Clinical Study Protocol

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

Study Number TV48125-CNS-30082

NCT04464707

Protocol with Amendment 09 Approval Date: 24 September 2023

Clinical Trial Protocol with Amendment 09

Trial Number TV48125-CNS-30082

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

Randomized, Double-Blind, Placebo-Controlled Trial of Fremanezumab in Participants (6 to 17 Years) with Chronic Migraine

A Trial to Test if Fremanezumab is Effective in Preventing Chronic Migraine in Participants 6 to 17 Years of Age

Efficacy, Safety, and Tolerability Trial (Phase 3)

IND number: 106,533; NDA number: not applicable; BLA number: 761089; EudraCT number: 2019-002053-33; EU CT number: not applicable

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

Article 45 or 46 of 1901/2006 applies

EudraVigilance Code for the IMP: SUB181665

EudraVigilance Code for the Drug Substance: not applicable

Version Date: 24 September 2023

Sponsor

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

United States of America

Sponsor's Authorized Representative

[redacted]

Teva Pharmaceutical Industries Ltd.

Name and contact information of the Medical Monitor are provided separately.

This clinical trial 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 trial); national country legislation; the protocol; and the Sponsor's Standard Operating Procedures (SOPs).

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INVESTIGATOR AGREEMENT

Clinical Trial Protocol with Amendment 09

Version Date: 24 September 2023

TV48125-CNS-30082

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IND number: 106,533; NDA number: not applicable; BLA number: 761089; EudraCT number: 2019-002053-33; EU CT number: not applicable

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

Article 45 or 46 of 1901/2006 applies

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 09 and agree that it contains all necessary details for carrying out this trial. I am qualified by education, experience, and training to conduct this clinical research trial. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this trial 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 trial personnel reporting to me who participate in this trial and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the trial. I agree to keep records on all participant information, IMP shipment and return forms, and all other information collected during the trial, 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

Clinical Trial Protocol with Amendment 09

Version Date: 24 September 2023

TV48125-CNS-30082

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

IND number: 106,533; NDA number: not applicable; BLA number: 761089; EudraCT number: 2019-002053-33; EU CT number: not applicable

I have read the protocol with Amendment 09 and approve the design of this trial.

Sponsor's Authorized Representative	**Signature**	**Date**

Executed signature pages are maintained within the Trial Master File

COORDINATING INVESTIGATOR AGREEMENT

Clinical Trial Protocol with Amendment 09

Version Date: 24 September 2023

TV48125-CNS-30082

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

IND number: 106,533; NDA number: not applicable; BLA number: 761089; EudraCT number: 2019-002053-33; EU CT number: not applicable

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

Article 45 or 46 of 1901/2006 applies

I have read the protocol with Amendment 09 and agree that it contains all necessary details for carrying out this trial. I am qualified by education, experience, and training to conduct this clinical research trial. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this trial 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 trial personnel reporting to me who participate in this trial and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the trial. I agree to keep records on participant information, IMPs shipment and return forms, and other information collected during the trial, 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: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel:

Coordinating Investigator	Signature	Date

Executed signature page is maintained within the Trial Master File.

PROTOCOL AMENDMENT DETAILS

A total of 8 prior amendments have occurred, as shown in the following table:

Document History	
Administrative Letter 06	21 December 2021
Amendment 08	09 December 2021 34 participants randomized/enrolled
Administrative Letter 05	10 May 2021
Administrative Letter 04	04 February 2021
Administrative Letter 03	05 November 2020
Amendment 07	20 August 2020 0 participants randomized/enrolled The management of study activities during the COVID-19 pandemic are detailed in Appendix O. The following sections are affected: Section 3.1 General Study Design and Study Schematic Section 3.5 Schedule of Study Procedures and Assessments Section 4.4 Replacement of Patients Section 9.5 Efficacy Analysis Appendix E. Quality Control and Quality Assurance Appendix F. Ethics
Amendment 06	27 July 2020 0 participants randomized/enrolled
Amendment 05	27 June 2020 0 participants randomized/enrolled
Administrative Letter 02	07 July 2020
Amendment 04	20 April 2020 0 participants randomized/enrolled
Administrative Letter 01	10 March 2020
Amendment 03	20 February 2020 0 participants randomized/enrolled
Amendment 02	05 December 2019 0 participants randomized/enrolled
Amendment 01	21 June 2019 0 participants randomized/enrolled
Original Protocol	28 March 2019

Current Amendment 09 24 September 2023

As of 18 September 2023, 180 participants have been randomized/enrolled.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The Sponsor took the opportunity of the protocol amendment procedure to already align the protocol with the upcoming new Clinical Trial Regulation requirements. This involved updating the protocol to a new template. This update may have caused changes and/or relocations to specific texts and/or sections, compared to the previous version of the protocol (ie, Protocol Amendment 08). An overview of the various relevant sections are presented below.

Section - Protocol Amendment 08	Section - Protocol Amendment 09	Comment
CLINICAL STUDY PROTOCOL SYNOPSIS	1. PROTOCOL SUMMARY	Alignment with new template
1. INTRODUCTION AND BACKGROUND INFORMATION	2. INTRODUCTION	Alignment with new template
2. STUDY OBJECTIVES AND ENDPOINTS	3. TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS	Alignment with new template
3. STUDY DESIGN	4. TRIAL DESIGN	Alignment with new template
3.1. General Study Design and Study Schematic Diagram – Figure 1: Overall Study Design Schematic Diagram	Moved Figure 1: Overall Trial Schematic Diagram to Section 1.2	Alignment with new template
3.4 Stopping Rules for the Study	7.4 Trial Stopping Rules	Alignment with new template
3.5. Schedule of Study Procedures and Assessments	Moved Table 1: Trial Procedures and Assessments to Section 1.3	Alignment with new template
4. SELECTION AND WITHDRAWAL OF PATIENTS	5. TRIAL POPULATION	Alignment with new template
4.3. Withdrawal Criteria and Procedures for the Patient	7.2. Participant Withdrawal from the Trial	Alignment with new template
4.3.1. Study-Specific Patient Withdrawal Criteria and Procedures	7.1. Discontinuation of Trial Intervention	Alignment with new template
4.4. Replacement of Patients	7.1. Discontinuation of Trial Intervention	Alignment with new template
4.5. Rescreening	Combined with section 5.6. Screen Failures	Alignment with new template
5. TREATMENTS	6. TRIAL INTERVENTION AND CONCOMITANT THERAPY	Alignment with new template.
5.5. Restrictions	5.5. Lifestyle Considerations	Alignment with new template.
5.9.3. Data Monitoring Committee	4.1.2. Data Monitoring Committee/Safety Review	Alignment with new template.

Section - Protocol Amendment 08	Section - Protocol Amendment 09	Comment
	Committee and 10.3. Informed Consent Process	
5.10. Total Blood Volume	8.13. Total Blood Volume	Alignment with new template.
6. ASSESSMENT OF EFFICACY	8. TRIAL ASSESSMENTS AND PROCEDURES	Alignment with new template
7. ASSESSMENT OF SAFETY	8.3. Safety Assessments and Procedures	Alignment with new template.
7.1. Adverse Events	8.4. Adverse Events and Serious Adverse Events	Alignment with new template.
7.2. Pregnancy	8.5. Pregnancy and Postpartum Information	Alignment with new template.
7.4.1 Table 4: Clinical Laboratory Tests	13.2. Table 7: Clinical Laboratory Tests	Alignment with new template.
8. ASSESSMENT OF PHARMACOKINETICS AND IMMUNOGENICITY	8.7. Pharmacokinetics	Alignment with new template.
8.3. Immunogenicity Testing	8.11. Immunogenicity Assessments	Alignment with new template.
9. STATISTICS	9. STATISTICAL CONSIDERATIONS	Alignment with new template.
10. QUALITY CONTROL AND QUALITY ASSURANCE	11. GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE	Alignment with new template.
11. COMPLIANCE STATEMENT	10. GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT	Alignment with new template.
12. DATA MANAGEMENT AND RECORD KEEPING	11. GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE	Alignment with new template.
13. FINANCING AND INSURANCE	13.4. Financial Disclosure	Alignment with new template.
14. PUBLICATION POLICY	13.7. Publication Policy	Alignment with new template.
15. REFERENCES	15. REFERENCES	Alignment with new template.
16. SUMMARY OF CHANGES TO PROTOCOL	13.3. Prior Protocol Amendments	Alignment with new template.
APPENDIX A. CLINICAL LABORATORIES AND OTHER	Removed Appendix	Alignment with new template to remove company confidential

Section - Protocol Amendment 08	Section - Protocol Amendment 09	Comment
DEPARTMENTS AND INSTITUTIONS		information and personal protected data.
APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT	13.9. Trial Procedures and Assessments by Visit	Alignment with new template.
APPENDIX C. PREVENTIVE MIGRAINE MEDICATIONS FOR ANY CONDITION ALLOWED FOR THE DURATION OF THE STUDY FOR APPROXIMATELY 30% OF PATIENTS	13.8. Preventive Migraine Medications for Any Condition Allowed for the Duration of the Trial	Alignment with new template.
APPENDIX D. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS	12.1. Further Details and Clarifications on the Adverse Event Definition	Alignment with new template.
APPENDIX E. QUALITY CONTROL AND QUALITY ASSURANCE	11.2. Data Quality Assurance	Alignment with new template.
APPENDIX F. ETHICS	10.1. Regulatory and Ethical Considerations 10.3. Informed Consent Process 10.4. Data Protection 13.6. Dissemination of Clinical Trial Data	Alignment with new template.
APPENDIX G. BIRTH CONTROL METHODS AND PREGNANCY TESTING	13.1. Contraception and Pregnancy Testing	Alignment with new template.
APPENDIX H. LOST TO FOLLOW-UP	7.3. Lost to Follow-Up	Alignment with new template.
APPENDIX I. GUIDANCE ON SAFETY MONITORING	12.2. Further Details and Clarifications on the Serious Adverse Event Definition	Alignment with new template.
APPENDIX J. TOTAL BLOOD VOLUME	8.13. Total Blood Volume	Alignment with new template.
APPENDIX K. PRODUCT COMPLAINTS	8.6. Clinical Product Complaints	Alignment with new template.
APPENDIX L. DATA MANAGEMENT AND RECORD KEEPING	11.2. Data Quality Assurance 11.3. Source Data	Alignment with new template.
APPENDIX M. PUBLICATION POLICY	13.7. Publication Policy	Alignment with new template.
APPENDIX N. STORAGE AND DESTRUCTION OF BIOLOGICAL SAMPLES	8.3.4. Clinical Laboratory Tests	Handling, storage, and shipping details were removed from protocol per new template instructions.
APPENDIX O. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19	Removed Appendix and all cross references throughout document	No longer relevant as pandemic passed.

Overall Rationale for the Amendment:

The primary reason for this protocol amendment was to reduce the trial population size and relaxation of the inclusion criteria. Consequently, there was reduction in statistical power and a removal of the interim analysis. In alignment with the new protocol template, the terms "study(ies)" and "patient(s)" were updated to "trial(s)" and "participant(s)", respectively, throughout the document. In addition, where appropriate the term "test IMP" is used for the Teva product under study and the term for "placebo" was updated to "placebo IMP". A high-level description of the changes, and a brief rationale are provided in the table below. All changes are reflected in the Protocol Synopsis (Section 1.1). Minor editorial changes (typos, punctuation, etc) have also been made to the protocol (and Protocol Synopsis, as appropriate). Table 1 (Trial Procedures and Assessment), Table 2 (Investigational Medicinal Products Used in the Trial), and Table 3 (The Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device) have been revised to reflect the changes below.

Section Number and Name	Description of Change	Brief Rationale
Title page, Investigator Agreement, and Coordinating Investigator Agreement	Updated paediatric investigation plan number from P/0411/2019 to P/0378/2023	Alignment with agreed modified paediatric investigation plan for fremanezumab
1.1. Protocol Synopsis	Protocol Synopsis is reduced to 2 pages.	Alignment with new template.
1.3. Schedule of Activities	Updated footnote d of Table 1 "The date of…administration of IMP".	Clarification.
2. Introduction	Reduced to 3 pages. For additional details the reader is referred to the Investigator's Brochure. Added statement about Trial TV48125-MH-40142.	Alignment with new template. Update.
2.1.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product and/or Device	Updating heading to include "and/or Device".	Alignment with new template.
2.2.2 Overall Benefit-Risk Conclusion	Removed text "Severe hypersensitivity reactions are regarded as a potential risk for fremanezumab."	Updated as hypersensitivity reactions are no longer a potential risk.
3.1. Primary and Secondary Trial Objectives and Endpoints	Primary efficacy endpoint was updated from "…headache days of at least moderate severity…" to "…migraine days…" First 2 secondary efficacy endpoint bullets were updated. Bullet 1: changed from "migraine days" to "headache days of at least moderate severity". Bullet 2: changed from "headache days of at least moderate severity" to "migraine days".	Updated to align with other pediatric and adult trials. Updated to align with other pediatric and adult trials.

Section Number and Name	Description of Change	Brief Rationale
3.1.1.Justification of Primary Endpoint	Aligning with the change to primary endpoint from "headache days" to "migraine days".	Clarification.
3.2. Primary Estimand	Update text from headache to migraine days: "…number of migraine days during…"	Alignment with objectives.
3.4. Exploratory/Other Objectives and Endpoints	[redacted]	[redacted]
4.1. Description of Trial Design 4.1.1. Planned Number of Participants and Countries	Enrollment target was reduced from "approximately 418 patients" to "approximately 278 patients". The number of evaluable participants is planned to be "approximately 266" based on the currently observed drop-out rate of 4%. In line with the current projections and reduced sample size, trial completion date was updated from "Q4 2023" to "Q3 2026". Trial start date was updated from Q1 2020 to Q2 2020. Text on interim analysis and/or sample size re-estimation was removed.	Mitigation to the observed recruitment constrains and further trial completion delays. Mitigation to the observed recruitment constrains and further trial completion delays. Removed due to recruitment constraints and to avoid further trial completion delays.
4.4 Start of Trial and End of Trial	Suggested template text added that "trial start date is the date on which the clinical trial will be open for recruitment of participants."	Alignment with new template.
5.3. Inclusion Criteria	Inclusion criteria c was revised to "…history of ≥15 headache days per month on average during the 3 months…" and inclusion criteria e was deleted. Inclusion criteria f was updated to specify that "approximately 35% of participants" are allowed preventive medications.	Aid with recruitment.
5.4. Exclusion Criteria	Inclusion criteria d was revised to clarify that the participant's current history of a clinically significant psychiatric condition, is at the discretion of the Investigator.	Clarification.

Section Number and Name	Description of Change	Brief Rationale
6.1.1. Investigational Medicinal Products Used in the Trial	Added line "intervention type" to Table 2.	Alignment with template.
6.2.1. Justification for Test Investigational Medicinal Product and/or Device and Dose	Updating heading to include "and/or Device".	Alignment with new template.
6.8. Prior and Concomitant Therapy	Update text to specify that "Approximately 35% of participants will be allowed to remain on no more than 2 migraine preventive medications for any condition…" Text in Section 4.2 was updated accordingly. Updated text in relation to the PRN and chronic use medications.	Aid with participant retention and clarification. Clarification.
7.2. Participant Withdrawal from the Trial	Updated format to unnumbered bullets. Updated 4th bullet to clarify that participants using prohibited concomitant medications chronically should be withdrawn. Added bullet regarding suicidal ideation and/or suicidal behavior and trial withdrawal. In alignment with added device vigilance text added "and/or Device" in relation relatedness to IMP and withdrawal from trial. Removed duplicate text "The participant will be…test IMP or trial procedure is made)."	Clarification. Alignment with new template. Clarification.
7.3. Lost to Follow-Up	Updated 2nd bullet on effort to regain contact with participant deemed lost to follow up.	Alignment with new template.
8.1. Screening/Baseline Assessments and Procedures	Added new template text.	Clarification.
8.3.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis	Added text that reflex tests may be triggered automatically.	Clarification.
8.3.4.2.1. Human Chorionic Gonadotropin Tests	Removed word "other" and to clarify that "urine β-HCG tests will be performed at all visits…"	Alignment with Table 1.
8.3.7. Medication Error and Special Situations Related to the Investigational Medicinal Products	Updated to mandatory template text and removed bullets on "off-label use" and "breastfeeding" present in protocol amendment 08 (Section 7.3). Added text referencing to Section 8.6	Alignment with new template. Alignment with new template.

