maximal Exposure to IMP: The total duration of patient participation in the study is planned to be 21 weeks, consisting of a screening period of up to 5 weeks (ranging from 17 to 35 days), and a double-blind treatment period of 16 weeks.

Study Duration: May 2019 until approximately July 2022.

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

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

There are currently no plans to make the treatment available after completion of this study. After Visit 7, all subsequent clinical care will be determined by or at the discretion of the treating physician.

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

a. approved for study participation by the Fibromyalgia Eligibility Review Committee (Section 5.8.1)

b. capable of giving signed informed consent

c. agree to comply with the requirements and restrictions listed in this protocol, including remaining at the clinic for the duration of each required visit during the study period to complete all scheduled procedures and assessments

d. male or female ≥18 to 75 years old at screening (inclusive) with FM

e. willing to comply with recording of once-daily scores using the PI-NRS, completed every evening (approximately the same time each day) starting at the BAPS Visit (Visit 2) and continuing to the EOT/EOS or ET Visit (Visit 7). A minimum of 12 of 14 daily average pain intensity ratings AND daily worst pain intensity ratings are required to be recorded in an e-diary during the baseline assessment period.

f. all of the following diagnostic criteria for FM according to 2016 American College of Rheumatology (Wolfe et al 2016) are met at the Screening Visit:
   - Generalized pain, defined as pain in at least 4 of 5 regions, is present.
   - Symptoms have been present at a similar level for at least 3 months.
   - Widespread pain index (WPI) ≥7 and a symptom severity (SS) scale score ≥5 OR WPI of 4 to 6 and SS scale score ≥9.
   - A diagnosis of FM is valid irrespective of other diagnoses. A diagnosis of FM does not exclude the presence of other clinically important illnesses.

g. PI-NRS score ≥4 in average daily FM pain assessed by self-report over the past week at Screening Visit

h. body mass index of 18.5 to 45 kg/m^2 and a body weight ≥45 kg

i. agree to use only acetaminophen as rescue medication for FM-related pain (up to 1000 mg per dose and not to exceed 3000 mg/day for any indication throughout the study period)

j. non-pharmacologic interventions (including normal daily exercise routines, chiropractic care, physical therapy, psychotherapy, and massage therapy) are unchanged for a minimum of 30 days prior to screening and will remain unchanged throughout the study

k. agree not to initiate or modify any non-pharmacologic or pharmacologic interventions for FM from washout through the EOT/EOS or ET Visit

l. agree to maintain a usual and unchanged physical exercise regimen

m. [Revision 1] must meet the following pregnancy-related criteria:
   - females must have a negative serum beta-human chorionic gonadotropin (β-HCG) test at screening or be sterile or postmenopausal; definitions of sterile and postmenopausal are provided in Appendix F
   - females 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) and for 6 months after the last dose of the IMP; further details are provided in Appendix F
   - males who are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile), and their female partners are of childbearing potential, should use highly effective birth control methods for the duration of the study (ie, starting at screening); further details are provided in Appendix F

n. must agree not to participate in another interventional study from the screening period through the EOT/EOS or ET Visit

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

a. unable or unwilling to discontinue/washout of prohibited medications (Appendix I); Note: Medications used to treat depression or anxiety are permitted provided they were started at least 90 days prior to screening, have been used at a stable dose for at least 90 days, and will be maintained at that dose for the duration of the study. Therefore, both over-the-counter medications used to treat depression or anxiety and selective serotonin reuptake inhibitors (SSRIs; with the exception of ≥60 mg/day of fluoxetine) are permitted.

b. in the investigator's opinion, history of no meaningful improvement to an adequate trial of 2 or more different pharmacological classes of medications indicated for FM adequately dosed for an adequate period of time

c. ongoing pain that would confound or interfere with the assessment of the patient's FM pain or require excluded therapies during the patient's participation in this study. Other sources of pain may include, but are not limited to, neuropathic pain attributable to an identifiable cause, post-herpetic neuralgia, traumatic injury, prior surgery, complex regional pain syndrome or failed back syndrome, infections or inflammatory arthritis (eg, rheumatoid arthritis [RA], ankylosing spondylitis, psoriatic arthritis, gout), other autoimmune diseases (eg, systemic lupus erythematosus), and other widespread rheumatic diseases (widespread osteoarthritis [OA]). Localized OA is permitted as long as it is subclinical (which does not require treatment with an analgesic[s]).

d. surgery planned during the study period

e. receiving prophylactic treatment for migraine-related disorders, including topiramate, valproic acid, onabotulinumtoxinA, amitriptyline, and nortriptyline

f. known history of clinically significant or unstable hematologic, cardiac, or thromboembolic events (ie, arterial or venous thrombotic or embolic events, including cerebrovascular accident [including transient ischemic attacks]; deep vein thrombosis or pulmonary embolism); renal, endocrine, pulmonary, gastrointestinal, genitourinary, or neurologic disorders [exclusive of FM]; infectious, hepatic, or ocular disease, at the discretion of the investigator, as determined by a medical and psychiatric history; and physical examination, 12-lead ECG, serum chemistry, hematology, coagulation, and urinalysis). Abnormal test results may be repeated for confirmation.

g. moderate or severe major depressive symptoms as assessed by the HADS Depression Subscore >14 (at the Screening Visit and/or the BAPS Visit)

h. known history of suicide attempt, suicidal behavior, or suicidal ideation within the last 12 months (a response of "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale) or have been assessed as a significant risk to commit suicide at the Screening Visit or Randomization Visit

i. lifetime history of any psychotic and/or bipolar disorder as assessed by the Mini-International Neuropsychiatric Interview (MINI)

j. current, untreated, moderate or severe major depressive disorder and/or anxiety disorders as assessed by the MINI. Patients with currently treated major depressive disorder and/or anxiety disorder can be included, provided that according to the investigator's judgment, there have been no clinically significant changes in symptoms while on a stable dose of allowed antidepressants or antianxiety medications for at least 90 days prior to screening, and that the dosage of antidepressant or antianxiety medication will be maintained for the duration of the study.

k. current eating disorders as assessed by the MINI

l. known infection or history of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection or are antigen positive for hepatitis B at screening

m. past or current history of cancer in the past 5 years, except for appropriately treated non-melanoma skin carcinoma (basal carcinoma)

n. known history of hypersensitivity reactions to injected proteins, including mAbs and animal venoms, or a history of Stevens-Johnson Syndrome/toxic epidermal necrolysis syndrome

o. known history of hypersensitivity or intolerance to the use of acetaminophen

p. known hypersensitivity or intolerance to the components in the formulation of fremanezumab

q. participation in an interventional clinical study of a chemical entity or device within 2 months or 5.5 half-lives (whichever is longer) prior to IMP administration

r. participation in an interventional clinical study of a mAb within 3 months or 5.5 half-lives (whichever is longer) prior to IMP administration

s. any prior exposure to mAbs targeting the CGRP pathway (including erenumab, eptinezumab, galcanezumab, or fremanezumab) at any time. If the patient has participated in a clinical study with any of these mAbs, it has to be confirmed that the patient received placebo in order to be eligible for this study.

t. clinically significant elevations in hepatic enzymes (alanine aminotransferase or aspartate aminotransferase) based on the upper limit of normal (ULN) or investigator judgment, which have been reconfirmed on a repeat test

u. suspected hepatocellular damage that fulfills criteria for Hy's law at screening

v. serum creatinine >1.5× ULN, clinically significant proteinuria, or evidence of renal disease at screening

w. known history of alcohol and/or drug abuse within the past 12 months per the MINI or have a positive urine drug screen for illegal drugs of abuse at the Screening Visit, BAPS Visit, or prior to randomization

x. [Revision 1] if using marijuana (cannabis), meets the MINI (v.7.0.2) criteria for greater than mild substance use disorder for marijuana (cannabis), cannabidiol, or other cannabinoids during the preceding 12 months; and/or the investigator is concerned that the use of marijuana (cannabis), cannabidiol, or other cannabinoids

could interfere with a subject's ability to provide reliable data or comply with the protocol

y. diagnosed with uncontrolled sleep apnea

z. employee of Teva Pharmaceuticals, the CRO involved, or the investigative site personnel directly affiliated with this study and/or immediate family members (spouse, parent, child, or sibling, whether biological or legally adopted, or legal guardian/custodian)

aa. involved in an active workers compensation case or is currently filing or seeking a work disability claim for any reason or condition

bb. currently experiencing acute, severe psychosocial stress (ie, recent death of a loved one, divorce)

cc. any condition or situation (ie, shift work) that, in the investigator's opinion, makes the patient unsuitable for study participation

dd. [New criterion] has received any CGRP pathway targeting treatment or compound (anti-CGRP antibodies, anti-CGRP receptor antibodies, or CGRP receptor antagonists/oral gepants) for migraine

ee. [New criterion] the patient is a pregnant or nursing female or plans to become pregnant during the study, including the 6-month period after the administration of the IMP

Statistical Considerations

Sample Size Rationale: The sample size of 80 subjects per treatment group was selected based on expert consensus agreement at a scientific advisory board meeting; this sample size is expected to provide sufficient precision to estimate the treatment effect of fremanezumab versus placebo. Moreover, assuming a standard deviation of 2.2 for change from baseline in the weekly average of the daily average PI-NRS score, 80 patients per treatment group will provide at least 90% probability to observe the half length of the 95% confidence interval of the treatment difference between fremanezumab 225 mg sc or fremanezumab 675 mg sc and placebo less than 0.74. In total, 240 patients will be enrolled in this study in a 1:1:1 randomization ratio.

Primary Efficacy Analysis: The primary efficacy variable, the change from baseline to week 16 in the weekly average of the daily average PI-NRS scores over the past 24 hours, will be analyzed using a Mixed Model Repeated Measures (MMRM) model with change from baseline in the weekly average of the daily average PI-NRS scores at each week as the dependent variable; sex, age group at FM onset, week, treatment, and treatment by week interaction as fixed factors; and baseline PI-NRS scores as a covariate. The heterogeneous autoregressive correlation structure for repeated observations within patients will be used; the denominator degrees of freedom will be estimated using Kenward-Roger's approximation. An adjustment for missing data due to lack of efficacy or adverse event assumes that the PI-NRS scores will, on average, return to baseline values. Missing data will be imputed 500 times to generate 500 complete data sets by using the SAS procedure PROC MI following the 3 steps below:

- Step 1: The monotone missing pattern will be induced by the Markov Chain Monte Carlo method in the PROC MI procedure using seed number 4751523.

- Step 2: The remaining missing data at subsequent weeks will be imputed using the regression method for the monotone pattern with seed number 4751523 and adjustment for covariates including treatment groups, randomization strata, relevant baseline, and all values at preceding visits.
- Step 3: The initially missing and now imputed data for patients discontinued from the study treatment due to lack of efficacy or adverse event will be center adjusted at the mean baseline value for that treatment group, ie, the final imputed score will be equal to the imputed score under missing at random minus (mean change from baseline score at the post-baseline time point for the treatment group).

Each imputed data set will be analyzed using the MMRM described above. The results from the 500 analyses will be combined using Rubin's formulae (PROC MIANALYZE). The least squares mean estimates for the mean change from baseline to each time point, as well as the difference of the estimates between the fremanezumab and placebo groups, with the corresponding standard error, p-value, and associated 95% confidence interval will be calculated.

Sensitivity Analysis: Sensitivity analyses will be included to address the assumptions in the primary model. The primary analysis will be repeated; however, the daily average pain scores measured on the days where the patient took rescue medication will be replaced with his or her PI-NRS score at the time of rescue medication use before the weekly average PI-NRS scores are derived. On days where a patient uses rescue medication more than once, the mean PI-NRS score at the time of rescue mediation use will be used as the pain score in place of the average pain intensity score for that day.

Three new sensitivity analyses will be conducted as part of the planned second interim analysis. Details of the new sensitivity analyses will be specified in the interim analysis statistical analysis plan.

Secondary Efficacy Analysis: The change from baseline to week 16 in the weekly average of the daily worst PI-NRS score over the past 24 hours and the change from baseline of the individual components of the FIQR score and total FIQR score will be analyzed in the same manner as the primary efficacy endpoint; however, the baseline pain intensity over the past 24 hours and the baseline FIQR score, respectively, will be used as a covariate in the MMRM model instead of the baseline PI-NRS score.

PGIC data will be dichotomized, where a patient who responds as either "much improved" or "very much improved" will be considered improved, and all other responses will be considered not improved. The response variable will be analyzed using a logistic regression model with the treatment, age group at FM onset, and sex as explanatory factors. In addition, PGIC data will be summarized as categorical variables by week and treatment group using descriptive statistics.

The percentage of patients who experience a ≥30% reduction and ≥50% reduction in the weekly average of the daily average PI-NRS score will be analyzed using a generalized estimating equation method, where the dependent variable experience ≥30% reduction and ≥50% reduction (Yes/No) will be modeled through the binomial link function, with treatment, sex, age group at FM onset, week, and treatment by week interaction as explanatory factors. In addition, a plot of percentage of improvement versus percentage of patients meeting the improvement level throughout the study will be presented by treatment group.

All other secondary efficacy endpoints will be analyzed in the same manner as the primary efficacy endpoint with the respective baseline assessment as a covariate in the MMRM model.

Other Efficacy Analysis: Statistical modeling to be used for other efficacy endpoints will be described and detailed in the statistical analysis plan as appropriate.

Multiple Comparisons and Multiplicity: No multiplicity adjustment is planned for this study.

[redacted]

Safety Analyses: 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.

Tolerability Analysis: Local tolerability findings (eg, erythema, induration, ecchymosis, and occurrence of injection site pain) will be listed and summarized descriptively.

Pharmacokinetic Analysis: Plasma concentrations will be tabulated at each planned sampling time point by treatment group. In addition, the most appropriate population pharmacokinetic model will be developed; covariates that may affect pharmacokinetic parameters will be tested for inclusion in the model. This analysis will be reported separately from the CSR; individual pharmacokinetic concentration data will be summarized and listed in the CSR.

Pharmacokinetic/Pharmacodynamic Analysis: If appropriate, further pharmacokinetic/pharmacodynamic relationship may be estimated by compartmental techniques. The pharmacokinetic parameters will be based on fremanezumab concentrations. The pharmacodynamic endpoint will be the efficacy and/or safety response(s).

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

Biomarker Analysis: Blood samples (approximately 19.0 mL) will be collected on day 1, prior to randomization and at the times specified in Table 1. [redacted]

Immunogenicity Analysis: A summary of immunogenicity results will be provided, and the incidence of immunogenicity and the antibody titers will be calculated.

Ancillary Studies Analysis: No ancillary analyses are planned for this study.

Planned Interim Analysis: Interim analyses are planned for this study.

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Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ACR	American College of Rheumatology
ADA	anti-drug antibody
ADL	activities of daily living
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration-time curve
BAPS	Baseline Assessment Period Start
BLA	Biological License Application
BP	blood pressure
CA	Competent Authority
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
CGRP	calcitonin gene-related peptide
CH	cluster headache
CM	chronic migraine
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EM	episodic migraine
EOS	end-of-study
EOT	end-of-treatment
EQ VAS	EQ Visual Analogue Scale
EQ-5D-5L	EuroQol-5D-5L
ET	early termination
EudraCT	European Clinical Trials
FIQR	Fibromyalgia Impact Questionnaire Revised

Abbreviation	Term
FM	fibromyalgia
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPSP	Global Patient Safety and Pharmacovigilance
HADS	Hospital Anxiety and Depression Scale
HBsAg	Hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IHS	International Headache Society
IMP	investigational medicinal product
IMD	Inventory of Medical Diagnoses
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
iv	intravenous
LSO	local safety officer
mAb	monoclonal antibody
MCMC	Markov Chain Monte Carlo
MINI	Mini-International Neuropsychiatric Interview
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
n	number
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NIH	National Institutes of Health
OA	osteoarthritis
OTC	over-the-counter
PEF	peak expiratory flow

Abbreviation	Term
PGIC	Patient Global Impression of Change
PI-NRS	Pain Intensity-Numerical Rating Scale
PP	per-protocol
PROC MI	SAS procedure
PROMIS	Patient-Reported Outcomes Measurement Information System
RA	rheumatoid arthritis
RIM	reserpine induced model
RTSM	Randomization and Trial Supply Management
sc	subcutaneous
SF	Short Form
SOP	Standard Operating Procedure
SS	symptom severity
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States (of America)
WOCBP	women of childbearing potential
WPI	widespread pain index

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

Fremanezumab (TEV-48125 [formerly PF-04427429, RN307, and LBR-101]), a humanized immunoglobulin G (IgG) 2Δa/kappa monoclonal antibody (mAb) derived from a murine precursor, is currently approved in the United States (US) for the preventive treatment of migraine in adults and marketed under the trade name AJOVY®. Fremanezumab is under development for chronic pain indications. Fremanezumab is a potent, selective calcitonin gene-related peptide (CGRP) binder and does not bind to the closely related family members such as amylin, calcitonin, adrenomedullin, or intermedin peptides. Fremanezumab binds both α- and β-CGRP and inhibits CGRP from binding to the CGRP receptor.

Calcitonin gene-related peptide and its receptor are widely expressed in the somatosensory and autonomic peripheral nerves as well as in the enteric system (Iyengar et al 2017). Dorsal root ganglion sensory neurons are pseudounipolar, and both their central and peripheral axonal endings release CGRP (Raddant and Russo 2011). Calcitonin gene-related peptide is found in the central nervous system primarily in the dorsal horn of the spinal cord. There is also a prominent localization of CGRP in sensory Aδ- and C-fiber neurons of peripheral nerves (Iyengar et al 2017, Poyner et al 2002, Pozo-Rosich et al 2015). Stimulation of sensory nerves can elicit an axon reflex, releasing CGRP and substance P from adjacent axonal branches. This results in evoked release of proinflammatory mediators that leads to sensitization of peripheral nerves and, with further stimulation, amplification of pain signals, which is manifested clinically as hyperalgesia and allodynia (Basbaum et al 2009, Willis 1999, Woolf 2011). In addition, satellite glia surrounding dorsal root ganglia release proinflammatory factors such as tumor necrosis factor alpha (TNFα) that promote CGRP release from nociceptive neurons, which in turn stimulates further release of proinflammatory factors from satellite glia in a positive-feedback loop. Furthermore, with inflammation, local mast cells may release both TNFα and CGRP, further driving the positive-feedback loop (Raddant and Russo 2011).

Chronic nerve injury or nerve inflammation may lead to a neuroplastic phenomenon termed pain sensitization, in which afferent nociceptive neurons display increased excitability in response to stimuli (eg, lower threshold for activation, repetitive discharges, and increased synaptic efficacy) (Iyengar et al 2017). Both central and peripheral pain sensitization essentially represent a reprogramming of the sensory nervous system that may occur with chronic nociceptive pain as well as chronic neuropathic pain. Although CGRP does not itself mediate pain, it plays an important role in both peripheral as well as central sensitization, phenomena that manifest clinically as allodynia and hyperalgesia, and which are prominent concomitant symptoms of migraine (photophobia, phonophobia, and cutaneous allodynia) [Cornelison et al 2016, Durham 2016, Iyengar et al 2017, Raddant and Russo 2011, Russell et al 2014]. Given the efficacy seen in treating migraine as well as the associated allodynia, by analogy, an anti-CGRP antibody has the potential to block or reduce pain sensitization in a variety of chronic pain indications in which sensitization has been shown to play a role, such as fibromyalgia (FM), osteoarthritis (OA), neuropathic pain, and visceral pain.

Fibromyalgia is a common cause of chronic widespread musculoskeletal pain, often accompanied by fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms. The prevalence of the condition ranges from 1.2% to 5.4% and is dependent on criteria used to diagnose FM (Jones et al 2015).

The diagnosis of FM is based primarily on the patient's symptoms of widespread pain, typically reported in the muscles and joints, and findings of multiple tender points in characteristic soft tissue locations, in the absence of evidence on physical examination and laboratory testing of joint or muscle inflammation that would explain the patient's symptoms. According to the 2016 American College of Rheumatology FM diagnostic criteria (Wolfe et al 2016), FM may be diagnosed when all of the following criteria are met:

1. Generalized pain, defined as pain in at least 4 of 5 regions, is present.
2. Symptoms have been present at a similar level for at least 3 months.
3. There is a widespread pain index (WPI) ≥7 and a symptom severity (SS) scale score ≥5 OR WPI of 4 to 6 and SS scale score ≥9.
4. A diagnosis of FM is valid irrespective of other diagnoses. A diagnosis of FM does not exclude the presence of other clinically important illnesses.

Fibromyalgia often occurs with other conditions currently considered to have a similar underlying pathophysiology (eg, irritable bowel syndrome, interstitial cystitis, and tension headache) or as a comorbidity in individuals with diseases characterized by ongoing peripheral damage or inflammation (eg, autoimmune disorders and osteoarthritis) (Clauw 2014).

The approach toward the treatment of FM integrates pharmacological and non-pharmacological interventions. Non-pharmacologic interventions include patient education (eg, regarding the importance of good sleep, treating common comorbidities), adhering to an exercise program, psychological interventions and cognitive behavioral therapy for pain management, and addressing the treatment of other common comorbidities (Clauw 2014, Macfarlane et al 2017).

If non-pharmacologic interventions do not yield a satisfactory improvement in FM, pharmacotherapy is often initiated. In the US, there are 3 drugs with an approved indication for the treatment of FM: 2 serotonin and norepinephrine reuptake inhibitors (SNRIs), duloxetine (CYMBALTA®) and milnacipran (SAVELLA®), and the anti-seizure medication pregabalin (LYRICA®). Other analgesic classes that have been used commonly in the treatment of FM include tricyclic antidepressants (eg, amitriptyline), anti-seizure medications (eg, gabapentin [NEURONTIN®]), muscle relaxants (eg, cyclobenzaprine, tizanidine [ZANAFLEX®]), or OTCs, including acetaminophen and nonsteroidal anti-inflammatory drugs. To date, these pharmacologic treatment options produce only marginal effectiveness and are accompanied by side effects necessitating the need to develop new treatments for patients with FM.

The etiology of the syndrome is unknown, and the pathophysiology is uncertain (Clauw 2014).

Fibromyalgia is considered a pain amplification syndrome characterized by widespread musculoskeletal pain with comorbidities of fatigue, cognitive/emotional, and poor sleep quality related symptoms (Staud and Rodriguez 2006, Wolfe et al 1995). Research over the past 2 decades has delivered consistent evidence to suggest abnormal nervous system findings in patients with FM (Clauw et al 2011). In addition to pain-related changes, patients with FM manifest hyperalgesia and allodynia with respect to mechanical and thermal stimuli, a composite

of reduced tolerance and abnormal brain processing of non-painful sensory stimuli (Carrillo-de-la-Pena et al 2006, Geisser et al 2008, Gibson et al 1994, Hollins et al 2009, Kosek et al 1996, López-Solá et al 2014, Wilbarger and Cook 2011). Central and/or peripheral mechanisms of nociception are altered in FM (Carrillo-de-la-Pena et al 2006, Geisser et al 2008, Gibson et al 1994, Hollins et al 2009, Kosek et al 1996, López-Solá et al 2014, Sann and Pierau 1998, Staud and Smitherman 2002, Wilbarger and Cook 2011). Studies suggest that pain in FM may be associated with hyperexcitability of the nociceptive system (ie, increased transmission [Oaklander et al 2013, Serra et al 2014, Üçeyler et al 2013], peripheral and central amplification [Cook et al 2004, Gracely et al 2002, Pujol et al 2014], reduced inhibitory control mechanisms [Julien et al 2005, Kosek and Hansson 1997]), and reduced opponent non-nociceptive sensory processing (Ichesco et al 2013, López-Solá et al 2014, Montoya et al 2006, Ozgocmen et al 2003, Pujol et al 2014).

Refer to the current Investigator's Brochure (IB) for detailed information on the background, pharmaceutical particulars, nonclinical experience, and clinical experience with fremanezumab.

1.2. Findings from Nonclinical and Clinical Studies

1.2.1. Nonclinical Studies

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

No toxicological concerns were identified following chronic dosing to experimental animals at dose levels up to 300 mg/kg/week. The calculated safety margin is 54-fold higher than the expected clinical exposure following 675 mg sc monthly.

In a GLP embryo-fetal development study in rabbits, sc injection of fremanezumab to pregnant rabbits was well tolerated and did not induce any obvious maternal toxicity or embryo-fetal toxicity in any dose group.

Based on the absence of findings in the safety pharmacology studies, no concerns were identified for fremanezumab to cause any biologically significant changes in the cardiovascular, respiratory, and central nervous systems.

The pharmacokinetics of fremanezumab in animals (rats and monkeys) is typical of a humanized IgG2 molecule, with low mean plasma clearance, low volume of distribution at steady state, and a long elimination half-life. Exposure increased linearly across doses following single and repeated weekly dosing. Following sc administration, mean systemic exposure ranged from 65% to 92% of the equivalent iv doses, demonstrating reasonably high sc bioavailability.

The overall nonclinical safety data (see also the IB) support the safe, repeated (monthly) administration of fremanezumab in human subjects for the duration of the Phase 3 pivotal trials (3 months) and the long-term safety extension (1 year).

1.2.2. Clinical Studies

As of 30 August 2019, approximately 4972 subjects/patients (4062 adult patients with migraine, 15 pediatric patients with migraine, 380 patients with cluster headache [CH], 37 patients with

persistent post-traumatic headache, an estimated 4 patients with FM, and 474 healthy subjects) have been exposed to fremanezumab. The fremanezumab clinical program comprises 24 clinical studies (10 Phase 1; 6 Phase 2, 2b, or 2b/3; and 8 Phase 3 studies), of which 19 have been completed.

The safety and tolerability of fremanezumab was studied in all of the 24 studies in the clinical program (ie, 10 Phase 1, 2 Phase 2, 2 Phase 2b, 2 Phase 2b/3, and 8 Phase 3 studies). Based on the safety results of the completed studies, the safety profile was assessed to include the following events as identified risks qualifying as adverse drug reactions: injection site induration, injection site erythema, injection site pruritus, injection site pain, and injection site rash. None of the identified risks was serious or considered as a clinically meaningful risk. No serious adverse reaction is considered expected by the sponsor for the purpose of expedited reporting of suspected unexpected serious adverse reactions (SUSAR) reporting.

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)

Benefits

Despite the available nonpharmacologic and pharmacologic interventions (approved and non-approved), acceptable pain relief in patients with FM is often inadequate. In a large proportion of patients, symptoms of FM are refractory to treatment and pharmacological treatments that have a minimal or moderate effect on pain. Patients do not experience acceptable efficacy and/or cannot tolerate the adverse effects of these medications, and therefore, FM continues to pose a clinically significant unmet medical need (Ablin and Häuser 2016, Macfarlane et al 2017). Fremanezumab inhibits the interaction of CGRP with its receptor and may alleviate pain and perhaps other symptoms associated with FM, based on the involvement of CGRP pathway in this condition; however, the benefits of fremanezumab in FM remain to be determined.

Risks

Fremanezumab (sc) has generally been well tolerated over the range of doses evaluated (single doses of 0.02 to 2000 mg in healthy subjects, multiple doses of 30 to 300 mg in healthy volunteers, and multiple doses of 225 to 900 mg sc in patients with migraine). The most common treatment-emergent adverse events in patients with migraine were mild to moderate transient general administration site disorders/reactions. Other commonly reported treatment-emergent adverse events were upper respiratory tract infection, back pain, nausea, and dizziness. Based on the exposure and body of evidence from Teva's studies of fremanezumab in other indications, the benefit and risk assessment for fremanezumab is expected to be favorable.

Known risks that do not impact the risk-benefit profile are as follows:

- injection site induration
- injection site erythema
- injection site pruritus

- injection site pain
- injection site rash

None of these risks are considered clinically meaningful.

Severe hypersensitivity reactions are regarded as a potential risk for fremanezumab based on the following considerations: mild and moderate drug hypersensitivity events were observed infrequently albeit with similar incidence in placebo and fremanezumab in the clinical development program for migraine, but no anaphylaxis or severe hypersensitivity reactions related to the investigational medicinal product (IMP) were seen. While no severe hypersensitivity or anaphylactic reactions occurred as a result of fremanezumab administration 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 anti-CGRP pathway monoclonal antibodies, along with concomitant medications including lamotrigine.

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 monkey and humans using fremanezumab have not identified clinically relevant changes in heart rate, blood pressure, or other cardiovascular parameters. No relevant cardiovascular event has been seen in the completed studies.

Refer to the current IB for additional information regarding benefits and risks to patients.

1.3.2. Overall Benefit and Risk Assessment for This Study

The efficacy of fremanezumab in the treatment of FM is unknown. This study serves as a proof of concept study. The benefit of fremanezumab in treating pain associated with FM remains to be determined.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

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

Objectives	Endpoints
The **primary objective** of the study is to estimate the treatment effect of fremanezumab administered subcutaneously in reducing pain in adult patients with FM.	The primary efficacy endpoint is the change from baseline up to week 16 in the weekly average of the daily average Pain Intensity-Numerical Rating Scale (PI-NRS) score over the past 24 hours.
A **secondary objective** is to evaluate the effect of fremanezumab on other efficacy measures, including pain, quality of life, sleep, fatigue, improvement in health, physical functioning, and mood.	The secondary efficacy endpoints are as follows: • change from baseline up to week 16 in the individual components of the Fibromyalgia Impact Questionnaire Revised (FIQR): symptom subscore, impact subscore, and functional subscore score • responder rate of the Patient Global Impression of Change (PGIC) rating (percentage of patients much improved or very much improved) up to week 16 • the percentage of patients who experience a ≥30% reduction in the weekly average of the daily average PI-NRS score up to week 16 • the percentage of patients who experience a ≥50% reduction in the weekly average of the daily average PI-NRS score up to week 16 • change from baseline up to week 16 in the weekly average of the daily worst PI-NRS score over the past 24 hours • change from baseline up to week 16 in the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short Form (SF) 8a score • change from baseline up to week 16 in the PROMIS Physical Function SF12a score • change from baseline up to week 16 in the PROMIS Fatigue SF8a score • number (%) of patients who did not complete the treatment (Kaplan-Meier Survival Analysis) due to

Objectives	Endpoints
	lack of efficacy
A **secondary objective** of the study is to evaluate the safety and tolerability of fremanezumab administered subcutaneously in adult patients with FM.	The safety and tolerability endpoints are as follows: • occurrence of adverse events • change from randomization up to week 16 in the clinical laboratory tests (serum chemistry, hematology, and urinalysis) • change from baseline up to week 16 in vital signs (pulse, respiratory rate, systolic and diastolic blood pressure, and oral body temperature measurements at each visit) • clinically significant changes in physical examination, including body weight • abnormal standard 12-lead electrocardiogram (ECG) findings • tolerability at the injection site including but not limited to pain, erythema, induration, and ecchymosis • occurrence of hypersensitivity/anaphylaxis reactions using standardized criteria (Appendix C) • suicidal ideation and behavior as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) • number (%) of patients who did not complete the treatment (Kaplan-Meier Survival Analysis) due to adverse events

2.1.1. Justification of Primary Endpoint

The change from baseline in the weekly average of the daily average PI-NRS score over the past 24 hours is a well-established and Food and Drug Administration-accepted endpoint in clinical studies of chronic pain, including FM. The PI-NRS is a validated numerical pain rating scale-based outcome measure (Arnold et al 2015, Farrar et al 2010).