Section Number and Name	Description of Change	Brief Rationale
	to evaluate whether the medication error or special situation may be due to a device deficiency.	
8.4.1.1. Adverse Events	Added text on medical device vigilance.	Alignment with new template.
8.4.1.2. Serious Adverse Events	Deleted definitions of Hy's law criteria.	Alignment with new template.
8.4.1.3. Adverse Device Effects and Serious Adverse Device Effects	Added new section.	Alignment with new template.
8.4.2. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Added text on treatment-emergent adverse events.	Alignment with new template.
8.4.4. Recording of Adverse Events and Serious Adverse Events	Added text on medical device vigilance. Updated text that reporting must occur within 24 hours. Added Figure 2 Decision Tree for Adverse Events and Adverse Device Effects Classification.	Alignment with new template. Alignment with new template. Alignment with new template.
8.4.4.2. Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device	Updated heading and added text on medical device vigilance. Also in Table 3.	Alignment with new template.
8.4.4.3. Expectedness of Serious Adverse Events	Added text on medical device vigilance.	Alignment with new template.
8.4.5. Follow-Up of Adverse Events and Serious Adverse Events	Added statements related to devices and types of follow-up procedures, documentation, and reporting of updated data on serious adverse events.	Alignment with new template.
8.4.6. Reporting of Serious Adverse Events	Added text on medical device vigilance.	Alignment with new template.
8.4.7. Regulatory Reporting Requirements for Serious Adverse Events	Added text on medical device vigilance. Added new text on submission of SUSARs. Combined 2 bullets points related to modifying the protocol and/or ICF.	Alignment with new template.
8.4.8.1. Protocol-Defined Adverse Events of Special Interest that Require Reporting to Sponsor's Global PV	Removed text on COVID-19. Added "Protocol-Defined Adverse Events of Special Interest Form".	COVID-19 is no longer adverse event of special interest and does not need to be reported via same procedure as serious adverse events. Alignment with new template.

Section Number and Name	Description of Change	Brief Rationale
	Updated text to " protocol-defined adverse events…that occur before IMP (and/or PFS)…"	
8.4.9. Disease-Related Events or Outcomes not Qualifying as Adverse Events or Serious Adverse Events	Added new section.	Alignment with new template.
8.5. Pregnancy and Postpartum Information	Added new template text to clarify that females who become pregnant during trial will be withdrawn from IMP (and/or PFS). Added new template text clarifying why partners of trial participants are requested to sign an ICF. Added number of days and 24 hour reporting requirement. Added clarification that both Pregnancy and Serious Adverse Event Forms should be completed for a spontaneous abortion and for an elective abortion due to developmental anomalies.	Clarification and alignment with new template. Alignment with new template. Clarification and alignment with new template.
8.6.1.Definition of Clinical Product Complaints	Added text on medical device vigilance. Updated text that Product Complaint Form should be emailed as soon as possible after becoming aware of the issue.	Alignment with new template. Alignment with new template.
8.6.2. Handling the IMP/Devices at the Investigational Center	Updated heading and section to also include device text.	Alignment with new template
8.6.5. Device Deficiency that Could Have Led to Serious Adverse Event	Added new section relating to device vigilance, including Tables 4 and 5.	Alignment with new template.
8.7.1.Pharmacokinetic Sampling	Deleted content on handling, storage and shipment and referred to Laboratory Manual instead.	Alignment with new template.
8.9. Genetics	New section added.	Alignment with new template.
8.12. Medical Resource Utilization and Health Economics	New section added.	Alignment with new template.
8.13. Total Blood Volume	Table 6: Total Blood Volumes to be Collected from an Individual Trial Participant was relocated to here (from	Alignment with new template.

Section Number and Name	Description of Change	Brief Rationale
	Appendix J in previous version of protocol).	
9. STATISTICAL CONSIDERATIONS	New template text added.	Alignment with new template.
9.1.4. Per Protocol Analysis Set	Updated text to specify this is a subset of the Full Analysis Set.	Clarification.
9.2. Analyses Supporting Primary Objective(s) 9.2.1.Primary Endpoint 9.2.1.1.Estimand for the Primary Endpoint 9.2.2. Secondary Endpoints 9.2.3.Exploratory/Other Endpoints 9.2.4.1. Primary Efficacy Analysis 9.2.4.2. Sensitivity and Supplementary Analyses 9.3.Analysis Supporting Secondary Objective(s)	In all subsections relevant text referring to “headache days of at least moderate severity” or “migraine days” was updated where needed. Update the definition of migraine day (Section 9.2)	Alignment with updating the primary endpoint. Alignment with updating the primary endpoint.
9.2.4.1. Primary Efficacy Analysis 9.3. Analysis Supporting Secondary Objective(s)	Added text on weight subgroup analysis.”	Update
9.5. Safety Analyses	Added text on medical device vigilance.	Alignment with new template.
9.6.3. Immunogenicity Analysis	Text updated “…if data allows. This analysis will be reported separately.”	Clarification.
9.7. Interim Analyses	Interim analysis for sample size re-estimation was removed.	Removed due to recruitment constraints and to avoid further trial completion delays.
9.8. Sample Size Determination	Enrollment target was reduced from “approximately 418 patients” to “approximately 278 patients”. The number of evaluable participants is planned to be “approximately 266” based on the currently observed drop-out rate of 4%. Statistical power is consequently reduced from “at least 90% power” to “at least 80%”. Text on interim analysis and/or sample size re-estimation was removed.	Mitigation to the observed recruitment constrains and further trial completion delays.
10.1. Regulatory and Ethical Considerations	Relocated text on ”Competent Authorities and Independent Ethics Committees/Institutional Review Boards”(in Appendix L of previous version of protocol) to here.	Alignment with new template.

Section Number and Name	Description of Change	Brief Rationale
	Added ISO 14155: Clinical investigation of medical devices for human subjects – Good Clinical Practice in alignment with added text on device vigilance. Added template text "Regulation [EU] No. 536/2014 [CTR]" to the statement on applicable GCP guidelines for trial conduct. Added text to clarify that Investigator should conduct and administer the clinical trial in accordance with the protocol "and applicable regulations".	Alignment with new template.
	Added new template text "The clinical trial agreement… and/or protocol."	Alignment with new template.
	Added standard text to include multicenter trials.	Alignment with new template.
10.3. Informed Consent Process	Added new template text on informed consent when a minor reaches the age of legal competence.	Alignment with new template.
10.4. Data Protection	Added new template text.	Alignment with new template.
10.5. Early Investigational Center Closure or Trial Termination	New section and text.	Alignment with new template.
11.1. Quality Tolerance Limits	New section added.	Alignment with new template.
11.2. Data Quality Assurance	Added new template text concerning Investigator responsibilities in relation to product complaints, CRF reviews, data corrections, important protocol deviations, trial monitoring and audit and inspection.	Clarification and alignment with new template.
	Added template text describing the main responsibilities of the trial monitor(s) "…are to explain… the Investigator"…	Clarification and alignment with new template.
11.3. Source Data	Deleted duplicate text "All participant data must … to the CRF."	Alignment with new template and lean writing.
13.1.3. Pregnancy Testing	New section added.	Clarification and alignment with new template.
13.3. Prior Protocol Amendments	Added Administrative letter 06.	Update.
13.5. Recruitment Strategy	New section added.	Alignment with new template.
13.8. Preventive Migraine Medications for	Update text to specify that "the chronic use of 2 of the following concomitant medications is allowed in approximately 35% of participants".	Aid with participant retention and clarification.

Section Number and Name	Description of Change	Brief Rationale
Any Condition Allowed for the Duration of the Trial	Updated text in relation to the PRN and chronic use medications and updated text to clarify that the "regular use" of medication containing opioids and barbiturates is not allowed. Update reference to "O'Brien et al 2015"..	Clarification. Correction.
13.9. Trial Procedures and Assessments by Visit	Update bullets to clarify that serum β-HCG and urine pregnancy tests will be conducted. 1. Procedures for Screening (Visit 1, Days -28 to -1): "serum beta-human gonadotropin (β-HCG) and urine…menstrual period…" 4. End of Treatment/Early Withdrawal (Visit 5 [Day 85±3 days]) "serum β-HCG and urine pregnancy tests…"	Alignment with Section 8.3.4.2.1.

For previous amendments, the Protocol Amendment History including the Summary of Changes to the Protocol and the corresponding rationale for each change is provided in Section 13.3.

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

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

Brief Title: Randomized, Double-Blind, Placebo-Controlled Trial of Fremanezumab in Participants (6 to 17 Years) with Chronic Migraine. A Trial to Test if Fremanezumab is Effective in Preventing Chronic Migraine in Patients 6 to 17 Years of Age.

Regulatory Agency Identifier Number(s): IND number: 106,533; NDA number: not applicable; BLA number: 761089; EudraCT number: 2019-002053-33; EU CT number: not applicable

Pediatric Investigation Plan Number: P/0378/2023

Rationale: Migraine is a prevalent condition characterized by attacks of headache and associated symptoms (such as nausea, photophobia, or phonophobia). Among populations of children of all ages, migraine prevalence ranges from 8% to 11%. There is an unmet medical need for a safe and effective prophylactic treatment for episodic migraine and chronic migraine (CM) in the pediatric population. Given the progression of the disease and the knowledge gained from the adult population, it is reasonable and important to evaluate fremanezumab in the pediatric population.

Name of IMP: Fremanezumab

Intervention Type: Drug (including placebo)

Primary and Secondary Objectives, Endpoints:

Objectives	Endpoints
The **primary objective** of the trial is to evaluate the efficacy of test investigational medicinal product (IMP) as compared to placebo IMP for the preventive treatment of chronic migraine (CM).	The **primary efficacy endpoint** is the mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of IMP.
A **secondary objective** is to evaluate the safety and tolerability of test IMP in the preventive treatment of CM.	The **safety and tolerability endpoints** are as follows: • occurrence of adverse events throughout the trial, including local injection site reaction/pain • abnormal standard 12-lead electrocardiogram (ECG) findings • changes from baseline in vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate), height, and weight measurements • changes from baseline in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results • abnormal physical examination findings

Objectives	Endpoints
	• suicidal ideation and behavior as suggested by the Columbia-Suicide Severity Rating Scale (C-SSRS)
A **secondary objective** of the trial is to further demonstrate the efficacy of test IMP as compared to placebo IMP for the preventive treatment of CM.	The **secondary efficacy endpoints** are as follows: • mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP • proportion of participants reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of IMP • mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of IMP • mean change from baseline (day 1) in migraine-related disability score, as measured by the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire, at 12 weeks after administration of the first dose of IMP • mean change from baseline (day 1) in quality of life, as measured by the Pediatric Quality of Life Inventory (PedsQL), at 12 weeks after administration of the first dose of IMP
A **secondary objective** of the trial is to evaluate the immunogenicity of test IMP and the impact of antidrug antibodies (ADAs) on clinical outcomes in participants exposed to test IMP.	• proportion of participants developing ADAs throughout the trial. The impact of ADAs on safety and efficacy will be analyzed if the number of ADA-positive participants allows.

Exploratory objectives and endpoints will be assessed as well.

Overall Design: This is a 4-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, and tolerability of 2 different doses (dependent on participants' body weight) of subcutaneous (sc) test investigational medicinal product (IMP) and placebo IMP. Enrollment will include male and female participants (6 to 17 years of age, inclusive). The dose of test IMP will be determined by the participant's weight at randomization.

Number of Participants: A planned total of approximately 278 CM participants will be randomized. The number of evaluable participants is planned to be approximately 266 (133 evaluable participants completing the trial per treatment group).

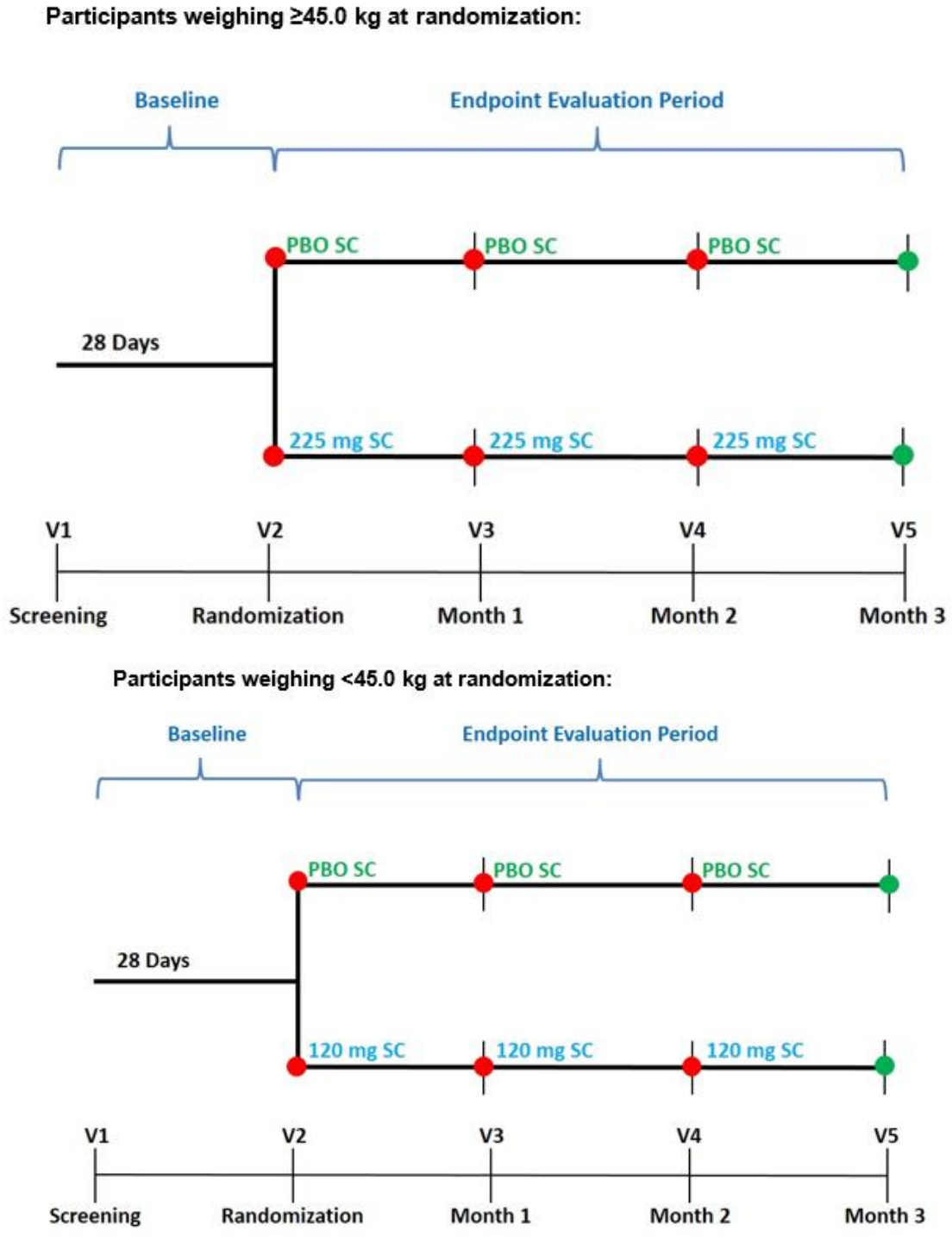
Trial Arms and Duration: Participants will be randomly assigned in a 1:1 ratio between test IMP and placebo IMP treatment groups. The total duration of the trial is planned to be 75 months (from quarter [Q]2 2020 to Q3 2026).

Data Monitoring/Other Committee: Not applicable.

Ethical Considerations: Based on the current safety profile and the demonstrated efficacy of the sc test IMP dosage form as observed in adults, the overall risk and benefit assessment for this trial is favorable.

1.2. Trial Schema

Figure 1: Overall Trial Schematic Diagram



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

1.3. Schedule of Activities

Trial 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 8 (Trial Assessments and Procedures) and Section 13.9.

Table 1: Trial Procedures and Assessments

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

Trial period	**Pretreatment period (incl. screening visit and baseline period)**	**Double-blind treatment period**			
Visit number	**V1**[a]	**V2**	**V3**	**V4**	**V5**[b]
Month number	**Month −1**	**Month 0**	**Month 1**	**Month 2**	**Month 3**
Procedures and assessments[c]	**Screening Days −28 to −1**	**Randomization Dose 1 Day 1**[d] **(+3 days)**	**Dose 2 Day 29**[d] **(±3 days)**	**Dose 3 Day 57**[d] **(±3 days)**	**EOT or early withdrawal Day 85**[d] **(±3 days)**
Vital signs measurement[l]	X	X	X	X	X
Adverse events[m,f]	X	X	X	X	X
Concomitant medication inquiry[f]	X	X	X	X	X
Clinical laboratory tests[c,n]	X		X		X
Pregnancy test[o]	X	X	X	X	X
Electronic headache diary device dispensation[p]	X				
Review electronic headache diary entries[p,f]		X	X	X	X
Electronic headache diary device return[p]					X
Blood samples for plasma drug concentration[c]		X	X		X
Blood samples for serum ADA assessment[c]		X	X		X
C-SSRS[q,f]	X	X	X	X	X
PedMIDAS[f]		X			X
PedsQL[f]		X	X	X	X
[redacted][f]					X
Administration of IMP[r]		X	X	X	

Trial period	**Pretreatment period (incl. screening visit and baseline period)**	**Double-blind treatment period**			
Visit number	**V1**[a]	**V2**	**V3**	**V4**	**V5**[b]
Month number	**Month −1**	**Month 0**	**Month 1**	**Month 2**	**Month 3**
Procedures and assessments[c]	**Screening Days −28 to −1**	**Randomization Dose 1 Day 1**[d] **(+3 days)**	**Dose 2 Day 29**[d] **(±3 days)**	**Dose 3 Day 57**[d] **(±3 days)**	**EOT or early withdrawal Day 85**[d] **(±3 days)**
Injection site assessment[c]		X	X	X	

[a] Participants will complete the screening visit no more than 28 (+3) days before the randomization visit (visit 2 [day 1]).
[b] After completing EOT assessments/procedures, all eligible participants will be offered enrollment in the long-term safety and tolerability trial (Trial TV48125-CNS-30084).
[c] Electrocardiograms will be performed, weight will be recorded (visit 2 only), urine pregnancy tests will be performed at all visits prior to dosing, and blood samples will be collected before IMP administration. Assessment of injection site reactions will be performed after administration of each dose of IMP, before the participant leaves the investigational site. All other trial procedures can be performed at any time during the visit.
[d] The date of the next visit will be calculated based on the actual date of the last administration of IMP.
[e] Must be performed prior to any trial procedure.
[f] [redacted]
[g] Eligibility criteria will be confirmed prior to randomization.
[h] Physical examination, including height and weight, will be performed at screening, randomization, and EOT. Body mass index will be calculated at screening and randomization.
[i] Puberty status (Tanner staging scale, see Section 8.3.1) will be assessed at randomization (visit 2) and EOT either by participants' self-report or by physical examination according to the Tanner staging card provided.
[j] Participants will be randomized to receive placebo IMP or 1 of 2 test IMP doses (based on body weight).
[k] Twelve-lead ECGs will be performed in triplicate at any time during the visit, prior to IMP administration.
[l] The method for measuring temperature in an individual participant must be the same at each timepoint.
[m] Inquiries about adverse events will be made before and after IMP administration.
[n] Serum chemistry, hematology, coagulation, and urinalysis.
[o] Females who are postmenarchal or ≥12 years of age only. Serum β-HCG tests will be performed at screening (visit 1) and visit 5; urine β-HCG tests will be performed at all visits. Inquire and record start/stop date of menstrual period at each visit.
[p] Eligible participants will be given an electronic headache diary device and they or a parent/caregiver will be trained in its use and compliance requirements on the day of screening. Participants or parents/caregivers will complete electronic headache diary entries about the previous day daily beginning on day -27 through the EOT/early withdrawal visit. If the participant is unable to complete the diary themselves, then a parent/caregiver will complete the diary for them.

[q] The C-SSRS will be completed by a qualified rater trained to administer the scale at the investigational center based on discussion with the participant/caregiver at the time points described. Any participant who demonstrates suicidal ideation and/or any suicidal behavior at any point during the trial should be withdrawn from the trial and discontinued from trial treatment. In addition, if a patient endorses suicidal ideation or behavior at any point during the trial (including during screening), the Investigator must explain to the participant/caregiver the need for follow-up with a mental health professional and make any necessary referrals.

[r] The location of the sc injection should be recorded at each administration visit.

β-HCG=beta-human chorionic gonadotropin; ADA=antidrug antibody; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=end-of-treatment; PedMIDAS=Pediatric Migraine Disability Assessment; PedsQL=Pediatric Quality of Life Inventory; [redacted]; sc=subcutaneous; V=visit.

2. INTRODUCTION

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

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

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

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

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

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

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

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

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

Detailed information on the test investigational medicinal product (IMP) (fremanezumab), nonclinical pharmacokinetics, toxicology studies, and clinical trials/studies are provided in the Investigator's Brochure (IB).

2.1. Purpose of Trial

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

The purpose of the trial is to determine whether the test IMP is safe and effective in the preventive treatment of migraine in pediatric participants with CM.

2.2. Summary of Benefits and Risks

2.2.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product and/or Device

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

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

2.2.2. Overall Benefit-Risk Conclusion

Mild and moderate drug hypersensitivity events were observed infrequently and with similar incidence in placebo and fremanezumab in the clinical development program, but no anaphylaxis or severe hypersensitivity reactions were seen. However, it cannot be excluded that severe events may occur in the future. Additional information regarding benefits and risks to participants may be found in the IB.

In summary, the benefit and risk assessment for fremanezumab is favorable following review of the observed clinical adult data.

3. TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Primary and Secondary Trial Objectives and Endpoints

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

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

Objectives	Endpoints
A **secondary objective** of the trial is to evaluate the immunogenicity of test IMP and the impact of antidrug antibodies (ADAs) on clinical outcomes in participants exposed to test IMP.	• proportion of participants developing ADAs throughout the trial. The impact of ADAs on safety and efficacy will be analyzed if the number of ADA-positive participants allows.

3.1.1. Justification of Primary Endpoint

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

By definition, the IHS diagnostic criteria for CM include patients that suffer ≥15 headache days per month and/or treat the headache with an acute migraine-specific medication. Headache and migraine days are defined differently in the protocol. This requirement is consistent with migraine preventive treatment guidelines and also with the Teva adult CM trial inclusion criteria.

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

3.2. Primary Estimand

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

3.3. Secondary Estimand(s)

Not applicable.

3.4. Exploratory/Other Objectives and Endpoints

[redacted]

[redacted]

4. TRIAL DESIGN

4.1. Description of Trial Design

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

The total duration of the trial is planned to be 75 months (from quarter [Q]2 2020 to Q3 2026). See Section 4.4 for the definition of the end of the trial.

Participants will be randomly assigned in a 1:1 ratio between test IMP and placebo IMP treatment groups:

- monthly sc administration of test IMP
- monthly sc administration of matching placebo IMP

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

- participants weighing ≥45.0 kg will receive monthly sc administration of test IMP at 225 mg.
- participants weighing <45.0 kg will receive monthly sc administration of test IMP at 120 mg.

The enrollment target is approximately 278 randomized participants in total. The trial consists of a screening visit, a 28-day baseline period, and a 12-week (84-day) treatment period, including a final evaluation at week 12 (end-of-treatment [EOT] visit, approximately 4 weeks [28 days] after the final dose IMP). See Section 13.5 for recruitment strategy.

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

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

Upon completion of the final trial assessments, all eligible participants will be offered enrollment in a long-term safety and tolerability trial (Trial TV48125-CNS-30084), consisting of 9 months (36 weeks) of open-label treatment and 5 months of follow-up commencing from the last IMP administration. In the long-term safety extension trial, participants rolling over from the current trial will be weighed at visit 2 and will receive monthly test IMP with dose adjusted every 3 months per weight category (225 mg in participants ≥45.0 kg or 120 mg in participants <45.0 kg). Participants who do not complete this trial and participants who complete this trial but do not wish to continue treatment may enroll in Trial TV48125-CNS-30084 for the purpose of

attending a follow-up visit for safety and antidrug antibodies (ADA) assessments approximately 5 months (150 days [5 half-lives]) after receiving the last dose of IMP.

Trial procedures and assessments with their time points are shown in Table 1. The trial schematic diagram is presented in Figure 1.

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

4.1.1. Planned Number of Participants and Countries

A planned total of approximately 278 participants will be randomized. The number of evaluable participants is planned to be approximately 266 (133 evaluable participants completing the trial per treatment group). Details on definition of evaluable participants and sample size are given in Section 9.

The trial is planned to be conducted in 6 to 10 countries in approximately 85 investigational centers.

4.1.2. Data Monitoring Committee/Safety Review Committee

There will be no Data Monitoring Committee (DMC) in this trial.

4.2. Rationale for Trial Design

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

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

Because headache consortium guidelines recommend preventive therapies for all participants with CM due to the frequency of headaches and high degree of disability, participants using no more than 2 migraine preventive medications for any condition at the time of trial enrollment will be allowed to remain on the medication if the medication has at least moderate evidence of efficacy for migraine (Silberstein et al 2012). For the purpose of this protocol, these medications are listed in Section 13.8. Participants on concomitant migraine preventive medications listed in Section 13.8 must be on a stable dose for at least 2 months prior to screening (visit 1), without anticipated changes during the trial. A list of migraine preventive medications allowed for any

condition for the duration of the trial for approximately 35% of participants is presented in Section 13.8. The total number of participants receiving concomitant preventive medication during the trial will not exceed approximately 35% of the total number of participants randomized. Randomization will be stratified by participants with and without migraine preventive medications in Section 13.8.

4.3. Access to Trial Intervention After End of Trial

For participants who do not wish to roll-over in the long term safety trial (TV48125-CNS-30084; Section 4.1) there is no access to test IMP (and/or pre-filled syringe [PFS]) after the end of the trial.

4.4. Start of Trial and End of Trial

The trial start date is the date on which the clinical trial will be open for recruitment of participants.

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

5. TRIAL POPULATION

5.1. Selection of Trial Population

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

5.2. Rationale for Trial Population

See Section 4.2.

Prospective waivers (exceptions) from trial inclusion and exclusion criteria to allow participants to be randomized/enrolled are not granted by Teva (Section 11.2).

5.3. Inclusion Criteria

Participants may be included in this trial only if they meet all of the following criteria:

a. The participants is a male or female between the ages of 6 to 17 years (inclusive) on the day of randomization to test IMP/placebo IMP.

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

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

c. [Revision 01]The participant has a clinical history of recurrent headache consistent with the diagnosis of migraine for at least 6 months before screening, consistent with ICHD-3 criteria, (Headache Classification Committee of the IHS 2013), and a history of ≥15 headache days per month on average during the 3 months prior to screening (visit 1).

d. The participant or parent/caregiver has maintained a prospectively collected headache diary during a 28-day baseline period in which headache days were recorded on 15 or more days, and 8 or more of these headache days had at least 1 of the following migraine characteristics:

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

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

- headache is preceded by an aura, as described by ICHD-3 criteria.
- headache was treated by a nonsteroidal anti-inflammatory drug, paracetamol, triptan, or ergot preparation.

e. This criterion was deleted

f. [Revision 01]Not using migraine preventive medications (listed in Section 13.8) or using no more than 2 migraine preventive medications (listed in Section 13.8) for migraine or other medical condition, as long as the dose and regimen have been stable for at least 2 months prior to screening (visit 1). A list of migraine preventive medications allowed for any condition for the duration of the trial for approximately 35% of participants is presented in Section 13.8 .

Note: A person is considered to be not using migraine preventive medications (listed in Section 13.8) when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinum toxin A or B prior to screening (visit 1). The use of other agents that are not included in Section 13.8 but used for migraine prevention is permitted during the trial; however, these participants will not be counted towards the approximately 35% participant limit threshold.

g. Females who are postmenarchal or ≥12 years of age may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at baseline or are sterile. Definitions of females of childbearing potential and females who are not of childbearing potential are given in Section 13.1.

h. Females who are postmenarchal or ≥12 years of age and sexually active must use highly effective birth control methods with their male partners for the duration of the trial (ie, starting at screening) and for 6 months after the last dose of IMP. Males who are sexually active with female partners must use a condom for the duration of the trial and for 6 months after the last administration of IMP. Further details are included in Section 13.1.

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

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

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

l. The participant weighs at least 17.0 kg on the day of randomization to test IMP/placebo IMP.

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

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

5.4. Exclusion Criteria

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

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

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

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

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

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

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

g. The participant is pregnant or nursing.

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

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

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

k. Previous participation in the Phase 1 pharmacokinetics trial (Trial TV48125-CNS-10141).

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

m. In the judgment of the Investigator, the participant has a significantly abnormal finding during the 28-day baseline period, including hematology, blood chemistry,

coagulation tests, or urinalysis values/findings (abnormal tests may be repeated for confirmation).

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

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

p. The participant has any history of alcohol or drug abuse. The definition of alcohol or drug abuse, including marijuana, is based on the Investigator's clinical judgement.

q. In the judgment of the Investigator, the participant cannot fully participate in or successfully complete the trial for its full duration for any of the following reasons:

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

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

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

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

t. The participant has a known hypersensitivity to the active substance or to any of the excipients of the IMP.

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

5.5. Lifestyle Considerations

Medications prohibited before and/or during the trial are described in Section 6.8 and the exclusion criteria (Section 5.4). Restrictions with regard to pregnancy and required laboratory values are provided in the inclusion and exclusion criteria (Section 5.3 and Section 5.4, respectively). Restrictions regarding contraception methods are detailed in the inclusion and

exclusion criteria (Section 5.3 and Section 5.4, respectively) and are also described in Section 13.1.

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

There are no additional restrictions in this trial.

5.6. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized in the trial. A minimal set of screening failure information will be entered in the Case Report Form (CRF). Minimal information includes but is not limited to demography, screening failure details, eligibility criteria, and any serious adverse events.

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

Participants may have individual parameters retested at the discretion of both the Investigator and the Sponsor.

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

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

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

6. TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1. Description of Trial Intervention(s)

6.1.1. Investigational Medicinal Products Used in the Trial

Investigational medicinal product is defined as the test IMPs and matching placebo IMPs to the respective test IMPs. The IMPs used in this trial are described in Table 2.

Table 2: Investigational Medicinal Products Used in the Trial

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

IMP name	Test IMP	Placebo IMP
Manufacturer	[redacted]	[redacted]

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

6.1.1.1. Test Investigational Medicinal Product

The formulation of test IMP to be used for clinical investigations in the pediatric population will be identical to the sc formulation of test IMP that will be used in the clinical program for adults.

Additional details may be found in the IB for test IMP.

6.1.1.1.1. Starting Dose and Dose Levels

Participants will be randomly assigned in a 1:1 ratio between test IMP and placebo IMP treatment groups:

- monthly sc administration of test IMP
- monthly sc administration of matching placebo IMP

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

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

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

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

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

6.1.1.2. Placebo Investigational Medicinal Product

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

6.2. Rationale for Trial Intervention(s)

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

Examination of the relationship between test IMP exposure and baseline body weight supports the consideration of a weight cutoff of 45.0 kg for dose selection. Participants weighing ≥45.0 kg will be administered the approved adult dose of 225 mg monthly, and participants weighing <45.0 kg will be administered 120 mg monthly based on the results of the modeling and simulation-based strategy described below.

Aside from the effects of weight on clearance and volume of distribution, other physiological differences between adults and children are not anticipated to have a significant influence on the pharmacokinetic profile of test IMP. Absorption of mAbs is believed to occur via convective transport through the lymphatic endothelium and by diffusion of antibody at the site of injection (Wang et al 2008). As such, differences in lymph flow between adults and pediatric participants may have an impact on the absorption of mAbs. Elimination of test IMP is expected to occur via proteolytic catabolism. Based on this mechanism, differences in endogenous immunoglobulin G (IgG) concentrations or neonatal Fc receptor expression may impact the pharmacokinetic profile of test IMP in children compared to adults. Although IgG1 concentrations reach adult levels by age 5, the concentrations of IgG2 (test IMP is recombinant humanized IgG2 mAb) reach adult levels more slowly (Edlund et al 2015). A 2013 investigation by Momper et al from the Food and Drug Administration (FDA) analyzed 92 products approved between 2007 and 2012 with similar adult and pediatric indications across different therapeutic areas, and 87 (94.5%) had equivalent dosing for adults and adolescent patients (Momper et al 2013).

Based on pharmacokinetic simulations, a body weight threshold of 40 kg can be generally used for pediatric participants to receive the same fixed adult dosage for mAbs (Yang et al 2019). In addition, mAbs tend to have wide therapeutic windows since they represent more targeted therapy with limited off-target toxicity; as a result, recommending a 40 kg threshold for receiving the adult dosage, with resultant pediatric exposure being within 20% to 30% above adult exposure, seems to be appropriate (Yang et al 2019). The test IMP weight cutoff is slightly higher (45 kg); hence, this reduces the likelihood to be above adult exposure. In addition, fremanezumab has a wide therapeutic dose range that was tested in Phase 2b and Phase 3 studies in adults of up to 900 mg sc monthly.

Thus, based on considerable data available in adult participants with migraine weighing ≥45 kg, in addition to the evidence supporting the lack of expected difference in pharmacokinetics between adults and adolescent participants, the use of 225 mg monthly was proposed in pediatric participants weighing ≥45 kg.

The final dose for participants <45.0 kg was determined by taking into account observed pharmacokinetic data from Trial TV48125-CNS-10141, a Phase 1 trial in pediatric participants 6 to 11 years of age (inclusive). Data from this trial (TV48125-CNS-10141) were used to refine the current adult population pharmacokinetic model (which was based on adult data from 2 Phase 1 trials [Trials LBR-101-011 and TV48125-PK-10078], 2 Phase 2b trials [Trials LBR-101-021 and LBR-101-022], and 3 Phase 3 trials [Trials TV48125-CNS-30049, TV48125-CNS-30050, and TV48125-CNS-30051 (cutoff date 30 May 2018)]), where allometric weight exponents for clearance and central volume were estimated, and a 2-compartment model with first-order absorption, elimination, and body weight effect on clearance and central volume adequately described the test IMP concentration-time data observed in pediatric participants with migraine.

This refined pediatric population pharmacokinetic model was used to simulate individual estimates of exposure for a virtual population of pediatric subjects over a range of possible test IMP doses. A population of 2400 virtual pediatric patients (6 to 17 years of age [inclusive]) was generated (200 patients per year of age) and used along with the final pediatric pharmacokinetic model estimates to simulate concentration-time data for monthly sc doses ranging from 60 to 225 mg. Virtual patients were assigned weight values based on a uniform distribution of age using growth chart data from the Centers for Disease Control. Simulated exposure measures

were calculated at steady state for the virtual pediatric patients and compared to exposure measured at steady state in the adult population receiving test IMP 225 mg sc monthly.

For virtual pediatric patients 6 to 17 years of age with baseline weight <45 kg administered 120 mg sc monthly, the simulated area under the concentration-time curve from time 0 to 28 days distribution was nearly identical to the adult participant distribution following administration of 225 mg sc monthly. Very similar patterns were observed for average concentration and minimum drug concentration. The simulated maximum concentration distribution following 120 mg sc monthly in the pediatric population suggests slightly higher maximum concentration than that achieved in the adult population following 225 mg sc monthly; however, overall, the upper exposure range extends only slightly above the upper range of the adult exposures.