2.2. [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.3. Immunogenicity Objective and Endpoint

The immunogenicity objective and endpoint are as follows:

Objective	Endpoint
To evaluate the immunogenicity of fremanezumab and the impact of anti-drug antibodies (ADAs) on clinical outcomes	• incidence and characteristics of ADAs (eg, titers, kinetics, and neutralizing activities)

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a 21-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fremanezumab in adult patients with FM. Fremanezumab 225 mg, fremanezumab 675 mg, or placebo will be administered sc for 4 monthly doses. The study will consist of a 17- to 35-day screening period (Visit 1, phone contact, and Baseline Assessment Period Start [BAPS] Visit [Visit 2]), and a 16-week double-blind treatment period (Visits 3, 4, 5, 6, and 7). Patients enrolled in the study will be male or female patients with FM. Patients will be required to wash out of all prohibited concomitant medication(s) prior to the BAPS Visit (Visit 2).

Therefore, the total duration of patient participation in the study is planned to be 21 weeks, consisting of the screening period of up to 5 weeks (ranging from 17 to 35 days) and the double-blind treatment period of 16 weeks; details are given in Section 5.

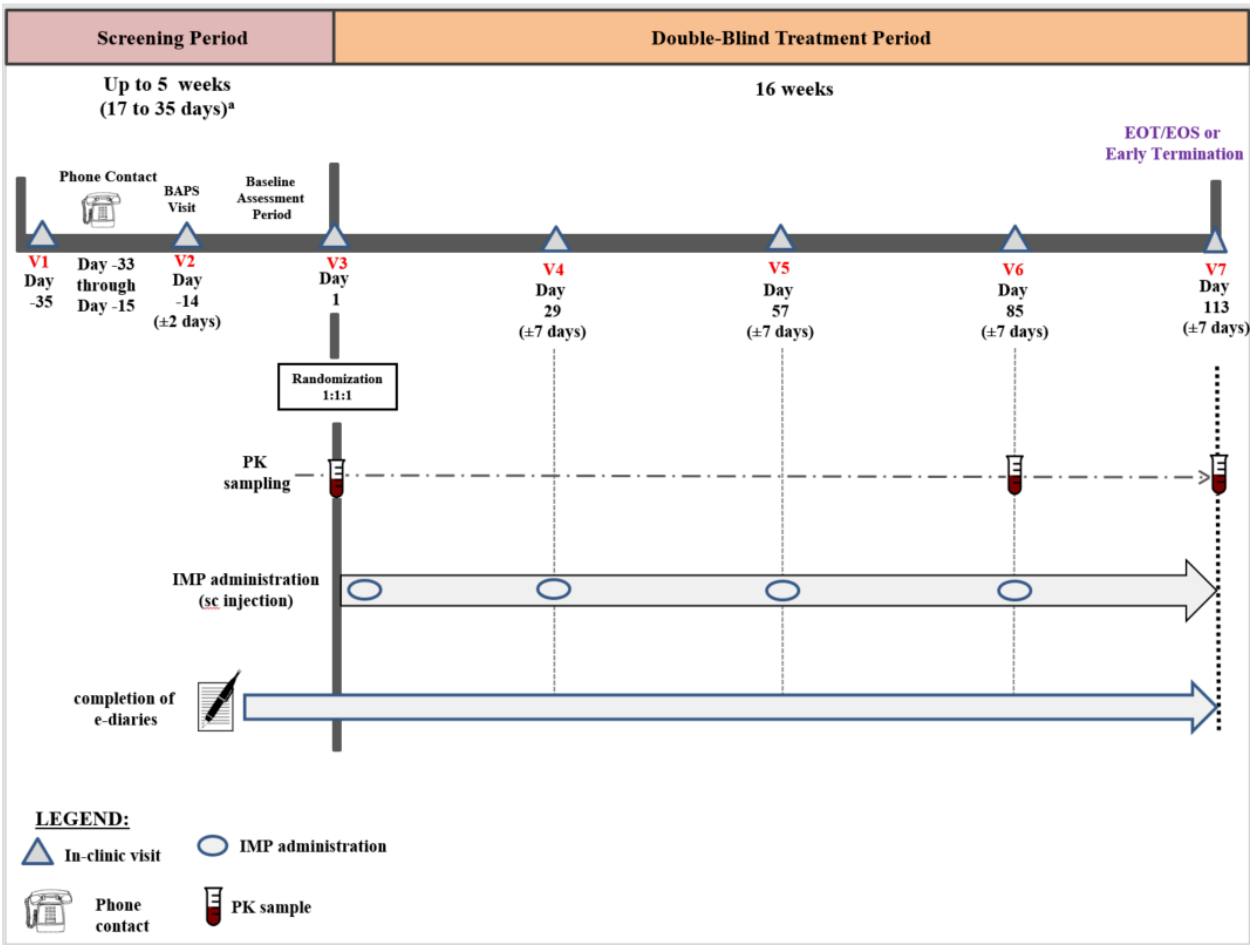
The end-of-study (EOS) is defined as completion of the last visit of the last patient.

The study duration will be from May 2019 until approximately July 2022.

For Coronavirus Disease 2019 (COVID-19) updates, see Appendix O.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



[a] The screening period is up to 5 weeks and can range from 17 to 35 days. The duration of the washout period will be 7 to 19 days; suggested washout periods for commonly used analgesics are listed in Table 4.
Note: For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center (see Section 3.5).
BAPS = Baseline Assessment Period Start; COVID-19 = Coronavirus Disease 2019; e-diary = electronic diary; EOS = end-of-study; EOT = end-of-treatment; PK = pharmacokinetic; sc = subcutaneous; V = visit.

3.2. Planned Number of Patients and Countries

Approximately 240 patients will be randomized.

The study is planned to be conducted in the United States of America in approximately 40 investigational centers.

3.3. Justification for Study Design and Selection of Population

The 2016 ACR Classification Criteria for diagnosis of FM will be utilized to ensure that the study's patient population is representative of current practice. Although these have been less widely used than past criteria, specifically within clinical studies of FM, these current criteria avoid regional pain disorder misclassification and eliminate the restriction of diagnosis to

patients who have no other condition that would explain their widespread pain (Wolfe et al 2016).

A randomized, double-blind, placebo-controlled, parallel-group design has been chosen because this study design best controls for bias. A crossover study design is not feasible given the long half-life of fremanezumab. The use of placebo is necessary because there is no alternative method for controlling for placebo effects. In order to assess a possible dose response, both a 225-mg and a 675-mg dose regimen have been included.

To maintain full blinding, reduce bias, improve scientific integrity, and increase assay sensitivity, a Concealed Protocol approach will be used. All study sites and staff will be blinded to eligibility criteria for randomization, treatment randomization, and the timing of the primary endpoint. Investigators, site personnel, and study staff (ie, contract research organization [CRO]) will work from the Concealed Protocol.

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list. This system will be used to ensure a balance across treatment groups; no effort will be made to maintain a balance among treatment groups within a study site.

The doses planned for administration at Visits 3 (1st dose), 4, 5, and 6 for patients randomized to receive fremanezumab 225 mg, fremanezumab 675 mg, or placebo will require administration of three 1.5-mL sc injections. In order to blind the treatment groups based on both dose volume and number of injections, patients will receive the following injection schedule:

	Fremanezumab 225 mg	**Fremanezumab 675 mg**	**Placebo**
Visits 3 to 6	1× 1.5 mL sc 225 mg active drug 2× 1.5 mL sc placebo	3× 1.5 mL sc 225 mg active drug	3× 1.5 mL sc placebo

3.4. Stopping Rules for the Study

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

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

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

If the whole study or specific arms of the study will be stopped, the patients that are terminated early will be followed according to Section 4.3.

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 1. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix B.

Central surveillance monitoring will be carried out in real time, and a data review coordinator will perform daily review of the blinded data (eg, e-diary) to identify missing or conflicting data so that corrective action may be implemented as quickly as possible.

For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center. Home visits may be completed by a Home Care Visiting Service Provider (ie, home care, visiting nurse, or other medical professional) under supervision by the investigational center staff, as required, to complete assessments/procedures. The Home Care Visiting Service Provider will be a centralized provider identified by the sponsor. The investigational center must contact the sponsor before any home visits are initiated. Home visits will be documented.

Visits should be conducted in accordance with the timelines specified in the protocol (see Table 1), whenever feasible. Averting a missed visit is considered a high priority. Therefore, if additional time is required beyond the specified visit window to complete the visit, the Medical Monitor should be contacted, and the visit window may be extended for appropriate reasons. In such instances, the reasons for deviation in the date of the visit will be clearly documented.

Table 1: Study Procedures and Assessments

Study Period	**Screening Period (up to 5 weeks [17 to 35 days])[a]**			**Double-Blind Treatment Period (16 weeks)**				
	Screening Visit	**Phone Contact (Washout)[b]**	**Baseline Assessment Period**	**Randomization (Dose 1)**	**Dose 2**	**Dose 3**	**Dose 4**	
Visit number	**V1**	**Phone Contact**	**V2 (BAPS Visit)**	**V3**	**V4[c]**	**V5[c]**	**V6**	**V7 (EOT/EOS or ET)**
Day and allowed time windows	**Week -5 Day -35**	**Day -33 through Day -15**	**Day -14 (±2 days)**	**Day 1**	**Day 29 ±7 days**	**Day 57 ±7 days**	**Day 85 ±7 days**	**Day 113 ±7 days**
Procedures and assessments[d, e]	**Screening**	**Scheduling and Instructions[f]**	**BAPS Visit**	**W 1**	**W 4**	**W 8**	**W 12**	**W 16**
Informed consent	X							
Inclusion and exclusion criteria	X		X	X				
Medical and psychiatric history	X							
Record demographic characteristics	X							
Pain reporting (tablet) training[g]	X		X	X	X	X	X	
E-diary training[h]	X		X	X	X	X	X	
Dispense/account/ collect rescue medication (APAP)[i]	X		X	X	X	X	X	X
Prior medication tapering		X						
Assign randomization/ treatment number				X				

Study Period	**Screening Period (up to 5 weeks [17 to 35 days])**[a]			**Double-Blind Treatment Period (16 weeks)**				
	Screening Visit	**Phone Contact (Washout)**[b]	**Baseline Assessment Period**	**Randomization (Dose 1)**	**Dose 2**	**Dose 3**	**Dose 4**	
Visit number	**V1**	**Phone Contact**	**V2 (BAPS Visit)**	**V3**	**V4**[c]	**V5**[c]	**V6**	**V7 (EOT/EOS or ET)**
Day and allowed time windows	**Week -5 Day -35**	**Day -33 through Day -15**	**Day -14 (±2 days)**	**Day 1**	**Day 29 ±7 days**	**Day 57 ±7 days**	**Day 85 ±7 days**	**Day 113 ±7 days**
Procedures and assessments[d, e]	**Screening**	**Scheduling and Instructions**[f]	**BAPS Visit**	**W 1**	**W 4**	**W 8**	**W 12**	**W 16**
PI-NRS[j]	X		X	X				
ACR 2016 WPI[k]	X							
ACR 2016 SS[k]	X							
MINI	X							
Prior medication and treatment history	X		X	X				
Clinical laboratory tests (serum chemistry, hematology, and urinalysis)[l]	X			X			X	X
Urine drug screen	X		X	X	X	X	X	X
Alcohol (social history)[m]	X							
Marijuana (cannabis), cannabidiol, or other cannabinoids (medicinal and social history)	X							
Physical examination[n, o]	X		X	X	X	X	X	X

Study Period	**Screening Period (up to 5 weeks [17 to 35 days])**[a]			**Double-Blind Treatment Period (16 weeks)**				
	Screening Visit	**Phone Contact (Washout)**[b]	**Baseline Assessment Period**	**Randomization (Dose 1)**	**Dose 2**	**Dose 3**	**Dose 4**	
Visit number	**V1**	**Phone Contact**	**V2 (BAPS Visit)**	**V3**	**V4**[c]	**V5**[c]	**V6**	**V7 (EOT/EOS or ET)**
Day and allowed time windows	**Week -5 Day -35**	**Day -33 through Day -15**	**Day -14 (±2 days)**	**Day 1**	**Day 29 ±7 days**	**Day 57 ±7 days**	**Day 85 ±7 days**	**Day 113 ±7 days**
Procedures and assessments[d, e]	**Screening**	**Scheduling and Instructions**[f]	**BAPS Visit**	**W 1**	**W 4**	**W 8**	**W 12**	**W 16**
Electrocardiography[p, q]	X			X			X	X
Vital signs measurement[r]	X		X	X	X	X	X	X
Serum β-HCG test for women	X							
Urine pregnancy test for WOCBP[s]			X	X	X	X	X	X
FSH[t]	X							
Inform patients of study restrictions and compliance requirements	X		X	X	X	X	X	
Assess concomitant medication	X	X	X	X	X	X	X	X
Provide e-diary			X					
Review study compliance[u]			X	X	X	X	X	X
EQ-5D-5L (tablet)			X	X	X	X	X	X
HADS (tablet)	X		X	X	X	X	X	X

Study Period	**Screening Period (up to 5 weeks [17 to 35 days])**[a]			**Double-Blind Treatment Period (16 weeks)**				
	Screening Visit	**Phone Contact (Washout)**[b]	**Baseline Assessment Period**	**Randomization (Dose 1)**	**Dose 2**	**Dose 3**	**Dose 4**	
Visit number	**V1**	**Phone Contact**	**V2 (BAPS Visit)**	**V3**	**V4**[c]	**V5**[c]	**V6**	**V7 (EOT/EOS or ET)**
Day and allowed time windows	**Week -5 Day -35**	**Day -33 through Day -15**	**Day -14 (±2 days)**	**Day 1**	**Day 29 ±7 days**	**Day 57 ±7 days**	**Day 85 ±7 days**	**Day 113 ±7 days**
Procedures and assessments[d, e]	**Screening**	**Scheduling and Instructions**[f]	**BAPS Visit**	**W 1**	**W 4**	**W 8**	**W 12**	**W 16**
FIQR (tablet)			X	X	X	X	X	X
PGIC (tablet)							X	X
PROMIS Physical Function SF12a (tablet)			X	X	X	X	X	X
PROMIS Fatigue SF8a (tablet)			X	X	X	X	X	X
PROMIS Sleep Disturbance SF8a (e-diary)[v]			X					
IMD (tablet)[w]	X						X	X
Blood samples for plasma concentration of IMP[x]				X			X	X
Blood samples for serum ADA concentration[y]				X			X	X
[redacted]				X			X	X

Study Period	**Screening Period (up to 5 weeks [17 to 35 days])**[a]			**Double-Blind Treatment Period (16 weeks)**				
	Screening Visit	**Phone Contact (Washout)**[b]	**Baseline Assessment Period**	**Randomization (Dose 1)**	**Dose 2**	**Dose 3**	**Dose 4**	
Visit number	**V1**	**Phone Contact**	**V2 (BAPS Visit)**	**V3**	**V4**[c]	**V5**[c]	**V6**	**V7 (EOT/EOS or ET)**
Day and allowed time windows	**Week -5 Day -35**	**Day -33 through Day -15**	**Day -14 (±2 days)**	**Day 1**	**Day 29 ±7 days**	**Day 57 ±7 days**	**Day 85 ±7 days**	**Day 113 ±7 days**
Procedures and assessments[d, e]	**Screening**	**Scheduling and Instructions**[f]	**BAPS Visit**	**W 1**	**W 4**	**W 8**	**W 12**	**W 16**
Adverse events inquiry[aa]		X	X	X	X	X	X	X
C-SSRS[bb]	X		X	X	X	X	X	X
Administration of IMP				X	X	X	X	
Review e-diaries			X	X	X	X	X	X
Collect patient e-diary								X

[a] The Screening Visit should occur no more than 35 days before randomization. The screening period should be a minimum duration of 17 days (if no washout period is required), and the length of the screening period will be contingent on the duration of the washout period for the prohibited medication.

[b] Patients will be instructed to start the washout period during the screening period phone contact. The duration of the washout period will be 7 to 19 days; suggested washout periods for commonly used analgesics are listed in Table 4. Laboratory values will be checked prior to the phone call by the investigator. Visit 2 will be scheduled and the monitoring plan for washout will be defined by the investigator. The washout period will need to be completed before the BAPS Visit (Visit 2). Training and Instructions will be provided to patients regarding the monitoring of withdrawal symptoms during the washout period.

[c] For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center (see Section 3.5).

[d] All assessments listed before IMP administration in the Study Procedures and Assessments are to be performed before IMP administration.

[e] For unscheduled visits, procedures and assessments will be completed as needed, at the investigator's discretion. For further details, see Appendix B.

[f] Patients who do not require a washout may be scheduled for the BAPS Visit (Visit 2) following review by the Fibromyalgia Eligibility Review Committee (Section 5.8.1).

[g] Training patients on accurate pain reporting and placebo response reduction on the site's tablet will occur at Screening (Visit 1), the BAPS Visit (Visit 2), and as needed for subsequent retraining throughout the study.

[h] Training for the e-diary will occur at Screening (Visit 1), the BAPS Visit (Visit 2), and as needed for subsequent retraining throughout the study. Site personnel will also instruct patients on the requirement for timely and daily completion of the e-diary. During the BAPS Period, a minimum of 12 of 14 days' compliance with e-diary recording is required. At least 75% compliance with e-diary recordings on a weekly basis is expected after the randomization period. Site personnel will monitor patients' compliance that e-diary entry is at least 75% every week during the double-blind treatment period. If weekly 75% compliance is not maintained, a reminder and any other corrective actions, as deemed necessary, will be issued to the patient.

[i] Rescue medication will need to be brought back to the investigational center (or reviewed in the patient's home if a home visit is conducted at Visit 4 and/or Visit 5) for pill counts at each visit. Collect, perform accountability, and re-dispense at all visits. Final collection is at the EOT/EOS or ET Visit (Visit 7) or at the Randomization Visit (Visit 3) if the patient is not randomized. From the BAPS Visit (Visit 2) onward, if the patient needs rescue medication, their pain intensity score should be entered into the e-diary before taking the rescue medication.

[j] At screening, patients will record their average pain over the past 7 days using the site's tablet. For the baseline assessment period (ie, between the BAPS Visit [Visit 2] and the Randomization Visit [Visit 3]) and the double-blind treatment period, patients will record their daily average pain intensity score and daily worst pain intensity score using the PI-NRS in the e-diary every evening at approximately the same time between 1800 and 2200 hours. Pain intensity scores will be entered in the e-diary prior to every use of rescue medication.

[k] The 2016 ACR diagnostic criteria for fibromyalgia (Wolfe et al 2016) must be met at the Screening Visit.

[l] Clinical laboratory tests will include serum chemistry, hematology, urinalysis, and urine drug screen. HIV, HBsAg, hepatitis C antibody, and TSH will also be completed only at the Screening Visit (Visit 1).

[m] Alcohol screening will be done by query of alcohol consumption history.

[n] Height and weight will be obtained at the Screening Visit. Weight only will be obtained during each physical examination.

[o] A full physical examination will be conducted at Screening (Visit 1). Physical examinations will be abbreviated and supplemented by the collection of AEs and SAEs at Visits 2 to 7.

[p] A single ECG will be performed.

[q] Procedure will be performed before other assessments (eg, blood draws and administration of questionnaires).

[r] Vital signs, including heart rate, respiratory rate, oral body temperature, and blood pressure, will be measured after ECGs and before scheduled blood draws, when applicable. Additionally, vital signs must be recorded immediately in case of suspected anaphylaxis and severe hypersensitivity.

[s] A serum pregnancy test may be completed as a confirmatory test, if warranted. In the event pregnancy is confirmed, the IMP will not be administered, and the patient will undergo early termination from the study.

[t] Postmenopausal women only (at least 1 year since last menses and FSH level above 35 U/L).

[u] Review of study compliance includes review of e-diary recordings, rescue medication use, concomitant medication use, and use of non-pharmacologic therapies (including normal daily exercise routines, chiropractic care, physical therapy, psychotherapy, and massage therapy).

[v] The PROMIS Sleep Disturbance SF8a (e-diary) should be performed weekly on awakening. Collection of the PROMIS Sleep Disturbance SF8a will start the day of the BAPS Visit (Visit 2) to assess the previous week's sleep and is completed in the e-diary.

[w] At the Screening Visit (Visit 1), the IMD (tablet) will be administered by the investigator; any condition that the patient has been diagnosed with will be recorded. At Visit 6 and the EOT/EOS or ET Visit (Visit 7), the IMD will be administered by the investigator; any condition recorded at Visit 1 will be assessed for improvement or non-improvement.

[x] Blood samples (4 mL) for plasma drug concentration will be collected at designated visits. Blood samples will be collected before dosing when IMP is administered. Samples from patients who were randomized to receive placebo will not be analyzed.

[y] Blood samples (5 mL) for serum ADA assessment will be collected prior to dosing at the designated visits, as well as upon observation of any severe hypersensitivity reaction or anaphylaxis. Samples from patients who were randomized to receive placebo will not be analyzed.

[z] [redacted]

[aa] Adverse events will be captured from the time informed consent is signed until end-of-study. Postdose inquiries will be made before the patient leaves the investigational center.

[bb] The C-SSRS Baseline/Screening version will be completed at Visit 1, and the C-SSRS Since Last Visit version will be completed at all other time points.

ACR = American College of Rheumatology; ADA = anti-drug antibody; AE = adverse event; APAP = acetaminophen; β-HCG = beta-human chorionic gonadotropin; BAPS = Baseline Assessment Period Start; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; e-diary = electronic diary; EOS = end-of-study; EOT = end-of-treatment; EQ-5D-5L = EuroQol-5D-5L; ET = early termination; FIQR = Fibromyalgia Impact Questionnaire Revised; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety and Depression Scale; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IMD = Inventory of Medical Diagnoses; IMP = investigational medicinal product; MINI = Mini-International Neuropsychiatric Interview; PGIC = Patient Global Impression of Change; PI-NRS = Pain Intensity-Numerical Rating Scale; PROMIS = Patient-Reported Outcomes Measurement Information System; SAE = serious adverse event; SF = Short Form; SS = symptom severity; TSH = thyroid stimulating hormone; V = visit; WOCBP = women of childbearing potential; WPI = widespread pain index.

3.6. e-Diary and Tablet Data Collection

The primary data collection tools that will be used in this study are the e-diary and the tablet, administered by [redacted] (Appendix A).

3.6.1. e-diary

The e-diary will be dispensed to each patient at the BAPS Visit (Visit 2). The e-diary will be used to record the following data:

- Average PI-NRS rating
- Worst PI-NRS rating
- At-the-moment PI-NRS rating
- Rescue medication use
- Amount of rescue medication used for a specific breakthrough pain episode
- Time of rescue medication used for a specific breakthrough pain episode
- PROMIS Sleep Disturbance SF8a (Morning Report only)

The e-diary will be completed per the Study Procedures and Assessments (Table 1). The e-diary will contain the following reports, which will guide the patient through completion of the necessary data collection on any respective day during the study: Evening Report, Make-up Evening Report, Morning Report, and Make-up Morning Report. The Evening Report will be available to patients each evening for completion between 1800h and 2200h. The Evening Report will have audible alarms that will sound at 3 different times before the entry window expires or upon completion of the report. If a patient cannot complete or forgets to complete the Evening Report, a Make-up Evening Report will become available for completion between 0300h and 1300h the next day. The Make-up Evening Report will also have audible alarms that will sound 3 times during this interval but will cease to sound upon completion of the report.

The Morning Report will be available to patients for completion between 0300h and 1300h on the respective day as scheduled in Table 1. The Morning Report will have audible alarms that will sound at 3 different times during this interval but will cease to sound upon completion of the report. If a patient cannot complete or forgets to complete the Morning Report, a Make-up Morning Report will become available for completion between 1800h and 2200h the same day. The Make-up Morning Report will not have separate audible alarms because it becomes available during the same time interval as the Evening Report for that day, which does have audible alarms.

The Rescue Medication tab will be available to patients 24 hours per day; tapping this tab will automatically display all required information for the patient to complete. The e-diary main menu will have tabs for each of the aforementioned reports, which the patient will tap to access the respective report. Patients will be trained by the site staff on the use of the e-diary at Visits 1 and 2, and as needed for subsequent retraining throughout the study. Additional information on the e-diary can be found in the Study Manual.

3.6.2. Tablet

The tablet will be dispensed to each clinical site. Patients and study site staff will use the tablet at their visits to complete the required assessments. The tablet will be used to record the following information:

- FIQR
- PGI-C
- PROMIS 12a Physical Function
- PROMIS Fatigue SF8a
- EQ-5D-5L
- HADS
- IMD

The tablet assessments will be completed per the Study Procedures and Assessments (Table 1). Additional information collected on the tablet only at the Screening Visit includes the patient-reported average PI-NRS rating over the past 7 days. The tablet main menu will contain individual tabs for each of the visits. Assessments will be completed by study site staff and/or the patient at the study site in the same order. Patients will be trained by the site staff via the tablet on accurate pain reporting and placebo response reduction at Visits 1 and 2, and as needed for subsequent retraining throughout the study. Additional information on the tablet can be found in the Study Manual.

4. SELECTION AND EARLY TERMINATION OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled will not be granted by Teva or the Medical Monitor.

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

4.1. Patient Inclusion Criteria

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

a. approved for study participation by the Fibromyalgia Eligibility Review Committee (Section 5.8.1)

b. capable of giving signed informed consent

c. agree to comply with the requirements and restrictions listed in this protocol, including remaining at the clinic for the duration of each required visit during the study period to complete all scheduled procedures and assessments

d. male or female between ≥18 to 75 years old at screening (inclusive) with FM

e. willing to comply with recording of once daily scores using the PI-NRS, completed every evening (approximately the same time each day) starting at the BAPS Visit (Visit 2) and continuing to the end-of-treatment (EOT)/EOS or early termination (ET) Visit (Visit 7). A minimum of 12 of 14 daily average pain intensity ratings AND daily worst pain intensity ratings are required to be recorded in an e-diary during the baseline assessment period (Section 3.6.1).

f. all of the following diagnostic criteria for FM according to 2016 American College of Rheumatology (Wolfe et al 2016) are met at the Screening Visit:

   – Generalized pain, defined as pain in at least 4 of 5 regions, is present.

   – Symptoms have been present at a similar level for at least 3 months.

   – WPI ≥7 and SS scale score ≥5 OR WPI of 4 to 6 and SS scale score ≥9.

   – A diagnosis of FM is valid irrespective of other diagnoses. A diagnosis of FM does not exclude the presence of other clinically important illnesses.

g. PI-NRS score ≥4 in average daily FM pain assessed by self-report over the past week at Screening Visit

h. body mass index of 18.5 to 45 kg/m^2 and a body weight ≥45 kg

i. agree to use only acetaminophen as rescue medication for FM-related pain (up to 1000 mg per dose and not to exceed 3000 mg/day for any indication throughout the study period)

j. non-pharmacologic interventions (including normal daily exercise routines, chiropractic care, physical therapy, psychotherapy, and massage therapy) are unchanged for a minimum of 30 days prior to screening and will remain unchanged throughout the study

k. agree not to initiate or modify any non-pharmacological or pharmacological interventions for FM from washout through the EOT/EOS or ET Visit

l. agree to maintain a usual and unchanged physical exercise regimen

m. [Revision 1] must meet the following pregnancy-related criteria:

- females must have a negative serum beta-human chorionic gonadotropin (β-HCG) test at screening or be sterile or postmenopausal; definitions of sterile and postmenopausal are provided in Appendix F
- females 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) and for 6 months after the last dose of the IMP; further details are provided in Appendix F
- males who are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile), and their female partners are of childbearing potential, should use highly effective birth control methods for the duration of the study (ie, starting at screening); further details are provided in Appendix F

n. must agree not to participate in another interventional study from the screening period through the EOT/EOS or ET Visit

4.2. Patient Exclusion Criteria

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

a. unable or unwilling to discontinue/washout of prohibited medications (Appendix I); Note: Medications used to treat depression or anxiety are permitted provided they were started at least 90 days prior to screening, have been used at a stable dose for at least 90 days, and will be maintained at that dose for the duration of the study. Therefore, both over-the-counter (OTC) medications used to treat depression or anxiety and selective serotonin reuptake inhibitors (SSRIs; with the exception of ≥60 mg/day of fluoxetine) are permitted.

b. in the investigator's opinion, history of no meaningful improvement to an adequate trial of 2 or more different pharmacological classes of medications indicated for FM adequate dosing for an adequate period of time

c. ongoing pain that would confound or interfere with the assessment of the patient's FM pain or require excluded therapies during the patient's participation in this study. Other sources of pain may include, but are not limited to, neuropathic pain attributable to an identifiable cause, post-herpetic neuralgia, traumatic injury, prior surgery, complex regional pain syndrome or failed back syndrome, infections or inflammatory arthritis (eg, rheumatoid arthritis [RA], ankylosing spondylitis, psoriatic arthritis, gout), other autoimmune diseases (eg, systemic lupus erythematosus), and other widespread rheumatic diseases (widespread osteoarthritis [OA]). Localized OA is permitted as long as it is subclinical (which does not require treatment with an analgesic[s]).

d. surgery planned during the study period

e. receiving prophylactic treatment for migraine-related disorders, including topiramate, valproic acid, onabotulinumtoxinA, amitriptyline, and nortriptyline

f. known history of clinically significant or unstable hematological, cardiac, or thromboembolic events (ie, arterial or venous thrombotic or embolic events, including cerebrovascular accident [including transient ischemic attacks], deep vein thrombosis, or pulmonary embolism); renal, endocrine, pulmonary, gastrointestinal, genitourinary, or neurologic disorders [exclusive of FM]; infectious, hepatic, or ocular disease, at the discretion of the investigator, as determined by a medical and psychiatric history; and physical examination, 12-lead ECG, serum chemistry, hematology, coagulation, and urinalysis). Abnormal test results may be repeated for confirmation.

g. moderate or severe major depressive symptoms as assessed by the HADS Depression Subscore >14 (at the Screening Visit and/or the BAPS Visit)

h. known history of suicide attempt, suicidal behavior, or suicidal ideation within the last 12 months (a response of "yes" to questions 4 or 5 on the suicidal ideation portion of the C-SSRS), or have been assessed as a significant risk to commit suicide at the Screening Visit or Randomization Visit

i. lifetime history of any psychotic and/or bipolar disorder as assessed by the MINI

j. current, untreated, moderate or severe major depressive disorder and/or anxiety disorder as assessed by the MINI. Patients with currently treated major depressive disorder and/or anxiety disorder can be included, provided that according to the investigator's judgment, there have been no clinically significant changes in symptoms while on a stable dose of allowed antidepressants or antianxiety medications for at least 90 days prior to screening, and that the dosage of antidepressant or antianxiety medication will be maintained for the duration of the study.

k. current eating disorders as assessed by the MINI

l. known infection or history of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection, or are antigen positive for hepatitis B at screening

m. past or current history of cancer in the past 5 years, except for appropriately treated non-melanoma skin carcinoma (basal carcinoma)

n. known history of hypersensitivity reactions to injected proteins, including mAbs and animal venoms, or a history of Stevens-Johnson Syndrome/toxic epidermal necrolysis syndrome

o. known history of hypersensitivity or intolerance to the use of acetaminophen

p. known hypersensitivity or intolerance to the components in the formulation of fremanezumab

q. participation in an interventional clinical study of a chemical entity or device within 2 months or 5.5 half-lives (whichever is longer) prior to IMP administration

r. participation in an interventional clinical study of a mAb within 3 months or 5.5 half-lives (whichever is longer) prior to IMP administration

s. any prior exposure to mAbs targeting the CGRP pathway (including erenumab, eptinezumab, galcanezumab, or fremanezumab) at any time. If the patient has participated in a clinical study with any of these mAbs, it has to be confirmed that the patient received placebo in order to be eligible for this study.

t. clinically significant elevations in hepatic enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) based on the upper limit of normal (ULN) or investigator judgment, which have been reconfirmed on a repeat test

u. suspected hepatocellular damage that fulfills criteria for Hy's law at screening

v. serum creatinine >1.5× ULN, clinically significant proteinuria, or evidence of renal disease at screening

w. known history of alcohol and/or drug abuse within the past 12 months per the MINI or have a positive urine drug screen for illegal drugs of abuse at the Screening Visit, BAPS Visit, or prior to randomization

x. [Revision 1] if using marijuana (cannabis), meets the MINI (v.7.0.2) criteria for greater than mild substance use disorder for marijuana (cannabis), cannabidiol, or other cannabinoids during the preceding 12 months; and/or the investigator is concerned that the use of marijuana (cannabis), cannabidiol, or other cannabinoids could interfere with a subject’s ability to provide reliable data or comply with the protocol

y. diagnosed with uncontrolled sleep apnea

z. employee of Teva Pharmaceuticals, the CRO involved, or the investigative site personnel directly affiliated with this study and/or immediate family member (spouse, parent, child, or sibling, whether biological or legally adopted, or legal guardian/custodian)

aa. involved in an active workers compensation case or is currently filing or seeking a work disability claim for any reason or condition

bb. currently experiencing acute, severe psychosocial stress (ie, recent death of a loved one, divorce)

cc. any condition or situation (ie, shift work) that, in the investigator’s opinion, makes the patient unsuitable for study participation

dd. [New criterion] has received any CGRP pathway targeting treatment or compound (anti-CGRP antibodies, anti-CGRP receptor antibodies, or CGRP receptor antagonists/oral gepants) for migraine

ee. [New criterion] the patient is a pregnant or nursing female or plans to become pregnant during the study, including the 6-month period after the administration of the IMP

4.3. Discontinuation from IMP/Early Termination from Study Criteria and Procedures for the Patient

There are no study-specific patient discontinuation/early termination criteria and procedures. The following general criteria apply.