Additional simulations of dose selection for pediatric participants weighing <45 kg was also performed with an alternative pediatric population pharmacokinetic model with the fixed allometric exponents (ie, 0.75 for clearance and 1.0 for volume). However, the apparent over-prediction of observed exposures from the Phase 1 pharmacokinetic pediatric trial (Trial TV48125-CNS-10141) with this model led to an under prediction of the selected dose needed to achieve exposures comparable to those in adults receiving 225 mg sc test IMP.

Considering the wide safety margin for f test IMP with substantial evidence supporting the safety of the approved dose of 225 mg sc monthly in adults, the expected exposures in pediatric participants weighing <45 kg after administration of 120 mg sc monthly fall well within the exposure range of adults receiving doses up to 900 mg sc monthly; where 675 mg sc monthly and 900 mg sc monthly were administered in the adult Phase 2b trials and were found to be safe and well tolerated. Safety margin data from a nonclinical study in juvenile rats indicate that at the no observed adverse effect level dose of 450 mg/kg/week (see IB), calculated safety margins range from 16- to 22-fold higher than expected pediatric clinical exposure based on a population pharmacokinetic model. It is therefore concluded that in nonclinical studies, adequate safety margins are calculated even when considering higher exposure in the pediatric population.

Given the wide safety margin of test IMP with considerable evidence supporting the safety of the approved dose of 225 mg sc monthly in adults, and to minimize the risk of decreased efficacy in this pediatric population, the 120 mg monthly dose level was selected for participants aged 6 to 17 years (inclusive) with weight values <45.0 kg based on targeting the achievement of a similar distribution of test IMP exposure levels (following multiple dosing) of 225 mg monthly in adult participants with EM and CM.

The formulation of test IMP to be used for clinical investigations in the pediatric population will be identical to the sc formulation of test IMP that was used in the clinical program for adults.

6.2.2. Justification for Use of Placebo Investigational Medicinal Product

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

The use of a placebo IMP rather than an active comparator is justified in this trial because of the limited availability of a suitable comparator. Topiramate is the only migraine preventive

medication approved for pediatric populations, but it is not approved in all regions of the EU and is limited to adolescents ages 12 through 17, so this medication would be off-label for those participants ages 6 through 11.

6.3. Dosing and Administration

See Section 6.1.1.1.1.

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

6.4. Treatment of Overdose

See Section 8.3.7.

6.5. Preparation, Handling, Labeling, Storage, and Accountability

6.5.1. Storage Conditions and Handling

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

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

Further guidance is provided in the Pharmacy Manual.

6.5.2. Labeling

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

6.5.3. Accountability

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

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

Only participants enrolled in the trial 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 trial materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal Investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused PFS and vials of IMP will be destroyed at the investigational center in accordance with investigational center Standard Operating Procedures (SOPs) or will be disposed of, retained, or returned to the Sponsor or designee per Sponsor instructions.

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

6.6. Participant Assignment, Randomization, and Blinding

6.6.1. Participant Assignment and Randomization

This is a double-blind trial. The Sponsor, Investigators, trial staff (except for staff involved in bioanalytical analyses), and participants will be blinded to treatment assignment. A computer-generated master randomization list will be provided to drug packaging facilities. Packaging vendor(s) will package active and placebo into single-visit kits according to Good Manufacturing Practice procedures. The active drug and placebo kits for each dose will be identical in appearance and will contain 1 PFS (for the 225 mg dose and its matching placebo) or 2 vials (for the 120 mg dose and its matching placebo). Adequate kit supply for upcoming trial visits will be managed by interactive response technology (IRT) and kept (refrigerated at 2°C to 8°C) on site.

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

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

6.6.2. Maintenance of Randomization

Participant randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of analysis (after the end of trial), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant SOP.

6.6.3. Blinding and Unblinding

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

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 participant's IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes, indicating the IMP assignment for each randomized participant, will be available to the Investigator(s) or pharmacist(s) at the investigational center via the Randomization and Trial Supply Management system, both via telephone and internet. Breaking of the treatment code can always be performed by the Investigator without prior approval by the Sponsor; however, the Sponsor should be notified following breaking of the treatment code. The participant's IMP assignment should not be revealed to the Sponsor.

When a blind is broken, the participant will be withdrawn from the trial and the event will be recorded on the CRF. The circumstances leading to the breaking of the code should be fully documented in the Investigator's trial files and in the participant's source documentation. Assignment of IMP should not be recorded in any trial documents or source document.

In blinded trials, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 8.4.4.2), Global Pharmacovigilance (Global PV) 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 trial, and analysis and reporting of the data.

6.7. Trial Intervention Compliance

The Investigator will be responsible for monitoring participant compliance. If the Investigator or the Sponsor determines that the participant is not in compliance with the trial protocol, the Investigator and the Sponsor should determine whether the participant should be withdrawn from the trial. The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) should be notified.

6.8. Prior and Concomitant Therapy

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

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

Approximately 35% of participants will be allowed to remain on no more than 2 migraine preventive medications for any condition, provided the medication is recognized to have at least moderate evidence of efficacy or is commonly used. For the purpose of this protocol, these medications are listed in Section 13.8. Additional details on migraine preventive medications are provided in Section 13.8. For chronic use of these medications for any indication, participants must have been on a stable, well-tolerated dose of this migraine preventive medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the trial. For the remaining approximately 65% of participants, these medications are not allowed for migraine or for any other indications. As needed (PRN) use of these medications are allowed during the course of the trial for any indications and do not have to have established dosing regimens. PRN use of these medications should be reported in the eCRF as concomitant medications. Participants should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the prescribing information or local treatment guidelines.

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

The chronic use of concomitant therapies not listed in Section 13.8 for any indication is allowed throughout the course of the trial. All participants must have been on a stable dose of these concomitant medications for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the trial. PRN use of medications for adverse events or intercurrent acute situations are allowed.

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

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

Concomitant medication and treatment will be recorded until visit 5.

7. DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1. Discontinuation of Trial Intervention

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

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

The participant must be withdrawn from the IMP if the participant experiences a severe hypersensitivity reaction or anaphylaxis.

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

A participant who is randomized/enrolled but does not complete the treatment period will not be replaced (see Section 9.8).

All protocol-specified procedures/assessments should be performed at the EOT/early withdrawal visit (see Table 1).

7.2. Participant Withdrawal from the Trial

Each participant is free to withdraw from the trial or discontinue from IMP at any time, without prejudice to their continued care. Participants must be withdrawn from the trial if any of the following events occur:

- Participant withdraws consent or requests discontinuation from the IMP or withdrawal from the trial for any reason.
- Participant develops an illness that would interfere with his/her continued participation.
- Participant is noncompliant with the trial procedures and assessments or administration of IMPs in the opinion of the Investigator.
- Participant takes prohibited concomitant medications chronically.

- A female participant has a confirmation of pregnancy during the trial from a positive pregnancy test.
- The Sponsor requests withdrawal of the participant.
- Participant experiences an adverse event or other medical condition indicating to the Investigator that continued participation is not in the best interest of the participant.
- Any participant who demonstrates suicidal ideation and/or any suicidal bahavior at any point during the trial should be withdrawn from the trial and discontinued from trial treatment.

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

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

See Section 7.3 for information regarding how the trial will define and address lost to follow-up participants to help limit the amount and impact of missing data.

If the reason for withdrawal from the trial 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 participant is referred to the care of a health care professional, or until a determination of a cause unrelated to the IMP [and/or PFS] or trial procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; both the adverse events page and the relevant page of the CRF will be completed at that time.

The Investigator must inform the Trial Leader as soon as possible of each participant who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a participant is withdrawn from the trial for multiple reasons that also include adverse events, the relevant page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the Investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the participant. In such a case, the reason for discontinuation would be “need to take a prohibited medication,” not the adverse event.

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

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

7.3. Lost to Follow-Up

A participant 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 participant fails to return to the investigational center for a required trial visit:

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

7.4. Trial Stopping Rules

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

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

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

If the whole trial or arms of the trial are stopped, the participants that are terminated early will be followed according to criteria outlined in Section 7.2.

8. TRIAL ASSESSMENTS AND PROCEDURES

8.1. Screening/Baseline Assessments and Procedures

A signed and dated ICF will be obtained before screening procedures commence (see Section 10.3). Procedures performed at screening are listed in Table 1 and Section 13.9.

Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations. Participants will acknowledge and agree to the possible use of this information for the trial by giving informed consent.

Participants may have individual parameters retested at the discretion of both the Investigator and the Sponsor (also see Section 5.6).

Participants who fulfil the inclusion criteria and meet none of the exclusion criteria at the screening visit may be enrolled in the trial.

8.2. Efficacy Assessments and Procedures

Data from any efficacy assessments performed after the specified time (see Table 1) will not be collected on the CRF; in the event, however, that such data are collected, these data will not be analyzed.

8.2.1. Electronic Headache Diary

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

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

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

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

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

8.2.2. Pediatric Migraine Disability Assessment

The Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire is a 6-item instrument to assess migraine-related disability in pediatric participants, which can be self-administered by the participant or administered by a caregiver. It has been validated in patients aged 4 through 18 years (Hershey et al 2001) and includes questions related to the impact of headache on school performance, disability at home (eg, inability to do chores or homework), and social/sport functioning.

8.2.3. [redacted]

[redacted]

8.2.4. Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) 4.0 is a brief 23-item health-related quality of life instrument that evaluates quality of life in 4 areas of functioning: physical, emotional, social, and school functioning. The PedsQL 4.0 has 4 age ranges: toddlers (2 through 4 years), young child (5 through 7 years), child (8 through 12 years), and adolescent (13 through 18 years). This trial will use the young child, child, and adolescent formats. The PedsQL version that will be

used for the participant for the duration of the trial will be based on the age of the participant at visit 2 and will not change during the course of the trial.

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

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

8.3. Safety Assessments and Procedures

In this trial, safety will be assessed by qualified trial personnel by evaluating reported adverse events, vital signs measurements, clinical laboratory test results, ECG findings, physical examination findings (including body weight and height measurements), suicidal ideation and behavior (as suggested by the Columbia-Suicide Severity Rating Scale [C-SSRS]), and use of concomitant medication.

8.3.1. Physical Examinations

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

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

A complete physical examination will include the following organ systems: general appearance; head, eyes, ears, nose, and throat; chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Any physical examination finding that is judged by the Investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 8.4.5.

8.3.2. Vital Signs

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

Before pulse and BP are measured, the participant must be in a supine or semi-erect/seated position and resting for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given participant. For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the Investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 8.4.5.

8.3.3. Electrocardiograms

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

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

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

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

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

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

Any ECG finding that is judged by the Investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 8.4.5.

8.3.4. Clinical Laboratory Tests

Safety samples will be stored for a short period of time in the central laboratory until analysis and destruction.

Specific details regarding central laboratory storage and destruction can be found in the trial Laboratory Manual and the central laboratory's SOPs.

8.3.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis

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

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the Investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event and monitored as described in Section 8.4.5. An adverse event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the participant from the trial, the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic work-up. (Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a participant from entering the trial or receiving IMP are not considered adverse events.)

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

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected hepatitis, HIV, or Lyme disease, a blood sample may be taken at screening at the discretion of the Investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed in Section 13.2. Note, reflex tests (eg, red blood cell [RBC] shapes, RBC morphology, and other microscopic findings) may be triggered automatically.

8.3.4.2. Other Laboratory Tests

8.3.4.2.1. Human Chorionic Gonadotropin Tests

Serum β-HCG tests will be performed for all female participants who are postmenarchal or ≥12 years of age at screening (visit 1) and visit 5; urine β-HCG tests will be performed at all visits (Table 1). Any participant who becomes pregnant during the trial will be withdrawn. Procedures for reporting the pregnancy are provided in Section 8.5.

8.3.5. Suicidal Ideation and Behavior Risk Monitoring

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

8.3.6. Assessment of Local Tolerability and Pain

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

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

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

Injection site reactions will be recorded as adverse events as described in Section 8.4.1.1 and Section 9.5.1.

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

Any administration of IMP that is not in accordance with the trial protocol should be reported as a protocol deviation and documented in the participant's source documents (see Section 11.2), regardless of whether or not an adverse event occurs as a result.

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care professional, participant, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the Sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.

The Investigator should refer to Section 8.6 to evaluate whether the medication error or special situation may be due to a device deficiency.

8.4. Adverse Events and Serious Adverse Events

8.4.1. Definitions of Adverse Events and Serious Adverse Events

8.4.1.1. Adverse Events

Adverse events are categorized according to ICH guidelines and adverse device effects are categorized and classified according to ISO standard 14155. The procedures for device deficiencies that are not associated with an adverse event, as well as those that are associated with an adverse event or that have the potential to cause a serious adverse event, are described in Section 8.6.

An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily 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 trial, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to fremanezumab.

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

- a new condition or the worsening of a preexisting condition
- intercurrent illnesses
- physical injuries and the mechanism that caused the injury
- events possibly related to concomitant medication
- drug/drug or drug/device interactions
- events occurring during diagnostic procedures or during any washout phase of this trial
- laboratory or diagnostic test abnormalities (note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a participant from entering the trial or receiving trial treatment are not considered adverse events

Worsening of the disease under study that occurs during the trial that is not typical of the participant's daily symptoms or leads to the participant's discontinuation will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before trial entry and do not worsen during this trial will not be considered adverse events.

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

8.4.1.2. Serious Adverse Events

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 a life-threatening adverse event (ie, the participant 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 participant signed the ICF will not be considered serious adverse events, unless there was worsening of the preexisting condition during the participant's participation in this trial.
- 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 participant 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 liver injury that meets the criteria for Hy's Law; 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.

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

See Section 12.2 for guidance regarding monitoring participants with elevated liver function tests.

8.4.1.3. Adverse Device Effects and Serious Adverse Device Effects

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

A serious adverse device effect results in any of the consequences characteristic of a serious adverse event (Section 8.4.1.2) and is reported per Section 8.4.7.

8.4.2. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

For recording of serious adverse events, the trial period is defined for each participant as that time period from signature of the ICF to visit 5 (EOT visit). Serious adverse events occurring in a participant after visit 5 (EOT visit) should be reported to the Sponsor if the Investigator becomes aware of them, following the procedures described in Section 8.4.7.

Treatment-emergent adverse events are defined as adverse events that occurred after the first dose of IMP (and/or PFS) was administered through the end of the trial.

8.4.3. Identifying Adverse Events and Serious Adverse Events

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

8.4.4. Recording of Adverse Events and Serious Adverse Events

All adverse events that occur during the defined trial period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP (and/or PFS). The Investigator will record all relevant information regarding every adverse event/serious adverse event and will categorize each as guided in Figure 2. For serious adverse events and protocol-defined adverse events of special interest for expedited reporting to Global PV, the Serious Adverse Event and Protocol-Defined Adverse Events of Special Interest Form must be completed and the serious adverse event and the protocol-defined adverse events of special interest must be reported within 24 hours (Section 8.4.7). The Investigator does not need to actively monitor participants for new adverse events after the end of the trial.

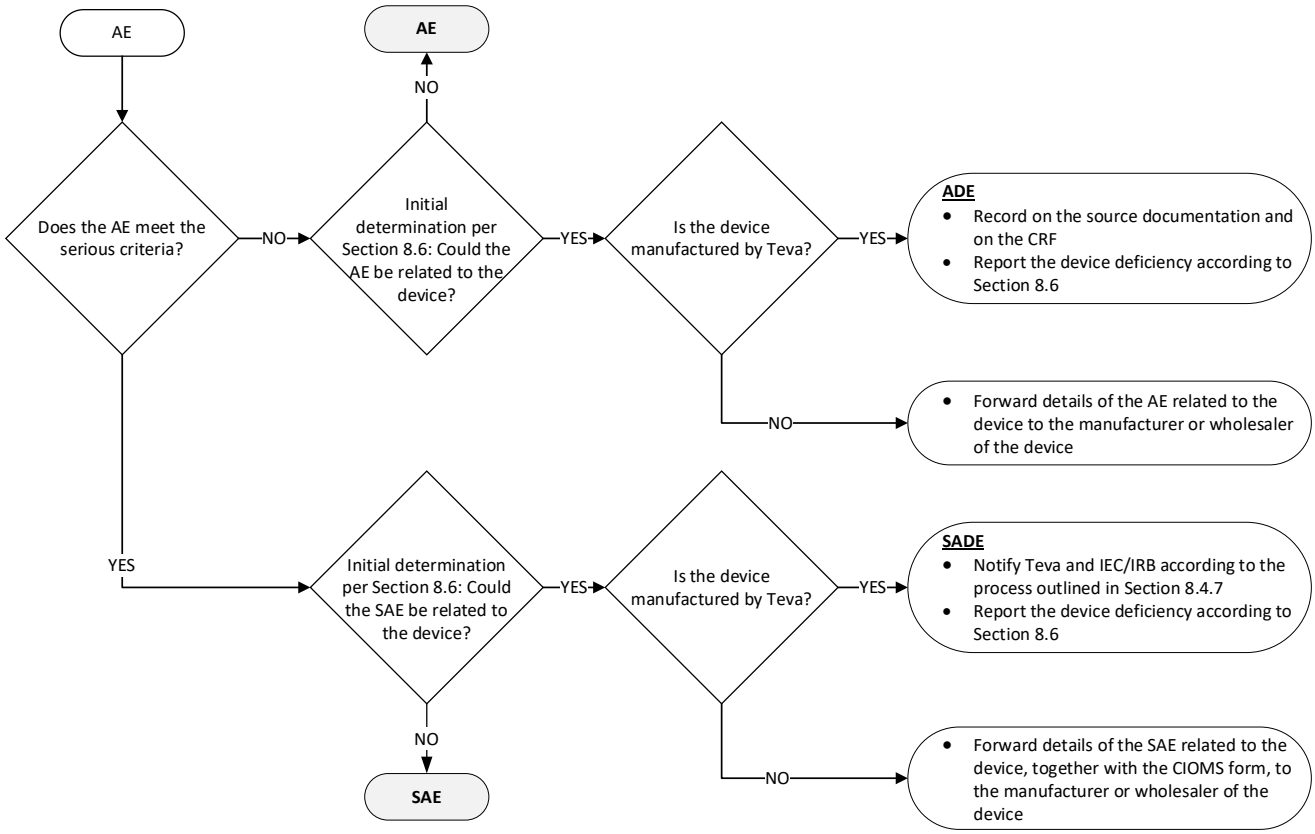
Serious adverse events and/or serious adverse device effects occurring in a participant after the end of trial should be reported to the Sponsor if the Investigator becomes aware of them, following the procedures described in Section 8.4.7.

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

The relationship of each adverse event to IMP (and relationship to the device, if applicable), and the severity and seriousness of each adverse event, as judged by the Investigator, must be recorded.

The Investigator should make an initial determination whether the adverse event may be related to a device deficiency, using Figure 2, Table 4, and Table 5.

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



AE=adverse event; ADE=adverse device effect; CIOMS=Council for International Organizations of Medical Sciences; CRF=case report form; IEC=Independent Ethics Committee; IRB=Institutional Review Board; SADE=serious adverse device effect; SAE=serious adverse event.

Further details are given in the Safety Monitoring Plan.

8.4.4.1. 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

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

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

Table 3: The Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device

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

IMP=investigational medicinal product; PFS=pre-filled syringe.

8.4.4.3. Expectedness of Serious Adverse Events

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 trial is the IB.

The Sponsor's Global PV will determine the expectedness for all serious adverse events.

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

An unanticipated serious adverse device effect for the integral medical device developed by the Sponsor is a serious adverse effect caused by, or associated with, the device that is not listed in Section 8.6.5, Table 4 and Table 5.

8.4.5. Follow-Up of Adverse Events and Serious Adverse Events

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the participant is referred for continued care to a healthcare professional; or until a determination of a cause unrelated to the IMP (and/or PFS) or trial procedure is made.

The Investigator may perform additional laboratory tests or investigations, histopathological examinations, or consult with other healthcare professionals to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible.

If a participant dies during participation in the trial or during a recognized follow-up period, the Investigator will provide postmortem findings including histopathology, if available, within the Serious Adverse Event Form.

New or updated information will be recorded in the originally submitted documents.

The Investigator will submit any updated data on serious adverse events to Global PV within 24 hours of receipt of the information, following the process described in Section 8.4.7.

8.4.6. Reporting of Serious Adverse Events

To satisfy regulatory requirements, the Investigator must report all serious adverse events that occur during the trial, regardless of the judgment of relationship to administration of the IMP (and/or PFS), to the Sponsor except for serious adverse events listed in Section 8.4.9. The Investigator must report the event within 24 hours of learning 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 Serious Adverse Event Form should be sent to the Local Safety Officer (LSO) or designee (as applicable, for eg, a contract research organization [CRO]) in a country without a Sponsor LSO); the LSO will forward the report to the Sponsor's Global PV.

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 (and/or PFS), trial procedures, and to underlying disease.

The Investigator should forward additional information (follow-up) about any serious adverse event unavailable at the initial reporting within 24 hours of when it becomes known, following the same process as for the initial report.

The process for serious adverse device effect reporting to Global PV is the same as for serious adverse event reporting.

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

- trial number
- Investigator and investigational center identification
- participant number
- onset date and detailed description of adverse event

- Investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility, reasonable possibility)

Additional information includes:

- age and sex of participant
- 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)

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the Pregnancy Form (see Section 8.5).

8.4.7. Regulatory Reporting Requirements for Serious Adverse Events

If a serious unexpected adverse event (ie, the event fulfills the criteria for a SUSAR) or serious adverse device effect is believed to be related to the IMP (and/or PFS), the Sponsor will take appropriate steps to notify all Investigators participating in sponsored clinical trials of fremanezumab and the appropriate competent authorities (and IRB/IEC, as applicable).

For all countries, the Sponsor's Global PV will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for submission to the competent authorities, IRBs/IECs, and Investigators, according to regulations. For trials in the EEA, submission of SUSARs is done centrally to European Medicines Agency (EMA) by the Global PV. The Investigator must ensure that the IRB/IEC is also informed of the event, in accordance with national and local regulations.

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

In addition to notifying the Investigators and competent authorities (and IRB/IEC, if appropriate), other measures may be required, including the following:

- modifying the protocol and/or ICF
- discontinuing or suspending the trial
- modifying listings of expected toxicities to include adverse events newly identified as related to fremanezumab (and/or PFS).

8.4.8. Adverse Events of Special Interest

8.4.8.1. Protocol-Defined Adverse Events of Special Interest that Require Reporting to Sponsor's Global PV

For purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to the Sponsor's Global PV for evaluation: ophthalmic-related adverse events of at least moderate severity and severe hypersensitivity or anaphylactic reactions. Hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al 2006). The clinical criteria for diagnosing anaphylaxis are provided in Section 12.1. In the event of suspected anaphylaxis, vital signs (including oxygen saturation and respiration rate) will be measured.

The process for reporting a protocol-defined adverse event of special interest is the same as that for reporting a serious adverse event (Section 8.4.6), using the same Serious Adverse Event/Protocol-Defined Adverse Events of Special Interest Form. Protocol-defined adverse events of special interest to be reported to Global PV can be either serious or nonserious, according to the criteria outlined in Section 8.4.1. Protocol-defined adverse events of special interest that occur before IMP (and/or PFS) administration do not require reporting to Global PV.

Adverse events of special interest for pediatric participants are not listed in the Pediatric Investigation Plan or Pediatric Study Plan.

8.4.9. Disease-Related Events or Outcomes not Qualifying as Adverse Events or Serious Adverse Events

Disease state is an efficacy variable for this trial and should be captured on the eCRF; accordingly, disease-related manifestations should not be recorded as adverse events unless assessed as more severe than the participant's usual disease course. Disease manifestations that are more severe than the participant's usual course of disease and meet the criteria for a serious adverse event should be reported as a serious adverse event.

8.4.10. Protocol Deviations Because of an Adverse Event

If a participant experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure participant safety, after the event has stabilized or treatment has been administered (or both), the Investigator or other physician in attendance must contact the Clinical Leader as soon as possible to discuss the situation. The Investigator, in consultation with the Sponsor, will decide whether the participant should continue to participate in the trial.

8.5. Pregnancy and Postpartum Information

Any female participant becoming pregnant during the trial will discontinue IMP (and/or PFS) and will be withdrawn from the trial.

All pregnancies of women participating in the trial and female partners of men participating in the trial , if applicable that occur during the trial or within at least 5 half-lives (ie, 6 months) or 180 days from last IMP dose, whichever is longer, are to be reported within 24 hours from Investigator awareness. The completed Pregnancy Form should be sent to the LSO/CRO (as applicable, for eg, a CRO in a country without a Sponsor LSO); the LSO will forward the report to the Sponsor's Global PV. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the Pregnancy Form (Section 8.4.7).

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

Because there is lack of data on human teratogenicity, genotoxicity, fetotoxicity, or spermatoxicity for this IMP, female partners of men participating in the trial who become pregnant will be asked to sign an ICF. All female participants and female partners of men participating in the trial 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 trial and any complication of pregnancy that the Investigator becomes aware of after withdrawal from the trial will be reported as an adverse event or serious adverse event, as appropriate.

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

- For a spontaneous abortion, report as a serious adverse event (both Pregnancy and Serious Adverse Event Forms should be completed).
- For an elective abortion due to developmental anomalies, report as a serious adverse event (both Pregnancy and Serious Adverse Event Forms should be completed).
- For an elective abortion **not** due to developmental anomalies, report on the Pregnancy Form; do not report as an adverse event.

8.6. Clinical Product Complaints

8.6.1. Definition of 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 and/or clinical device supplies used in a clinical research trial sponsored by Teva.

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

Examples of a clinical product complaint include, but are not limited to, the following:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling)
- 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 deficiency eg, any inadequacy of an investigational medical device or combination product with respect to its identity, quality, durability, reliability, usability, safety, or performance. This includes malfunctions, use errors, inadequate labeling (eg, unintelligible label, incorrect expiry date)

Each investigational center will be responsible for detecting, documenting, and reporting a clinical product complaint by completing the Product Complaint Form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com as soon as possible after becoming aware of the issue.

Reporting a complaint must not be delayed even if not all the required information can be immediately obtained. Known information must be immediately reported. The Sponsor will collaborate with the Investigator to obtain any outstanding information.

Once the complaint has been investigated by the Sponsor, when required, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

If the clinical product complaint is related to a device, comparator, co-medication, rescue medication, or any other product planned in the protocol not manufactured by Teva, the complaint will be forwarded to the manufacturer/wholesaler of that product.

8.6.2. Handling the IMP/Devices at the Investigational Center

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

If it is determined that the investigational center must return all IMP (and/or PFS), the Sponsor will provide the information needed to handle the return.

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

8.6.3. Product Complaint Associated with Adverse Events or Serious Adverse Events

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting of the adverse event or serious adverse event (Section 8.4.2 to Section 8.4.7).

8.6.4. 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
- participant identifier (participant trial number) and corresponding visit numbers, if applicable
- product name and strength for open-label trials
- participant number, bottle, and kit numbers (if applicable) for double-blind or open-label trials
- 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 trials) Yes/No
- date and name of person receiving the complaint

8.6.5. Device Deficiency that Could Have Led to Serious Adverse Event

Device deficiencies that could have led to serious adverse events are defined as deficiencies that might have led to a serious adverse device effect if (see Figure 2):

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

These device deficiencies shall be reported to the IRB/IEC by the Investigator and to the regulatory authorities by the Sponsor or manufacturer (for devices not manufactured by the Sponsor) according to the national and local regulations.

The Investigator will record in the source documentation a description of the complaint, the initial determination whether the device deficiency could have led to a serious adverse event, and any actions taken to resolve the complaint and to preserve the safety of the participant.

The Investigator should use Table 4, and Table 5 to help make an initial determination whether the device deficiency could have led to a serious adverse event and include this assessment in the Product Complaint Form.

Table 4: Anticipated Use-Related Deficiencies and Their Potential Hazards and Serious Harms

Use step	Use error	Potential hazard situation	Potential harm
Obtain sharps container and dispose of the device	Syringe not disposed of correctly after use	Needle stick third party	Third party death
Check that IMP name appears on device	Failure to check IMP information.	Incorrect medicament injected	Participant death
Store carton within the refrigerator	Fail to store product correctly	Participant exposed to toxic substance due to degraded drug	Permanent impairment or life threatening injury
Inspect the device	Fail to perceive or recognize a need to visually inspect the device; Incorrect mental model of what would be considered to constitute 'damage'; Expiration date check not completed; Misread the expiration date; etc.	Inject degraded or expired IMP	Toxicity – Permanent impairment or life threatening injury

IMP=investigational new drug.

Table 5: Anticipated Design-Related Deficiencies and Their Potential Hazards and Serious Harms

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

Device component	Failure mode	Potential hazard situation	Potential harm
Syringe label	Label is illegible	User is exposed to toxic substance	Toxicity - Permanent impairment or life threatening injury
Syringe label	Misinformation or label is incorrect.	User is exposed to toxic substance or degraded drug	Permanent impairment or life threatening injury
Product IFU	Misinformation or missing information. IFU is incorrect or incomplete.	User is exposed to toxic substance or degraded drug	Permanent impairment or life threatening injury

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

8.7. Pharmacokinetics

Sampling for pharmacokinetics will be sparse. Thus, the test IMP pharmacokinetic samples will be analyzed using a population pharmacokinetic approach and will be reported separately from the clinical study report (CSR).

Samples from participants who receive test IMP will be analyzed for fremanezumab using a validated method. Samples from participants who receive placebo IMP will not be analyzed.

8.7.1. Pharmacokinetic Sampling

Blood samples (2 mL) will be collected via venipuncture or indwelling catheter at the time points detailed in Table 1 for plasma concentration measurements of fremanezumab.

The dates and times of IMP administration and each pharmacokinetic sample will be recorded on the source documentation and transcribed onto the CRF.

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

Assessment of ECG should precede pharmacokinetic blood sampling (see Table 1).

8.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this trial.

8.9. Genetics

Genetic parameters are not evaluated in this trial.

8.10. Biomarkers

Biomarkers are not evaluated in this trial.

8.11. Immunogenicity Assessments

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

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

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

8.12. Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this trial.

8.13. Total Blood Volume

The total blood volume to be collected for each participant in this trial is approximately 48 mL, as summarized in Table 6.

Table 6: Total Blood Volumes to be Collected from an Individual Trial Participant

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

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

9. STATISTICAL CONSIDERATIONS

This section describes the statistical analysis as foreseen at the time of planning the trial. 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.

The analysis will be conducted on all participant data at the time the trial ends.

9.1. Analysis Sets

9.1.1. Safety Analysis Set

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

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

9.1.2. Intent-to-Treat Analysis Set

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

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

9.1.3. Full Analysis Set

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

9.1.4. Per-Protocol Analysis Set

The per-protocol analysis set will consist of all participants in the FAS who have completed the trial without any important deviations, such as important inclusion/exclusion criteria deviations, important deviations or omissions of the IMP administration, or unexpected drug concentration findings, and who have at least 75% diary compliance after the start of treatment.

9.1.5. Trial Population

The ITT analysis set (Section 9.1.2) will be used for all trial population summaries unless otherwise specified. Summaries will be presented by treatment group and for all participants.

9.1.5.1. Participant Disposition

Data from participants screened; participants screened but not randomized and reason not randomized; participants who are randomized; participants randomized but not treated; participants in the ITT, safety, and other analysis sets;participants who complete the trial; and participants who withdraw from the trial will be summarized using descriptive statistics. Data from participants who withdraw from the trial will also be summarized by reason for withdrawal using descriptive statistics.

9.1.5.2. Demographic and Baseline Characteristics

Participants demographic and baseline characteristics, including medical history, prior medications, and 12-lead ECG findings, will be summarized by treatment group using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be provided. For categorical variables, participant counts and percentages will be provided. Categories for missing data will be presented, if necessary.

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

9.2. Analyses Supporting Primary Objective(s)

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

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

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

9.2.1. Primary Endpoint

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

9.2.1.1. Estimand for the Primary Endpoint

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

9.2.2. Secondary Endpoints

The secondary efficacy endpoints are as follows:

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

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

9.2.3. Exploratory/Other Endpoints

[redacted]

[redacted]

9.2.4. Planned Method of Analysis

The FAS (see Section 9.1.3) will be used for all efficacy analyses. Summaries will be presented by treatment group.

9.2.4.1. Primary Efficacy Analysis

The primary efficacy endpoint, the mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of IMP, will be analyzed using an analysis of covariance method. The model will include treatment, sex, puberty status, region, baseline weight category (<45.0 kg or ≥45.0 kg), and preventive medication use at baseline (Yes/No) as fixed effects and baseline number of migraine days as a covariate. Ninety-five percent confidence intervals will be constructed for the least squares mean differences between the test IMP group and the placebo IMP group. A hierarchical procedure will be used to control Type 1 error rate, as described in Section 9.2.6.

9.2.4.2. Sensitivity and Supplementary Analyses

A sensitivity analysis for the primary efficacy endpoint will be conducted by using multiple imputation method for missing data. Sensitivity analysis using Mixed-Effect Model Repeated Measure method also will be conducted for change from baseline to months 1 through 3 in migraine days. A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint. Additional subgroup analyses will be performed to investigate treatment effect among relevant sub-populations, such as sex, region, receiving preventive migraine therapy or not, receiving 2 preventive medications (Section 13.8), and receiving alternative preventive medications that belong to the same classes but are not listed in Section 13.8. The details will be described in the statistical analysis plan.

9.2.5. Data Handling Conventions

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

9.2.5.1. Handling of Withdrawals and Missing Data

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

9.2.6. Multiple Comparisons and Multiplicity

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

The order of secondary endpoint analyses will in general follow the sequence listed in Section 9.2.2. Final order and details will be confirmed in the statistical analysis plan, which will be finalized before database lock.

9.3. Analysis Supporting Secondary Objective(s)

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

9.4. Analysis of Exploratory Objective(s)

[redacted]

9.5. Safety Analyses

Safety analyses will be performed on the safety analysis set (Section 9.1.1).

Safety assessments and time points are provided in Table 1.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each participant will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the Investigator to be related to test IMP (and/or PFS) (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, serious adverse device effects, protocol-defined adverse events of special interest, adverse events, and adverse device effects causing withdrawal from the trial. Summaries will be presented by treatment group and for all participants. Participant listings of serious adverse events, serious adverse device effects, adverse events, and adverse device effects leading to withdrawal will be presented.