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

1. Patient withdraws consent or requests discontinuation from the IMP or early termination 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 confirmed pregnancy during the study based on a positive pregnancy test result (positive urine pregnancy tests will need a blood β-HCG confirmation of the result).
6. Patient experiences an adverse event or other medical condition, which indicates to the investigator that continued participation is not in the best interest of the patient.
7. The investigator and/or sponsor may terminate an individual patient from the study at any time for any reason (eg, lack of efficacy, protocol deviation, noncompliance, or adverse event). In addition, patients with hypersensitivity reactions, positive C-SSRS, positive HADS findings, or abnormal hepatic laboratory values along with bilirubin increases that are consistent with hepatic injury may meet criteria for discontinuation from the IMP.

Efficacy endpoints (primary, secondary, [redacted]) will be derived from subjective pain ratings collected daily using an e-diary. Eligible patients will receive comprehensive training from site personnel on the correct use of the e-diary. Site personnel will also instruct patients on the requirement for timely and daily completion of the e-diary. At least 75% compliance with e-diary recordings on a weekly basis is expected after the randomization visit. Site personnel will monitor patients' compliance that e-diary entry is at least 75% every week during the double-blind treatment period. If weekly 75% compliance is not maintained, a reminder and any other corrective actions, as deemed necessary, will be issued to the patient (Section 3.6.1).

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

1. any increase in ALT or AST to ≥3× the ULN, combined with INR >1.5× the ULN or total bilirubin >2× the ULN
2. any increase in ALT or AST to ≥3× the ULN, which is accompanied by symptoms clearly associated with impaired liver function (eg, vomiting, nausea, fever, rash, eosinophilia) and not deemed related to other diseases (eg, vomiting or nausea triggered by migraine)

3. any increase in ALT or AST to levels ≥5 but <8× the ULN, which is persistent for ≥2 weeks of repeated measurements
4. any increase in ALT or AST to levels ≥8× the ULN
5. in any case where monitoring of liver enzymes cannot be performed according to the protocol guidance

Patients should be treated with standard of care after discontinuation from IMP or early termination of the study, as appropriate. All protocol-specified procedures/assessments should be performed at the EOT/EOS or ET Visit (Visit 7) (see Table 1).

Investigators should attempt to obtain information on patients in the case of early termination from the study or discontinuation from IMP (EOT/early termination; see Appendix B). Results of any evaluations and observations, together with a narrative describing the reason(s) for early termination from the study or discontinuation from IMP, must be recorded in the source documents. The electronic case report form (eCRF) must document the primary reason for early termination from the study or discontinuation from IMP.

See Appendix G 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 early termination from the study or discontinuation from IMP is an adverse event and/or clinically significant abnormal laboratory test result, monitoring will be continued as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the eCRF; both the adverse events page and the relevant page of the eCRF will be completed at that time.

The investigator must inform the Study Leader as soon as possible of each patient who is being considered for early termination due to adverse events. Additional reports must be provided when requested.

If a patient early terminates from the study or discontinues IMP for multiple reasons that also include adverse events, the relevant page of the eCRF should indicate that the early termination 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 early termination by itself, but that requires the use of a prohibited medication, thereby requiring early termination of the patient. In such a case, the reason for termination would be “need to take a prohibited medication”, not the adverse event.

In the case of patients lost to follow-up, attempts to contact the patient must be made and recorded in the patient’s medical records and entered into the eCRF.

4.4. Replacement of Patients

A patient who is terminated early from the study will not be replaced.

4.5. Rescreening

Rescreening will not be routinely allowed for patients who are screened but not enrolled (eg, because eligibility criteria were not met [inclusion criteria not met and/or exclusion criteria met]). However, patients who were screened but not enrolled due to technical issues (eg, diary malfunction) or are out of Visit 2 window due to urgent extenuating circumstances (eg, public health emergency) may be considered for screening one additional time. Only patients who were not enrolled due to these limited issues/circumstances may be screened a second time.

If the patient is screened again, a new informed consent form (ICF) will need to be signed and a new screening number will be assigned.

For Coronavirus Disease 2019 updates, see Appendix O.

4.6. Screen Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. Data for screen failure reason and minimal information including but not limited to demography, adverse events from the time of informed consent, and subject disposition, will be entered into the eCRF.

5. TREATMENTS

5.1. Investigational Medicinal Products Used in the Study

Investigational medicinal product is defined as the test IMPs and matching placebo IMP to the test IMP. Patients will receive the IMP at Visits 3, 4, 5, and 6. Patients randomized to the 225 mg dose level will receive 1 injection of 225 mg fremanezumab and 2 injections of placebo; patients randomized to the 675 mg dose level will receive 3 injections of 225 mg fremanezumab; and patients randomized to placebo will receive 3 injections of placebo at each visit.

5.1.1. Test Investigational Medicinal Product

Fremanezumab is a humanized IgG2Δa/kappa monoclonal antibody derived from a murine precursor. Additional details are provided in Table 2 and in the current IB.

5.1.1.1. Starting Dose and Dose Levels

A high and low dose level will be studied: 675 mg sc monthly and 225 mg sc monthly. For each dose regimen, the starting dose will be the same as the subsequent dose. Patients will receive either placebo or 1 of 2 IMP dose levels for a total of 3 sc injections at each dosing visit.

The recommended sc injection sites follow the National Institutes of Health (NIH) Clinical Center Patient Education Materials (NIH Clinical Center Patient Education Materials 2016). The suggested injection site locations for sc administration are the following: back of upper arms, lower abdomen/belly/waistline, and front of thighs. The sc injection and location will be recorded for each administration visit (Visits 3, 4, 5, and 6).

5.1.1.2. Dosing Visits and Dose Modification

Visits 1, 2, 3, and 6 must occur at the study site. For Visits 4 and/or 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center for any extenuating circumstances (see Section 3.5). After such extenuating circumstances resolve, home visits may be permitted to continue.

Doses will be administered at the study site or at home, as applicable, at the time of visits via a fixed dose pre-filled syringe; no dose modifications will be allowed. There will be a time window for doses that do not occur on the scheduled days. If a scheduled visit cannot occur within the ±7-day time window due to extenuating circumstances, the Medical Monitor should be contacted to determine if the window can be lengthened. Medical Monitor notification and consultation for all missed scheduled visits and related rescheduling and necessary plans of action is required.

For COVID-19 updates, see Appendix O.

5.1.2. Placebo Investigational Medicinal Product

Fremanezumab placebo is the same vehicle as the test IMP formulation but does not contain active fremanezumab.

Table 2: Investigational Medicinal Products Used in the Study

IMP Name	Test IMP	Placebo IMP	Reference IMP
Trade name and INN, if applicable, or company-assigned number	Fremanezumab; recombinant humanized IgG2Δa/kappa mAb against CGRP	Fremanezumab placebo	None
Formulation	Solution for injection is a sterile, unpreserved, and colorless to slightly yellow aqueous solution for sc injection for single-use administration. The drug product contains fremanezumab at 150 mg/mL nominal concentration in 16 mM histidine, 6.6% w/v sucrose, 0.136 mg/mL disodium EDTA, 0.02% w/v polysorbate 80 at pH 5.5. Fremanezumab will be provided in pre-filled syringes	Fremanezumab placebo is the same vehicle as the test IMP formulation but does not contain active fremanezumab Placebo will be provided in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Pre-filled syringes will contain the same vehicle and excipients as those for active injection. Fremanezumab placebo will be provided in pre-filled syringes.	
Unit dose strength(s)/Dosage level(s)	225 mg/1.5 mL	1.5 mL	
Route of Administration	sc administration	sc administration	
Packaging	IMP will be provided in a pre-filled syringe.	Pre-filled syringe	
[redacted]	[redacted]	[redacted]	
Dosing instructions/Dosing schedule/Treatment periods	sc fremanezumab or placebo on Visits 3, 4, 5, and 6 (days 1, 29, 57, and 85)		

CGRP = calcitonin gene related peptide; EDTA = ethylenediaminetetraacetic acid; IgG = immunoglobulin G; IMP = investigational medicinal product; INN = international nonproprietary name; mAb = monoclonal antibody; sc = subcutaneous; w/v = weight/volume.

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

5.2.1. Storage and Security

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

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

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

5.2.2. Labeling

Supplies of IMPs will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

5.2.3. Accountability

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

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

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

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

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty syringes must be destroyed at the investigational center in accordance with the investigational center's Standard Operating Procedures (SOPs) following sponsor approval. In the event that the investigational center is unable to destroy the empty units of IMP, the IMP must be returned to the sponsor or its

designee per sponsor instructions. Unused syringes and/or kits are to be returned to the depot for destruction.

For visits conducted at the patient's home, it is the responsibility of the site to ensure the correct IMP is provided. If a sharps container is to be supplied to the patient, the site is responsible for arranging the container and ensuring it is available to be provided along with the IMP.

Detailed procedures are provided in Appendix H.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The fremanezumab doses and dosing regimens to be evaluated in this double-blind study were selected on the basis of animal pharmacodynamic and pharmacokinetic data, 8 pharmacokinetic/safety studies in healthy volunteers, 5 safety/efficacy studies in patients with migraine, and population pharmacokinetic and pharmacokinetic/pharmacodynamic modeling and simulations.

The pharmacodynamics of fremanezumab were examined in animal models by characterization of the ability of fremanezumab to block CGRP functions in vivo (see Section 1.2.1). Specifically, neurogenic vasodilation by capsaicin application on the skin was used to induce a CGRP-mediated increase in vasodilatation or skin blood flow in cynomolgus monkeys. In the study, fremanezumab (dosed as a single iv bolus at 1, 10, or 100 mg/kg) produced a dose-dependent inhibition of the capsaicin-induced skin flare response. The magnitude and duration of the inhibition produced by fremanezumab were dose dependent, with the 10 and 100 mg/kg doses showing inhibition out to 56 days postdose. Based on body surface area conversion, these doses are equivalent to single doses of approximately 225 mg sc and 2000 mg iv, respectively, in patients with migraine. Therefore, the 225 mg sc dose was considered to be a reasonable and pragmatic choice for the lowest dose with potential for effectiveness.

Based on data from the pharmacokinetic and pharmacodynamic studies in animal models and the pharmacokinetics, safety, and tolerability of fremanezumab from Phase 1 studies in healthy volunteers, 2 dose regimens were selected for sc administration in the Phase 2b study in patients with episodic migraine (EM) for a treatment period of 3 months. The 2 active arms were 225 mg and 675 mg sc administered monthly. The results of the Phase 2b study demonstrated that both dose regimens were effective, safe, and well tolerated by patients with EM. The mean changes in number of migraine days relative to baseline for both fremanezumab dose arms were significantly different from the placebo arm at 3 months (primary endpoint), and the study was also strikingly positive at 2 months and 1 month. Although a maximum tolerated dose was not reached in the Phase 2b study, and single doses up to 2000 mg iv were observed to be safe in healthy volunteers, it is considered best practice to select the lowest effective dose known for administration. Therefore, the lowest dose from the Phase 2b study, 225 mg fremanezumab administered monthly, was preserved for the Phase 3 study in patients with EM. A second active treatment group will receive fremanezumab at 675 mg quarterly to determine efficacy using a higher dose in case the lower dose of 225 mg sc monthly is not effective or is minimally effective. The 225-mg monthly and 675-mg quarterly dose regimens demonstrated similar exposure over a 3-month period in clinical studies of patients with EM.

For the current proof of concept study, 2 active dose regimens will be administered: a lower dosing regimen of 225 mg monthly and a higher dosing regimen of 675 mg monthly. The 675-mg monthly dose will provide a discerningly higher exposure separation from the lower dose of 225 mg monthly. The calculated safety margin is 54-fold higher than the expected clinical exposure following 675 mg sc monthly. As indicated above, the 675-mg monthly dosing regimen was also found to be safe and well tolerated in patients with EM.

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. A placebo-controlled design allows for negative control, which facilitates measure of the actual effect of the treatment being tested in the clinical study.

5.4. Other Medicinal Products/Non-Investigational Medicinal Products

Information regarding acetaminophen as a rescue medicinal product is provided in Table 3.

Table 3: Other Medicinal Products Used in the Study

Medicinal Product Name	**Rescue Medication**
Trade name and INN, if applicable, or company-assigned number	Acetaminophen
Formulation	To be sourced by the site
Unit dose strength(s)/Dosage level(s)	500 mg
Route of administration	Oral
Dosing instructions	1 to 2 caplets with dose up to 1000 mg per dose; maximum of 3000 mg/day
Packaging	To be sourced by the site
Manufacturer	To be sourced by the site

INN = International Nonproprietary Name.

5.5. Treatment after the End of the Study

Patients will not have access to sc fremanezumab as provided in this study after the EOT/EOS or ET Visit (Visit 7). After Visit 7, all subsequent clinical care will be determined by or at the discretion of the treating physician.

5.6. Restrictions

Patients will be required to comply with the following restrictions:

1. Agree not to initiate or modify any non-pharmacologic or pharmacologic interventions for FM during the study.
2. Agree to maintain usual level of activity during the study.

5.6.1. Activity

Patients must remain at the investigational center for safety observation for at least 30 minutes after IMP administration. Patients may be asked to remain at the investigational center longer if it is judged to be medically necessary by the investigator.

5.6.2. Blood Donation

Patients may not donate blood while taking the IMP and for 6 months after their last dose.

5.7. Prior and Concomitant Medication or Therapy

5.7.1. Permitted Concomitant Medication or Therapy

Selective serotonin reuptake inhibitors or OTC medications are permitted if started at least 90 days prior to screening, have been on a stable dose for at least 90 days, and are expected to remain on a stable dose throughout the study, except for ≥60 mg/day of fluoxetine.

Over-the-counter medications used to treat depression or anxiety are permitted provided the dose has been stable for at least 90 days prior to screening and is not changed during the study.

For rescue treatment of FM-related pain, only acetaminophen up to 1000 mg per dose and not to exceed 3000 mg/day (for any indication) may be used, if needed, after recording the PI-NRS score in the e-diary. Use of nasal, inhaled, and topical steroids is permitted.

Nonsteroidal anti-inflammatory drugs are permitted provided the use has been stable (ie, per patient's usual dosing regimen) for at least 1 month prior to screening and will remain unchanged throughout the study.

Antihistamines are permitted for sleep. In addition, tricyclic antidepressants at low doses (amitriptyline [≤25 mg] or trazodone [≤150 mg]) or cyclobenzaprine (up to 10 mg), zolpidem (up to 10 mg), and melatonin may be used for sleep per the patient's usual dosing regimen, with no dose change 1 month prior to screening and throughout the study.

Concomitant medications permitted during the study include the following: 1) SSRIs (stable use), 2) the use of acetaminophen as a rescue medication up to 1000 mg per dose and not to exceed 3000 mg/day as a rescue medication for pain, 3) medications required for the treatment of any adverse events, 4) aspirin (maximum daily dose 325 mg) for cardiovascular prophylaxis, 5) nonsteroidal anti-inflammatory drugs (stable use), and 6) selected sleep medications.

If using marijuana (cannabis), cannabidiol, or other cannabinoids, regardless of route of administration, subjects should be instructed to keep their use at approximately the same dose/amount, route of administration, and frequency throughout the study.

No other FM medications (prescription, OTC, behind-the-counter, IMPs other than those permitted in this study, or vaccine) will be allowed during the study. For details of allowed medications, see Appendix N.

5.7.2. Prohibited Medication or Therapy

A list of prohibited medications is provided in Appendix I. At each visit at the investigational center after the Screening Visit, the investigator will ask patients whether they have taken any

medications (other than IMP[s]), including OTC medications, vitamins, or herbal or nutritional supplements, since the previous visit.

Concomitant medication and treatment will be recorded until the EOT/EOS or ET Visit (Visit 7/week 16).

5.7.3. Recommended Washout Periods

The washout periods for common drugs are detailed in Table 4. While it is not mandatory to wash out of all concomitant medications, it is desirable to reduce the number of concomitant medications to a minimum, if possible. Note: Not all of these medications will require washout; see Section 5.7.1, Section 5.7.2, Appendix I, and Appendix N for further information about permitted concomitant medications.

Washout periods are recommendations; actual washout periods must be determined by the investigator based on his/her clinical practice/judgement, the medication, and the dose of the respective medication. If there are any questions, contact the medical monitor.

Table 4: List of Recommended Washout Periods for Common Medications

Name of Drug	Recommended Washout
Analgesic/antipyretic	
Acetaminophen	1 week
Anticonvulsants	
Gabapentin	1 week
Pregabalin	1 week
Antidepressants	
Duloxetine	2 weeks
Venlafaxine	2 weeks
Amitriptyline	2 weeks
Nortriptyline	2 weeks
Cox-2 inhibitor	
Celecoxib	1 week
Nonsteroidal anti-inflammatory drugs	
Aspirin (high dose)	2 weeks
Aspirin (low dose)	1 week
Choline magnesium trisalicylate	1 week
Diclofenac (gel)	1 week
Diclofenac (oral)	1 week
Diclofenac (patch)	1 week
Diflunisal	1 week
Etodolac	1 week

Name of Drug	**Recommended Washout**
Fenoprofen	1 week
Ibuprofen	1 week
Indomethacin	1 week
Meclofenamate	1 week
Meloxicam	1 week
Methyl salicylate (high dose)	2 weeks
Methyl salicylate (low dose)	1 week
Nabumetone	1 week
Naproxen	1 week
Oxaprozin	2 weeks
Piroxicam	2 weeks
Salsalate	1 week
Tolmetin	1 week
Opioids	
Codeine	1 week
Dihydrocodeine	1 week
Fentanyl	1 week
Hydrocodone	1 week
Methadone	2 weeks
Morphine	1 week
Oxycodone	1 week
Oxymorphone	1 week
Tramadol	1 week
Patches	
Lidocaine	1 week
Serotonin and norepinephrine reuptake inhibitors	
Desvenlafaxine	2 weeks
Duloxetine	2 weeks
Levomilnacipran	2 weeks
Milnacipran	2 weeks
Venlafaxine	2 weeks

5.8. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. If the investigator or the sponsor determines that the patient does not comply with the study protocol, the investigator and the sponsor should determine whether the patient should be terminated from the study (Section 4.3). The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) should be notified.

5.8.1. Fibromyalgia Eligibility Review Committee

The Fibromyalgia Eligibility Review Committee is a sponsor- and site-independent review committee comprised of one or more external experts with experience in fibromyalgia study design and execution. The review committee has been charged with determining if patients proposed for study enrollment are appropriate candidates. Such determination will be based upon assessment of clinical information obtained during the screening period relevant to the diagnosis and treatment of fibromyalgia, as well as potential confounds to diagnosis, treatment, and/or study participation.

5.9. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. All IMPs will be identical and indistinguishable. Patients, investigators, and all clinical study center staff will remain blinded to treatment assignment during the study. Eligible patients will be randomly assigned via a qualified Randomization and Trial Supply Management (RTSM) system in a 1:1:1 ratio to fremanezumab at 225 mg sc or fremanezumab 675 mg sc, or placebo sc. Randomization will be stratified by sex (male/female) and age at FM onset (<40 years old and ≥40 years old).

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list. The generation of the randomization list and management of the RTSM system will be done by a qualified service provider. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

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 released. However, if a prioritized sample analysis is needed, bioanalytical and clinical pharmacology personnel may be unblinded.

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

5.10. Maintenance of Randomization and Blinding

5.10.1. Maintenance of Randomization

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

patient randomization list, without indication of IMP assignment, from the Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant SOP. The unblinded IMP assignment will be requested by Data Management from the clinical study center.

Packaging vendor(s) will package test IMP and placebo IMP according to Good Manufacturing Practice procedures. Kits will be identical in appearance. Adequate kit supply for upcoming study visits will be managed by RTSM and kept (refrigerated at 2°C to 8°C) at the investigational centers.

At Visits 3 through 6, the RTSM will be queried, and investigational center personnel will retrieve and administer each pre-filled syringe contained in the appropriately numbered kit(s). Kit numbers will be entered into the eCRF.

5.10.2. Blinding and Unblinding

Blinded pharmacokinetic data may be assessed during the study. 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 who are not part of the study team 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), if needed.

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

When a blind is broken, the patient will be terminated early from the study and the event will be recorded on the eCRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP should not be recorded in any study documents or source document.

In blinded studies, for an adverse event defined as a 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 analysis and reporting of the data.

5.10.3. Independent Data Monitoring Committee

There will be no Independent Data Monitoring Committee (IDMC) for this study.

5.11. Total Blood Volume

The total blood volume that will be collected for each patient enrolling in this study for scheduled evaluation of ADAs, fremanezumab concentrations, clinical laboratory tests, and biomarkers is approximately 150.8 mL. Details are provided in Appendix J.

The total blood volume that will be collected over the duration of the study conforms to established blood volume collection for clinical research.

6. ASSESSMENT OF EFFICACY

6.1. Assessments of Efficacy

6.1.1. Pain Intensity-Numerical Rating Scale

The PI-NRS is an 11-point pain intensity numerical rating scale where 0=no pain and 10=worst possible pain. The PI-NRS is a widely used and validated pain scale in studies of approved therapies in FM (Arnold et al 2015, Farrar et al 2010). The PI-NRS will be used to rate average FM pain intensity over the past week at screening. This will be entered via the site tablet at screening. The remainder of the assessments are daily assessments from Visit 2 to Visit 7 and are recorded in the patient's e-diary. The average daily FM pain intensity over the past 24 hours, the worst FM pain intensity over the past 24 hours, and at-the-moment pain intensity just prior to the use of rescue medication.

6.1.2. Fibromyalgia Impact Questionnaire Revised

The FIQR is a commonly used instrument in the evaluation of FM patients. It contains 21 questions in 3 domains: function (9 questions), overall impact (2 questions), and symptoms (10 questions). Questions are graded on a 0 to 10 numeric scale with 10 being the worst. All questions are framed in the context of the **last 7 days**. The weighting of these 3 domains is that 30% of the total score is ascribed to "function," 50% is ascribed to "symptoms," and 20% is ascribed to "overall impact." The total maximal score of the FIQR is 100 (Bennet et al 2009).

6.1.3. EuroQol-5 Dimension Questionnaire

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of the descriptive system EQ Visual Analogue Scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale (0 to 100) with endpoints labelled "the best health you can imagine" and "the worst health you can imagine" (EQ-5D-5L User Guide 2018).

6.1.4. Patient Global Impression of Change

The PGIC scale evaluates all aspects of patients' health and assesses if there has been an improvement or decline in clinical status since the start of the study. Improvement is recorded on a 7-point scale, with 1 indicating very much improved and 7 indicating very much worse (Arnold et al 2015).

6.1.5. Patient-Reported Outcomes Measurement Information System

6.1.5.1. PROMIS Sleep Disturbance Short Form 8a

The PROMIS Sleep Disturbance SF8 Scale contains 8 items with a score range of 8 to 40 and measures quality of sleep and sleep-related impairment. The PROMIS Sleep Disturbance instrument assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. This includes perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. Sleep Disturbance does not focus on symptoms of specific sleep disorders, nor does it provide subjective estimates of sleep quantities (total amount of sleep, time to fall asleep, amount of wakefulness during sleep). The Sleep Disturbance SF8 assesses sleep disturbance over the past 7 days (PROMIS-Sleep Disturbance Scoring Manual). Collection of the PROMIS Sleep Disturbance SF8a will start the day of the BAPS Visit (Visit 2) and will be administered weekly via the e-diary Morning Report to assess the previous week's sleep.

6.1.5.2. PROMIS Physical Function Short Form 12a

The PROMIS Physical Function SF12a Scale contains 12 items with a score ranging from 12 to 60. The PROMIS Physical Function Scale measures self-reported capability rather than actual performance of physical activities. This includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands over the past over the past 7 days. A single Physical Function capability score is obtained from a SF. A lower score indicates more limited physical disability (PROMIS-Physical Function Scoring Manual).

6.1.5.3. PROMIS Fatigue Short Form 8a

The PROMIS Fatigue SF8a contains 8 items with a score range from 8 to 40. Each question has 5 response options ranging in value from 1 to 5 over the past 7 days. To find the total raw score for an SF with all questions answered, sum the values of the response to each question. For the adult 8-item form, the lowest possible raw score is 8; the highest possible raw score is 40, indicating worst sleep (PROMIS-Fatigue Scoring Manual).

6.1.6. Hospital Anxiety and Depression Scale

The HADS is a 14-item questionnaire that measures anxiety and depression in both hospital and community settings for a recall period of 7 days. It assesses the SS of anxiety disorders and depression in patients with illness and the general population. Scores of 0 to 7 in respective subscales are considered normal, with 8 to 10 borderline and 11 or over indicating clinical "caseness." The HADS has been used in the study of patients with FM (Nam et al 2014).

6.1.7. Inventory of Medical Diagnoses

The IMD is a 9-item, non-validated inventory that evaluates in patients (1) medical conditions diagnosed and present for at least 3 months at the Screening Visit and (2) improvement or non-improvement of these medical conditions at the end of the study.

Questions will be completed by the investigator at the Screening Visit (Visit 1) and at Visits 6 and 7. For those medical conditions that a patient identifies as present at screening, the

investigator will query at Visits 6 and 7 whether those conditions are improved or not improved compared with when the patient entered the study.

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, 12-lead ECG findings, physical examination findings (including body weight measurements), C-SSRS scores, local injection site assessments, use of concomitant medication, and laboratory test results. Study procedures and assessments are described in Table 1.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

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

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

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

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the early termination 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.)

Worsening of the disease under study will be assessed by the principal investigator and should be recorded as an adverse event only if the presentation or outcome is deemed more severe than would normally be expected from the normal course of the disease in a particular patient.

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the study or the ET visit for patients who discontinue from the study for any reason. Symptoms or signs of medication withdrawal during the weaning period should be recorded as a medication withdrawal adverse event. The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the eCRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events, the serious adverse event form must be completed, and the serious adverse event must be reported immediately (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period.

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

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

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

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

Table 5: The Relationship of an Adverse Event to the IMP

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

7.1.5. Serious Adverse Events

For recording of serious adverse events, the study period is defined for each patient as that time period from signature of the ICF to the end of the study or the ET visit for patients who discontinue from the study for any reason. Serious adverse events occurring in a patient after the end of the study should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

7.1.5.1. Definition of a Serious Adverse Event

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

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

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

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

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

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

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

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

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 CRO in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information, Appendix A); 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 the following:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

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

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

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

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

7.1.5.3.2. Sponsor Responsibility

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

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

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

- ophthalmic-related adverse events of at least moderate severity, as determined by the investigator
- severe hypersensitivity reactions or anaphylaxis (see Appendix C)

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 C. 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 will be 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 either be serious or nonserious, according to the criteria outlined in Section 7.1.5.1.

7.1.7. Protocol Deviations Because of an Adverse Event

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

7.2. Pregnancy

Any female patient becoming pregnant during the study will discontinue IMP.

All pregnancies of women participating in the study and female partners of men participating in the study that occur during the study, or within at least 6 months after administration of IMP, will be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section (Appendix A) of this protocol; the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3).

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

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

The Medical Monitor should be contacted in any of the following events:

1. All 3 syringes from the assigned kit are unable to be administered during the visit.
2. Any dose has been administered and a syringe is damaged.

If a syringe is damaged prior to dose administration, a new kit should be requested. Additional information is provided in the Study Manual.

Any administration of IMP that is not in accordance with the study protocol should be reported on the eCRF either as a violation, if it meets the violation criteria specified in the protocol (Appendix D), or as a deviation, in the patients source documents, regardless of whether or not an adverse event occurs as a result.