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

Suicidal ideation and behavior will be measured using the C-SSRS. Data for participants with positive findings will be listed.

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

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

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

9.5.1. Tolerability Analysis

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

- Assessment of injection site erythema, induration, and ecchymosis will be recorded according to measurements: 5 to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe).
- Injection site pain will be recorded using the 11-point numerical rating scale and will be mapped to mild, moderate, or severe, according to patricipant's self-report of pain intensity, as described for the recording of headache pain in Section 8.2.1.
- Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.

Tolerability will be assessed by the following:

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

Local tolerability findings will be listed and summarized descriptively.

9.6. Other Analyses

9.6.1. Pharmacokinetic Analysis

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

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

9.6.2. Pharmacokinetic/Pharmacodynamic Analysis

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

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

9.6.3. Immunogenicity Analysis

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

9.7. Interim Analyses

There will be no formal interim analysis.

9.8. Sample Size Determination

The sample size planned is approximately 266 participants (133 evaluable participants completing the trial per treatment group). Assuming a treatment difference of 1.7 days (reduction in monthly average number of headache days of at least moderate severity) and a common SD of 4.92, a sample size of 133 participants per treatment group gives at least 80% power for the trial to succeed at an alpha level of 0.05. Assuming a 4% discontinuation rate, approximately 278 participants (139 participants per treatment group) will be randomized. Participants will be randomized to receive either monthly sc administration of test IMP or placebo IMP.

9.9. Protocol Deviations

Information related to protocol amendments and deviations are provided in Section 11.2.

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

10. GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1. Regulatory and Ethical Considerations

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

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

Compliance Statement

This trial will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for GCP E6, ISO 14155: Clinical investigation of medical devices for human subjects – Good Clinical Practice, and any applicable national and local laws and regulations (eg, Title 21CFR Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, Regulation [EU] No. 536/2014 [CTR] regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The Investigator is responsible for performing the clinical trial 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 trial in accordance with the protocol and applicable regulations will be documented in separate clinical trial agreements with the Sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The clinical trial agreement shall outline the Investigator's and the institution's responsibilities with respect to the conduct of the clinical trial, including the Investigator's reporting obligation to the Sponsor for suspected cases of serious breach from GCP and/or protocol.

The Investigator is responsible for ensuring the privacy, health, and welfare of the participants during and after the clinical trial; and must ensure that trained personnel are immediately available in the event of a medical emergency. The Investigator and the involved clinical trial personnel must be familiar with the background and requirements of the trial; 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 trial at that/each investigational center and for contacts with trial management, with the IRB/IEC, and with competent authorities.

See Section 10.3 for the ethics expectations of informed consent or assent, Section 10.4 for confidentiality regarding trial participants, Section 13.6 for requirements for registration of the clinical trial, and Section 13.7 for the publication policy.

10.2. Committees

There will be no DMC in this trial.

10.3. Informed Consent Process

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

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

The Investigator, or a qualified person designated by the Investigator, should fully inform the participant and each parent/legally acceptable representative of all pertinent aspects of the trial, including the written information approved by the IRB/IEC, per local regulations. All written and oral information about the trial will be provided in a language as nontechnical as practical to be understood by each parent/legally acceptable representative and the participant. The participant and each parent/legally acceptable representative should be given ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. The above should be detailed in the source documents.

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

If, during the trial, a minor reaches the age of legal competence to give informed consent as defined in national law, his or her informed consent shall be obtained before that participant can continue to participate in the clinical investigation.

10.4. Data Protection

Data protection and confidentiality

All personal data will be processed in accordance with applicable data protection law.

Teva has implemented appropriate technical, physical, organizational, and administrative information, and privacy security measures to protect the confidentiality, integrity, and availability of data in its systems. Teva's Information Security Team keeps the measures under continuous review to align with state-of-the-art standards, taking into account the nature and context of the processing. Teva systems and policies are aligned with industry-standard

information security and privacy frameworks such as ISO 27001 covering categories of security controls including:

- Access Control
- Awareness and Training
- Backup and Recovery
- Change Control
- Encryption and Communication Controls
- Identity and Authentication
- Incident Response and Recovery
- Logging, Monitoring, and Alerting
- Media Protection
- Operations Control
- Personnel Security
- Physical and Environmental
- Program and Risk Management
- System and Communications Protection
- Third Party/Supplier Relationship Control

Teva employs an Information Security Team and where needed, Teva also leverages independent data security experts.

Teva employs a Cyber Defense Center to direct and coordinate all security incident activity.

Teva has implemented Incident Response and Recovery policies and processes to identify and respond to security incidents and/or data breaches both internally as well as from other involved third parties. These policies cover the full Incident Response and Recovery lifecycle from initial response/notification through triage and mitigation activities to recovery and root-cause resolution. Teva also has a "Global Privacy Incident and Breach Reporting Policy" to address a privacy incident or breach (suspected or confirmed).

Where personal data is stored, transmitted, or processed externally utilizing third parties, Teva employs appropriate contractual language, and other controls requiring the third party to employ appropriate information security controls and protections to guard the confidentiality, integrity, and availability of such data.

Teva has completed Data Protection Impact Assessments in respect of the processing of personal data gathered in the course of clinical trials.

Teva trains its staff as regarding the handling of personal data in accordance with applicable law. This includes training on how to recognize, respond to, and mitigate a personal data breach.

Teva has implemented role-based access which means that personal data will only be available to those who need access.

The confidentiality of participant data is protected. For eg, participant data will be randomized and blinded in accordance with Section 6.6; and Teva staff are subject to a contractual obligation of confidentiality.

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

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

10.5. Early Investigational Center Closure or Trial Termination

For clinical investigational centers located in the EU, a declaration of the end of the clinical trial will be made in accordance with the procedures outlined in Directive 2001/20/EC, Article 10(c) or Regulation (EU) No. 536/2014 (CTR), as applicable, for other countries, local regulations will be followed.

The Sponsor or designee reserves the right to close the investigational center or terminate the trial at any time for any reason at the sole discretion of the Sponsor. In such cases, investigational centers will be closed upon trial completion. An investigational center is considered closed when all required documents and trial supplies have been collected and an investigational center closure visit has been performed.

The Investigator may initiate investigational center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational center by the Sponsor or Investigator may include but are not limited to:

For trial termination:

- Discontinuation of further trial intervention development.

For investigational center termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor’s procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

11. GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1. Quality Tolerance Limits

Quality Tolerance Limits are not evaluated in this trial.

11.2. Data Quality Assurance

Refer to Section 8.6 for the definition of a clinical product complaint or device deficiency and Investigator responsibilities in the management of a clinical product complaint or device deficiency. Further details are given in a Pharmacy Manual.

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this trial.

Oversight will be carried out as described in the Sponsor's SOPs for clinical trials. Day to day data management tasks for this trial are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical trials at that organization. These SOPs will be reviewed by the Sponsor before the start of data management activities.

Data will be verified by the trial 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 Clinical Data Management System (CDMS) and any discrepancies will be queried.

CRFs received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this trial. Logical checks will be implemented to ensure data quality and accuracy. 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. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the trial, the CDMS and all other trial data will be locked to further additions or corrections. Locking the trial 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.

Protocol Amendments and Protocol Deviations

Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IRB/IEC and national and local

competent authorities, as applicable, except when necessary to address immediate safety concerns to the participants or when the change involves only nonsubstantial logistics or administration. The Principal Investigator at each investigational center, the Coordinating Investigator (if applicable), and the Sponsor will sign the protocol amendment.

Important Protocol Deviations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the participants in the trial and/or (b) the scientific value of the trial will be considered an important protocol deviation. Important protocol deviations may include non-adherence on the part of the participant, 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. Important protocol deviations will be documented by investigational center personnel. All important protocol deviations will be reported to the responsible IRB/IEC, as required.

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

If a participant experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure participant safety, the Investigator or other physician in attendance must contact the Clinical Leader as soon as possible to discuss the situation. The Investigator, in consultation with the Sponsor, will decide whether the participant should continue to participate in the trial.

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

Information to Trial Personnel

The Investigator is responsible for giving information about the trial to all personnel members involved in the trial or in any element of participant management, both before starting the trial and during the course of the trial (eg, when new personnel become involved). The Investigator must ensure that all trial personnel are qualified by education, experience, and training to perform their specific task. These trial 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 trial, as necessary.

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

Trial Monitoring

To ensure compliance with GCP guidelines, the trial monitor or representative is responsible for ensuring that participants have signed the ICF and the trial is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines. Details of the

monitoring procedures are outlined in the trial's monitoring plan which is maintained by the Sponsor.

The trial monitor is the primary association between the Sponsor and the Investigator. The main responsibilities of the trial monitor(s) are to explain the protocol to all trial staff including the Investigator, visit the Investigator before, during, and after the trial 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 participants before they participate in the trial and when changes to the consent form are warranted, in accordance with IRB/IEC approvals.

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

If electronic CRFs are used for the trial, the trial monitor will indicate verification by electronically applying source document verification flags to the CRF and will ensure that all required electronic signatures are being implemented accordingly.

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

In case of an emergency situation (eg, the COVID-19 pandemic), where trial monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with global and/or local regulations.

Audit and Inspection

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

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

In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be audited remotely, where allowed, and in accordance with global and/or local regulations.

11.3. Source Data

Direct Access to Source Data and Documents

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

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

The medical experts, trial monitors, auditors, IRB/IEC, 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, video images, and recordings) for source data verification, provided that participant confidentiality is maintained in accordance with national and local requirements.

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

Data Collection

Data will be collected using CRFs that are specifically designed for this trial. The data collected on the CRFs will be captured in a 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 trial-specific training. After they are trained, users will be provided with individual system access rights.

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

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, eDiary data, electronic patient reported outcomes tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol.

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

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

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

Investigator Responsibilities

The Investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the trial 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 ICFs

- participant identification lists
- CRFs for each participant on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, eDiary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with Sponsor, the IRB/IEC, and any competent authority

The Investigator will retain all records related to the trial 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 trial completion, or earlier in the case of the investigational center closing or going out of business, the Investigator reasonably determines that trial 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 trial 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 trial records.

See Section 13.4 for financial and insurance information.

12. APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

12.1. Further Details and Clarifications on the Adverse Event Definition

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 BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

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

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

Source: Sampson et al 2006.

12.2. Further Details and Clarifications on the Serious Adverse Event Definition

12.2.1. Guidance on Safety Monitoring

Guidance on Monitoring Participants with Elevated Liver Function Tests

Liver enzymes (ALT, AST, gamma glutamyl transpeptidase [GGT], and ALP) as well as total bilirubin[1] will be measured at each trial visits 1, 3, and 5.

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

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

Elevation of Either ALT or AST to ≥3× ULN

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

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

[1] In case total bilirubin is >ULN, then direct bilirubin will be checked.

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

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

- the baseline value was within the normal range and ALT or AST is still ≥3× the ULN
- the baseline value was above the ULN and ALT or AST is ≥2× the baseline value

Additional Tests/Evaluations

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

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

ALT or AST ≥3× (>3.5× the ULN if the Baseline Value Is >2.5× the ULN) but Less Than 5× the ULN

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

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

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

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

- ALT, AST, GGT, ALP, total and direct bilirubin, CBC and differential count (to assess for eosinophilia), and INR should be monitored twice a week.
- At least for every other measurement, the tests should be sent to the central laboratory. The rest of the tests may be sent to a local laboratory. The INR should always be sent to a local laboratory.

ALT or AST ≥8× the ULN

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

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

Stopping Rules

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

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

Follow-Up of Liver Enzymes After Stopping Rules Are Met

- A participant who meets the above criteria for discontinuation of the IMP should be invited to the site to return the IMP. Early withdrawal visit activities should be performed as soon as possible.
- Liver enzymes should be monitored until normalization or stabilization of the abnormality, according to the discretion of the Investigator.
- In any case, following the early withdrawal visit, the minimal follow-up period will be 30 days and will include measurement of liver enzymes at least once weekly (may be performed in local laboratory, with at least 1 test being sent to the central laboratory).
- Every effort should be made to complete the additional tests/evaluations, as described above.
- Every effort should be made to ensure that the participant continues to receive ongoing evaluation and treatment by their primary care physician after withdrawal from the trial.

13. APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1. Contraception and Pregnancy Testing

13.1.1. Definitions Related to Childbearing Potential

Females of childbearing potential are defined as the following:

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

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

- premenarchal and <12 years of age

13.1.2. Contraception

Description of different birth control methods

Highly effective birth control methods:

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

- Progestogen-only hormonal contraception (oral, injectable, and implantable) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP
- Progestin and estrogen contraceptives (oral only) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP
- Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before screening
- Bilateral tubal occlusion
- Vasectomized partner, provided that he is the sole sexual partner and has received medical assessment of the surgical process
- Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

Unacceptable birth control methods:

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

Male contraception

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

13.1.3. Pregnancy Testing

Beta-human chorionic gonadotropin (β-HCG) tests in serum or urine will be performed for all woman of childbearing potential at the time points as specified in Table 1 and, if clinically indicated, thereafter:

- Refer to Section 5.3 for pregnancy testing inclusion criteria.
- Additional pregnancy tests (HCG in urine or serum) may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the trial.

13.2. Clinical Laboratory Tests

Table 7: Clinical Laboratory Tests

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

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

13.3. Prior Protocol Amendments

Administrative Letter 06 Dated 21 December 2021

ADMINISTRATIVE LETTER 06

Study number: TV48125-CNS-30082

Clinical Study Protocol with Amendment 08

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

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002053-33

21 December 2021

Dear Investigator:

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

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

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

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

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

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VV-00067507 v2.0

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

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

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

Before	After
Each patient is free to withdraw from the study or discontinue from IMP at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur: (New bullet added)	*Each patient is free to withdraw from the study or discontinue from IMP at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur:* • ***Any patient who demonstrates suicidal ideation and/or any suicidal behavior at any point during the study should be withdrawn from the study and discontinued from study treatment.***

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

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

Sincerely [redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

Amendment 08 Dated 09 December 2021

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

Original text with changes shown	New wording	Reason/justification for change
3.1. General Study Design and Study Schematic (Other sections affected by this change: 3.2, 9.1, and 9.12)		
An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (standard deviation [SD]) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% of patients have completed at least 3 months of treatment or have withdrawn from the study early. If the pooled SD is less than 5.4, the sample size will not be changed; if the pooled SD is greater than 6, the sample size ~~may~~ will increase to approximately 600 patients; and if the pooled SD is between 5.4 and 6, the sample size ~~may~~ will increase to approximately 500 patients total.	An interim analysis with blinded sample size re-estimation will be conducted by evaluating the pooled variability (standard deviation [SD]) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% of patients have completed at least 3 months of treatment or have withdrawn from the study early. If the pooled SD is less than 5.4, the sample size will not be changed; if the pooled SD is greater than 6, the sample size will increase to approximately 600 patients; and if the pooled SD is between 5.4 and 6, the sample size will increase to approximately 500 patients total.	Added interim analysis language.
The enrollment target is approximately 418 patients in total with potential increase (up to approximately 600 patients total) depending on the planned interim analysis of blinded sample size re-estimation (Section 9.12). ~~The goal in the 12- through 17-year-old age group is to enroll similar numbers of patients who are 12 through 14 years old and 15 through 17 years old~~.	The enrollment target is approximately 418 patients in total with potential increase (up to approximately 600 patients total) depending on the planned interim analysis of blinded sample size re-estimation (Section 9.12).	Removal of language regarding similar number of patients for each age group and the addition of interim analysis language.
3.3. Justification for Study Design and Selection of Population (Other sections affected by this change: 4.1)		
A list of migraine preventive medications allowed for any condition for the duration of the study for up to 30% of patients is presented in Appendix C.	A list of migraine preventive medications allowed for any condition for the duration of the study for up to 30% of patients is presented in Appendix C.	Clarification
Table 1: Study Procedures and Assessments		

Original text with changes shown	New wording	Reason/justification for change
[c] Electrocardiograms will be performed, weight will be recorded (visit 2 only), urine pregnancy tests will be performed at all visits prior to dosing, and blood samples will be collected before study drug administration. Assessment of injection site reactions will be performed after administration of each dose of study drug, before the patient leaves the investigational site. All other study procedures can be performed at any time during the visit.	[c] Electrocardiograms will be performed, weight will be recorded (visit 2 only), urine pregnancy tests will be performed at all visits prior to dosing, and blood samples will be collected before study drug administration. Assessment of injection site reactions will be performed after administration of each dose of study drug, before the patient leaves the investigational site. All other study procedures can be performed at any time during the visit.	Clarification
4.1. Patient Inclusion Criteria		
-headache was treated by a nonsteroidal anti-inflammatory drug (NSAID), paracetamol, triptan, or ergot preparation.	-headache was treated by a nonsteroidal anti-inflammatory drug (NSAID), paracetamol, triptan, or ergot preparation.	Paracetamol is added as it is a commonly used acute medication
f. Note: A person is considered to be not using preventive medications when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinum toxin A or B prior to screening (visit 1). The use of other agents that are not included in Appendix C but used for migraine prevention is permitted during the study; however, these patients will not be counted towards the 30% patient limit threshold.	f. Note: A person is considered to be not using preventive medications when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinum toxin A or B prior to screening (visit 1). The use of other agents that are not included in Appendix C but used for migraine prevention is permitted during the study; however, these patients will not be counted towards the 30% patient limit threshold.	Clarification
m. The patient has a body mass index ranging from the 5th to 120% of the 95th percentile, inclusive, at screening, based on the local standard.	m. The patient has a body mass index ranging from the 5th to 120% of the 95th percentile, inclusive, at screening, based on the local standard.	Expansion of patient body mass index to allow representation of real-world patient population
4.2. Patient Exclusion Criteria		
b. The patient has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine or in the head or neck area for any condition during the 2 months prior to the day of the screening visit.	b. The patient has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine or in the head or neck area for any condition during the 2 months prior to the day of the screening visit.	Clarification
g. The patient is pregnant~~, nursing, or taking a combined estrogen and progestogen hormonal contraceptive~~ or nursing.	g. The patient is pregnant or nursing.	Change reflecting allowance of combination contraception

Original text with changes shown	New wording	Reason/justification for change
o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <~~90~~ 75 mL/min/1.73m^2, as calculated by the revised Schwartz formula (~~CrCl=[~~eGFR=[0.413×Ht]/serum creatinine), or evidence of renal disease during the 28-day baseline period.	o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <75 mL/min/1.73m^2, as calculated by the revised Schwartz formula (eGFR=[0.413×Ht]/ serum creatinine), or evidence of renal disease during the 28-day baseline period.	Clarification of Schwartz formula, reflecting the administrative letter
p. The patient has any history of alcohol or drug abuse. The definition of alcohol or drug abuse, including marijuana, is based on the investigator's clinical judgement.	p. The patient has any history of alcohol or drug abuse. The definition of alcohol or drug abuse, including marijuana, is based on the investigator's clinical judgement.	Clarification on alcohol and drug abuse, including marijuana.
See New wording column.	u. The patient has a current or past medical history of hemiplegic migraine.	Addition of an exclusion criterion
Table 2: Investigational Medicinal Products Used in the Study		
[redacted]	[redacted]	Change updating manufacturer name for the test and placebo investigational medicinal product s
5.6. Prior and Concomitant Medication or Therapy		
All prior therapy, medication, or procedure (ie, procedures for the treatment of migraine [eg, nerve blocks]) for the treatment of migraine a patient has had during their lifetime will be recorded on the CRF.	All prior therapy, medication, or procedure (ie, procedures for the treatment of migraine [eg, nerve blocks]) for the treatment of migraine a patient has had during their lifetime will be recorded on the CRF.	Clarification
6.1.4. Pediatric Quality of Life Inventory		
The Pediatric Quality of Life Inventory (PedsQL) 4.0 is a brief 23-item health-related quality of life instrument that evaluates quality of life in 4 areas of functioning: physical, emotional, social, and school functioning. The PedsQL 4.0 has 4 age ranges: toddlers (2 through 4 years), young child (5 through 7 years), child (8 through 12 years), and adolescent (13 through 18 years). This study will use the young child, child, and adolescent formats. The PedsQL version that will be used	The Pediatric Quality of Life Inventory (PedsQL) 4.0 is a brief 23-item health-related quality of life instrument that evaluates quality of life in 4 areas of functioning: physical, emotional, social, and school functioning. The PedsQL 4.0 has 4 age ranges: toddlers (2 through 4 years), young child (5 through 7 years), child (8 through 12 years), and adolescent (13 through 18 years). This study will use the young child, child, and adolescent formats. The PedsQL version that will be used for the patient	Clarification

Original text with changes shown	New wording	Reason/justification for change
for the patient for the duration of the study will be based on the age of the patient at visit 2 and will not change during the course of the study.	for the duration of the study will be based on the age of the patient at visit 2 and will not change during the course of the study.	
7.9. Assessment of Suicidality		
The C-SSRS, combined with the investigator's clinical evaluation, will be used to assess whether the patient has suicidal ideation or behavior and its severity (Posner et al 2011).	The C-SSRS, combined with the investigator's clinical evaluation, will be used to assess whether the patient has suicidal ideation or behavior and its severity (Posner et al 2011).	Clarification
9.5.4.2. Sensitivity and Supplementary Analyses		
A sensitivity analysis for the primary efficacy endpoint will be conducted by using multiple imputation method for missing data. Sensitivity analysis using Mixed-Effect Model Repeated Measure method also will be conducted for change from baseline to months 1 through 3 in headache days of at least moderate severity. A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint. Additional subgroup analyses will be performed to investigate treatment effect among relevant sub-populations, such as sex, region, receiving preventive migraine therapy or not, receiving 2 preventive medications from Appendix C, and receiving alternative preventive medications that belong to the same classes but are not listed in Appendix C. The details will be described in the statistical analysis plan.	A sensitivity analysis for the primary efficacy endpoint will be conducted by using multiple imputation method for missing data. Sensitivity analysis using Mixed-Effect Model Repeated Measure method also will be conducted for change from baseline to months 1 through 3 in headache days of at least moderate severity. A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint. Additional subgroup analyses will be performed to investigate treatment effect among relevant sub-populations, such as sex, region, receiving preventive migraine therapy or not, receiving 2 preventive medications from Appendix C, and receiving alternative preventive medications that belong to the same classes but are not listed in Appendix C. The details will be described in the statistical analysis plan.	Clarification of additional subgroup analyses
Appendix C. PREVENTIVE MIGRAINE MEDICATIONS FOR ANY CONDITION ALLOWED FOR THE DURATION OF THE STUDY FOR UP TO 30% OF PATIENTS (Other sections affected by this change: 3.3, 4.1, 5.6)		
The chronic use of two of the following concomitant ~~preventive migraine~~ medications are allowed in up to ~~20~~ 30% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients using no more than 2 migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication. Patients must have been on a stable,	The chronic use of two of the following concomitant medications are allowed in up to 30% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients using no more than 2 migraine preventive medications for any condition at the time of study enrollment will be allowed to remain on the medication. Patients must have been on a stable, well-tolerated dose of this medication for at least	Clarification of preventative migraine medications to reflect real-world use

Original text with changes shown	New wording	Reason/justification for change
well-tolerated dose of this medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 70% of patients, the chronic use of these medications are not allowed for migraine or for any other indications. As-needed (PRN) use of these medications are allowed during the course of the study. PRN use of these medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary PRN use is defined as any treatment regimen outside of the locally approved prescribing information or local treatment guidelines.	2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 70% of patients, the chronic use of these medications are not allowed for migraine or for any other indications. As-needed (PRN) use of these medications are allowed during the course of the study. PRN use of these medications should be reported in the eCRF as concomitant medications. Patients should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the locally approved prescribing information or local treatment guidelines.	
~~• Other: riboflavin, magnesium~~	See Original text with changes shown	Removal of riboflavin and magnesium from the Appendix C as they are not prescribed medicines
Other agents that are not on this list but used for migraine prevention that may be used per local guidelines or clinical practice preference are considered to have doubtful efficacy for migraine prevention and therefore are treated the same as other concomitant medications and DO NOT need to be captured in eCRF pages specific for migraine preventive medications.	Other agents that are not on this list but used for migraine prevention that may be used per local guidelines or clinical practice preference are considered to have doubtful efficacy for migraine prevention and therefore are treated the same as other concomitant medications and DO NOT need to be captured in eCRF pages specific for migraine preventive medications.	Clarification
APPENDIX G. BIRTH CONTROL METHODS AND PREGNANCY TESTING		
• Progestin and estrogen contraceptives (oral only) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP	• Progestin and estrogen contraceptives (oral only) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP	Change allowing for oral progestin and estrogen contraceptives
Appendix O. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19		
See New wording column.	Section 5.6 Prior and Concomitant Medication or Therapy There is currently no data available regarding the concomitant use of fremanezumab and the new COVID-19 vaccines. Based on Teva's knowledge of both fremanezumab and what has been	Clarification regarding the COVID-19 vaccination.

Original text with changes shown	New wording	Reason/justification for change
	published about the respective vaccines, Teva has no reason to believe there would be an interaction. However, the investigator should use his/her medical judgement regarding any concerns related to an individual patient. We do recommend not giving the 2 injections, the study drug, and the vaccines in the same arm if the injections are administered close together in time, as it would be difficult to tell which one caused any potential reaction. If logistically possible, we would recommend waiting at least 72 hours between the receipt of the vaccine and the subsequent dose of fremanezumab in order to allow for better attribution of causality should an adverse event occur after administration. As with any concomitant medicaion, the vaccine should be recorded in the source documentation and in the electronic data capture.	

Administrative Letter 05 Dated 10 May 2021

ADMINISTRATIVE LETTER 05

Study number: TV48125-CNS-30082

Clinical Study Protocol with Amendment 07

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

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002053-33

10 May 2021

Dear Investigator:

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

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

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

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

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

5/10/2021 | 1:13:43 PM EDT

Administrative Letter 04 Dated 04 February 2021

ADMINISTRATIVE LETTER 04

Study number: TV48125-CNS-30082

Clinical Study Protocol with Amendment 07

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

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002053-33

04 February 2021

Dear Investigator:

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

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

Before	After
[redacted]	[redacted]

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

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

DocuSigned by:
[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

2/4/2021 | 12:22:01 PM EST

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

Administrative Letter 03 Dated 05 November 2020

ADMINISTRATIVE LETTER 03

Study number: TV48125-CNS-30082

Clinical Study Protocol with Amendment 07

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

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002053-33

05 November 2020

Dear Investigator:

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

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

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

The final wording without tracked changes will be as follows:

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

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

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

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

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

Amendment 07 Dated 20 August 2020

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

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

Changes to the Protocol

Original text with changes shown	New wording	Reason/justification for change
TITLE PAGE		
See New wording column.	**COVID-19 pandemic-related operational updates are provided in Appendix O.**	Sentence was added to provide a link to the operational guidance for COVID-19 contained in Appendix O.
1.1. Introduction		
See New wording column.	In September 2018, fremanezumab was approved in the United States of America (US) for the preventive treatment of migraine in adults and marketed under the trade name AJOVY®. Fremanezumab has also been approved in the European Union (EU) and a number of countries worldwide.	Sentences were added to provide context regarding the regulatory status of fremanezumab in the adult population.
3.1. General Study Design and Study Schematic (Other sections affected by this change: 3.5)		
The total duration of the study is planned to be 48 months (from ~~approximately~~ Q1 2020 to Q4 2023).	The total duration of the study is planned to be 48 months (from Q1 2020 to Q4 2023).	Revised as quarter is an approximation.
See New wording column.	For coronavirus disease 2019 (COVID-19) updates, see Appendix O.	Updated sections to cross-references the addition of Appendix O.

Original text with changes shown	New wording	Reason/justification for change
3.2. Planned Number of Patients and Countries		
The study is expected to start in Q1 2020 and last until ~~approximately~~ Q4 2023.	The study is expected to start in Q1 2020 and last until Q4 2023.	Revised as quarter is an approximation.
Table 1 Study Procedures and Assessments		
c Electrocardiograms will be performed and blood samples will be collected before study drug administration. Assessment of injection site reactions will be performed after administration of each dose of study drug, before the patient leaves the investigational site. All other study procedures can be performed at any time during the visit.	c Electrocardiograms will be performed and blood samples will be collected before study drug administration. Assessment of injection site reactions will be performed after administration of each dose of study drug, before the patient leaves the investigational site. All other study procedures can be performed at any time during the visit.	Footnote "c" was modified to specify that ECGs will be performed before study drug administration.
See New wording column.	Table 1 has been modified as follows: f This procedure/assessment may be performed remotely for patients who are not able to go to the investigational center or if the investigational center staff are not able to see patients at the investigational center due to unforeseen circumstances.	Footnote "f" was added to identify the procedures/assessments that may be performed remotely.
k Twelve-lead ECGs will be performed in triplicate at any time during the visit, prior to study drug administration.	k Twelve-lead ECGs will be performed in triplicate at any time during the visit, prior to study drug administration.	Footnote "k" was modified to specify that ECGs will be performed before study drug administration.
m Inquiries about adverse events will be made before and after study drug administration. ~~Postdose inquiries will be made before the patient leaves the study center.~~	m Inquiries about adverse events will be made before and after study drug administration.	Revised as adverse event inquiries are not mandated to occur on site.
q The C-SSRS ~~Baseline/Screening version~~ will be completed by a qualified rater trained to administer the scale at the investigational center ~~the physician based on discussion with the patient/caregiver at visit 1 (screening visit), and the C-SSRS Since Last Visit version will be completed by the physician~~ based on discussion with the patient/caregiver at ~~all other~~ the time points described.	q The C-SSRS will be completed by a qualified rater trained to administer the scale at the investigational center based on discussion with the patient/caregiver at the time points described.	Revised for simplicity as the C-SSRS does not need to be completed specifically by a physician.
4.1. Patient Inclusion Criteria		
m. The patient has a body mass index ranging from the 5th to the ~~90~~95th	m. The patient has a body mass index ranging from the 5th to the 95th percentile, inclusive, at screening.	This inclusion criterion was changed to allow patients at a higher BMI percentile to be

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

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

Amendment 06 Dated 27 July 2020

The primary reason for this amendment is to revise the protocol in accordance with the conditions for approval of the clinical trial application received from the Voluntary

Harmonisation Procedure (VHP). This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment and Written Request agreements. All major changes to the protocol body are listed below in the table and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Changes to the Protocol

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

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

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

Administrative Letter 02 Dated 07 July 2020

ADMINISTRATIVE LETTER 02

Study number: TV48125-CNS-30082

Clinical Study Protocol with Amendment 05

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

IND number: 106,533; BLA number: 761089; EudraCT number: 2019-002053-33

07 July 2020

Dear Investigator:

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

[redacted]

The change to Section 6.1.3 is provided below:

[redacted]

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

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

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

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

Amendment 05 Dated 27 June 2020

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

Changes to the Protocol

Original text with changes shown	New wording	Reason/justification for change
3.3. Justification for Study Design and Selection of Population		
Migraine is a condition that starts from childhood or adolescence and progresses into adulthood. Among populations of children of all ages, migraine prevalence ranges from 8% to 11% (Abu-Arafeh et al 2010, Abu-Arefeh and Russell 1994, Laurell et al 2004, Ozge et al 2013, Stovner and Andree 2010). Additionally, there is an unmet need for the treatment of migraine in pediatric patients as there are limited therapy options available for this patient population. Throughout Teva's development program for adults, fremanezumab had demonstrated statistically and clinically significant superior efficacy over placebo. It is also well tolerated in the adult migraine population. Given the progression of the disease and the knowledge gained from the adult population, it is reasonable and important to evaluate fremanezumab in the pediatric population.	Migraine is a condition that starts from childhood or adolescence and progresses into adulthood. Among populations of children of all ages, migraine prevalence ranges from 8% to 11% (Abu-Arafeh et al 2010, Abu-Arefeh and Russell 1994, Laurell et al 2004, Ozge et al 2013, Stovner and Andree 2010). Additionally, there is an unmet need for the treatment of migraine in pediatric patients as there are limited therapy options available for this patient population. Throughout Teva's development program for adults, fremanezumab had demonstrated statistically and clinically significant superior efficacy over placebo. It is also well tolerated in the adult migraine population. Given the progression of the disease and the knowledge gained from the adult population, it is reasonable and important to evaluate fremanezumab in the pediatric population.	This paragraph was added to provide context for conducting a study in vulnerable patients.
Section 4.1. Patient Inclusion Criteria		
b. The patient's parent(s) or legal guardian(s) must give written informed consent, and the patient must give assent (in accordance with local regulations). **Note:** In some countries, patients aged 15 to 17 years (inclusive) may give written informed consent; however, the patient's parent(s) or legal guardian(s) must be informed, per local regulations.	b. The patient's parent(s) or legal guardian(s) must give written informed consent, and the patient must give assent (in accordance with local regulations). **Note:** In some countries, patients aged 15 to 17 years (inclusive) may give written informed consent; however, the patient's parent(s) or legal guardian(s) must be informed, per local regulations.	Inclusion criterion b was revised to specify that some countries may allow patients aged 15 to 17 years to give written informed consent, per local regulations.
Section 4.2. Patient Exclusion Criteria		
d. The patient has a current history of a clinically significant psychiatric condition, any prior history of a suicide attempt, or a history of suicidal ideation with a specific plan within the past 2	d. The patient has a current history of a clinically significant psychiatric condition, any prior history of a suicide attempt, or a history of suicidal ideation with a specific plan within the past 2	Exclusion criterion was revised to specify that exclusion of a patient based on clinically significant

Original text with changes shown	New wording	Reason/justification for change
years, at the discretion of the investigator.	years, at the discretion of the investigator.	psychiatric condition is at the discretion of the investigator.
e. The patient has an ongoing infection or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, ~~or~~ chronic hepatitis B or C, or a known active infection of coronavirus disease 2019 (COVID-19).	e. The patient has an ongoing infection or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, chronic hepatitis B or C, or a known active infection of coronavirus disease 2019 (COVID-19).	Exclusion criterion was revised to exclude those with a known active COVID-19 infection.
g. The patient is pregnant, nursing, or taking a combined estrogen and progestogen hormonal contraceptive.	g. The patient is pregnant, nursing, or taking a combined estrogen and progestogen hormonal contraceptive.	Revised to exclude patients taking a combined estrogen and progestogen hormonal contraceptive.
h. The patient has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome, or the patient is concomitantly using lamotrigine.	h. The patient has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome, or the patient is concomitantly using lamotrigine.	Revised to exclude patients concomitantly using lamotrigine.
o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <90 mL/min/1.73m2, or evidence of renal disease during the 28-day baseline period.	o. The patient has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate of <90 mL/min/1.73m2, or evidence of renal disease during the 28-day baseline period.	An exclusion of patients with an estimated glomerular filtration rate of <90 $mL/min/1.73m^2$ was added as another means of evidence of renal disease.
t. The patient has a known hypersensitivity to the active substance or to any of the excipients of the study drug.	t. The patient has a known hypersensitivity to the active substance or to any of the excipients of the study drug.	This exclusion criteria was added to ensure patients with a known hypersensitivity are not enrolled in the study.
4.3.1. Study-Specific Patient Withdrawal Criteria and Procedures		
The patient must be withdrawn from the study if the patient experiences a severe hypersensitivity reaction or anaphylaxis.	The patient must be withdrawn from the study if the patient experiences a severe hypersensitivity reaction or anaphylaxis.	The sentence was added to specify that patients must be withdrawn if they experience a severe hypersensitivity reaction of anaphylaxis.
~~4.7.1.1~~3.1 General Study Design and Study Schematic Diagram	3.1 General Study Design and Study Schematic Diagram	Section 4.7.1.1 was moved within the protocol to be Section 3.1 as it was inadvertently placed in the incorrect section.
4.5. Rescreening		
If the history of migraine classification (EM or CM) as taken by the investigator differs from the classification determined by the diary data (28- day	If the history of migraine classification (EM or CM) as taken by the investigator differs from the classification determined by the diary data (28- day baseline	Clarification to avoid confusion by referencing a screening period.