The following are types of medication errors and special situations:

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

7.4. Clinical Laboratory Tests

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

- abnormal and not clinically significant
- abnormal and clinically significant

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

that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

Table 6: Clinical Laboratory Tests

Serum Chemistry	**Hematology and Coagulation**	**Urinalysis**
Calcium Phosphate Sodium Potassium Chloride Creatinine Glucose Blood urea nitrogen (BUN) Urate Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Lactate dehydrogenase (LDH) Gamma-glutamyl transpeptidase (GGT) Alkaline phosphatase Bicarbonate Carbon dioxide Protein Albumin Bilirubin Direct bilirubin Hepatitis B	Hemoglobin Hematocrit Erythrocytes Platelets Leukocytes – Neutrophils – Lymphocytes – Eosinophils – Monocytes – Basophils Lymphocytes atypical Prothrombin International Normalized Ratio (INR)	Protein Glucose Ketones Hemoglobin pH Specific gravity Microscopic tests – Bacteria – Erythrocytes – Leucocytes – Crystals – Casts
Tests to be performed at screening only		**Tests to be performed as indicated in** Table 1
Human immunodeficiency virus (HIV) Hepatitis B surface antigen (HBsAg) Hepatitis C antibody Thyroid stimulating hormone (TSH) Beta-human chorionic gonadotropin (β-HCG; women of childbearing potential only)		Drug screening β-HCG (women of childbearing potential only)

7.4.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis) will be performed at the time points detailed in Table 1. Clinical laboratory tests will be performed using a central laboratory; details will be specified in the Laboratory Manual. Specific laboratory tests to be performed are provided in Table 6.

7.4.2. Other Clinical Laboratory Tests

At screening, patients will be tested for human immunodeficiency virus, hepatitis B surface antigen (HBsAg), hepatitis C antibody, and thyroid stimulating hormone (Table 6).

7.4.2.1. Beta-human Chorionic Gonadotropin Tests

Beta-human chorionic gonadotropin tests in serum will be performed for all women of childbearing potential at screening (Visit 1). Urine will be used for all subsequent visits and will be tested on site via β-HCG dipstick. Serum may be tested if clinically indicated, or as a confirmatory test for a positive dipstick result.

7.4.2.2. Urine Drug Screen

A urine drug screen will be performed at the time points specified in Table 1, but patients should not be told at which visits the urine drug screen will be performed. The urine drug screen detects the presence of drugs of abuse, including opioids, and marijuana/cannabis (see details in the Laboratory Manual).

A positive result for any of the above drugs or their metabolites, except marijuana/cannabis, without medical explanation, will preclude the patient from randomization/enrollment or continued participation in the study.

7.5. Physical Examinations

Physical examinations, including height and weight (to be obtained at the Screening Visit; and weight during each physical examination), will be performed at the time points detailed in Table 1. Any physical examination finding that is judged by the investigator as clinically significant (except at the Screening Visit) will be considered an adverse event, recorded on the eCRF, and monitored as described in Section 7.1.2.

A full physical examination will include at a minimum skin, lungs, cardiovascular, respiratory, gastrointestinal, and neurologic assessments.

An abbreviated physical examination will include at a minimum skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious diseases and record in the eCRF.

7.6. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, oral body temperature, and pulse) will be measured at the time points detailed in Table 1. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

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

7.7. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 1. A qualified physician at a central diagnostic center will be interpreting the ECG.

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

- abnormal and not clinically significant
- abnormal and clinically significant

Any ECG finding that is judged by the investigator as clinically significant (except at the Screening Visit) will be considered an adverse event, recorded on the source documentation and in the eCRF, and monitored as described in Section 7.1.2.

7.8. Immunogenicity

Blood samples for ADA assessment will be collected prior to dosing at the designated visits, as well as upon observation of any severe hypersensitivity reaction or anaphylaxis.

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

7.10. Assessment of Suicidality

The sponsor considers it important to monitor for events of suicidal ideation or behavior during this clinical study.

The C-SSRS will be used to assess the patient's suicidal ideation (severity and intensity) and behavior (Posner et al 2011). The C-SSRS Baseline/Screening version will be administered by certified site staff at Visit 1, and the C-SSRS Since Last Visit version will be completed by certified site staff at all other time points, as described in Table 1. Appropriate study staff should review the results. Any significant findings on the C-SSRS require evaluation by the site investigator.

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

8.1. Pharmacokinetic Assessment

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

Blood samples (4 mL) will be collected via venipuncture or indwelling catheter (for details, see the Laboratory Manual) at the time points detailed in Table 1 for plasma concentration measurements of fremanezumab. The dates and times of IMP administration and the date and time of each pharmacokinetic sample collection will be recorded in the source documentation and entered into the eCRF.

Samples from patients who received 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 will be included in the Laboratory Manual.

8.2. Pharmacodynamics Assessment

Pharmacodynamic parameters will not be evaluated in this study.

8.3. Immunogenicity Testing

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

Blood samples (6 mL) will be collected via venipuncture or indwelling catheter (for details, see the Laboratory Manual) at the time points detailed in Table 1 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 documentation and entered into the eCRF.

8.4. [redacted]

[redacted]

[redacted]

9. STATISTICS

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

9.1. Study Design and Randomization

This is a multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fremanezumab treatment in patients with FM. Patients will be randomly assigned to receive treatment with fremanezumab 225 mg sc, fremanezumab 675 mg sc, or matching placebo sc in a 1:1:1 ratio. Randomization and blinding will be as described in Section 5.9.

9.2. Sample Size and Power Considerations

The sample size of 80 subjects per treatment group was selected based on expert consensus agreement at a scientific advisory board meeting; this sample size is expected to provide sufficient precision to estimate the treatment effect of fremanezumab versus placebo. Moreover, assuming a standard deviation of 2.2 for change from baseline in the weekly average of the daily average PI-NRS score, 80 patients per treatment group will provide at least 90% probability to observe the half length of the 95% confidence interval of the treatment difference between fremanezumab 225 mg sc or fremanezumab 675 mg sc and placebo less than 0.74. In total, 240 patients will be enrolled in this study in a 1:1:1 randomization ratio.

9.3. Analysis Sets

9.3.1. 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.

Patient disposition, demographics, and baseline characteristics will use the ITT analysis set, as appropriate.

9.3.2. 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 received at least 1 dose of study medication and at least 1 post-baseline entry of daily average pain intensity using the PI-NRS.

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.

All efficacy analyses will use the mITT analysis set unless noted otherwise.

9.3.3. Safety Analysis Set

The safety analysis set will include all randomized patients who received at least 1 dose of study medication. 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.

All safety analyses will use the safety analysis set unless noted otherwise.

9.3.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the mITT analysis set including only patients without major protocol violations defined in the statistical analysis plan before study unblinding. The PP analysis set will serve as support for the efficacy analyses.

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

The primary efficacy endpoint and selected secondary efficacy endpoints will be analyzed using PP analysis set; details will be specified in the statistical analysis plan.

9.3.5. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include those patients from the safety analysis set who have at least 1 plasma concentration value for fremanezumab.

9.4. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the by-visit descriptive summaries. Data imputation rule(s) will be described in relevant sections and detailed in the statistical analysis plan.

9.4.1. Handling Early Terminations and Missing Data

Details for handling early terminations and missing data will be provided in the statistical analysis plan; observed data will be analyzed and presented without data imputation unless specified otherwise in the statistical analysis plan.

9.5. Study Population

Male and female patients, ≥18 to 75 years old, inclusive, with FM.

The ITT analysis set (Section 9.3) will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment group and for all patients.

9.5.1. Patient Disposition

Descriptive statistics will be used to summarize data from the following groups: patients screened; patients screened but not randomized and reason not randomized; patients who are randomized; patients randomized but not treated (and reason); patients in the ITT, mITT, safety, PP, and pharmacokinetic analysis sets; patients who complete the treatment and the study; and patients who discontinue from the treatment and the study. Data from patients who discontinue from treatment and the study will also be summarized by reason for discontinuation using descriptive statistics.

9.5.2. Demographic and Baseline Characteristics

Patient demographic characteristics (age, sex, ethnicity, and race) and baseline characteristics (medical history, prior medications, 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, standard deviation, standard error, 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.

9.6. Efficacy Analysis

9.6.1. Primary Endpoint

The primary efficacy endpoint is the change from baseline up to week 16 in the weekly average of the daily average PI-NRS score over the past 24 hours.

9.6.2. Secondary Endpoints

- change from baseline up to week 16 in the individual components of the FIQR: symptom subscore, impact subscore, and functional subscore score
- responder rate of the PGIC rating (percentage of patients much improved or very much improved) up to week 16
- percentage of patients who experience a ≥30% reduction in the weekly average of the daily average PI-NRS score up to week 16
- percentage of patients who experience a ≥50% reduction in the weekly average of the daily average PI-NRS score up to week 16
- change from baseline up to week 16 in the weekly average of the daily worst PI-NRS score over the past 24 hours
- change from baseline up to week 16 in the PROMIS Sleep Disturbance SF8a score
- change from baseline up to week 16 in the PROMIS Physical Function SF12a score
- change from baseline up to week 16 in the PROMIS Fatigue SF8a score
- number (%) of patients who did not complete the treatment (Kaplan-Meier Survival Analysis) due to lack of efficacy

9.6.3. [redacted]

- [redacted]

9.6.4. Planned Method of Analysis

9.6.4.1. Primary Efficacy Analysis

The primary efficacy variable will be analyzed using an MMRM model with the change from baseline up to week 16 in the weekly average of the daily average over the past 24 hours PI-NRS scores as the dependent variable; sex, age group at FM onset, week, treatment, and treatment by week interaction as fixed factors; and baseline PI-NRS scores as a covariate. The heterogeneous autoregressive correlation structure for repeated observations within patients will be used, and the denominator degrees of freedom will be estimated using Kenward-Roger's approximation. An adjustment for missing data due to lack of efficacy or adverse event assumes the PI-NRS scores will, on average, return to baseline values. Missing data will be imputed 500 times to generate 500 complete data sets by using the SAS procedure PROC MI following the 3 steps below:

- Step 1: The monotone missing pattern will be induced by the Markov Chain Monte Carlo method in the PROC MI procedure using seed number 4751523.
- Step 2: The remaining missing data at subsequent weeks will be imputed using the regression method for the monotone pattern with seed number 4751523 and adjustment for covariates including treatment groups, randomization strata, relevant baseline and all values at preceding visits.
- Step 3: The initially missing and now imputed data for patients discontinued from the study treatment due to lack of efficacy or adverse event will be center adjusted at the mean baseline value for that treatment group, ie, the final imputed score will be equal to the imputed score under missing at random minus (mean change from baseline score at the post-baseline time point for the treatment group).

Each imputed data set will be analyzed using the MMRM described above. The results from the 500 analyses will be combined using Rubin's formulae (PROC MIANALYZE). The least squares means estimates for the mean change from baseline to each time point, as well as the difference of the estimates between the fremanezumab and placebo groups, with the corresponding standard error, p-value and associated 95% confidence interval will be provided.

9.6.4.2. Sensitivity Analysis

Sensitivity analyses will be included to address the assumptions in the primary model. The primary analysis will be repeated; however, the daily average pain scores measured on the days where the patient took rescue medication will be replaced with his or her PI-NRS score at the time of rescue medication use before the weekly average PI-NRS scores are derived. On days where a patient uses rescue medication more than once, the mean PI-NRS score at the time of

rescue mediation use will be used as the pain score in place of the average pain intensity score for that day.

Three subgroup analyses will be conducted as part of the planned second interim analysis for the primary endpoint using descriptive statistics.

- analysis by baseline pain level (PI-NRS ≥4, PI-NRS ≥5, and PI-NRS ≥6)
- analysis by normalizing data for use of analgesia at baseline by adding 1 to the baseline pain score for those using analgesia
- analysis by use of analgesia during baseline

Details of the subgroup analyses will be specified in the interim analysis statistical analysis plan.

9.6.4.3. Secondary Efficacy Analysis

The change from baseline in weekly average of the daily worst PI-NRS over the past 24 hours up to week 16 and the baseline FIQR score will be analyzed in the same manner as the primary efficacy endpoint; however, the baseline pain intensity over the past 24 hours and the baseline FIQR score, respectively, will be used as a covariate in the MMRM model instead of the baseline PI-NRS score.

The PGIC asks patients to rate their status on the following scale:

Since the start of the study, my overall status is:
1. Very Much Improved
2. Much Improved
3. Minimally Improved
4. No Change
5. Minimally Worse
6. Much Worse
7. Very Much Worse

The PGIC data will be dichotomized, where a patient who responds as either “much improved” or “very much improved” will be considered improved, and all other responses will be considered not improved. The response variable will be analyzed using a logistic regression model with the treatment, age group at FM onset, and sex as explanatory factors. In addition, the PGIC data will be summarized as categorical variable by week and treatment group using descriptive statistics.

The percentage of patients who experience ≥30% reduction and ≥50% reduction in the weekly average of the daily average PI-NRS score up to week 16 will be analyzed using a generalized estimating equation method, where the dependent variable experience ≥30% reduction and ≥50% reduction (Yes/No) will be modeled through the binomial link function, with treatment, sex, age group at FM onset, week, and treatment by week interaction as explanatory factors. In addition, a plot of percentage of improvement versus percentage of patients meeting the improvement level throughout the study will be presented by treatment group.

Change from baseline up to week 16 in the PROMIS Sleep Disturbance SF8a score, change from baseline up to week 16 in the PROMIS Physical Function SF12a score, change from baseline up to week 16 in PROMIS Fatigue SF8a score, and change from baseline up to week 16 in the HADS will be analyzed using an MMRM model with treatment, sex, age group at FM onset, week, treatment-by-week interaction, and baseline value of the corresponding variable as explanatory factors.

The number and percentage of patients who did not complete the treatment due to lack of efficacy or adverse event will be summarized using descriptive statistics, and the time to treatment discontinuation due to lack of efficacy or adverse event will be analyzed using the Kaplan-Meier Survival Analysis method.

9.6.4.4. Other Efficacy Analysis

Statistical modeling to be used for other efficacy endpoints will be described and detailed in the statistical analysis plan as appropriate.

9.6.4.5. [redacted]

[redacted]

9.7. Multiple Comparisons and Multiplicity

No multiplicity adjustment is planned for this study.

9.8. Safety Analysis

Safety analyses will be performed on the safety analysis set. The safety analysis set will include all randomized patients who receive at least 1 dose of IMP.

9.8.1. Safety Variables

The overall safety and tolerability of sc fremanezumab treatment will be assessed by evaluating adverse events and the following additional safety variables at the time points specified in Section 3.5:

- clinical laboratory tests
- vital signs
- physical examination

- 12-lead ECGs
- concomitant therapy or medication usage
- C-SSRS

9.8.2. Safety Analysis

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

The number and percentage of patients who did not complete the treatment due to lack of efficacy or adverse event will be summarized using descriptive statistics, and the time to treatment discontinuation due to lack of efficacy or adverse event will be analyzed using the Kaplan-Meier Survival Analysis method.

Changes in laboratory, ECG, vital signs measurements, and C-SSRS 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.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient early terminations 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.

9.8.3. Tolerability Analysis

Local tolerability findings (eg, erythema, induration, ecchymosis, and occurrence of injection site pain) will be listed and summarized descriptively.

9.9. Pharmacokinetic Analysis

Plasma concentrations will be tabulated at each planned sampling time point by treatment group. In addition, the most appropriate population pharmacokinetic model will be developed, and covariates that may affect pharmacokinetic parameters will be tested for inclusion in the model. This analysis will be reported separately from the CSR; individual pharmacokinetic concentration data will be summarized and listed in the CSR.

9.10. Pharmacodynamic Analysis

Efficacy will be the only pharmacodynamic parameter evaluated in this study.

9.11. Pharmacokinetic/Pharmacodynamic Analysis

Plasma concentration of fremanezumab will be summarized by visit using descriptive summary statistics.

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

9.12. Biomarker Analysis

Blood samples (approximately 19.0 mL) will be collected on day 1, prior to randomization and at the times specified in Table 1, [redacted]

9.13. Immunogenicity Analysis

The summary of immunogenicity results will be provided, and the incidence of immunogenicity and the antibody titers will be calculated.

9.14. Ancillary Studies Analysis

There are no ancillary studies planned for this study.

9.15. Planned Interim Analysis

A formal interim analysis for futility in this proof-of-concept study is planned after 68 patients have been enrolled; the interim analysis will be performed by an independent third party. A second interim analysis, for futility or continuation of the study, is planned after approximately 150 patients have completed the study; the interim analysis will be performed by a team, which is independent and isolated from the study team, who will be kept blinded. Details of the interim analyses will be specified in the interim analysis statistical analysis plan.

[redacted]

9.16. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in subsequent protocol amendments, if any, 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 D for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations and violations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

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

11. COMPLIANCE STATEMENT

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

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 recorded 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 and for contacts with study management, with the IEC/IRB, and with competent authorities.

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

12. DATA MANAGEMENT AND RECORD KEEPING

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

13. FINANCING AND INSURANCE

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

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

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

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

14. PUBLICATION POLICY

See Appendix M for information regarding the publication policy.

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 05 Dated 09 August 2021

The primary reason for this amendment is to update relevant sections of the protocol to include patients using marijuana (cannabis), cannabidiol, or other cannabinoids into the study. Another primary reason for this amendment is the addition of a planned second interim analysis. In addition, the removal of an appendix on liver function tests monitoring will also be implemented in alignment with other recent fremanezumab studies; the total blood volume to be collected from each patient will be updated as a result of the change in the blood collection tube for the INR and the removal of the second FSH assessment during Visit 2; and CGRP pathway targeting treatment or compound drug class will be added to the list of prohibited medications and its use added to the exclusion criteria. Table 1 (Schedule of Study Procedures and Assessments) has been revised to reflect changes described below. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc.) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/justification for change
PREFACE		
~~The protocol amendment 04 was approved on 16 June 2020. However, it was not submitted to a health authority or Institutional Review Board/Independent Ethics Committee (IRB/IEC). Subsequently, an interim analysis was added to the study. These circumstances led to a revised protocol amendment (Protocol Amendment 04 Revision 01).~~		The preface was removed to follow the protocol template; explanation for Protocol Amendment 04 Revision 01 was added to the amendment history
SPONSOR PROTOCOL APPROVAL and APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Sponsor's Authorized Representative [redacted]	**Sponsor's Authorized Representative** [redacted]	Administrative update
Section 3.5 Schedule of Study Procedures and Assessments		

Original text with changes shown	New wording	Reason/justification for change
See new wording column	Table 1. (Study Procedures and Assessments) has been modified as follows: • Marijuana (cannabis), cannabidiol, or other cannabinoids (medicinal and social history) assessment was added to Screening Visit (Visit 1) • FSH test was removed from Visit 2 Editorial changes and updates reflecting the revisions made to the table were applied to Table 1 footnotes.	Updated the table to reflect the collection of marijuana (cannabis), cannabidiol, or other cannabinoids medicinal and social history and the removal of the second FSH assessment during Visit 2
Section 4.1 Patient Inclusion Criteria		
m. [Revision 1] must meet the following pregnancy-related criteria: ~~– women surgically sterile by documented complete hysterectomy, bilateral oophorectomy, or~~ ~~– bitubal ligations or confirmed to be postmenopausal (at least 1 year since last menstrual period) and~~ ~~– menopausal women confirmed by a follicle-stimulating hormone >35 U/L~~ ~~– men surgically sterile by documented vasectomy OR~~ ~~If of childbearing potential, patients must meet any of the following criteria:~~ ~~– must use highly effective contraception method (Appendix F) with their partners during the entire study period and for 6 months after the last dose of the IMP~~ – ~~sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of~~ contraception.	m. [Revision 1] must meet the following pregnancy-related criteria: – females must have a negative serum beta-human chorionic gonadotropin (β-HCG) test at screening or be sterile or postmenopausal; definitions of sterile and postmenopausal are provided in Appendix F – females 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) and for 6 months after the last dose of the IMP; further details are provided in Appendix F – males who are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile), and their female partners are of childbearing potential, should use highly effective birth control methods for the duration of the study (ie, starting at screening); further details are provided in Appendix F	Updated the criterion with more concise descriptions

Original text with changes shown	New wording	Reason/justification for change
– females ~~patients of childbearing potential~~ must have a negative serum beta-human chorionic gonadotropin (β-HCG) ~~pregnancy~~ test at screening ~~(confirmed by urine dipstick β-HCG pregnancy test at baseline)~~or be sterile or postmenopausal; definitions of sterile and postmenopausal are provided in Appendix F – females 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) and for 6 months after the last dose of the IMP; further details are provided in Appendix F – males who are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile), and their female partners are of childbearing potential, should use highly effective birth control methods for the duration of the study (ie, starting at screening); further details are provided in Appendix F		
Section 4.2 Patient Exclusion Criteria		
x. [Revision 1]~~any marijuana use within 2 months prior to screening~~if using marijuana (cannabis), meets the MINI (v.7.0.2) criteria for greater than mild substance use disorder for marijuana (cannabis), cannabidiol, or other cannabinoids during the preceding 12 months; and/or the investigator is concerned that the use of marijuana (cannabis), cannabidiol, or other cannabinoids could interfere with a subject's ability to provide reliable data or comply with the protocol	x. [Revision 1] if using marijuana (cannabis), meets the MINI (v.7.0.2) criteria for greater than mild substance use disorder for marijuana (cannabis), cannabidiol, or other cannabinoids during the preceding 12 months; and/or the investigator is concerned that the use of marijuana (cannabis), cannabidiol, or other cannabinoids could interfere with a subject's ability to provide reliable data or comply with the protocol	The criterion was updated to include patients using marijuana (cannabis), cannabidiol, or other cannabinoids into the study
dd. [New criterion] has received any CGRP pathway targeting treatment or compound (anti-CGRP antibodies, anti-CGRP receptor antibodies, or CGRP receptor antagonists/oral gepants) for migraine	dd. [New criterion] has received any CGRP pathway targeting treatment or compound (anti-CGRP antibodies, anti-CGRP receptor antibodies, or CGRP receptor antagonists/oral gepants) for migraine	Added the use of CGRP pathway targeting treatment or compound to the exclusion criteria
ee. [New criterion] the patient is a pregnant or nursing female or plans to become pregnant during the study, including the 6-month period after the administration of the IMP	ee. [New criterion] the patient is a pregnant or nursing female or plans to become pregnant during the study, including the 6-month period after the administration of	Added pregnant or nursing females, or those with plans to become pregnant within a specified time period to the

Original text with changes shown	New wording	Reason/justification for change
	the IMP	exclusion criteria
Section 5.7.1 Permitted Concomitant Medication or Therapy		
If using marijuana (cannabis), cannabidiol, or other cannabinoids, regardless of route of administration, subjects should be instructed to keep their use at approximately the same dose/amount, route of administration, and frequency throughout the study.	If using marijuana (cannabis), cannabidiol, or other cannabinoids, regardless of route of administration, subjects should be instructed to keep their use at approximately the same dose/amount, route of administration, and frequency throughout the study.	Added to include patients using marijuana (cannabis) and other cannabinoids into the study
Section 5.11 Total Blood Volume		
The total blood volume that will be collected for each patient enrolling in this study for scheduled evaluation of ADAs, fremanezumab concentrations, clinical laboratory tests, and biomarkers is approximately ~~161.5~~150.8 mL. ~~An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes.~~ Details are provided in Appendix J.	The total blood volume that will be collected for each patient enrolling in this study for scheduled evaluation of ADAs, fremanezumab concentrations, clinical laboratory tests, and biomarkers is approximately 150.8 mL. Details are provided in Appendix J.	Updated to reflect the change in the blood volume to be collected as a result of the change in the blood collection tube for the INR requiring a decrease of 1.8 mL from the volume of blood to be collected from each patient during Visits 1, 3, 6, and 7, and the removal of the second FSH assessment during Visit 2
Section 7.4.2.2 Urine Drug Screen		
A urine drug screen will be performed at the time points specified in Table 1, but patients should not be told at which visits the urine drug screen will be performed. The urine drug screen detects the presence of drugs of abuse, including opioids, and marijuana/cannabis (see details in the Laboratory Manual). A positive result for any of the above drugs or their metabolites, except marijuana/cannabis, without medical explanation, will preclude the patient from randomization/enrollment or continued participation in the study.	A urine drug screen will be performed at the time points specified in Table 1, but patients should not be told at which visits the urine drug screen will be performed. The urine drug screen detects the presence of drugs of abuse, including opioids, and marijuana/cannabis (see details in the Laboratory Manual). A positive result for any of the above drugs or their metabolites, except marijuana/cannabis, without medical explanation, will preclude the patient from randomization/enrollment or continued participation in the study.	Updated to remove the alert flag for marijuana/cannabis or other cannabinoids at study sites to include patients using cannabis/marijuana or other cannabinoids, as specified in Section 5.7.1, into the study
Section 9.6.4.2 Sensitivity Analysis		
Three subgroup analyses will be conducted as part of the planned second interim analysis for the primary endpoint using descriptive statistics.	Three subgroup analyses will be conducted as part of the planned second interim analysis for the primary endpoint using descriptive statistics.	Added a general description pertaining to the 3 subgroup analyses to be conducted as part

Original text with changes shown	New wording	Reason/justification for change
• analysis by baseline pain level (PI-NRS ≥4, PI-NRS ≥5, and PI-NRS ≥6) • analysis by normalizing data for use of analgesia at baseline by adding 1 to the baseline pain score for those using analgesia • analysis by use of analgesia during baseline Details of the subgroup analyses will be specified in the interim analysis statistical analysis plan.	• analysis by baseline pain level (PI-NRS ≥4, PI-NRS ≥5, and PI-NRS ≥6) • analysis by normalizing data for use of analgesia at baseline by adding 1 to the baseline pain score for those using analgesia • analysis by use of analgesia during baseline Details of the subgroup analyses will be specified in the interim analysis statistical analysis plan.	of the planned second interim analysis
Section 9.15 Planned Interim Analysis		
~~There will be 1~~A formal interim analysis for futility in this proof-of-concept study is planned after 68 patients ~~are~~have been enrolled; the interim analysis will be performed by an independent third party. A second interim analysis, for futility or continuation of the study, is planned after approximately 150 patients have completed the study; the interim analysis will be performed by a team, which is independent and isolated from the study team, who will be kept blinded. ~~The d~~Details of the interim ~~analysis~~analyses will be specified in ~~an~~the interim analysis statistical analysis plan. ~~If the study continues after the first interim analysis, a second interim analysis may be performed; the nature and timing of the second interim analysis will be prespecified in a subsequent protocol amendment. To ensure study integrity, all of the interim analyses will be performed by an independent third party; the study team will be kept blinded.~~ [redacted]	A formal interim analysis for futility in this proof-of-concept study is planned after 68 patients have been enrolled; the interim analysis will be performed by an independent third party. A second interim analysis, for futility or continuation of the study, is planned after approximately 150 patients have completed the study; the interim analysis will be performed by a team, which is independent and isolated from the study team, who will be kept blinded. Details of the interim analyses will be specified in the interim analysis statistical analysis plan. [redacted]	Updated to include details of a planned second interim analysis [redacted]
APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		

Original text with changes shown	New wording	Reason/justification for change
1. Procedures for screening (Visit 1, day -35 [week -5]) The Screening Visit (Visit 1) will take place not more than 3 weeks before the Baseline Assessment Period Start (BAPS) Visit (Visit 2). The following procedures will be performed at Visit 1: … • marijuana (cannabis), cannabidiol, or other cannabinoids (medicinal and social history) …	1. Procedures for screening (Visit 1, day -35 [week -5]) The Screening Visit (Visit 1) will take place not more than 3 weeks before the Baseline Assessment Period Start (BAPS) Visit (Visit 2). The following procedures will be performed at Visit 1: … • marijuana (cannabis), cannabidiol, or other cannabinoids (medicinal and social history) …	Added the collection of marijuana (cannabis), cannabidiol, or other cannabinoids medicinal and social history as patients using marijuana (cannabis), cannabidiol, or other cannabinoids will be included into the study
3. Procedures Before Administration of Investigational Medicinal Product(s) (BAPS Visit [Visit 2, day -14 (week -3) (±2 days)]) Patients who meet the inclusion and exclusion criteria at Visit 1 will continue to Visit 2, when initial baseline assessments will be conducted. The following procedures will be performed at Visit 2: • review inclusion and exclusion criteria • study assessments/pain reporting training • e-diary data review training • dispense/account rescue medication • provide e-diary • PI-NRS (recorded daily) • prior medication and treatment history • urine drug screen • abbreviated physical examination • vital signs measurements • ~~serum FSH test (for postmenopausal women only)~~ …	3. Procedures Before Administration of Investigational Medicinal Product(s) (BAPS Visit [Visit 2, day -14 (week -3) (±2 days)]) Patients who meet the inclusion and exclusion criteria at Visit 1 will continue to Visit 2, when initial baseline assessments will be conducted. The following procedures will be performed at Visit 2: • review inclusion and exclusion criteria • study assessments/pain reporting training • e-diary data review training • dispense/account rescue medication • provide e-diary • PI-NRS (recorded daily) • prior medication and treatment history • urine drug screen • abbreviated physical examination • vital signs measurements …	Updated to reflect the removal of serum FSH test during Visit 2
APPENDIX F. BIRTH CONTROL METHODS AND PREGNANCY TESTING		
Women/Girls of nonchildbearing potential are defined as: • surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally	**Women/Girls of nonchildbearing potential are defined as:** • surgically (documented hysterectomy, bilateral	Added the definition of women/girls of non-childbearing potential to Appendix F for clarity

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/justification for change</th></tr>
<tr><td>sterile
• postmenopausal</td><td>oophorectomy, or bilateral salpingectomy) or congenitally sterile
• postmenopausal</td><td></td></tr>
<tr><td colspan="3">APPENDIX I. LIST OF PROHIBITED MEDICATIONS AND THERAPEUTIC INTERVENTIONS</td></tr>
<tr><td>CALCITONIN GENE-RELATED PEPTIDE PATHWAY TARGETING TREATMENT OR COMPOUND
<table><tr><td>Anti-CGRP Antibodies</td></tr><tr><td>Eptinezumab-jjmr (Vyepti)</td></tr><tr><td>Galcanezumab-gnlm (Emgality)</td></tr><tr><td>Anti-CGRP Receptor Antibodies</td></tr><tr><td>Erenumab-aooe (Aimovig)</td></tr><tr><td>CGRP Receptor Antagonists/Oral Gepants</td></tr><tr><td>Ubrogepant (Ubrelvy)</td></tr><tr><td>Rimegepant (Nurtec ODT)</td></tr></table></td><td>CALCITONIN GENE-RELATED PEPTIDE RECEPTOR PATHWAY TARGETING TREATMENT OR COMPOUND
<table><tr><td>Anti-CGRP Antibodies</td></tr><tr><td>Eptinezumab-jjmr (Vyepti)</td></tr><tr><td>Galcanezumab-gnlm (Emgality)</td></tr><tr><td>Anti-CGRP Receptor Antibodies</td></tr><tr><td>Erenumab-aooe (Aimovig)</td></tr><tr><td>CGRP Receptor Antagonists/Oral Gepants</td></tr><tr><td>Ubrogepant (Ubrelvy)</td></tr><tr><td>Rimegepant (Nurtec ODT)</td></tr></table></td><td>Added CGRP pathway targeting treatment or compound to Appendix I</td></tr>
<tr><td>OTHER THERAPEUTIC INTERVENTIONS
<table><tr><td>Herbal agents (eg, St. John’s Wort)</td></tr><tr><td>Topical lidocaine within 1 month prior to screening</td></tr><tr><td>Capsaicin within 6 months prior to screening</td></tr><tr><td>~~Cannabinoids~~</td></tr><tr><td>Oral corticosteroids</td></tr></table></td><td>OTHER THERAPEUTIC INTERVENTIONS
<table><tr><td>Herbal agents (eg, St. John’s Wort)</td></tr><tr><td>Topical lidocaine within 1 month prior to screening</td></tr><tr><td>Capsaicin within 6 months prior to screening</td></tr><tr><td>Oral corticosteroids</td></tr></table></td><td>Cannabinoids was removed to include patients using marijuana (cannabis), cannabidiol, or other cannabinoids into the study</td></tr>
<tr><td colspan="3">APPENDIX J. TOTAL BLOOD VOLUME</td></tr>
</table>

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/justification for change</th></tr>
<tr>
<td>Total blood volume to be collected for each patient in this study is approximately ~~161.5~~150.8 mL for scheduled tests. ~~An additional 30 mL of blood may be collected in the event of follow up for liver enzymes.~~ Refer to the Laboratory Manual for details on blood sampling.
Total Blood Volumes
<table>
<tr><th>Visit number</th><th>Visit 1</th><th>Visit 2</th><th>Visit 3</th><th>Visit 6</th><th>Visit 7</th><th>Total</th></tr>
<tr><th>Visit type</th><th>Screening visit</th><th>BAPS visit</th><th colspan="2">Double-blind treatment</th><th>EOT/ EOS or ET visit</th><th></th></tr>
<tr><td>Number of samples</td><td>6</td><td>~~1~~ 0</td><td>9</td><td>9</td><td>9</td><td>~~34~~33</td></tr>
<tr><td>Volume (mL)</td><td>~~33.5~~ 31.7</td><td>~~3.5~~0</td><td>~~41.5~~ 39.7</td><td>~~41.5~~ 39.7</td><td>~~41.5~~ 39.7</td><td>~~161.5~~ 150.8</td></tr>
</table>
~~a~~ ~~This sample is for FSH assessment and will be drawn from postmenopausal women only.~~
See FDA Guidance (Guidance for Industry 2007) for acceptable blood volume loss per collection procedure.
BAPS = Baseline Assessment Period Start; EOS = end-of-study; EOT = end-of-treatment; ET = early termination; FDA = Food and Drug Administration~~; FSH = follicle stimulating hormone.~~.</td>
<td>Total blood volume to be collected for each patient in this study is approximately 150.8 mL for scheduled tests. Refer to the Laboratory Manual for details on blood sampling.
Total Blood Volumes
<table>
<tr><th>Visit number</th><th>Visit 1</th><th>Visit 2</th><th>Visit 3</th><th>Visit 6</th><th>Visit 7</th><th>Total</th></tr>
<tr><th>Visit type</th><th>Screening visit</th><th>BAPS visit</th><th colspan="2">Double-blind treatment</th><th>EOT/ EOS or ET visit</th><th></th></tr>
<tr><td>Number of samples</td><td>6</td><td>0</td><td>9</td><td>9</td><td>9</td><td>33</td></tr>
<tr><td>Volume (mL)</td><td>31.7</td><td>0</td><td>39.7</td><td>39.7</td><td>39.7</td><td>150.8</td></tr>
</table>
See FDA Guidance (Guidance for Industry 2007) for acceptable blood volume loss per collection procedure.
BAPS = Baseline Assessment Period Start; EOS = end-of-study; EOT = end-of-treatment; ET = early termination; FDA = Food and Drug Administration.</td>
<td>Updated to reflect the change in the blood volume to be collected as a result of the change in the blood collection tube for the INR requiring a decrease of 1.8 mL from the volume of blood to be collected from each patient during Visits 1, 3, 6, and 7, and the removal of the second FSH assessment during Visit 2</td>
</tr>
<tr><td colspan="3">APPENDIX O. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19</td></tr>
<tr>
<td>APPENDIX O. ~~GUIDANCE ON SAFETY MONITORING~~
~~APPENDIX N.~~ MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19</td>
<td>APPENDIX O. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19</td>
<td>An entire appendix containing the guidance on monitoring patients with elevated liver function tests was removed, because the level of monitoring of liver function tests described in it is no longer required, as liver function is no longer a protocol-defined adverse event of special interest in fremanezumab studies; the</td>
</tr>
</table>

Original text with changes shown	New wording	Reason/justification for change
		deletion resulted to an update to the lettering of subsequent appendices and their in-text cross references

16.2. Amendment 04 with Revision 01 Dated 25 June 2020

The primary reason for this revision is to include interim analyses. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/justification for change
PREFACE		
The protocol amendment 04 was approved on 16 June 2020. However, it was not submitted to a health authority or Institutional Review Board/Independent Ethics Committee (IRB/IEC). Subsequently, an interim analysis was added to the study. These circumstances led to a revised protocol amendment (Protocol Amendment 04 Revision 01).	The protocol amendment 04 was approved on 16 June 2020. However, it was not submitted to a health authority or Institutional Review Board/Independent Ethics Committee (IRB/IEC). Subsequently, an interim analysis was added to the study. These circumstances led to a revised protocol amendment (Protocol Amendment 04 Revision 01).	A preface was added to explain why Protocol Amendment 04 was updated with Revision 01, and the date of approval of Amendment 04, which was previously listed as 12 June 2020, was corrected to 16 June 2020 (when the approval signature was obtained)
Section 9.15 Planned Interim Analysis		
There will be ~~no~~1 formal interim analysis for futility in this study after 68 patients are enrolled. The details of the interim analysis will be specified in an interim analysis statistical analysis plan. If the study continues after the first interim analysis, a second interim analysis may be performed; the nature and timing of the second interim analysis will be prespecified in a subsequent protocol amendment. To ensure study integrity, all of the interim analyses will be performed by an independent third party; the study team will be kept blinded.	There will be 1 formal interim analysis for futility in this study after 68 patients are enrolled. The details of the interim analysis will be specified in an interim analysis statistical analysis plan. If the study continues after the first interim analysis, a second interim analysis may be performed; the nature and timing of the second interim analysis will be prespecified in a subsequent protocol amendment. To ensure study integrity, all of the interim analyses will be performed by an independent third party; the study team will be kept blinded.	Updated to include futility and interim analyses

16.3. Amendment 04 Dated 16 June 2020

The primary reasons for this amendment are to add to the exclusion criterion related to prior hypersensitivity reactions in patients with a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome. A second primary reason for this amendment is to provide flexibility and reduce patient burden. In addition, rescreening will be available to patients who could not be randomized due to technical issues, or who were in screening and not randomized because of the Coronavirus Disease 2019 (COVID-19) pandemic. All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Additionally, COVID-19 pandemic-related operational updates were added to the study as a new appendix (Appendix P).

The Clinical Study Protocol Synopsis, Table 1 (Study Procedures and Assessments), and Figure 1 (Overall Study Schematic Diagram) have been revised to reflect changes described below.

Original text with changes shown	New wording	Reason/justification for change
TITLE PAGE		
Teva Branded Pharmaceutical Products R&D, Inc. ~~41 Moores Road~~145 Brandywine Parkway ~~Frazer~~West Chester, Pennsylvania 1938~~055~~ United States of America	**Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, Pennsylvania 19380 United States of America**	Administrative update
SPONSOR PROTOCOL APPROVAL		
Sponsor's Authorized Representative [redacted]	**Sponsor's Authorized Representative** [redacted]	Provided additional information on title/credentials for Sponsor's Authorized Representative

Original text with changes shown	New wording	Reason/justification for change
COORDINATING INVESTIGATOR AGREEMENT		
Executed signature pages are maintained within the Investigator Site File and the Trial Master File	**Executed signature pages are maintained within the Investigator Site File and the Trial Master File**	Clarified that the coordinating investigator signature will be on file in the official repository
Section 1.1 Introduction (Other sections affected by this change: Section 5.1.1 and Section 5.1.2 [Table 2])		
Fremanezumab (~~also known as~~ TEV-48125 [formerly PF-04427429, RN307, and LBR-101~~, TEV-48125, or Ajovy~~]), a humanized immunoglobulin G (IgG) 2Δa/kappa monoclonal antibody (mAb) derived from a murine precursor, is currently approved in the United States (US) for the preventive treatment of migraine in adults ~~(episodic and chronic)~~ and marketed under the trade name AJOVY®. Fremanezumab is under development for ~~cluster headache (CH), persistent post traumatic headache, and~~ chronic pain indications. Refer to the current Investigator's Brochure (IB) for detailed information on the background, pharmaceutical particulars, nonclinical experience, and clinical experience with fremanezumab.	Fremanezumab (TEV-48125 [formerly PF-04427429, RN307, and LBR-101]), a humanized immunoglobulin G (IgG) 2Δa/kappa monoclonal antibody (mAb) derived from a murine precursor, is currently approved in the United States (US) for the preventive treatment of migraine in adults and marketed under the trade name AJOVY®. Fremanezumab is under development for chronic pain indications. Refer to the current Investigator's Brochure (IB) for detailed information on the background, pharmaceutical particulars, nonclinical experience, and clinical experience with fremanezumab.	The history of the names representing fremanezumab was clarified. Delta symbol added for accuracy in describing the antibody Added a sentence referring the reader where information on fremanezumab is located
Section 1.2.2 Clinical Studies		
As of 30 August ~~2018~~2019, approximately ~~4080~~4972 subjects/patients (~~3333~~4062 adult patients with migraine, 15 pediatric patients with migraine, ~~250~~380 patients with cluster headache [CH], ~~23~~37 patients with persistent post-traumatic headache, an estimated 4 patients with FM, and 474 healthy subjects) have been exposed to fremanezumab. The fremanezumab clinical program comprises ~~23~~24 clinical studies (10 Phase 1; ~~5~~4 Phase 2, 2b, or 2b/3; and ~~8~~10 Phase 3 studies), of which ~~12~~19 have been completed. The safety and tolerability of fremanezumab was studied in all of the ~~12 completed~~ 24 studies in the ~~migraine~~ clinical program (ie, ~~8 Phase 1 studies in healthy subjects, and 2 Phase 2b studies and 2 Phase 3 studies in patients with migraine~~10 Phase 1, 2 Phase 2, 2 Phase 2b, 2 Phase 2b/3, and 8 Phase 3 studies). Based on the safety results of the completed studies, the safety profile was assessed to include the following events	As of 30 August 2019, approximately 4972 subjects/patients (4062 adult patients with migraine, 15 pediatric patients with migraine, 380 patients with cluster headache [CH], 37 patients with persistent post-traumatic headache, an estimated 4 patients with FM, and 474 healthy subjects) have been exposed to fremanezumab. The fremanezumab clinical program comprises 24 clinical studies (10 Phase 1; 4 Phase 2, 2b, or 2b/3; and 10 Phase 3 studies), of which 19 have been completed. The safety and tolerability of fremanezumab was studied in all of the 24 studies in the clinical program (ie, 10 Phase 1, 2 Phase 2, 2 Phase 2b, 2 Phase 2b/3, and 8 Phase 3 studies). Based on the safety results of the completed studies, the safety profile was assessed to include the following events as identified risks qualifying as adverse drug reactions: injection site induration, injection site	Updated text with current information

Original text with changes shown	New wording	Reason/justification for change
as identified risks qualifying as adverse drug reactions: injection site induration, injection site erythema, injection site pruritus, injection site pain, and injection site rash.	erythema, injection site pruritus, injection site pain, and injection site rash.	
Section 1.3.1 Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)		
Risks Fremanezumab (sc) has generally been well tolerated over the range of doses evaluated (single doses of 0.02 to 2000 mg in healthy subjects, multiple doses of 30 to 300 mg in healthy volunteers, and multiple doses of 225 to 900 mg sc in patients with migraine). The most common treatment-emergent adverse events in patients with migraine were mild to moderate transient general administration site disorders/reactions. Other commonly reported treatment-emergent adverse events were upper respiratory tract infection, back pain, nausea, and dizziness. Based on the exposure and body of evidence from Teva's studies of fremanezumab in other indications, the benefit and risk assessment for fremanezumab is expected to be favorable. Known risks that do not impact the risk-benefit profile are as follows: • injection site induration • injection site erythema • injection site pruritus • injection site pain • injection site rash None of these risks are considered clinically meaningful. Severe hypersensitivity reactions are regarded as a potential risk for fremanezumab based on the following considerations: mild and moderate drug hypersensitivity events were observed infrequently albeit with similar incidence in placebo and fremanezumab in the clinical development program for migraine, but no anaphylaxis or severe hypersensitivity reactions related to the investigational medicinal product (IMP) were seen. ~~However, it cannot be excluded that severe events may occur in the future~~While no severe	Risks Fremanezumab (sc) has generally been well tolerated over the range of doses evaluated (single doses of 0.02 to 2000 mg in healthy subjects, multiple doses of 30 to 300 mg in healthy volunteers, and multiple doses of 225 to 900 mg sc in patients with migraine). The most common treatment-emergent adverse events in patients with migraine were mild to moderate transient general administration site disorders/reactions. Other commonly reported treatment-emergent adverse events were upper respiratory tract infection, back pain, nausea, and dizziness. Based on the exposure and body of evidence from Teva's studies of fremanezumab in other indications, the benefit and risk assessment for fremanezumab is expected to be favorable. Known risks that do not impact the risk-benefit profile are as follows: • injection site induration • injection site erythema • injection site pruritus • injection site pain • injection site rash None of these risks are considered clinically meaningful. Severe hypersensitivity reactions are regarded as a potential risk for fremanezumab based on the following considerations: mild and moderate drug hypersensitivity events were observed infrequently albeit with similar incidence in placebo and fremanezumab in the clinical development program for migraine, but no anaphylaxis or severe hypersensitivity reactions related to the investigational medicinal product (IMP) were seen. While no severe hypersensitivity or anaphylactic reactions	Updated text to include new information on injection site reactions, one case of Stevens-Johnson Syndrome, clarification for anaphylaxis reactions, and theoretical risks of unfavorable cardiovascular effects

Original text with changes shown	New wording	Reason/justification for change
hypersensitivity or anaphylactic reactions occurred as a result of fremanezumab administration 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 anti-CGRP pathway monoclonal antibodies, along with concomitant medications including lamotrigine. 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 monkey and humans using fremanezumab have not identified clinically relevant changes in heart rate, blood pressure, or other cardiovascular parameters. No relevant cardiovascular event has been seen in the completed studies. Refer to the current IB for a~~A~~dditional information regarding benefits and risks to patients~~ may be found in the IB~~.	occurred as a result of fremanezumab administration 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 anti-CGRP pathway monoclonal antibodies, along with concomitant medications including lamotrigine. 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 monkey and humans using fremanezumab have not identified clinically relevant changes in heart rate, blood pressure, or other cardiovascular parameters. No relevant cardiovascular event has been seen in the completed studies. Refer to the current IB for additional information regarding benefits and risks to patients.	
[redacted]		
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/justification for change
Section 3.1 General Study Design and Study Schematic Diagram (Other sections affected by this change: Section 3.5, Section 4.1, Section 7.1.2, Section 7.1.5, Appendix B, and Appendix J)		
This is a 21~~35~~-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fremanezumab in adult patients with FM. Fremanezumab 225 mg, fremanezumab 675 mg, or placebo will be administered sc for 4 monthly doses. The study will consist of a 17- to 35-day screening period (Visit 1, phone contact, and Baseline Assessment Period Start [BAPS] Visit [Visit 2]), and a 16-week double-blind treatment period (Visits 3, 4, 5, 6, and 7)~~, and a 14-week follow-up period with 1 follow-up visit (Visit 8)~~. Patients enrolled in the study will be male or female patients with FM. Patients will be required to wash out of all prohibited concomitant medication(s) prior to the BAPS Visit (Visit 2). Therefore, the total duration of patient participation in the study is planned to be ~~35~~21 weeks, consisting of the screening period of up to 5 weeks (ranging from 17 to 35 days)~~,~~ and the double-blind treatment period of 16 weeks~~, and the 14-week follow-up period~~; details are given in Section 5. The end-of-study (EOS) is defined as completion of the last ~~follow-up~~ visit of the last patient. The study duration will be from May 2019 until approximately ~~May 2021~~July 2022.	This is a 21-week, multicenter, randomized, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of fremanezumab in adult patients with FM. Fremanezumab 225 mg, fremanezumab 675 mg, or placebo will be administered sc for 4 monthly doses. The study will consist of a 17- to 35-day screening period (Visit 1, phone contact, and Baseline Assessment Period Start [BAPS] Visit [Visit 2]), and a 16-week double blind treatment period (Visits 3, 4, 5, 6, and 7). Patients enrolled in the study will be male or female patients with FM. Patients will be required to wash out of all prohibited concomitant medication(s) prior to the BAPS Visit (Visit 2). Therefore, the total duration of patient participation in the study is planned to be 21 weeks, consisting of the screening period of up to 5 weeks (ranging from 17 to 35 days) and the double blind treatment period of 16 weeks; details are given in Section 5. The end-of-study (EOS) is defined as completion of the visit of the last patient. The study duration will be from May 2019 until approximately July 2022.	Removed Visit 8 to shorten the duration of patient participation and reduce patient burden In addition, the estimated overall study duration was updated based on study activities to date
Section 3.1 General Study Design and Study Schematic Diagram, Figure 1 (Other sections affected by this change: Section 3.5 [Table 1, new footnote c, revised footnote i], Section 5.1.1.2, Section 5.3, Appendix B, and Appendix O)		
Note: For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center (see Section 3.5).	Note: For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center (see Section 3.5).	Added note in Study Schematic Diagram to reflect home dosing at Visits 4 and 5
Section 3.2 Planned Number of Patients and Countries		
Approximately ~~369 patients will be screened to achieve~~ 240 patients will be randomized.	Approximately 240 patients will be randomized. The study is planned to be conducted in the United States	Increased planned number of investigational centers based on

Original text with changes shown	New wording	Reason/justification for change
The study is planned to be conducted in the United States of America in approximately ~~30~~40 investigational centers.	of America in approximately 40 investigational centers.	study activities to date
Section 3.5 Schedule of Study Procedures and Assessments (Table 1) (Other sections affected by one or more of these changes: Section 3.6.2, Section 5.1.1.2, Section 6.1.5, Appendix B, and Appendix J)		
For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center. Home visits may be completed by a Home Care Visiting Service Provider (ie, home care, visiting nurse, or other medical professional) under supervision by the investigational center staff, as required, to complete assessments/procedures. The Home Care Visiting Service Provider will be a centralized provider identified by the sponsor. The investigational center must contact the sponsor before any home visits are initiated. Home visits will be documented. Visits should be conducted in accordance with the timelines specified in the protocol (see Table 1), whenever feasible. Averting a missed visit is considered a high priority. Therefore, if additional time is required beyond the specified visit window to complete the visit, the Medical Monitor should be contacted, and the visit window may be extended for appropriate reasons. In such instances, the reasons for deviation in the date of the visit will be clearly documented.	For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center. Home visits may be completed by a Home Care Visiting Service Provider (ie, home care, visiting nurse, or other medical professional) under supervision by the investigational center staff, as required, to complete assessments/procedures. The Home Care Visiting Service Provider will be a centralized provider identified by the sponsor. The investigational center must contact the sponsor before any home visits are initiated. Home visits will be documented. Visits should be conducted in accordance with the timelines specified in the protocol (see Table 1), whenever feasible. Averting a missed visit is considered a high priority. Therefore, if additional time is required beyond the specified visit window to complete the visit, the Medical Monitor should be contacted, and the visit window may be extended for appropriate reasons. In such instances, the reasons for deviation in the date of the visit will be clearly documented.	To provide information on home visits
Visit 8 (EOS) was removed. Accordingly, the following assessments were added at Visit 7 (EOT/EOS or ET): • Blood sample for serum ADA concentration • [redacted]	Visit 7 (EOT/EOS or ET)	Removed Visit 8 to shorten the duration of patient participation and reduce patient burden. Given this removal, added more assessments (eg, ADA blood sample collection) to Visit 7 to serve the purpose of Visit 8.
Day and allowed time window for Days 29, 57, 85, and 113 ±~~3~~7 days	Day and allowed time window for Days 29, 57, 85, and 113 ±7 days	To provide flexibility and reduce patient burden

Original text with changes shown	New wording	Reason/justification for change
At Visits 4 and 5, the following assessments were removed: • Clinical laboratory tests (serum chemistry, hematology, and urinalysis) • Blood samples for plasma concentration of IMP • Blood sample for serum ADA concentration • [redacted]		To reduce patient burden
At Visits 4 and 6, the following procedure was added: Inform patients of study restrictions and compliance		To improve patient compliance
Alcohol ~~screen~~ (social history)[m]	Alcohol (social history)[m]	Clarification
The injection site reactions assessment was deleted		Injections site reactions will be spontaneously reported and included in adverse event assessment
A footnote c was added to Visits 4 and 5. c For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center (see Section 3.5).	c For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center (see Section 3.5).	Clarified that visits can also occur at home
~~h~~e ~~Assessment will be completed at any unscheduled visit.~~For unscheduled visits, procedures and assessments will be completed as needed, at the investigator's discretion. For further details, see Appendix B.	e For unscheduled visits, procedures and assessments will be completed as needed, at the investigator's discretion. For further details, see Appendix B.	Clarified footnote on unscheduled visits and moved its location to indicate that investigator has discretion on all assessments and procedures at such visits
~~j~~k The 2016 ACR diagnostic criteria for fibromyalgia (Wolfe et al 2016) must be met at the Screening Visit ~~and at the Randomization Visit~~.	k The 2016 ACR diagnostic criteria for fibromyalgia (Wolfe et al 2016) must be met at the Screening Visit.	Removed extraneous detail
~~aa~~bb The C-SSRS Baseline/Screening version will be completed at Visit 1, and the C-SSRS Since Last Visit version will be completed at all other time points ~~except for Visit 7~~.	bb The C-SSRS Baseline/Screening version will be completed at Visit 1, and the C-SSRS Since Last Visit version will be completed at all other time points.	Correction

Original text with changes shown	New wording	Reason/justification for change
Section 3.6.1 e-Diary (Other sections affected by this change: Section 3.5 [Table 1, footnote h] and Appendix B)		
Patients will be trained by the site staff on the use of the e-diary at Visits 1 and 2, and as ~~necessary at~~ needed for subsequent ~~visits~~ retraining throughout the study.	Patients will be trained by the site staff on the use of the e-diary at Visits 1 and 2, and as needed for subsequent retraining throughout the study.	Clarified that training can also occur in between the visits and not just at specified visits
Section 3.6.2 Tablet (Other sections affected by this change: Section 3.5 [Table 1, footnote g] and Appendix B)		
Patients will be trained by the site staff via the tablet on accurate pain reporting and placebo response reduction at Visits 1 and 2, and as ~~necessary at~~ needed for subsequent ~~visits~~ retraining throughout the study.	Patients will be trained by the site staff via the tablet on accurate pain reporting and placebo response reduction at Visits 1 and 2, and as needed for subsequent retraining throughout the study.	Clarified that training can also occur in between the visits and not just at specified visits
Section 4.1 Patient Inclusion Criteria (Other section affected by this change: Section 3.5 [Table 1], for second change only)		
c. agree to comply with the requirements and restrictions listed in this protocol, including remaining at the clinic for the duration of each required visit during the study period to complete all scheduled procedures and assessments~~, and returning to the clinic for the follow-up procedures and assessments as specified in this protocol~~	c. agree to comply with the requirements and restrictions listed in this protocol, including remaining at the clinic for the duration of each required visit during the study period to complete all scheduled procedures and assessments	Removed follow-up visit to shorten the duration of patient participation and reduce patient burden
e. willing to comply with recording of once daily scores using the PI-NRS, completed every evening (approximately the same time each day) starting at the BAPS Visit (Visit 2) and continuing to the end-of-treatment (EOT)/EOS or early termination (ET) Visit (Visit 7). A minimum of 12 of 14 daily average pain intensity ratings AND daily worst pain intensity ratings are required to be recorded in an e-diary during the baseline assessment period (Section 3.6.1).	e. willing to comply with recording of once daily scores using the PI-NRS, completed every evening (approximately the same time each day) starting at the BAPS Visit (Visit 2) and continuing to the end-of-treatment (EOT)/EOS or early termination (ET) Visit (Visit 7). A minimum of 12 of 14 daily average pain intensity ratings AND daily worst pain intensity ratings are required to be recorded in an e-diary during the baseline assessment period (Section 3.6.1).	Clarified that the minimal recording requirement for daily pain ratings during the baseline assessments period applies to both the daily average and the daily worst pain ratings
f. all of the following diagnostic criteria for FM according to 2016 American College of Rheumatology (Wolfe et al 2016) are met at the Screening Visit ~~and at randomization:~~	f. all of the following diagnostic criteria for FM according to 2016 American College of Rheumatology (Wolfe et al 2016) are met at the Screening Visit	A duplicate of the screening assessment was not needed
n. must agree not to participate in another interventional study from the screening period through the EOT/EOS or ET Visit	n. must agree not to participate in another interventional study from the screening period through the EOT/EOS or ET Visit	Clarification

Original text with changes shown	New wording	Reason/justification for change
Section 4.2 Patient Exclusion Criteria		
a. unable or unwilling to discontinue/washout of prohibited medications (Appendix ~~J~~I); ~~selective serotonin reuptake inhibitors (SSRIs; with the exception of <60 mg/day of fluoxetine) or over-the-counter (OTC) medications used to treat depression or anxiety (Appendix J) are permitted if started at least 90 days prior to screening, have been on a stable dose for at least 90 days, and are expected to remain on a stable dose throughout the study~~ Note: Medications used to treat depression or anxiety are permitted provided they were started at least 90 days prior to screening, have been used at a stable dose for at least 90 days, and will be maintained at that dose for the duration of the study. Therefore, both over-the-counter (OTC) medications used to treat depression or anxiety and selective serotonin reuptake inhibitors (SSRIs; with the exception of ≥60 mg/day of fluoxetine) are permitted.	a. unable or unwilling to discontinue/washout of prohibited medications (Appendix I); Note: Medications used to treat depression or anxiety are permitted provided they were started at least 90 days prior to screening, have been used at a stable dose for at least 90 days, and will be maintained at that dose for the duration of the study. Therefore, both over-the-counter (OTC) medications used to treat depression or anxiety and selective serotonin reuptake inhibitors (SSRIs; with the exception of ≥60 mg/day of fluoxetine) are permitted.	Clarification of text
n. known history of hypersensitivity reactions to injected proteins, including mAbs and animal venoms, or a history of Stevens-Johnson Syndrome/toxic epidermal necrolysis syndrome	n. known history of hypersensitivity reactions to injected proteins, including mAbs and animal venoms, or a history of Stevens-Johnson Syndrome/toxic epidermal necrolysis syndrome	Updated to align with program-wide safety update
s. any prior exposure to mAbs targeting the CGRP pathway (including erenumab, ~~ALD304~~eptinezumab, galcanezumab, or fremanezumab) at any time. If the patient has participated in a clinical study with any of these mAbs, it has to be confirmed that the patient received placebo in order to be eligible for this study.	s. any prior exposure to mAbs targeting the CGRP pathway (including erenumab, eptinezumab, galcanezumab, or fremanezumab) at any time. If the patient has participated in a clinical study with any of these mAbs, it has to be confirmed that the patient received placebo in order to be eligible for this study.	Updated to use the approved generic name of ALD304
w. known history of alcohol and/or drug abuse within the past 12 months per the MINI or have a positive urine drug screen for illegal drugs of abuse ~~or alcohol test~~ at the Screening Visit, BAPS Visit, or prior to randomization	w. known history of alcohol and/or drug abuse within the past 12 months per the MINI or have a positive urine drug screen for illegal drugs of abuse at the Screening Visit, BAPS Visit, or prior to randomization	Updated to reflect that reference to urine alcohol testing is no longer required
Section 4.5 Rescreening (Other section affected by this change: Section 4.6)		
~~There is no provision for rescreening.~~ Rescreening will not be routinely allowed for patients who are screened but not enrolled (eg, because eligibility criteria were not met [inclusion criteria not met and/or exclusion criteria met]).	Rescreening will not be routinely allowed for patients who are screened but not enrolled (eg, because eligibility criteria were not met [inclusion criteria not met and/or exclusion criteria met]). However, patients who were	Updated rescreening criterion to account for extraordinary situations and technical problems

Original text with changes shown	New wording	Reason/justification for change
However, patients who were screened but not enrolled due to technical issues (eg, diary malfunction) or are out of Visit 2 window due to urgent extenuating circumstances (eg, public health emergency) may be considered for screening one additional time. Only patients who were not enrolled due to these limited issues/circumstances may be screened a second time. If the patient is screened again, a new informed consent form (ICF) will need to be signed and a new screening number will be assigned.	screened but not enrolled due to technical issues (eg, diary malfunction) or are out of Visit 2 window due to urgent extenuating circumstances (eg, public health emergency) may be considered for screening one additional time. Only patients who were not enrolled due to these limited issues/circumstances may be screened a second time. If the patient is screened again, a new informed consent form (ICF) will need to be signed and a new screening number will be assigned.	
Section 4.6 Screen Failure		
~~Patients who fail screening will not be allowed to rescreen.~~Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. Data for screen failure reason and minimal information, including but not limited to demography, adverse events from the time of informed consent, and subject disposition, will be entered into the eCRF.	Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. Data for screen failure reason and minimal information, including but not limited to demography, adverse events from the time of informed consent, and subject disposition, will be entered into the eCRF.	Provided additional details on screen failures
Section 5.1.1 Test Investigational Medicinal Product		
Fremanezumab is a humanized IgG2Δa/kappa monoclonal antibody derived from a murine precursor. Additional details ~~may be found~~ are provided in Table 2 and in the current IB ~~for fremanezumab~~.	Fremanezumab is a humanized IgG2Δa/kappa monoclonal antibody derived from a murine precursor. Additional details are provided in Table 2 and in the current IB.	Clarification
Section 5.1.1.2 Dosing Visits and Dose Modification		
Section 5.1.1.2 Dosing Visits and Dose Modification ~~and Dose Stratification~~ Visits 1, 2, 3, and 6 must occur at the study site. For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center for any extenuating circumstances (see Section 3.5). After such extenuating circumstances resolve, home visits may be	**Section 5.1.1.2 Dosing Visits and Dose Modification** Visits 1, 2, 3, and 6 must occur at the study site. For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center for any extenuating circumstances (see Section 3.5). After such extenuating circumstances resolve, home visits may be permitted to continue.	Clarification of the title of the section Clarification of the continuation of home visits In conjunction with increasing the window length for scheduled visits, allowed for potential further extension of the window

Original text with changes shown	New wording	Reason/justification for change
permitted to continue. Doses will be ~~delivered~~ administered at the study site or at home, as applicable, at the time of visits via a fixed dose pre-filled syringe; no dose modifications will be allowed. There will be a time window for doses that do not occur on the scheduled days. ~~A visit ±3 days from a scheduled visit is acceptable, a visit between 4 and 7 days of a scheduled visit is allowed but will be considered a protocol deviation, and a visit >7 days after the scheduled visit is not permitted.~~ If a scheduled visit cannot occur within the ±7-day time window due to extenuating circumstances, the Medical Monitor should be contacted to determine if the window can be lengthened. Medical Monitor notification and consultation for all missed scheduled visits and related rescheduling and necessary plans of action ~~is~~are required.	Doses will be administered at the study site or at home, as applicable, at the time of visits via a fixed dose pre-filled syringe; no dose modifications will be allowed. There will be a time window for doses that do not occur on the scheduled days. If a scheduled visit cannot occur within the ±7-day time window due to extenuating circumstances, the Medical Monitor should be contacted to determine if the window can be lengthened. Medical Monitor notification and consultation for all missed scheduled visits and related rescheduling and necessary plans of action are required.	due to COVID-19 pandemic
Section 5.2.3 Accountability		
For visits conducted at the patient's home, it is the responsibility of the site to ensure the correct IMP is provided. If a sharps container is to be supplied to the patient, the site is responsible for arranging the container and ensuring it is available to be provided along with the IMP.	For visits conducted at the patient's home, it is the responsibility of the site to ensure the correct IMP is provided. If a sharps container is to be supplied to the patient, the site is responsible for arranging the container and ensuring it is available to be provided along with the IMP.	Provided additional details on the newly allowed at-home visits as relates to IMP accountability
Section 5.5 Treatment after the End of the Study		
Patients will not have access to sc fremanezumab as provided in this study after the EOT/EOS or ET Visit (Visit 7). After Visit 7, ~~the study patients advised to return to their~~ all subsequent clinical care will be determined by or at the discretion of the treating physician ~~to resume their treatment for FM~~.	Patients will not have access to sc fremanezumab as provided in this study after the EOT/EOS or ET Visit (Visit 7). After Visit 7, all subsequent clinical care will be determined by or at the discretion of the treating physician.	Given the removal of Visit 8, clarified that study patients will not be directed or advised on care following Visit 7
Section 5.6.1 Activity		
Patients must remain at the investigational center for safety observation for at least ~~60~~ 30 minutes after IMP administration.	Patients must remain at the investigational center for safety observation for at least 30 minutes after IMP administration.	The vast majority of hypersensitivity reactions occur within 30 minutes of dosing

Original text with changes shown	New wording	Reason/justification for change
Section 5.7 Prior and Concomitant Medication or Therapy (Other section affected by this change: Section 3.1 [Figure 1, footnote a], Section 3.5 [Table 1, footnote b] and Appendix N)		
Section 5.7.1 Permitted Concomitant Medication or Therapy Nonsteroidal anti-inflammatory drugs are permitted provided the use has been stable (ie, per patient's usual dosing regimen) for at least 1 month prior to screening and will remain unchanged throughout the study. Antihistamines are permitted for sleep. In addition, tricyclic antidepressants at low doses (amitriptyline [≤25 mg] or trazodone [≤150 mg]) or cyclobenzaprine (~~5~~ up to 10 mg), zolpidem (up to 10 mg), and melatonin may be used for sleep per the patient's usual dosing regimen, with no dose change 1 month prior to screening and throughout the study. Concomitant medications permitted during the study include the following: 1) SSRIs (stable use), 2) the use of acetaminophen as a rescue medication up to 1000 mg per dose and not to exceed 3000 mg/day as a rescue medication for pain, 3) medications required for the treatment of any adverse events, 4) aspirin (maximum daily dose 325 mg) for cardiovascular prophylaxis, ~~and~~ 5) ~~some analgesics, such as~~ nonsteroidal anti-inflammatory drugs ~~may be permitted only to treat acute events (eg, injuries such as muscle sprains) for up to 3 days~~ (stable use), and 6) selected sleep medications. No other FM medications (prescription, OTC, behind-the-counter, IMPs other than those permitted in this study, or vaccine) will be allowed during the study. ~~Full~~ For details of allowed medications, ~~are provided in~~ see Appendix ~~O~~N. Section 5.7.2 Prohibited Medication or Therapy A list of prohibited medications is ~~given~~ provided in Appendix ~~J~~I. At each visit at the investigational center after the Screening Visit, the investigator will ask patients whether they have taken any medications (other than IMP[s]), including OTC medications, vitamins, or herbal or nutritional supplements, since the previous visit. Section 5.7.3 Recommended Washout Periods The washout periods for common drugs are detailed in	Section 5.7.1 Permitted Concomitant Medication or Therapy Nonsteroidal anti-inflammatory drugs are permitted provided the use has been stable (ie, per patient's usual dosing regimen) for at least 1 month prior to screening and will remain unchanged throughout the study. Antihistamines are permitted for sleep. In addition, tricyclic antidepressants at low doses (amitriptyline [≤25 mg] or trazodone [≤150 mg]) or cyclobenzaprine (up to 10 mg), zolpidem (up to 10 mg), and melatonin may be used for sleep per the patient's usual dosing regimen, with no dose change 1 month prior to screening and throughout the study. Concomitant medications permitted during the study include the following: 1) SSRIs (stable use), 2) the use of acetaminophen as a rescue medication up to 1000 mg per dose and not to exceed 3000 mg/day as a rescue medication for pain, 3) medications required for the treatment of any adverse events, 4) aspirin (maximum daily dose 325 mg) for cardiovascular prophylaxis, 5) nonsteroidal anti-inflammatory drugs (stable use), and 6) selected sleep medications. No other FM medications (prescription, OTC, behind-the-counter, IMPs other than those permitted in this study, or vaccine) will be allowed during the study. For details of allowed medications, see Appendix N. Section 5.7.2 Prohibited Medication or Therapy A list of prohibited medications is provided in Appendix I. At each visit at the investigational center after the Screening Visit, the investigator will ask patients whether they have taken any medications (other than IMP[s]), including OTC medications, vitamins, or herbal or nutritional supplements, since the previous visit. Section 5.7.3 Recommended Washout Periods	Section headers 5.7.1 and 5.7.2 added for clarity Allowed additional concomitant medications (with limitations) based on patient population In addition, the order of the text within this section was changed, and edits were made for consistency both within the section and with Appendix O (only additions, but not moves of unchanged text, are indicated) Section 5.7.3 was created for clarity. The information including Table 4 are from the original Appendix D, which was deleted.

Original text with changes shown	New wording	Reason/justification for change
Table 4. While it is not mandatory to wash out of all concomitant medications, it is desirable to reduce the number of concomitant medications to a minimum, if possible. Note: Not all of these medications will require washout; see Section 5.7.1, Section 5.7.2, Appendix I, and Appendix N for further information about permitted concomitant medications. Washout periods are recommendations; actual washout periods must be determined by the investigator based on his/her clinical practice/judgement, the medication, and the dose of the respective medication. If there are any questions, contact the medical monitor. Table 4, which lists the recommended washout periods for common medications was created.	The washout periods for common drugs are detailed in Table 4. While it is not mandatory to wash out of all concomitant medications, it is desirable to reduce the number of concomitant medications to a minimum, if possible. Note: Not all of these medications will require washout; see Section 5.7.1, Section 5.7.2, Appendix I, and Appendix N for further information about permitted concomitant medications. Washout periods are recommendations; actual washout periods must be determined by the investigator based on his/her clinical practice/judgement, the medication, and the dose of the respective medication. If there are any questions, contact the medical monitor.	
Section 5.10.1 Maintenance of Randomization		
At Visits 3 through ~~7~~6, the RTSM will be queried, and investigational center personnel will retrieve and administer each pre-filled syringe contained in the appropriately numbered kit(s). Kit numbers will be entered into the eCRF.	At Visits 3 through 6, the RTSM will be queried, and investigational center personnel will retrieve and administer each pre-filled syringe contained in the appropriately numbered kit(s). Kit numbers will be entered into the eCRF.	Clarification
Section 6.1.5.2 PROMIS Physical Function Short Form 12a		
The PROMIS Physical Function SF12a Scale contains 12 items with a score ranging from 12 to ~~36~~60.	The PROMIS Physical Function SF12a Scale contains 12 items with a score ranging from 12 to 60.	Corrected description of assessment scale
Section 7.1.6 Protocol-Defined Adverse Events of Special Interest		
• severe hypersensitivity reactions or anaphylaxis (see Appendix C)	• severe hypersensitivity reactions or anaphylaxis (see Appendix C)	Updated to include anaphylactic reactions
Section 15 References		
~~Curran SL, Andrykowski MA, Studts JL. Short Form of the Profile of Mood States (POMS-SF): Psychometric information. Psychol Assess 1995;7(1):80-3.~~ ~~Lindgren KN, Mastren VL, Tiburzi MJ, Ford DP, Bleecker ML. The factor structure of the Profile of Mood States (POMS) and its relationship to occupational lead exposure. J~~	National Institutes of Health. NIH Clinical Center Patient Education Materials Giving a Subcutaneous Injection. Bethesda, MD: National Institutes of Health Clinical Center; 2016.	Two references were deleted because they were no longer cited in the document and 1 reference was added

Original text with changes shown	New wording	Reason/justification for change
~~Occup Environ Med 1999;41(1):3-10.~~ National Institutes of Health. NIH Clinical Center Patient Education Materials Giving a Subcutaneous Injection. Bethesda, MD: National Institutes of Health Clinical Center; 2016.		
Appendix A Clinical Laboratories and Other Departments and Institutions		
[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted]	[redacted], Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted]	Updated as outlined in Administrative Letter 01
[redacted] Teva Branded Pharmaceutical Products R&D, Inc. ~~Tel:~~ [redacted] Cell: [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Cell: [redacted]	Updated contact information
Appendix B. Study Procedures and Assessments by Visit (Other section affected by this change: Section 3.5 [Table 1])		
IMD was removed from subsection 3 (Visit 2).		Corrected to align with Section 3.5 [Table 1]
• alcohol ~~screen~~ (social history) (for Visit 1	• alcohol (social history) (for Visit 1	Corrected to align with Section 3.5 [Table 1]
Appendix D. Washout Periods For Common Medications		
Appendix D was deleted. The contents of this appendix were moved to the newly created Section 5.7.3.		Clarification
Appendix F. Birth Control Methods And Pregnancy Testing		
~~Assessment of likelihood of possible interaction between IMP or concomitant medications and hormonal contraception should be conducted.~~ While ~~H~~hormonal contraception may be susceptible to interaction with ~~the~~ an IMP~~, which may~~ that reduces the efficacy of the ~~contraception~~ contraceptive	While hormonal contraception may be susceptible to interaction with an IMP that reduces the efficacy of the contraceptive method, eg, CYP 4A inducers, no adjustment in dosing should be necessary.	Language updated to align with other fremanezumab protocols.

Original text with changes shown	New wording	Reason/justification for change
method, eg, CYP 4A inducers, no adjustments in dosing should be necessary. Although d~~D~~rug interaction studies have not been conducted with fremanezumab, like other therapeutic antibodies, fremanezumab is expected to be primarily metabolized via proteolytic catabolism. Therefore, interaction with and impact on drug metabolizing enzymes (eg, CYP isoforms) is considered unlikely in humans. Furthermore, fremanezumab was tested for stimulation of pro-inflammatory cytokine release in human whole blood (Study PF-04427429/24Aug09/111320) and did not elicit significant cytokine release (tumor necrosis factor α, interleukin-6, interferon-γ, or interleukin-1β) in any donor including at concentrations up to 100 µg/mL. As such, there is also no reason to suspect that fremanezumab may influence CYP activity via cytokine release. ~~In case of suspected interaction, hormonal contraceptive alone may not be sufficient. In the absence of clinical pharmacokinetic interaction study data in IMPs with demonstrated or suspected human teratogenicity/fetotoxicity, recommendation for use of hormonal contraceptives should be thoroughly justified by the sponsor. Additional contraceptive methods, including supplementary barrier methods, may be considered.~~	Although drug interaction studies have not been conducted with fremanezumab. Like other therapeutic antibodies, fremanezumab is expected to be primarily metabolized via proteolytic catabolism. Therefore, interaction with and impact on drug metabolizing enzymes (eg, CYP isoforms) is considered unlikely in humans. Furthermore, fremanezumab was tested for stimulation of pro-inflammatory cytokine release in human whole blood ([redacted]) and did not elicit significant cytokine release (tumor necrosis factor α, interleukin-6, interferon-γ, or interleukin-1β) in any donor including at concentrations up to 100 µg/mL. As such, there is also no reason to suspect that fremanezumab may influence CYP activity via cytokine release.	
Postmenopausal women: • 1 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 ~~Recommendations for application of birth control methods:~~ ~~• IMPs with Marketing Authorisation (MA)~~ ~~– In case of no contraception recommendations, the principles of IMPs without MA should be applied~~ ~~• IMPs without MA~~ ~~– In case of clinical trials with IMPs that have not yet~~	Postmenopausal women: • 1 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	Language updated to align with other fremanezumab protocols.

Original text with changes shown	New wording	Reason/justification for change
~~received MA, there is usually limited or no information about the outcome of pregnancies in humans following in utero or gonadal exposure. Depending on the stage of clinical development there may also be limited or no information from non-clinical reproduction toxicity studies.~~ ~~The general recommendation in the ICH M3(R2) guideline is that "all female reproduction toxicity studies and standard battery of genotoxicity tests should be completed prior to the inclusion, in any clinical trial, of women of childbearing potential (WOCBP) not using highly effective birth control or whose pregnancy status is unknown".~~ ~~In case of insufficient or unavailable non-clinical data, the impact on the risk categorization should be evaluated. Unavailable or insufficient nonclinical data should be considered as "effects detected" and the highest risk category assumed.~~ ~~• IMP with demonstrated or suspected human teratogenicity/fetotoxicity~~ ~~Highly effective contraception using methods with low user dependency~~ ~~Contraception during treatment and until the end of relevant systemic exposure. This period should be extended by 30 days in case of genotoxicity.~~ ~~○ Monthly pregnancy testing~~ ~~○ Pregnancy testing during treatment and until end of relevant systemic exposure. In case of genotoxicity, this period should be extended by 30 days. Shorter testing intervals are to be considered depending on drug dosing schedule.~~ ~~In case of genotoxicity, methods of birth control for male participants must be used until end of relevant systemic exposure and in addition for further 90 days.~~ ~~• IMP with possible human teratogenicity/fetotoxicity~~ ~~Highly effective method of contraception~~ ~~Contraception during treatment and until the end of~~		

Original text with changes shown	New wording	Reason/justification for change
~~relevant systemic exposure~~ ~~– Additional pregnancy testing to be considered; as a minimum, at the end of relevant systemic exposure~~ ~~– In each case of delayed menstrual period (over 1 month between menstruations) confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles.~~ ~~• IMP with unlikely risk of human teratogenicity/fetotoxicity, for which assessment of the completed necessary nonclinical studies does not indicate teratogenicity/fetotoxicity, in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient evidence for lack of risk based on human data~~ ~~– An acceptable effective method of contraception unless an absence of risk of human teratogenicity/fetotoxicity in early pregnancy can be justified~~ ~~– As a minimum, contraception until treatment discontinuation~~		
Description of different birth control methods **Highly effective birth control methods:** Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include the following: • Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days ~~(for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic)~~ before the first dose of IMP • Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 7 days ~~(for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic)~~ before the first	**Description of different birth control methods** **Highly effective birth control methods:** Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include the following: • Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP • Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP • Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2	Language updated to align with other fremanezumab protocols.

Original text with changes shown	New wording	Reason/justification for change
dose of IMP • Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2 months before screening visit (V1) • Bilateral tubal occlusion • ~~Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical process~~ • Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. • Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency). **~~Acceptable birth control methods:~~** ~~Acceptable birth control methods that result in a failure rate of more than 1% per year include the following: progestogen-only oral hormonal contraception for which the inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide. The combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable but not highly effective methods of birth control.~~ **Unacceptable birth control methods:** Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together. **Male contraception** Male patients must always use a condom including	months before screening visit (V1) • Bilateral tubal occlusion • Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. • Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency). **Unacceptable birth control methods:** Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together. **Male contraception** Male patients must always use a condom including vasectomized men if their partners are of child-bearing potential. **Vasectomy:** Use of contraceptive methods applies also to vasectomized men.	

Original text with changes shown	New wording	Reason/justification for change
vasectomized men if their partners are of child-bearing potential~~, except in cases of no genotoxicity; or no demonstrated or suspected human teratogenicity/fetotoxicity~~. **Vasectomy:** Use of contraceptive methods applies also to vasectomized men~~, because of the risk associated with transfer of a drug via seminal fluid~~. **~~Contraception for female partners of male study participants:~~** ~~Female partners (who are not pregnant) of male study participants must use contraception for non-pregnant WOCBP until the end of relevant systemic exposure in case of IMPs with genotoxicity or IMPs with no genotoxicity but demonstrated or suspected human teratogenicity/fetotoxicity.~~ **~~Pregnancy tests in WOCBP:~~** ~~1. Conduct monthly pregnancy testing from first dose of IMP until last dose of IMP and additional 30 days in case the IMP does not have a marketing authorization and has suspected human teratogenicity/genotoxicity/fetotoxicity. Conduct monthly pregnancy testing and in case the IMP has a marketing authorization, if the IMP has a demonstrated or suspected human teratogenicity/genotoxicity/fetotoxicity according to Risk Safety Information. Shorter testing intervals are to be considered depending on drug dosing schedule.~~ ~~2. Consider additional pregnancy testing, but at least at the end of relevant systemic exposure, in case of possible human teratogenicity/fetotoxicity. This refers to IMPs, for which human data on pregnancies is limited or not available, there is no suspicion of human teratogenicity based on class effects or genotoxic potential, and nonclinical reproductive toxicity studies of relevance for early human pregnancy show positive findings that do not generate a strong suspicion of human teratogenicity/ fetotoxicity.~~ ~~3. For IMPs with unlikely risk of human teratogenicity/fetotoxicity, additional pregnancy testing is generally not necessary. This refers to IMPs for which~~		

Original text with changes shown	New wording	Reason/justification for change
~~assessment of the completed necessary nonclinical studies does not indicate teratogenicity/fetotoxicity in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient evidence for lack of risk based on human data.~~		
Appendix I. List of Prohibited Medications and Therapeutic Interventions		
These medication lists are not exhaustive; the investigator should check with the Medical Monitor ~~on~~ about any drug not listed in this appendix. For ~~those medications listed in Section 5.7,~~ the medications fluoxetine (Prozac) and naltrexone that are listed in the table below, only doses greater than the maximum listed dose are prohibited.	These medication lists are not exhaustive; the investigator should check with the Medical Monitor about any drug not listed in this appendix. For the medications fluoxetine (Prozac) and naltrexone that are listed in the table below, only doses greater than the maximum listed dose are prohibited.	Clarification
Vortioxetine (~~Brintellix~~ Trintellix) (formerly called Brintellix)	Vortioxetine (Trintellix) (formerly called Brintellix)	Updated trade name
Naltrexone ~~≤~~≥4.5 mg	Naltrexone ≥4.5 mg	Updated to correct a typographical error
Appendix J. Total Blood Volume (Other section affected by this change: Section 5.11)		
Total blood volume to be collected for each patient in this study is approximately ~~248~~161.5 mL for scheduled tests. Number of samples: Visit 4 ~~9~~0; Visit 5 ~~9~~0; Visit 7 ~~4~~9; Visit 8 ~~6~~0 Volume (mL): Visit 4 ~~41.5~~0; Visit 5 ~~41.5~~0; Visit 7 ~~16.5~~41.5; Visit 8 ~~29.0~~0	Total blood volume to be collected for each patient in this study is approximately 161.5 mL for scheduled tests. Number of samples: Visit 4 0; Visit 5 0; Visit 7 9; Visit 8 0 Volume (mL): Visit 4 0; Visit 5 0; Visit 7 41.5; Visit 8 0	Updated the total blood volume because of the changes in blood collection occasions, namely, removal of blood collection at Visits 4 and 5, updated sample volume at Visit 7, and removal of Visit 8; updated the table of blood volumes, accordingly
Appendix P Management of Study Activities During COVID-19 (Other sections affected by this change: Title Page, Amendment History, Section 3.1, Section 4.5, Section 5.1.1.2, Appendix D, and Appendix E)		
New appendix and text.	Additional text too numerous to include in this table; refer to Appendix P of this protocol.	Provided new appendix with details on how to manage study conduct during the COVID-19 pandemic In addition, cross-references to the new appendix were added to the indicated sections, as relevant

16.4. Administrative Letter 01 Dated 28 February 2020

ADMINISTRATIVE LETTER 01

Study number: TV48125-PN-20028

Clinical Study Protocol with Amendment 03

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Proof of Concept Study of the Efficacy and Safety of Fremanezumab for Treatment of Patients with Fibromyalgia, version date 22 July 2019

IND number: 141519; BLA number: 761089

28 February 2020

Dear Investigator:

The purpose of this letter is to provide the change of sponsor address and sponsor representative phone numbers. These updates are provided in the table below.

Contact information in the current protocol	**New contact information**	**Affected protocol sections**
Teva Branded Pharmaceutical Products R&D, Inc. 41 Moores Road Frazer, Pennsylvania 19355 United States of America	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, Pennsylvania 19380 United States of America	Title Page
[redacted]	[redacted]	Appendix A
[redacted]	[redacted]	Appendix A

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

Please feel free to contact [redacted], [redacted], [redacted] if you have any questions or concerns regarding this letter.

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel. 610.344.0200 | www.tevapharm.com

16.5. Amendment 03 Dated 22 July 2019

The primary reason for this amendment is to update the protocol-defined adverse events of special interests. This amendment is considered to be substantial (ie, requires approval by CA, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.2.1 Nonclinical Studies (Other sections affected by this change: Section 5.3.1)		
The calculated safety ~~margins ranged from~~ is 54-fold higher ~~to at least 158-fold higher~~ than the expected clinical exposure following 675 mg sc monthly~~, depending on the proposed indication and dosing regimen~~.	The calculated safety margin is 54-fold higher than the expected clinical exposure following 675 mg sc monthly.	This correction was made to account for exposure at the single dose used in this study.
Section 2.1 Primary and Secondary Study Objectives and Endpoints (Other Sections affected by this change: Sections 2.2, 9.6.2, and 9.6.3)		
number (%) of patients who did not complete the ~~study~~treatment (Kaplan-Meier Survival Analysis) due to lack of efficacy	number (%) of patients who did not complete the treatment (Kaplan-Meier Survival Analysis) due to lack of efficacy	This correction was made to identify patients identified for this endpoint.
Added "up to week 16" for relevant endpoints	The primary efficacy endpoint is the change from baseline up to week 16 in the weekly average of the daily average Pain Intensity-Numerical Rating Scale (PI NRS) score over the past 24 hours.	Changed to align with clinicaltrials.gov listing that clarifies the timeframe for endpoints
	change from baseline up to week 16 in the individual components of the Fibromyalgia Impact Questionnaire Revised (FIQR): symptom subscore, impact subscore, and functional subscore score	
	responder rate of the Patient Global Impression of Change (PGIC) rating (percentage of patients much improved or very much improved) up to week 16	
	the percentage of patients who experience a ≥30% reduction in the weekly average of the daily average PI NRS score up to week 16	
	the percentage of patients who experience a ≥50% reduction in the weekly average of the daily average PI NRS score up to week 16	

Original text with changes shown	New wording	Reason/Justification for change
	change from baseline up to week 16 in the weekly average of the daily worst PI-NRS score over the past 24 hours	
	change from baseline up to week 16 in the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short Form (SF) 8a score	
	change from baseline up to week 16 in the PROMIS Physical Function SF12a score change from baseline up to week 16 in the PROMIS Fatigue SF8a score	
	change from randomization up to week 16 in the clinical laboratory tests (serum chemistry, hematology, and urinalysis)	
	change from baseline up to week 16 in vital signs (pulse, respiratory rate, systolic and diastolic blood pressure, and oral body temperature measurements at each visit)	
[redacted]		
[redacted]	[redacted]	[redacted]
Section 3.5 Schedule of Study Procedures and Assessments (Other Sections affected by these changes: Section 5.1.2, Appendix B)		
Several rows and footnotes in the table were rearranged and updated.		These minor changes were made to clarify and temporally align the assessments.
Addition of C-SSRS to Visit 7		C-SSRS was added to Visit 7 in the event a patient terminates from the study early.
Study days for visits 4, 5, 6, 7, and 8	day 29, day 57, day 85, day 113, and	This correction was made to ensure

Original text with changes shown	New wording	Reason/Justification for change
were updated by 1 day (previously day 28, day 56, day 84, day 112, and day 210)	day 211	28 days between visits 3 and 4.
Separated footnote 'e' for tablet and e-diary	Training patients on accurate pain reporting and placebo response reduction to use the site's tablet will occur at Screening (Visit 1), the BAPS Visit (Visit 2), and as needed for subsequent visits.	This footnote was added to distinguish the tablet training from the e-diary training.
Review of study compliance includes review of e-diary recordings, rescue medication use, and other factors.	Review of study compliance includes review of e-diary recordings, rescue medication use, concomitant medication use, and use of non-pharmacologic therapies (including normal daily exercise routines, chiropractic care, physical therapy, psychotherapy, and massage therapy).	This change was made to specify compliance factors.
Section 3.6.2 Tablet		
~~• WPI and SS scale~~ • ~~Mini International Neuropsychiatric Interview (MINI)~~ • FIQR • PGI-C • PROMIS 12a Physical Function • PROMIS Fatigue SF8a • POMS-2A Short Form • EQ-5D-5L • ~~C-SSRS (Baseline and Since Last Visit)~~ • HADS • IMD The tablet assessments will be completed per the Study Procedures and Assessments (Table 1). Additional information collected on the tablet only at the Screening Visit includes the patient-reported average PI-NRS rating~~, worst PI-NRS rating, and at-the-moment PI-NRS rating~~ over the past 7 days…Patients will be trained by the site staff via~~on~~ the ~~use of the~~ tablet on accurate pain reporting and placebo response reduction at Visits 1 and 2, and as necessary at subsequent visits	• FIQR • PGI-C • PROMIS 12a Physical Function • PROMIS Fatigue SF8a • POMS-2A Short Form • EQ-5D-5L • HADS • IMD The tablet assessments will be completed per the Study Procedures and Assessments (Table 1). Additional information collected on the tablet only at the Screening Visit includes the patient-reported average PI-NRS rating over the past 7 days… Patients will be trained by the site staff via the tablet on accurate pain reporting and placebo response reduction at Visits 1 and 2 and as necessary at subsequent visits throughout the study.	This text was modified to clarify the tablet assessments.

Original text with changes shown	New wording	Reason/Justification for change
throughout the study.		
Section 4.1 Patient Inclusion Criteria (Other changes affected by these changes: Section 5.6.2 and 7.2)		
e. willing to comply with recording of once daily scores using the PI-NRS, completed every evening (approximately the same time each day) starting at the BAPS Visit (Visit 2) ~~up~~and continuing to the ~~Randomization~~ EOT (Visit ~~(Visit 3~~7). A minimum of 12 of 14 daily average pain ratings are required to be recorded in an e-diary during the baseline assessment period (Section 3.6.1)	e. willing to comply with recording of once daily scores using the PI-NRS, completed every evening (approximately the same time each day) starting at the BAPS Visit (Visit 2) and continuing to the EOT (Visit 7). A minimum of 12 of 14 daily average pain ratings are required to be recorded in an e-diary during the baseline assessment period (Section 3.6.1)	This change was made to ensure patient compliance in the study.
m. .. must use highly effective contraception method with their partners during the entire study period and for ~~5~~6 months after the last dose of the IMP	m. ...must use highly effective contraception method with their partners during the entire study period and for 6 months after the last dose of the IMP	This correction was made to account for the half-life of fremanezumab.
Section 5.1.1.1 Starting Dose and Dose Levels		
The recommended sc injection sites follow the National Institutes of Health (NIH) Clinical Center Patient Education Materials (NIH Clinical Center Patient Education Materials 2016). The suggested injection site locations for sc administration are the following: back of upper arms, lower abdomen/belly/waistline, and front of thighs. The sc injection and location will be recorded for each administration visit (Visits 3, 4, 5, and 6).	The recommended sc injection sites follow the National Institutes of Health (NIH) Clinical Center Patient Education Materials (NIH Clinical Center Patient Education Materials 2016). The suggested injection site locations for sc administration are the following: back of upper arms, lower abdomen/belly/waistline, and front of thighs. The sc injection and location will be recorded for each administration visit (Visits 3, 4, 5, and 6).	This change was made to clarify identification of sc injection sites.
Section 5.1.1.2 Dose Modification and Dose Stratification		
Doses will be delivered at the study site at the time of visits via a fixed dose pre-filled syringe; no dose modifications will be allowed. There will be a time window for ~~missed doses – these are visits that do not occur on the scheduled days~~doses that do not occur on the scheduled days. A visit ±3 days from a scheduled visit is acceptable, a visit between 4 and 7 days of a scheduled visit is allowed but will be considered a protocol deviation, and a visit >7 days after the scheduled visit is not permitted. Medical Monitor notification and	Doses will be delivered at the study site at the time of visits via a fixed dose pre-filled syringe; no dose modifications will be allowed. There will be a time window for doses that do not occur on the scheduled days. A visit ±3 days from a scheduled visit is acceptable, a visit between 4 and 7 days of a scheduled visit is allowed but will be considered a protocol deviation, and a visit >7 days after the scheduled visit is not permitted. Medical Monitor notification and consultation for all missed scheduled visits and related rescheduling and necessary plans of	This change was made to clarify the process in the event of dose modification.

Original text with changes shown	New wording	Reason/Justification for change
consultation for all missed scheduled visits and related rescheduling and necessary plans of action is required.	action is required.	
Section 5.2.3 Accountability		
Changes in how unused syringes are accounted for.	Unused syringes and/or kits are to be returned to the depot for destruction.	These changes were made to account for difference in accounting for unused syringes vs empty syringes.
Section 6.1.5 Profile of Mood States 2 – Adult Short Form (Other Sections affected by this change: Sections 2.2, 3.5, 3.6.2, 6.1.5, 9.6.3, and Appendix B)		
The POMS-2A Short Form is a psychological rating scale for the assessment of patients' specific mood states.	The POMS-2A Short Form is a psychological rating scale for the assessment of patients' specific mood states.	The 35-item POMS short form has a very high correlation with the full 65-item POMS and is less time consuming and burdensome for patients.
Section 6.1.8 Inventory of Medical Diagnoses (Other sections affected by this change: Section 2.2 and 9.6.3)		
For those medical conditions that a patient identifies as present at screening ~~Visits 6 and 7~~, the investigator will query at Visits 6 and 7 whether those conditions present at screening are improved or not improved compared with when the patient entered the study.	For those medical conditions that a patient identifies as present at screening, the investigator will query at Visits 6 and 7 whether those conditions are improved or not improved compared with when the patient entered the study.	This correction was made to ensure and include all conditions are determined at screening rather than only including conditions updated at later visits.
Section 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 ~~The severity of each adverse event will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).~~ ~~Adverse events that are not included in the NCI CTCAE lists will be graded according to the NCI CTCAE general guideline for grades:~~ ~~**Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated~~ ~~**Grade 2:** Moderate; minimal,~~	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	This change was made to reflect the decision that severity will not be graded by NCI CTCAE criteria.

Original text with changes shown	New wording	Reason/Justification for change
~~local intervention or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money)~~ ~~**Grade 3:** Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)~~ ~~**Grade 4:** Life-threatening consequences; urgent intervention indicated~~ ~~**Grade 5:** Death related to adverse event~~		
Section 7.1.6 Protocol-Defined Adverse Events of Special Interest		
~~Severe hypersensitivity reactions are considered protocol-defined adverse events to be sent to the sponsor's GPSP Department for evaluation. The process for reporting a protocol-defined adverse event of special interest will be the same as that for reporting a serious adverse event (see Section 7.1.5.3).~~	For purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to the sponsor's GPSP Department for evaluation: • ophthalmic-related adverse events of at least moderate severity, as determined by the investigator • severe hypersensitivity reactions (see Section 7.9) 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 C. 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 will be the same as that for	The new text was added to update protocol-defined adverse events of special interest, to clarify the investigator's role in determining adverse event severity, and to align with recent fremanezumab protocols.

Original text with changes shown	New wording	Reason/Justification for change
	reporting a serious adverse event (Section 7.1.5.3). Protocol-defined adverse events of special interest to be reported to GPSP can either be serious or nonserious, according to the criteria outlined in Section 7.1.5.1.	
Section 7.3 Medication Error and Special Situations Related to the Investigational Medicinal Products		
Text added for additional scenarios in which Medical Monitor should be contacted.	The Medical Monitor should be contacted in any of the following events: 1. All 3 syringes from the assigned kit are unable to be administered during the visit. 2. Any dose has been administered and a syringe is damaged. If a syringe is damaged prior to dose administration, a new kit should be requested. Additional information is provided in the Study Manual.	This text was added to align with other recent protocols.
Section 7.4 Clinical Laboratory Tests		
Added screening laboratory tests to Table 5		These assessments were added to ensure that a more comprehensive outline of clinical laboratory tests is provided.
Section 7.9 Assessment of Local Tolerability and Pain		
~~Local tolerability at the injection site (eg, pain, erythema, ecchymosis, induration) will be evaluated immediately (ie, within 20 minutes) and at 1 hour postdose (ie, postinjection). The allowed time windows for these assessments are provided below.~~ The table describing assessment time windows was removed. ~~Erythema, ecchymosis, and induration will be considered only if they reach a diameter of at least 5 mm. The surface diameter in millimeters should be recorded, and erythema, induration, and ecchymosis at the injection site will be graded according to the diameter measurements: Absent, 5 mm to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by~~	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 assessed and recorded by site personnel and categorized according to the following measurements: 5 to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). • Spontaneous reports of	This change was made to highlight fremanezumab program changes in the assessment and reporting of injection site reactions.

Original text with changes shown	New wording	Reason/Justification for change
~~careful superficial palpation avoiding pressuring or squeezing the injection site.~~ ~~Severity of local tolerability symptoms should be assessed as described below. Severe cases should be recorded as an adverse event. Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.~~ The table describing Severity Assessment of Local Tolerability was removed.	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.	
Section 9.6.4.3 Secondary Efficacy Analysis (Other sections affected by this change: Section 9.8.2)		
The PGIC data will be dichotomized, where a patient who responds as either "much improved" or "very much improved" will be considered improved, and all other responses will be considered not improved. The response variable will be analyzed using a ~~generalized estimating equation (GEE) method~~logistic regression model with the ~~logit link function, with~~ treatment, ~~sex,~~ age group at FM onset, ~~month,~~ and ~~treatment by month interaction~~sex as explanatory factors. In addition, the PGIC data will be summarized as categorical variable by ~~month~~week and treatment group using descriptive statistics~~. Data collected from patients after discontinuing treatment will be excluded and considered missing for this analysis~~. ... Change from baseline in the PROMIS Sleep Disturbance SF8a score~~ will be analyzed using the same MMRM model as the primary efficacy endpoint with baseline Sleep Disturbance SF8a score as a covariate.~~ Change from baseline in the PROMIS Physical Function SF12a score, change from baseline in PROMIS Fatigue SF8a score, and change from baseline in the HADS will be analyzed using an MMRM model with treatment, sex, age group	The PGIC data will be dichotomized, where a patient who responds as either "much improved" or "very much improved" will be considered improved, and all other responses will be considered not improved. The response variable will be analyzed using a logistic regression model with the treatment, age group at FM onset, and sex as explanatory factors. In addition, the PGIC data will be summarized as categorical variable by week and treatment group using descriptive statistics. ... Change from baseline in the PROMIS Sleep Disturbance SF8a score, change from baseline in the PROMIS Physical Function SF12a score, change from baseline in PROMIS Fatigue SF8a score, and change from baseline in the HADS will be analyzed using an MMRM model with treatment, sex, age group at FM onset, week, treatment-by-week interaction, and baseline value of the corresponding variable as explanatory factors. The number and percentage of patients who did not complete the treatment due to lack of efficacy or adverse event will be summarized using descriptive statistics, and the time to treatment discontinuation due to lack of efficacy or adverse event will be analyzed using the	This change was made to correct the analysis for secondary efficacy endpoints.

Original text with changes shown	New wording	Reason/Justification for change
at FM onset, ~~month~~week, treatment-by-~~ month~~week interaction, and baseline value of the corresponding variable as explanatory factors. The number and percentage of patients who did not complete the treatment due to lack of efficacy or adverse event will be summarized using descriptive statistics, and the time to treatment discontinuation due to lack of efficacy or adverse event will be analyzed using the Kaplan-Meier Survival Analysis method.	Kaplan-Meier Survival Analysis method.	

16.6. Amendment 02 Dated 16 April 2019

The primary reasons for this amendment are to describe the method and timing of the collection of e-diary assessments, to reflect the change in the assessment scale used to evaluate concurrent conditions, and to correct errors surrounding the timing of visits during the screening period. This amendment is considered to be substantial (ie, requires approval by a CA, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Table 1 (Study Procedures and Assessments) and Figure 1 (Overall Study Schematic Diagram) have been revised to reflect changes described below.

Original text with changes shown	**New wording**	**Reason/Justification for change**
Section 1.1 Introduction (Other sections affected by this change: Sections 3.3, 3.5, 4.1)		
According to the ~~2010/2011~~ 2016 American College of Rheumatology FM diagnostic criteria (Wolfe et al 2016), FM may be diagnosed when all of the following criteria are met: ~~1. There is a widespread pain index (WPI) ≥7 and a symptom severity (SS) scale score ≥5 or WPI of 3 to 6 and SS score ≥9.~~ ~~2. Symptoms have been present at a similar level for at least 3 months.~~ ~~3. The patient does not have a disorder that would otherwise explain the pain.~~ 1. Generalized pain, defined as pain in at least 4 of 5 regions, is present. 2. Symptoms have been present at a similar level for at least 3 months. 3. Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 OR WPI of 4 to 6 and SS scale score ≥9. 4. A diagnosis of FM is valid irrespective of other diagnoses. A diagnosis of FM does not exclude the presence of other clinically	According to the 2016 American College of Rheumatology FM diagnostic criteria (Wolfe et al 2016), FM may be diagnosed when all of the following criteria are met: 1. Generalized pain, defined as pain in at least 4 of 5 regions, is present. 2. Symptoms have been present at a similar level for at least 3 months. 3. Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 OR WPI of 4 to 6 and SS scale score ≥9. 4. A diagnosis of FM is valid irrespective of other diagnoses. A diagnosis of FM does not exclude the presence of other clinically important illnesses.	This change was made to ensure FM diagnosis is made using current diagnostic criteria.

Original text with changes shown	New wording	Reason/Justification for change
important illnesses.		
[redacted]		
[redacted]	[redacted]	[redacted]
Section 3.1 General Study Design and Study Schematic Diagram		
The study duration will be from ~~March~~ May 2019 until approximately ~~March~~ May 2021.	The study duration will be from May 2019 until approximately May 2021.	This change was made to reflect the shift in study start and completion date.
Section 3.2 Planned Number of Patients and Countries		
The study is planned to be conducted in the United States of America in approximately ~~25~~ 30 investigational centers.	The study is planned to be conducted in the United States of America in approximately 30 investigational centers.	This change was made to accommodate shifts in the program timeline.
Section 3.6 e-Diary and Tablet Data Collection (Other sections affected by this change: Sections 3.5, 4.1, 4.3, Appendix A, Appendix B)		
e-Diary and Tablet Data Collection The primary data collection tools that will be used in this study are the e-diary and the tablet administered by Stefanini (Appendix A). **e-Diary** The e-diary will be dispensed to each patient at the BAPS Visit (Visit 2). The e-diary will be used to record the following data: • Average PI-NRS rating • Worst PI-NRS rating • At-the-moment PI-NRS rating • Rescue medication use • Amount of rescue medication used for a specific breakthrough pain episode • Time of rescue medication used for a specific breakthrough pain episode • PROMIS Sleep Scale (Morning Report only)	**e-Diary and Tablet Data Collection** The primary data collection tools that will be used in this study are the e-diary and the tablet administered by Stefanini (Appendix A). **e-Diary** The e-diary will be dispensed to each patient at the BAPS Visit (Visit 2). The e-diary will be used to record the following data: • Average PI-NRS rating • Worst PI-NRS rating • At-the-moment PI-NRS rating • Rescue medication use • Amount of rescue medication used for a specific breakthrough pain episode • Time of rescue medication used for a specific	This change was made to specify the method and timing of collection of electronic assessments throughout the study.

Original text with changes shown	New wording	Reason/Justification for change
The e-diary will be completed per the Study Procedures and Assessments (Table 1). The e-diary will contain the following reports, which will guide the patient through completion of the necessary data collection on any respective day during the study: Evening Report, Make-up Evening Report, Morning Report, and Make-up Morning Report. The Evening Report will be available to patients each evening for completion between 1800h and 2200h. The Evening Report will have audible alarms that will sound at 3 different times before the entry window expires or upon completion of the report. If a patient cannot complete or forgets to complete the Evening Report, a Make-up Evening Report will become available for completion between 0300h and 1300h the next day. The Make-up Evening Report will also have audible alarms that will sound 3 times during this interval but will cease to sound upon completion of the report. The Morning Report will be available to patients for completion between 0300h and 1300h on the respective day as scheduled in Table 1. The Morning Report will have audible alarms that will sound at 3 different times during this interval but will cease to sound upon completion of the report. If a patient cannot complete or forgets to complete the Morning Report, a Make-up Morning Report will become available for completion between 1800h and 2200h the same day. The Make-up Morning Report will not have separate audible alarms because it becomes available during the same time interval as the Evening Report for that day, which does have audible alarms. The Rescue Medication tab will be available to patients 24 hours per day; tapping this tab will automatically display all required information for the patient to complete. The e-diary main menu will have tabs for each of the aforementioned reports, on which the patient will tap to access the respective report. In the case of a missed report, the respective report will have "Missed" as an indicator to the patient on the main menu. Patients will be trained by the site staff on the use of the e-diary at Visits 1 and 2, and at each visit throughout the study. Additional information on the e-diary can be found in the Study Manual. **Tablet** The tablet will be dispensed to each clinical site. Patients will use the tablet at their visits to complete the required assessments. The tablet	breakthrough pain episode • PROMIS Sleep Scale (Morning Report only) The e-diary will be completed per the Study Procedures and Assessments (Table 1). The e-diary will contain the following reports, which will guide the patient through completion of the necessary data collection on any respective day during the study: Evening Report, Make-up Evening Report, Morning Report, and Make-up Morning Report. The Evening Report will be available to patients each evening for completion between 1800h and 2200h. The Evening Report will have audible alarms that will sound at 3 different times before the entry window expires or upon completion of the report. If a patient cannot complete or forgets to complete the Evening Report, a Make-up Evening Report will become available for completion between 0300h and 1300h the next day. The Make-up Evening Report will also have audible alarms that will sound 3 times during this interval but will cease to sound upon completion of the report. The Morning Report will be available to patients for completion between 0300h and 1300h on the respective day as scheduled in Table 1. The Morning Report will have audible alarms that will sound at 3 different times during this interval but will cease to sound upon completion of the report. If a patient cannot complete or forgets to complete the Morning Report, a Make-up Morning Report will become available for completion between 1800h and 2200h the same day. The Make-up Morning Report will not have separate audible alarms because it becomes available during the same time interval as the Evening Report for that day, which does have audible alarms. The Rescue Medication tab will be available to patients 24 hours per day; tapping this tab will automatically display all required information for the patient to complete. The e-diary main menu will have	

Original text with changes shown	New wording	Reason/Justification for change
will be used to record the following information: • WPI and SS scale • Mini-International Neuropsychiatric Interview (MINI) • FIQR • PGI-C • PROMIS 12a Physical Function • PROMIS Fatigue 8a • POMS • EQ-5D-5L • C-SSRS (Baseline and Since Last Visit) • IMD The tablet will be completed per the Study Procedures and Assessments (Table 1). The tablet main menu will contain individual tabs for each of the visits. Assessments will be completed by study site staff and/or the patient at the study site in the same order. Patients will be trained by the site staff on the use of the tablet at Visits 1 and 2, and at each visit throughout the study. Additional information on the tablet can be found in the Study Manual.	tabs for each of the aforementioned reports, on which the patient will tap to access the respective report. In the case of a missed report, the respective report will have "Missed" as an indicator to the patient on the main menu. Patients will be trained by the site staff on the use of the e-diary at Visits 1 and 2, and at each visit throughout the study. Additional information on the e-diary can be found in the Study Manual. **Tablet** The tablet will be dispensed to each clinical site. Patients will use the tablet at their visits to complete the required assessments. The tablet will be used to record the following information: • WPI and SS scale • Mini-International Neuropsychiatric Interview (MINI) • FIQR • PGI-C • PROMIS 12a Physical Function • PROMIS Fatigue 8a • POMS • EQ-5D-5L • C-SSRS (Baseline and Since Last Visit) • IMD The tablet will be completed per the Study Procedures and Assessments (Table 1). The tablet main menu will contain individual tabs for each of the visits. Assessments will be completed by study site staff and/or the patient at the study site in the same order. Patients will be trained by the site staff on the use of the tablet at Visits 1 and 2, and at each visit throughout the study. Additional information on the tablet can be found in the Study Manual.	

Original text with changes shown	New wording	Reason/Justification for change
Section 4.1 Patient Inclusion Criteria (Other sections affected by this change: Section 5.8.1)		
a. approved for study participation by the Fibromyalgia Eligibility Review Committee (Section 5.8.1)	a. approved for study participation by the Fibromyalgia Eligibility Review Committee (Section 5.8.1)	This inclusion criterion was added to indicate there will be an independent review of patient enrollment eligibility.
Section 4.2 Patient Exclusion Criteria (Other sections affected by this change: Section 5.7, Appendix O)		
a. unable or unwilling to discontinue/washout of prohibited medications (Appendix J)~~.~~; ~~S~~selective serotonin reuptake inhibitors (SSRIs; with the exception of <60 mg/day of fluoxetine) or over-the-counter (OTC) medications used to treat depression or anxiety (Appendix J) are permitted if started at least 90 days prior to screening, have been on a stable dose for at least ~~6~~90 days, and are expected to remain on a stable dose throughout the study~~, except for ≥60 mg of fluoxetine~~	a. unable or unwilling to discontinue/washout of prohibited medications (Appendix J); selective serotonin reuptake inhibitors (SSRIs; with the exception of <60 mg/day of fluoxetine) or over-the-counter (OTC) medications used to treat depression or anxiety (Appendix J) are permitted if started at least 90 days prior to screening, have been on a stable dose for at least 90 days, and are expected to remain on a stable dose throughout the study	This change was made to align the number of days since starting a depression/anxiety medication with the number of days for which the drug dose should be stable.
Section 5.1 Investigational Medicinal Products Used in the Study		
Investigational medicinal product is defined as the test IMP and matching placebo IMP to the test IMP. Patients will receive the IMP at Visits 3, 4, 5, and 6. Patients randomized to the 225 mg dose level will receive 1 injection of 225 mg fremanezumab and 2 injections of placebo; patients randomized to the 675 mg dose level will receive 3 injections of 225 mg fremanezumab; and patients randomized to placebo will receive 3 injections of placebo at each visit.	Investigational medicinal product is defined as the test IMP and matching placebo IMP to the test IMP. Patients will receive the IMP at Visits 3, 4, 5, and 6. Patients randomized to the 225 mg dose level will receive 1 injection of 225 mg fremanezumab and 2 injections of placebo; patients randomized to the 675 mg dose level will receive 3 injections of 225 mg fremanezumab; and patients randomized to placebo will receive 3 injections of placebo at each visit.	This change was made to specify the administration of IMP.
Section 5.11 Total Blood Volume (Other sections affected by this change: Appendix K)		
The total blood volume that will be collected for each patient enrolling in this study for scheduled evaluation of ADAs, fremanezumab concentrations, clinical laboratory tests, and biomarkers is approximately ~~195~~248.5 mL for scheduled tests.	The total blood volume that will be collected for each patient enrolling in this study for scheduled evaluation of ADAs, fremanezumab concentrations, clinical laboratory tests, and biomarkers is approximately 248.5 mL for scheduled tests.	

Original text with changes shown	New wording	Reason/Justification for change
Section 6.1.1 Pain Intensity-Numerical Rating Scale		
The PI-NRS will be used to collect average daily pain intensity over the past 24 hours, the worst pain intensity over the past 24 hours, and at-the-moment pain intensity just prior to the use of rescue medication.	The PI-NRS will be used to collect average daily pain intensity over the past 24 hours, the worst pain intensity over the past 24 hours, and at-the-moment pain intensity just prior to the use of rescue medication.	This change was made to clarify how pain scores will be collected.
Section 6.1.8 Inventory of Medical Diagnoses (Other sections affected by this change: Sections 2.2, 3.5, 3.6.2, 9.6.3, 9.6.4.5, and Appendix B)		
~~**Complex**~~ **Inventory of Medical** ~~**Inventory**~~ **Diagnoses** The ~~Complex~~ Inventory of Medical ~~Inventory (CMSI~~ Diagnoses (IMD) is a ~~52~~9-item, non-validated inventory that ~~measures~~ evaluates in patients ~~the presence or absence of~~ (1) medical conditions diagnosed and present ~~physical symptoms (lasting~~ for at least 3 months~~) over the past year~~ at the Screening Visit.- and (2) their improvement or non-improvement at the end of the study. Questions ~~1 to 51, with exception of question 15,~~ will be completed by the investigator at the Screening Visit (Visit 1) and ~~baseline~~ at Visits 6 and 7. ~~If the~~ For those medical conditions that a patient ~~answered "yes" at~~ identifies as present at Visits 6 and 7 ~~screening to any of the questions~~, the investigator will query ~~the patient as to~~ whether ~~the pain is better~~ those conditions present at screening are improved or not improved~~, or worse than~~ compared with when the patient ~~they~~ entered the study.	**Inventory of Medical Diagnoses** The Inventory of Medical Diagnoses (IMD) is a 9-item, non-validated inventory that evaluates in patients (1) medical conditions diagnosed and present for at least 3 months at the Screening Visit and (2) their improvement or non-improvement at the end of the study. Questions will be completed by the investigator at the Screening Visit (Visit 1) and at Visits 6 and 7. For those medical conditions that a patient identifies as present at Visits 6 and 7, the investigator will query whether those conditions present at screening are improved or not improved compared with when the patient entered the study.	This text was added to reflect the change in assessment scales used. The Complex Medical Symptoms Inventory will be replaced with the IMD to collect data on concurrent medical conditions.
Section 7.1.6 Protocol-Defined Adverse Events of Special Interest		
Severe hypersensitivity reactions~~ For purposes of this protocol, the adverse events~~ are considered protocol-defined adverse events ~~of special interest for expedited reporting to pharmacovigilance and to be followed during the study~~ to be sent to the sponsor's GPSP Department for evaluation. ~~ophthalmic related adverse events (nonserious of at least moderate severity, and and serious), or events of suspected anaphylaxis and Cardiovascular events are~~ The process for reporting a protocol-defined ~~defined as adverse events of special interest that will be periodically analyzed by the Product Safety Group. Adverse events~~ adverse event of special interest will be the same as that for reporting a serious adverse event (see	Severe hypersensitivity reactions are considered protocol-defined adverse events to be sent to the sponsor's GPSP Department for evaluation. The process for reporting a protocol-defined adverse event of special interest will be the same as that for reporting a serious adverse event (see Section 7.1.5.3).	These changes were made to align the reporting of adverse events of special interest with other fremanezumab studies.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.1.5.3). ~~presented in the clinical study report (CSR), but there are no special requirements for expedited reporting~~		
Section 7.4.2.1 Beta-human Chorionic Gonadotropin Tests (Other sections affected by this change: Section 3.5 and Appendix B)		
Beta-human chorionic gonadotropin tests in serum ~~or urine~~ will be performed for all women of childbearing potential at screening (Visit 1~~)~~). Urine will be used for all subsequent visits and~~,~~ will be tested on site via β-HCG dipstick. Serum may be tested if clinically indicated, ~~thereafter~~ or as a confirmatory test for a positive dipstick result.	Beta-human chorionic gonadotropin tests in serum will be performed for all women of childbearing potential at screening (Visit 1). Urine will be used for all subsequent visits and will be tested on site via β-HCG dipstick. Serum may be tested if clinically indicated, or as a confirmatory test for a positive dipstick result.	This change was made to clarify that urine pregnancy tests will be used throughout the study and will be confirmed with serum testing if necessary.
[redacted]		
[redacted]	[redacted]	[redacted]

16.7. Amendment 01 Dated 08 February 2019

The primary reason for this amendment is to correct errors surrounding the timing of visits during the screening period. This amendment is considered to be substantial (ie, requires approval by a Competent Authority (CA), IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Table 1 (Study Procedures and Assessments) and Figure 1 (Overall Study Schematic Diagram) have been revised to reflect changes described below.

Original text with changes shown	New wording	Reason/Justification for change
Section 2.1 Primary and Secondary Objectives and Endpoints (Other sections affected by this change: Sections 9.6.2 and 9.6.4.)		
• the percentage of patients who experience a ≥30% reduction in the weekly average of the daily average PI-NRS score	• the percentage of patients who experience a ≥30% reduction in the weekly average of the daily average PI-NRS score	This change was made throughout to clarify which score is being used as an endpoint.
[redacted]		
[redacted]	[redacted]	[redacted]
Section 3.1 General Study Design and Study Schematic Diagram; Other sections affected by this change: Section 3.5 and Appendix B		
Day 210~~1~~	Day 210	This change is a correction of the study day for the End-of-Study Visit (Visit 8).
Sections 3.1 General Study Design and Study Schematic Diagram; Other sections affected by this change: Sections 3.5, 4.1, 4.2, and Appendix B		
1~~7~~4~~-~~ to 35-day screening period (Visit 1, phone contact, a Baseline Assessment Period Start [BAPS] Visit [Visit 2])	17- to 35-day screening period (Visit 1, phone contact, a Baseline Assessment Period Start	This change to the name of the visit was made throughout the protocol to reflect that the

Original text with changes shown	New wording	Reason/Justification for change
	[BAPS] Visit [Visit 2])	baseline assessments are started at Visit 2 and continue through Visit 3 (Randomization Visit).
Section 3.2 Planned Number of Patients and Countries		
Number of Patients Planned (total): Approximately 369 patients will be screened to achieve 240 randomized patients. ~~The number of evaluable patients is planned to be 180.~~	**Number of Patients Planned (total):** Approximately 369 patients will be screened to achieve 240 randomized patients.	This change was made to eliminate redundant text.
Section 3.5 Schedule of Study Procedures and Assessments; Other sections affected by this change: Section 3.1 and Appendix B		
~~**Week -3**~~ ~~**Day -21**~~ ~~**±5 days**~~ ~~**Washout**~~ **Day -33 through Day -15** **Scheduling and Instructions[d]**		**Day -33 through Day -15** **Scheduling and Instructions[d]**	This change was made to reflect the change to the length of the longest washout period (from 3 weeks to 2 weeks, maximum; see Appendix D).
Inclusion and exclusion criteria X ... Assess concomitant medication X		Inclusion and exclusion criteria X ... Assess concomitant medication X	These changes were made to correct the Schedule of Assessments.
V8 (EOS) ... Serum β-HCG test for women ~~X~~ Urine pregnancy test for WOCBP[o] X		V8 (EOS) ... Serum β-HCG test for women Urine pregnancy test for WOCBP[o] X	This change was made because this is the end of the study, and a serum pregnancy test for women is not necessary unless confirmation is required.
[b] Patients will be instructed to start the washout period during the screening period prior to phone contact. The duration of the washout period will be 7 to ~~30~~19 days; suggested washout periods for commonly used analgesics are listed in Appendix D. Laboratory values will be	[b] Patients will be instructed to start the washout period during the screening period prior to phone contact. The duration of the washout period will be 7 to 19 days; suggested	These changes were made to clarify timing of the phone call and to reflect the changes made to the recommended washout

Original text with changes shown	New wording	Reason/Justification for change
checked prior to the phone call by the investigator. V2 will be scheduled and the monitoring plan for washout will be defined by the investigator. The washout period will need to be completed before the ~~Baseline Assessment~~ BAPS Visit (Visit 2). Training and Instructions will be provided to patients regarding the monitoring of withdrawal symptoms during the washout period.	washout periods for commonly used analgesics are listed in Appendix D. Laboratory values will be checked prior to the phone call by the investigator. V2 will be scheduled and the monitoring plan for washout will be defined by the investigator. The washout period will need to be completed before the BAPS Visit (Visit 2). Training and Instructions will be provided to patients regarding the monitoring of withdrawal symptoms during the washout period.	periods made in Appendix D.
[c] ~~All baseline assessments will take place on day 1, except for the PI-NRS scores, which will be recorded days -14 to -1 (±3 days), inclusive.~~ [~~c~~d] Patients who do not require a washout may be scheduled for the BAPS Visit (Visit 2) following the availability of laboratory results. [d] Training on each assessment and the e-diary will occur at all visits after the e-diary is provided, except for Visit 5.	[c] Patients who do not require a washout may be scheduled for the BAPS Visit (Visit 2) following the availability of laboratory results. [d] Training on each assessment and the e-diary will occur at all visits after the e-diary is provided, except for Visit 5.	Footnote c was removed as it provided information already in the table. Footnote 'c' was added to clarify actions for those patients who are not on medications requiring a washout period as outlined in Appendix D.
[f] For the baseline assessment ~~14-day period before~~ (ie, between the BAPS Visit [Visit 2] and the ~~Baseline~~ Randomization Visit [Visit 3~~2~~]), patients will record their daily average pain intensity score and daily worst pain intensity score ~~o~~n the PI-NRS ~~once~~ daily ~~and will continue to taper off of other prohibited medications. Patients will record their scores~~ in the e-diary every evening at approximately the same time between 1800 and 2200 hours. Pain intensity scores prior to the use of rescue medication will also be entered in the e-diary daily if rescue medication is used. [~~g~~] ~~Record PI-NRS average and worst pain intensity score daily in the e-diary every evening between 1800 and 2200 hours during the study.~~	[f] For the baseline assessment period (ie, between the BAPS Visit [Visit 2] and the Randomization Visit [Visit 3]), patients will record their daily average pain intensity score and daily worst pain intensity score using the PI-NRS in the e-diary every evening at approximately the same time between 1800 and 2200 hours. Pain intensity scores prior to the use of rescue medication will also be entered in the e-diary daily if rescue medication is used.	This change was made to refer to the correct study visit, to include timing information from the protocol synopsis that was not in the protocol body, and to clarify that the PI-NRS score must be documented before rescue meds are taken.
[~~i~~h] Clinical laboratory tests will include serum chemistry, hematology, and urinalysis. HIV, HBsAg, hepatitis C antibody, and TSH will also be completed only at the Screening Visit (Visit 1).	[h] Clinical laboratory tests will include serum chemistry, hematology, and urinalysis. HIV, HBsAg, hepatitis C antibody, and TSH will also be completed only at the Screening Visit (Visit 1).	This change was made to include all clinical laboratory tests as outlined in Section 7.4
[o] A serum pregnancy test may be completed as a confirmatory test, if warranted.	[o] A serum pregnancy test may be completed as a confirmatory test, if warranted.	This change was made to clarify that a urine dipstick test may be confirmed with a serum

Original text with changes shown	New wording	Reason/Justification for change
		pregnancy test, if needed.
Section 3.5 Schedule of Study Procedures and Assessments; Other sections affected by this change: Section 6.1.6.1		
[q] The sleep e-diary or PROMIS Sleep Disturbance SF8a should be performed weekly on awakening. Collection of the PROMIS Sleep Disturbance SF8a will start at the BAPS Visit (Visit 2) at the study site to assess the previous week's sleep.	[q] The sleep e-diary or PROMIS Sleep Disturbance SF8a should be performed weekly on awakening. Collection of the PROMIS Sleep Disturbance SF8a will start at the BAPS Visit (Visit 2) at the study site to assess the previous week's sleep.	This footnote was modified to clearly state when the SF8a assessment will begin.
Section 4.1 Patient Inclusion Criteria		
b. agree to comply with the requirements and restrictions listed in this protocol, including remaining at the clinic for the duration of each ~~the~~ required visit ~~duration~~ during the study period to complete all scheduled procedures and assessments, and returning to the clinic for the follow-up ~~evaluation~~ procedures and assessments~~,~~ as specified in this protocol. ... ~~m. must be willing and able to comply with study restrictions and to remain at the investigational center during visits to complete all scheduled procedures and assessments, and be willing to return to the investigational center for further visits, as applicable, and the follow-up procedures and assessments as specified in this protocol~~	b. agree to comply with the requirements and restrictions listed in this protocol, including remaining at the clinic for each required visit duration during the study period to complete all scheduled procedures and assessments, and returning to the clinic for the follow-up procedures and assessments as specified in this protocol	This change was made to eliminate a redundant inclusion criterion.
d. willing to comply with recording of once-daily scores using the PI-NRS, completed every evening (approximately the same time each day) starting 14 days ~~before the Baseline Visit~~ at the BAPS Visit (Visit 2) up to the Randomization Visit (Visit 3). A minimum of 12 of 14 daily average pain ratings are required to be recorded in an e-diary during the baseline assessment period.	d. willing to comply with recording of once-daily scores using the PI-NRS, completed every evening (approximately the same time each day) starting at the BAPS Visit (Visit 2) up to the Randomization Visit (Visit 3). A minimum of 12 of 14 daily average pain ratings are required to be recorded in an e-diary during the baseline assessment period	This change was made to clarify the time boundaries of the washout period and to clarify the baseline assessment period.
e. all of the following diagnostic criteria for FM according to 2010/2011 American College of Rheumatology (Wolfe et al 2010) are met at the Screening Visit and at randomization:	e. all of the following diagnostic criteria for FM according to 2010/2011 American College of Rheumatology (Wolfe et al 2010) are met at the Screening Visit and at randomization:	This change was made to match criterion 'e' text from the synopsis and provide description of the resource.
Section 4.2 Patient Exclusion Criteria		

Original text with changes shown	New wording	Reason/Justification for change
~~c. known history of noncompliance leading to unsuccessful completion after enrollment in 1 or more FM registrational trials~~	Deleted criteria	This change was made as it was non-specific.
~~d. known history of intolerability or allergy to 2 or more medications~~	Deleted criteria	This change was made as it was non-specific.
~~h~~f. known history of clinically significant or unstable hematologic, cardiac, or thromboembolic events (ie, arterial or venous thrombotic or embolic events, including cerebrovascular accident [including transient ischemic attacks], deep vein thrombosis, or pulmonary embolism); renal, endocrine, pulmonary, gastrointestinal, genitourinary, or neurologic disorders [exclusive of FM]; ~~psychotic disorders, dementia, bipolar disorder, major depressive disorders, anxiety disorders, suicidality, and substance use disorders as diagnosed using the Mini-International Neuropsychiatric Interview [MINI];~~ infectious, hepatic, or ocular disease, at the discretion of the investigator, as determined by a medical and psychiatric history; and physical examination, 12-lead ECG, serum chemistry, hematology, coagulation, and urinalysis). Abnormal test results may be repeated for confirmation	f. known history of clinically significant or unstable hematologic, cardiac, or thromboembolic events (ie, arterial or venous thrombotic or embolic events, including cerebrovascular accident [including transient ischemic attacks], deep vein thrombosis, or pulmonary embolism); renal, endocrine, pulmonary, gastrointestinal, genitourinary, or neurologic disorders [exclusive of FM]; infectious, hepatic, or ocular disease, at the discretion of the investigator, as determined by a medical and psychiatric history; and physical examination, 12-lead ECG, serum chemistry, hematology, coagulation, and urinalysis). Abnormal test results may be repeated for confirmation	This change was made to align with other exclusion criteria to clarify inclusion/exclusion of patients with mental disorders and/or who may be on prohibited medications.
~~v~~t. clinically significant elevations in hepatic enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) based on the upper limit of normal (ULN) or investigator judgment, which have been reconfirmed on a repeat test	t. clinically significant elevations in hepatic enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) based on the ULN or investigator judgement, which have been reconfirmed on a repeat test	This change was made to define "clinically significant" for this criterion.
~~y~~w. known history of alcohol and/or drug abuse within the past 12 months ~~that in the investigator's opinion could interfere with the study evaluations or the patient's safety~~ per the MINI or have a positive urine drug screen for illegal drugs of abuse or alcohol test at the Screening Visit, ~~Baseline Assessment~~ BAPS Visit, or prior to randomization	w. known history of alcohol and/or drug abuse within the past 12 months per the MINI or have a positive urine drug screen for illegal drugs of abuse or alcohol test at the Screening Visit, BAPS Visit, or prior to randomization	This change was made for clarification.
Section 4.3 Discontinuation from IMP/Early Termination from Study Criteria and Procedures for the Patient; Other sections affected by this change: Section 3.5		
Efficacy endpoints (primary, secondary, [redacted]) will be derived from subjective pain ratings collected daily using an e-diary. Eligible patients will receive comprehensive training from site personnel on the	Efficacy endpoints (primary, secondary, [redacted] will be derived from subjective pain ratings collected daily using an e-diary.	This text was added to outline procedures for e-diary compliance.

Original text with changes shown	New wording	Reason/Justification for change
correct use of the e-diary. Site personnel will also instruct patients on the requirement for timely and daily completion of the e-diary. At least 75% compliance with e-diary recordings on a weekly basis is expected after the randomization period. Site personnel will monitor patients' compliance that e-diary entry is at least 75% every week during the double-blind treatment period. If weekly 75% compliance is not maintained, a reminder and any other corrective actions, as deemed necessary, will be issued to the patient. In the following circumstances, the IMP will be discontinued immediately:	Eligible patients will receive comprehensive training from site personnel on the correct use of the e-diary. Site personnel will also instruct patients on the requirement for timely and daily completion of the e-diary. At least 75% compliance with e-diary recordings on a weekly basis is expected after the randomization period. Site personnel will monitor patients' compliance that e-diary entry is at least 75% every week during the double-blind treatment period. If weekly 75% compliance is not maintained, a reminder and any other corrective actions, as deemed necessary, will be issued to the patient. In the following circumstances, the IMP will be discontinued immediately:	
Section 5.2.3 Accountability		
~~Partially used~~ Empty and unused pre-filled syringes must be destroyed at the investigational center in accordance with the investigational center's Standard Operating Procedures (SOPs) following sponsor approval. In the event that the investigational center is unable to destroy the empty and/or unused units of IMP, the IMP must be returned to the sponsor or its designee per sponsor instructions. ~~and unused pre-filled syringes of IMP will be returned to the sponsor or designee.~~	Empty and unused pre-filled syringes must be destroyed at the investigational center in accordance with the investigational center's Standard Operating Procedures (SOPs) following sponsor approval. In the event that the investigational center is unable to destroy the empty and/or unused units of IMP, the IMP must be returned to the sponsor or its designee per sponsor instructions.	This change was made to correct procedures for disposal of used and unused IMP.
Section 5.4 Other Medicinal Products		
Dosing Instructions: 1 to 2 caplets with dose up to 1000 mg~~/day~~ per dose; maximum of 3000 mg per day	Dosing Instructions: 1 to 2 caplets with dose up to 1000 mg~~/day~~ per dose; maximum of 3000 mg per day	This change was made to correct the acetaminophen dose used as rescue medication.
Section 5.7 Prior and Concomitant Medication or Therapy		
In addition, tricyclic antidepressants at low doses (amitriptyline [≤25 mg]~~)~~, cyclobenzaprine [2.5 mg sublingual or 5 to 10 mg], or trazodone-[≤150 mg]) may be used for sleep.	In addition, tricyclic antidepressants at low doses (amitriptyline [≤25 mg], cyclobenzaprine [2.5 mg sublingual or 5 to 10 mg], or trazodone [≤150 mg]) may be used	This change was made to clarify and organize which dosages applied to which medication.

Original text with changes shown	New wording	Reason/Justification for change
	for sleep.	
Section 5.11 Total Blood Volume		
The total blood volume that will be collected for each patient enrolling in this study for scheduled evaluation of ADAs, fremanezumab concentrations, clinical laboratory tests, and biomarkers ~~treatment with fremanezumab~~ is approximately 195.5 mL ~~for scheduled tests~~. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes. ~~The total blood volume that will be collected for each patient enrolling in this study for evaluation of ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) is approximately 195.5 mL~~. Details are provided in Appendix K.	The total blood volume that will be collected for each patient enrolling in this study for scheduled evaluation of ADAs, fremanezumab concentrations, clinical laboratory tests, and biomarkers is approximately 195.5 mL. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes. Details are provided in Appendix K.	This change was made to clarify the total blood volume to be collected.
Section 6.1.6.1 PROMIS Sleep Disturbance Short Form 8a		
The PROMIS Sleep Disturbance SF8 Scale contains 8 items with a score range of 8 to 40 and measures quality of sleep and sleep-related impairment ~~within the previous 24 hours~~.	The PROMIS Sleep Disturbance SF8 Scale contains 8 items with a score range of 8 to 40 and measures quality of sleep and sleep-related impairment.	This change was made to correct an error in the text.
Section 7.4 Clinical Laboratory Tests		
Albumin Bilirubin Direct bilirubin Hepatitis B	Albumin Bilirubin Direct bilirubin Hepatitis B	This change was made to clarify that assessment for Hepatitis B should be conducted as part of serum chemistry clinical laboratory testing.
Section 7.9 Assessment of Local Tolerability and Pain		
±15 min	±15 min	This change was made to reflect the correction to the assessment window.
Section 9.2 Sample Size and Power Considerations; Other sections affected by this change: Section 9.6.4.2		
Moreover, assuming a standard deviation of 2.2 for change from baseline in the weekly average of the daily average PI-NRS score, 80 patients per treatment group will provide at least 90% probability to observe the half length of the 95% confidence of the treatment difference between fremanezumab 225 mg sc or fremanezumab 675 mg sc and placebo ~~of~~ less	Moreover, assuming a standard deviation of 2.2 for change from baseline in the weekly average of the daily average PI-NRS score, 80 patients per treatment group will provide at least 90% probability to observe the half	This change was made to clarify how the score is being used as an endpoint.

Original text with changes shown	New wording	Reason/Justification for change
than 0.74.	length of the 95% confidence of the treatment difference between fremanezumab 225 mg sc or fremanezumab 675 mg sc and placebo less than 0.74.	
Section 9.6.2 Secondary Endpoints		
~~• change from baseline in the PI NRS score over the past 24 hours~~ • change from baseline in the individual components of the FIQR: symptom subscore, impact subscore, and functional subscore score	• change from baseline in the individual components of the FIQR: symptom subscore, impact subscore, and functional subscore score	This change was made because this endpoint does not appear in either protocol.
Appendix A CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
[redacted] Tel: [redacted]	[redacted] Tel: [redacted]	This change was made to include the Coordinating Investigator's contact information in Appendix A.
[redacted] Teva Pharmaceutical Industries Ltd. Tel: [redacted] Cell: [redacted] ~~Teva Pharmaceutical Industries Ltd.~~ ~~Tel:~~ [redacted] ~~Cell:~~ [redacted]	[redacted] Teva Pharmaceutical Industries Ltd. Tel: [redacted] Cell: [redacted]	This change was made to reflect a personnel change at the Sponsor.
~~TBD~~ [redacted]	[redacted]	This change was made to provide an information update.

Original text with changes shown	New wording	Reason/Justification for change
~~TBD~~ [redacted]	[redacted]	This change was made to provide an information update
[redacted] TBD	TBD	This change was made to provide an information update
~~TBD~~ [redacted]	[redacted]	This change was made to provide an information update
~~TBD~~ [redacted]	[redacted]	This change was made to provide an information update
Clinical Data Management System [redacted]	**Clinical Data Management System** [redacted]	This change was made to provide an information update
Appendix B STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
[Visit 2, day -14 (week -3) (±~~2~~3 days)]	**[Visit 2, day -14 (week -3) (±2 days)])**	This change was made to correct the Visit 2 visit window respective to inclusion criterion 'd'.
• serum FSH test (for postmenopausal women only) and β-HCG serum pregnancy test (women) • urine pregnancy test for women of childbearing potential • inform patients of study restrictions and compliance requirements	• serum FSH test (for postmenopausal women only) and β-HCG serum pregnancy test (women) • urine pregnancy test for women of childbearing potential • inform patients of study restrictions and compliance requirements	This change was made to accurately reflect those assessments given at Visit 2.
• assess for injection site reactions	• assess for injection site reactions	This change was made to clarify that injection site reactions are not assumed to occur, rather injection site reactions will be assessed if/when they occur.
• review of IMP accountability and rescue medication • collect ~~IMP~~ rescue medication	• review of IMP accountability and rescue medication • collect rescue medication	This change was made to account for the review and collection of rescue medication at unscheduled visits.
Appendix D WASHOUT PERIODS FOR COMMON MEDICATIONS		

Original text with changes shown	New wording	Reason/Justification for change
Duloxetine ~~1~~2 weeks ... Venlafaxine ~~1~~2 weeks Nortriptyline ~~3~~2 weeks ... Desvenlafaxine ~~3~~2 weeks Duloxetine ~~3~~2 weeks Levomilnacipran ~~3~~2 weeks Milnacipran ~~3~~2 weeks Venlafaxine ~~3~~2 weeks	Duloxetine 2 weeks ... Venlafaxine 2 weeks Nortriptyline 2 weeks ... Desvenlafaxine 2 weeks Duloxetine 2 weeks Levomilnacipran 2 weeks Milnacipran 2 weeks Venlafaxine 2 weeks	This change was made to clarify the washout periods.
Appendix J LIST OF PROHIBITED MEDICATIONS AND THERAPEUTIC INTERVENTIONS		
These medication lists are not exhaustive; the investigator should check with the Medical Monitor on any drug not listed in this appendix. For those medications listed in Section 5.7, doses greater than the listed dose are prohibited.	These medication lists are not exhaustive; the investigator should check with the Medical Monitor on any drug not listed in this appendix. For those medications listed in Section 5.7, doses greater than the listed dose are prohibited.	This change was made to ensure the medications listed in Appendix J do not conflict with those listed in Section 5.7.
Any new therapy taken within 90 days of the Screening Visit (Visit 1) or planned therapy concurrent with the study that could affect pain or any other symptom associated with FM (eg, physical therapy, massage, chirotherapy, psychotherapy, and counseling).	Any new therapy taken within 90 days of the Screening Visit (Visit 1) or planned therapy concurrent with the study that could affect pain or any other symptom associated with FM (eg, physical therapy, massage, chirotherapy, psychotherapy, counseling).	This change was made to clarify the period of non-pharmacologic interventions.
APPENDIX K TOTAL BLOOD VOLUME		
Total blood volume to be collected for each patient in this study is approximately 195.5 mL for scheduled tests ~~(at maximum)~~. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes.	Total blood volume to be collected for each patient in this study is approximately 195.5 mL for scheduled tests. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes.	This change was made to be consistent with the non-concealed version of the protocol.

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted], Teva Branded Pharmaceutical Products R&D, Inc. [redacted]
Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. [redacted]
Coordinating Investigator	[redacted]
Sponsor's Representative of Global Patient Safety and Pharmacovigilance	[redacted] Teva Pharmaceutical Industries Ltd. [redacted]
Contract Research Organization	[redacted]
Contract Manufacturing Organization	[redacted]
Central Clinical Laboratory	[redacted]
Central Electrocardiogram Evaluation	[redacted]
Bioanalytical Pharmacokinetics Evaluation	Teva Branded Pharmaceutical Products R&D, Inc. - Special Bioanalytics
Bioanalytical Immunogenicity Evaluation	Teva Branded Pharmaceutical Products R&D, Inc. - Special Bioanalytics
Biomarker Evaluation	TBD
Randomization and Trial Supply Management (RTSM) Vendor	[redacted]
e-diary Vendor	[redacted]
e-diary and Tablet Administrator	[redacted]

Clinical Data Management System	[redacted]

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. **Procedures for screening (Visit 1, day -35 [week -5])**

The Screening Visit (Visit 1) will take place not more than 3 weeks before the Baseline Assessment Period Start (BAPS) 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
- study assessments/pain reporting training
- electronic diary (e-diary) training
- dispense rescue medication
- Pain Intensity-Numerical Rating Scale (PI-NRS)
- 2016 Fibromyalgia American College of Rheumatology (ACR; widespread pain index [WPI] and symptom severity [SS] scale score) examination
- Mini-International Neuropsychiatric Interview
- prior medication and treatment history
- clinical laboratory tests
- urine drug screen
- alcohol (social history)
- marijuana (cannabis), cannabidiol, or other cannabinoids (medicinal and social history)
- full physical examination
- electrocardiography
- vital signs measurements (including height and weight)
- serum follicle-stimulating hormone (FSH) test (for postmenopausal women only) and beta-human chorionic gonadotropin (β-HCG) serum pregnancy test (women)
- inform patients of study restrictions and compliance requirements
- assess concomitant medication
- [redacted]

2. **Procedures for Phone Contact (Scheduling and Instructions [Day -33 through Day -15); Washout Period [7 to 19 days])**

Phone contact will occur no later than day -15. The following procedures will take place:

- prior medication tapering and washout
- assess concomitant medication
- inquire about adverse events
- schedule BAPS Visit (Visit 2)

3. **Procedures Before Administration of Investigational Medicinal Product(s) (BAPS Visit [Visit 2, day -14 (week -3) (±2 days)])**

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

The following procedures will be performed at Visit 2:

- review inclusion and exclusion criteria
- study assessments/pain reporting training
- e-diary data review/training
- dispense/account rescue medication
- provide e-diary
- PI-NRS (recorded daily)
- prior medication and treatment history
- urine drug screen
- abbreviated physical examination
- vital signs measurements
- urine pregnancy test for women of childbearing potential (serum pregnancy test may be completed to confirm, if warranted)
- inform patients of study restrictions and compliance requirements
- assess concomitant medication
- review study compliance
- [redacted]

- PROMIS Sleep Disturbance SF8a weekly in e-diary
- inquire about adverse events
- [redacted]
- review e-diary

4. **Procedures During Administration of Investigational Medicinal Product (Double-Blind Treatment Period)**

a. Randomization (Visit 3, day 1 [week 1])

The following procedures and assessments will be performed at Visit 3:

- review inclusion and exclusion criteria
- assign randomization/treatment number
- study assessments/pain reporting training
- e-diary data review/training
- dispense/account rescue medication
- [redacted]
- prior medication and treatment history
- clinical laboratory tests
- urine drug screen
- abbreviated physical examination
- electrocardiography
- vital signs measurements
- urine pregnancy test for women of childbearing potential (serum pregnancy test may be completed to confirm, if warranted)
- inform patients of study restrictions and compliance requirements
- assess concomitant medication
- review study compliance
- [redacted]

- blood sample for serum anti-drug antibody (ADA) concentration
- [redacted]
- inquire about adverse events
- [redacted] Since Last Visit version
- administration of IMP
- review e-diary

b. Administration of Investigational Medicinal Product (Visits 4, 5, and 6, days 29 [week 4], 57 [week 8], and 85 [week 12] ±7 days, respectively)

For Visits 4 and 5 (when at-home dosing is available), home visits are permitted for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center.

The following procedures and assessments will be performed at Visits 4, 5, and 6 (days 29 [week 4], 57 [week 8], and 85 [week 12] ±7 days, respectively):

- study assessments/pain reporting training (and as needed, for subsequent retraining throughout the study)
- e-diary data review/training (and as needed, for subsequent retraining throughout the study)
- dispense/account rescue medication
- PI-NRS (recorded daily)
- clinical laboratory tests (Visit 6 [day 85] only)
- urine drug screen
- abbreviated physical examination
- electrocardiography (Visit 6 [day 85] only)
- vital signs measurements
- urine pregnancy test for women of childbearing potential (serum pregnancy test may be completed to confirm, if warranted)
- inform patients of study restrictions and compliance requirements
- assess concomitant medication
- review study compliance
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- blood sample for plasma concentration of IMP (Visit 6 [day 85] only)
- blood sample for serum ADA concentration (Visit 6 [day 85] only)
- [redacted]
- inquire about adverse events
- [redacted] Since Last Visit version
- administration of IMP
- review e-diary

5. **End-of-Treatment/End-of-Study or Early Termination (Visit 7, day 113 [week 16] ±7 days)**

The following procedures/assessments will be performed at Visit 7 (day 113 [week 16]):

- account/collect rescue medication
- PI-NRS (daily in e-diary) (Note: Collection ends the day before or the morning of Visit 7 if missed the day before)
- clinical laboratory tests
- urine drug screen
- abbreviated physical examination
- electrocardiography
- vital signs measurements
- urine pregnancy test for women of childbearing potential (serum pregnancy test may be completed to confirm, if warranted)
- assess concomitant medication
- review study compliance
- [redacted]

- [redacted] Sleep Disturbance SF8a weekly in e-diary
- IMD
- blood sample for plasma concentration of IMP
- blood sample for serum ADA concentration
- [redacted]
- inquire about adverse events
- [redacted] Since Last Visit version
- review e-diary
- collect patient e-diary

6. Unscheduled Visits

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

APPENDIX C. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

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

a. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

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

c. Reduced BP after exposure to known allergen for that subject (minutes to several hours):
   - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Source: Modified from Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report. Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium [reprint in Ann Emerg Med 2006;47(4):373-80; PMID:16546624]. J Allergy Clin Immunol 2006;117(2):391-7.

APPENDIX D. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations and Violations

Protocol Amendments

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

Protocol Violations

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

When a protocol violation is reported, the sponsor will determine whether to terminate 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 protocol violation. If such patient has already completed the study or has terminated the study early, no action will be taken but the violation will be recorded.

For Coronavirus Disease 2019 updates, see Appendix O.

Information to Study Personnel

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

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

Study Monitoring

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

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

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

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

Audit and Inspection

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

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

APPENDIX E. ETHICS

Informed Consent

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

Written informed consent will be obtained from each patient before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be recorded in the informed consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original informed consent forms, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to terminate 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.

For Coronavirus Disease 2019 updates, see Appendix O.

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 eCRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

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

APPENDIX F. BIRTH CONTROL METHODS AND PREGNANCY TESTING

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

While hormonal contraception may be susceptible to interaction with an IMP that reduces the efficacy of the contraceptive method, eg, CYP 4A inducers, no adjustments in dosing should be necessary.

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

Furthermore, fremanezumab was tested for stimulation of pro-inflammatory cytokine release in human whole blood (Study PF-04427429/24Aug09/111320) and did not elicit significant cytokine release (tumor necrosis factor α, interleukin-6, interferon-γ, or interleukin-1β) in any donor including at concentrations up to 100 μg/mL. As such, there is also no reason to suspect that fremanezumab may influence CYP activity via cytokine release.

Women/Girls of childbearing potential are defined as:

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

Women/Girls of nonchildbearing potential are defined as:

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

Postmenopausal women:

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

Description of different birth control methods

Highly effective birth control methods:

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

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of IMP
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 7 before the first dose of IMP
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2 months before screening visit (V1)
- Bilateral tubal occlusion
- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are **not** acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency).

Unacceptable birth control methods:

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

Male contraception

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

Vasectomy:

Use of contraceptive methods applies also to vasectomized men.

Pregnant female partners of male study participants:

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

APPENDIX G. LOST TO FOLLOW-UP

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

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

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

APPENDIX H. HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR IMP(S)

Storage and Security

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

The test IMPs (fremanezumab and placebo IMP) must be stored under refrigeration at 2°C to 8°C (36°F to 46°F), do not freeze, protect from light and avoid vigorous shaking.

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

Labeling

Supplies of IMPs will be labeled in accordance with the current ICH guidelines on GCP and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

Accountability

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

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR), and used in accordance with this protocol.

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

The investigator (or designee) will instruct the patient to store the IMP according to the instructions on the label, if applicable; or will give instructions in an appropriate form.

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

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Pre-filled 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 pre-filled syringes of IMP will be returned to the sponsor or designee.

Further guidance and information pertaining to the preparation, handling, labeling, storage, and accountability for the IMP used in this study are provided in the Pharmacy Manual.

APPENDIX I. LIST OF PROHIBITED MEDICATIONS AND THERAPEUTIC INTERVENTIONS

These medication lists are not exhaustive; the investigator should check with the Medical Monitor about any drug not listed in this appendix. For the medications fluoxetine (Prozac) and naltrexone that are listed in the table below, only doses greater than the maximum listed dose are prohibited.

ANTIDEPRESSANTS

TCAs and related compounds
Amitriptyline
Amoxapine
Clomipramine (Anafranil)
Desipramine (Norpramin)
Doxepin
Imipramine (Tofranil, Tofranil-PM)
Maprotiline
Nortriptyline (Pamelor)
Protriptyline (Vivactil)
Trimipramine (Surmontil)
Serotonin-Norepinephrine Reuptake Inhibitors
Desvenlafaxine (Pristiq)
Duloxetine (Cymbalta, Irenka)
Levomilnacipran (Fetzima)
Milnacipran (Savella)
Venlafaxine (Effexor, Effexor XR)
5-HT3 Receptor Antagonists
Vortioxetine (Trintellix) (formerly called Brintellix)
Noradrenergic Antagonists
Mirtazapine (Remeron, Remeron SolTab)
Monamine Oxidase Inhibitors
Isocarboxazid (Marplan)
Phenelzine (Nardil)
Tranylcypromine (Parnate)
Selegiline (EmSam)

ANTIPSYCHOTICS/MOOD STABILIZERS

Antipsychotics
Aripiprazole (Abilify, Abilify Maintenna)
Asenapine (Saphris)
Cariprazine (Vraylar)
Chlorpromazine
Loxapine (Adasuve)
Olanzapine (Zyprexa, Zyprexa Zydis)
Quetiapine (Seroquel, Seroquel XR)
Risperidone (Risperdal, Risperdal Consta, Risperdal M-Tab)
Ziprasidone (Geodon)
Fluoxetine (Prozac) 60 mg or higher
Olanzapine and fluoxetine (Symbyax)

NEUROTOXINS

Botulinum Toxin A

NON BENZODIAZEPINE HYPNOTIC AGENTS

Eszopiclone (Lunesta)

OREXIN RECEPTOR ANTAGONISTS

Suvorexant (Belsomra)

MELATONIN RECEPTOR AGONISTS

Ramelteon (Rozerem)

PSYCHOTROPIC AGENTS

Armodafinil
Modafinil
Sodium Oxybate (Zyrem)

OPIOIDS/OPIOID ANTAGONISTS

Oxycodone
Hydrocodone
Hydromorphone
Oxymorphone
Morphine
Fentanyl
Methadone
Buprenorphine
Meperidine
Codeine
Tramadol
Levorphanol
Tapentadol
Naltrexone ≥4.5 mg

ALPHA2-DELTA CALCIUM CHANNEL MODULATORS

Gabapentin (Fanatrex FusePaq; Gralise; Gralise Starter; Neuraptine; Neurontin)
Pregabalin (Lyrica; Lyrica CR)

SKELETAL MUSCLE RELAXANTS

Baclofen
Carisoprodol
Methocarbamol

CENTRAL NERVOUS SYSTEM ACTING AGENTS-BENZODIAZEPINES

Alprazolam
Chlordiazepoxide Hydrochloride
Clobazam
Clonazepam
Clorazepate Dipotassium
Diazepam
Estazolam
Flurazepam Hydrochloride
Lorazepam
Midazolam Hydrochloride
Oxazepam

Quazepam
Temazepam
Triazolam

CALCITONIN GENE-RELATED PEPTIDE PATHWAY TARGETING TREATMENT OR COMPOUND

Anti-CGRP Antibodies
Eptinezumab-jjmr (Vyepti)
Galcanezumab-gnlm (Emgality)
Anti-CGRP Receptor Antibodies
Erenumab-aooe (Aimovig)
CGRP Receptor Antagonists/Oral Gepants
Ubrogepant (Ubrelvy)
Rimegepant (Nurtec ODT)

OTHER THERAPEUTIC INTERVENTIONS

Herbal agents (eg, St. John's Wort)
Topical lidocaine within 1 month prior to screening
Capsaicin within 6 months prior to screening
Oral corticosteroids

NON-PHARMACOLOGIC INTERVENTIONS

- Any procedures or mechanical/invasive interventions that could affect pain or any other symptom associated with FM (eg, nerve block, tender point injections, laser therapy, acupuncture, dry needling, spinal cord stimulation, transcutaneous electrical nerve stimulation [use of a TENS machine], intra thecal drug delivery by electronic pump.
- Any new therapy taken within 90 days of the Screening Visit (Visit 1) or planned therapy concurrent with the study that could affect pain or any other symptom associated with FM (eg, physical therapy, massage, chirotherapy, psychotherapy, and counseling).

APPENDIX J. TOTAL BLOOD VOLUME

Total blood volume to be collected for each patient in this study is approximately 150.8 mL for scheduled tests. Refer to the Laboratory Manual for details on blood sampling.

Total Blood Volumes

Visit number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Total**
Visit type	Screening visit	BAPS visit	Double-blind treatment				EOT/EOS or ET visit	
Number of samples	6	0	9	0	0	9	9	**33**
Volume (mL)	31.7	0	39.7	0	0	39.7	39.7	**150.8**

See FDA Guidance (Guidance for Industry 2007) for acceptable blood volume loss per collection procedure.
BAPS = Baseline Assessment Period Start; EOS = end-of-study; EOT = end-of-treatment; ET = early termination; FDA = Food and Drug Administration.

APPENDIX K. PRODUCT COMPLAINTS

Clinical Product Complaints

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. **Documenting a Product Complaint**

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

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

APPENDIX L. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

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

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

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

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

Data Collection

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

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

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

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

Data Quality Control

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

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

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

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

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

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

Investigator Responsibilities

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

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

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

APPENDIX M. PUBLICATION POLICY

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

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

The sponsor will comply with the requirements for publication of study results: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (ICMJE 2017). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

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

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

APPENDIX N. RELEVANT MEDICATIONS ALLOWED FOR THE DURATION OF THE STUDY

Antidepressant Medications

- Selective serotonin reuptake inhibitors including:
  - Fluoxetine (maximum daily dose <60 mg)
  - Citalopram (Celexa®, Cipramil)
  - Escitalopram (Lexapro®, Cipralex)
  - Paroxetine (Paxil®, Seroxat)
  - Fluvoxamine (Luvox®, Faverin)
  - Sertraline (Zoloft®, Lustral)

Analgesic Medications

- Aspirin (maximum daily dose 325 mg) for cardiovascular prophylaxis; acetaminophen as a rescue medication (up to 1000 mg per dose and not to exceed 3000 mg/day for all indications)
- Nonsteroidal anti-inflammatory drugs are permitted provided the use has been stable (ie, per patient's usual dosing regimen) for at least 1 month prior to screening and will remain unchanged throughout the study

Medications for Sleep

- Zolpidem at doses ≤10 mg at bedtime
- Melatonin
- Antihistamines
- Tricyclic antidepressants at low doses (amitriptyline [≤25 mg] or trazodone [≤150 mg])
- Cyclobenzaprine (up to 10 mg)

Medications for Chronic Migraine Prevention

- Except for those listed in Appendix I, all other therapies/medications are permitted.

APPENDIX O. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19

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

The changes specified in this appendix will be effective for the duration of the COVID-19 pandemic. Once the centers/countries are able to resume normal functioning, this appendix will become void, except in the case of resurgence of COVID-19 or emergence of another crisis affecting normal per protocol conduct of the study.

The following sections are affected:

Section 3.1 General Study Design and Study Schematic Diagram

Patients who were either in the screening period or in the baseline assessment period, as of 26 March 2020, were designated as screen failures. These patients will be invited to rescreen once the COVID-19 crisis has abated and the sponsor has granted approval to restart screening; the timing of restarting screening may also be dependent on the investigational center's geographical location due to varying state and local regulations.

Patients randomized, as of 26 March 2020, will continue on study as per the protocol, if possible. The study staff at the investigational centers are to follow the guidelines provided by the Centers for Disease Control and Prevention with regards to COVID-19 personal protection and social distancing. The investigational center will inform the patient of the safeguards being taken with regards to COVID-19 and discuss their willingness to come to the site for upcoming visits. If an ongoing patient declines to go to the site, the Medical Monitor will be notified to discuss further plans for that patient.

The dates for the study duration will be revised as a result of the COVID-19 public health emergency.

Section 4.5 Rescreening

Any patient who is a screen fail due to the COVID-19 study enrollment hold will be allowed to screen one additional time.

Section 5.1.1.2 Dosing Visits and Dose Modification

Visits 1, 2, 3, and 6 must occur at the study site. For Visits 4 and/or 5 (when at-home dosing is available), home visits are permitted under the circumstances described above. Doses will be administered at the study site or at home, as applicable. IMP accountability remains the responsibility of the site as discussed in Section 5.2.3.

Appendix D. Quality Control and Quality Assurance

Deviations from the study conduct due to emergency situations (eg, the COVID-19 pandemic), including implemented contingency measures and their impact (eg, patient discontinuation from treatment with investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data, etc), will be described in the appropriate sections of the CSR as applicable.

Appendix E. Ethics

For home visits, no new assessments are being implemented; only the location is changed. Hence, an Institutional Review Board (IRB) approval is not required prior to implementing the alternative options for assessments. The IRB will be notified for informational purposes if any alternate procedures are implemented.

A COVID-19 Consent Addendum has been approved for investigational center use if alternate procedures or assessments need to be instituted prior to the implementation of this protocol amendment.