Original text with changes shown	New wording	Reason/justification for change
~~screening~~baseline period), the patient may be rescreened one time; this information should be recorded in the CRF.	period), the patient may be rescreened one time; this information should be recorded in the CRF.	
Patients may be rescreened once if the repeated values for the laboratory, vital sign, or ECG screening criteria are within acceptable limits as judged by the investigator or if repeated values show normalization of the out-of-range values, but their initial ~~screening~~baseline period has expired.	Patients may be rescreened once if the repeated values for the laboratory, vital sign, or ECG screening criteria are within acceptable limits as judged by the investigator or if repeated values show normalization of the out-of-range values, but their initial baseline period has expired.	Clarification to avoid confusion by referencing a screening period.
5.3.1. Justification for Dose of Test Investigational Medicinal Product		
A 2013 investigation by Momper et al from the Food and Drug Administration (FDA) analyzed 92 products approved between 2007 and 2012 with similar adult and pediatric indications across different therapeutic areas, and 87 (94.5%) had equivalent dosing for adults and adolescent patients (Momper et al 2013~~The formulation of fremanezumab to be used for clinical investigations in the pediatric population will be identical to the sc formulation of fremanezumab that was used in the clinical program for adults.~~). Based on pharmacokinetic simulations, a body weight threshold of 40 kg can be generally used for pediatric patients to receive the same fixed adult dosage for mAbs (Yang et al 2019). In addition, mAbs tend to have wide therapeutic windows since they represent more targeted therapy with limited off-target toxicity; as a result, recommending a 40 kg threshold for receiving the adult dosage, with resultant pediatric exposure being within 20% to 30% above adult exposure, seems to be appropriate (Yang et al 2019). The fremanezumab weight cutoff is slightly higher (45 kg); hence, this reduces the likelihood to be above adult exposure. In addition, fremanezumab has a wide therapeutic dose range that was tested in Phase 2b and Phase 3 studies in adults of up to 900 mg sc monthly. Thus, based on considerable data available in adult patients with migraine weighing ≥45 kg, in addition to the	A 2013 investigation by Momper et al from the Food and Drug Administration (FDA) analyzed 92 products approved between 2007 and 2012 with similar adult and pediatric indications across different therapeutic areas, and 87 (94.5%) had equivalent dosing for adults and adolescent patients (Momper et al 2013). Based on pharmacokinetic simulations, a body weight threshold of 40 kg can be generally used for pediatric patients to receive the same fixed adult dosage for mAbs (Yang et al 2019). In addition, mAbs tend to have wide therapeutic windows since they represent more targeted therapy with limited off-target toxicity; as a result, recommending a 40 kg threshold for receiving the adult dosage, with resultant pediatric exposure being within 20% to 30% above adult exposure, seems to be appropriate (Yang et al 2019). The fremanezumab weight cutoff is slightly higher (45 kg); hence, this reduces the likelihood to be above adult exposure. In addition, fremanezumab has a wide therapeutic dose range that was tested in Phase 2b and Phase 3 studies in adults of up to 900 mg sc monthly. Thus, based on considerable data available in adult patients with migraine weighing ≥45 kg, in addition to the evidence supporting the lack of expected difference in pharmacokinetics between adults and adolescent patients, the use of 225 mg monthly was proposed in pediatric patients weighing ≥45 kg.	Additional information on the selected weight cutoff for the pediatric population has been added for investigator awareness.

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

Original text with changes shown	New wording	Reason/justification for change
evidence supporting the safety of the approved dose of 225 mg sc monthly in adults, and to minimize the risk of decreased efficacy in this pediatric population, the 120 mg monthly dose level was selected for patients aged 6 to 17 years (inclusive) with weight values <45.0 kg based on targeting the achievement of a similar distribution of fremanezumab exposure levels (following multiple dosing) of 225 mg monthly in adult patients with EM and CM. The formulation of fremanezumab to be used for clinical investigations in the pediatric population will be identical to the sc formulation of fremanezumab that was used in the clinical program for adults.	adults, and to minimize the risk of decreased efficacy in this pediatric population, the 120 mg monthly dose level was selected for patients aged 6 to 17 years (inclusive) with weight values <45.0 kg based on targeting the achievement of a similar distribution of fremanezumab exposure levels (following multiple dosing) of 225 mg monthly in adult patients with EM and CM. The formulation of fremanezumab to be used for clinical investigations in the pediatric population will be identical to the sc formulation of fremanezumab that was used in the clinical program for adults.	
5.5. Restrictions		
Patients must remain at the site, for safety observation, for at least 30 minutes after injection or longer if deemed necessary by medical judgment.	Patients must remain at the site, for safety observation, for at least 30 minutes after injection or longer if deemed necessary by medical judgment.	This sentence was added to provide a minimum time frame that the patient must be observed for safety evaluation.
5.6. Prior and Concomitant Medication or Therapy		
The following medications are prohibited during the study: opioids (including codeine), barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital), combined estrogen and progestogen hormonal contraceptives, and lamotrigine.	The following medications are prohibited during the study: opioids (including codeine), barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital), combined estrogen and progestogen hormonal contraceptives, and lamotrigine.	The sentence was added to specifically note which medications are prohibited during the study.
5.8. Randomization and Blinding		
~~Study personnel will be blinded to the results of the interim analysis other than the need (if any) for an adjustment in sample size.~~	-	This sentence was removed as the study personnel will not be unblinded to the results of the interim analysis.
7.4. Clinical Laboratory Tests (Other sections affected by this change: 8.1.1, 8.3)		
Details on sample handling, storage, shipment, and analysis are given in Appendix N and in the Laboratory Manual.	Details on sample handling, storage, shipment, and analysis are given in Appendix N and in the Laboratory Manual.	Reference to the newly added Appendix N has been added as it contains information on storage and destruction of samples.

Original text with changes shown	New wording	Reason/justification for change
9.5.1.1. Estimand for the Primary Endpoint		
The primary estimand for this study is the difference in means between the fremanezumab group and the placebo group in the target population who have received at least 1 dose of study drug and have at least 10 days of electronic diary efficacy data for the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug as if there were no intercurrent events. Data collected after treatment discontinuation or prohibited therapy will not be used for assessing the primary estimand.	The primary estimand for this study is the difference in means between the fremanezumab group and the placebo group in the target population who have received at least 1 dose of study drug and have at least 10 days of electronic diary efficacy data for the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug as if there were no intercurrent events. Data collected after treatment discontinuation or prohibited therapy will not be used for assessing the primary estimand.	Estimand language has been added to the protocol per recent ICH E9 guidance.
9.5.4.1. Primary Efficacy Analysis		
~~The group of patients 6 through 11 years of age will be analyzed descriptively.~~	-	This sentence was removed as patients aged 6 through 11 years will be analyzed as part of a subgroup analysis.
9.5.4.2. Sensitivity and Supplementary Analyses		
A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint.	A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint.	The sentence was added to provide information that a supplementary analysis using the ITT population will be conducted.
9.6. Multiple Comparisons and Multiplicity		
The order of secondary endpoint analyses will in general follow the sequence listed in Section 9.5.2. Final order and details will be confirmed in the statistical analysis plan, which will be finalized before database lock.	The order of secondary endpoint analyses will in general follow the sequence listed in Section 9.5.2. Final order and details will be confirmed in the statistical analysis plan, which will be finalized before database lock.	This sentence was added to provide clarity on the sequence of secondary efficacy endpoint comparisons.
9.8. Tolerability Analysis (Other sections affection by this change: 7.8)		
• Injection site pain will be recorded ~~as~~ using the 11-point numerical rating scale and will be mapped to mild, moderate, or severe, according to patient's self-report of pain intensity, as described for the recording of headache pain in Section 6.1.1.	• Injection site pain will be recorded using the 11-point numerical rating scale and will be mapped to mild, moderate, or severe, according to patient's self-report of pain intensity, as described for the recording of headache pain in Section 6.1.1.	Injection site pain assessments were revised to use the 11-point NRS to harmonize with the other pain assessments in the study.
9.12. Planned Interim Analysis (Other sections affected by this change: 3.1 and 9.5.4.1)		
An interim analysis ~~for~~with blinded sample size re-estimation will be	An interim analysis with blinded sample size re-estimation will be conducted by	This sentence was revised to ensure it is clear that the

Original text with changes shown	New wording	Reason/justification for change
conducted by ~~an independent statistical group~~evaluating the pooled variability (SD) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% of patients have completed at least 3 months of treatment or have withdrawn from the study early. ~~The sample size re-estimation will be based on the interim analysis result. The conditional power for the primary efficacy variable will be calculated. If the conditional power is less than 25% or greater than 75%, the sample size will not be increased. If the conditional power is between 25% and 75%, the sample size will be increased by up to 25%.~~	evaluating the pooled variability (SD) of the primary endpoint using the total number of patients regardless of the treatment assignment once 50% of patients have completed at least 3 months of treatment or have withdrawn from the study early.	sample size re-estimation will be blinded. Additionally, the conditional power description for the sample size re-estimation was removed as the planned sample size re-assess will use a more robust method to be described in the statistical analysis plan.
Appendix F. Ethics		
The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB).), per local regulations.	The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB).), per local regulations.	This stipulation was added as there may be different requirements for certain countries.
The investigator, or a qualified person designated by the investigator, should fully inform the patient and each parent/legally acceptable representative of all pertinent aspects of the study, including the written information approved by the IEC/IRB., per local regulations.	The investigator, or a qualified person designated by the investigator, should fully inform the patient and each parent/legally acceptable representative of all pertinent aspects of the study, including the written information approved by the IEC/IRB., per local regulations.	This stipulation was added as there may be different requirements for certain countries.
Appendix G. Birth Control Methods and Pregnancy Testing		
~~• Combined estrogen and progestogen hormonal contraception (oral, intravaginal, and transdermal) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP~~	-	This bullet was deleted from highly effective birth control methods as combined estrogen and progestogen hormonal contraception has been added as prohibited medications during the study.
Appendix L. Data Management and Record Keeping		
~~These data may also be sent electronically to the sponsor (or organization performing data management).~~	-	This sentence was deleted to avoid unintentional unblinding.
Appendix N. Storage and Destruction of Biological Samples		

Original text with changes shown	New wording	Reason/justification for change
Safety Samples Safety samples will be stored for a short period of time in the central laboratory until analysis and destruction. Specific details regarding central laboratory storage and destruction can be found in the study Laboratory Manual and the central laboratory's standard operating procedures (SOPs). **Pharmacokinetic and Immunogenicity Samples** Pharmacokinetic and immunogenicity samples will be stored at the sites at a temperature of 70°C ±20°C (or at/below -20°C if no 70°C freezer is available) in an upright position until they are shipped to the central laboratory. Samples will be stored at -70°C at the central laboratory, until shipped to the sponsor or designee for analysis, as described in the study Laboratory Manual. After analysis, the sponsor will store the residue (leftovers) from the pharmacokinetic and immunogenicity samples at 70°C at the designated bioanalytical archive facility for up to 5 years after the study results are submitted to the regulatory authorities. Destruction will take place at the sponsor's bioanalytical laboratory or designee, according to the applicable SOPs.	**Safety Samples** Safety samples will be stored for a short period of time in the central laboratory until analysis and destruction. Specific details regarding central laboratory storage and destruction can be found in the study Laboratory Manual and the central laboratory's standard operating procedures (SOPs). **Pharmacokinetic and Immunogenicity Samples** Pharmacokinetic and immunogenicity samples will be stored at the sites at a temperature of 70°C ±20°C (or at/below -20°C if no 70°C freezer is available) in an upright position until they are shipped to the central laboratory. Samples will be stored at -70°C at the central laboratory, until shipped to the sponsor or designee for analysis, as described in the study Laboratory Manual. After analysis, the sponsor will store the residue (leftovers) from the pharmacokinetic and immunogenicity samples at 70°C at the designated bioanalytical archive facility for up to 5 years after the study results are submitted to the regulatory authorities. Destruction will take place at the sponsor's bioanalytical laboratory or designee, according to the applicable SOPs.	Appendix N has been added to describe the storage and destruction of biological samples.

Amendment 04 Dated 20 April 2020

The primary reason for this amendment is to revise an exclusion criterion to exclude patients with a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome. This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment and Written Request agreements. The amendment is considered to be substantial (ie, requires approval by competent authorities, IEC, and/or IRB) by the sponsor’s Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Changes to the Protocol

Original text with changes shown	New wording	Reason/justification for change
TITLE PAGE (Other sections affected by this change: Amendment History, Investigator Agreement, Coordinating Investigator Agreement)		
Protocol with Amendment 04 Approval Date: 20 April 2020	**Protocol with Amendment 04 Approval Date: 20 April 2020**	Updated for Amendment 04
4.2. Patient Exclusion Criteria		
c. The patient has any clinically significant cardiovascular (including congenital cardiac anomalies or thromboembolic events), endocrine, gastrointestinal, genitourinary, hematologic, hepatic, immunologic, neurologic, ophthalmic, pulmonary, ~~or~~ renal disease, or complications of an infection, at the discretion of the investigator. e. The patient has an ongoing infection~~,~~ or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, or chronic hepatitis B or C. h. The patient has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome.	c. The patient has any clinically significant cardiovascular (including congenital cardiac anomalies or thromboembolic events), endocrine, gastrointestinal, genitourinary, hematologic, hepatic, immunologic, neurologic, ophthalmic, pulmonary, renal disease, or complications of an infection, at the discretion of the investigator. e. The patient has an ongoing infection or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, or chronic hepatitis B or C. h. The patient has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome.	Updated to specifically exclude patients with a history of chronic hepatitis B or C, and to exclude patients with a history of Stevens-Johnson Syndrome/toxic epidermal necrolysis syndrome from this study. It was also specified that patients with clinically significant complications of an infection may be excluded at the discretion of the investigator
4.5. Rescreening		
A patient who is screened but not enrolled (eg, because study eligibility criteria were not met [inclusion criteria not met or exclusion criteria met]) due to any of the following reasons: technical issues (eg, diary malfunction), out of visit 2 window due to an emergency situation (eg, pandemic or potential pandemic), a change in the patient's medical background, a modification of study inclusion and exclusion criteria, or upon the sponsor's discretion on a case-by-case basis, may be considered for rescreening 1 time. If the history of migraine classification (EM or CM) as taken by the investigator differs from the classification determined by the diary data (28-day screening period), the patient may be rescreened one time; this information should be recorded in the CRF.	A patient who is screened but not enrolled (eg, because study eligibility criteria were not met [inclusion criteria not met or exclusion criteria met]) due to any of the following reasons: technical issues (eg, diary malfunction), out of visit 2 window due to an emergency situation (eg, pandemic or potential pandemic), a change in the patient's medical background, a modification of study inclusion and exclusion criteria, or upon the sponsor's discretion on a case-by-case basis, may be considered for rescreening 1 time. If the history of migraine classification (EM or CM) as taken by the investigator differs from the classification determined by the diary data (28-day screening period), the patient may be rescreened one time; this information should be recorded in the CRF.	Clarification as a measure implementing to protect study participants and manage study conduct resulting from the COVID-19 or other potential pandemic.

Original text with changes shown	New wording	Reason/justification for change
7.1.6. Protocol-Defined Adverse Events of Special Interest		
Although coronavirus disease 2019 (COVID-19) is not suspected to be causally related to fremanezumab treatment, suspected or confirmed COVID-19, based on local standard of care, will be considered a protocol-defined adverse event of special interest to be sent to the sponsor's GPSP for the purpose of timely and robust adverse event data collection.	Although coronavirus disease 2019 (COVID-19) is not suspected to be causally related to fremanezumab treatment, suspected or confirmed COVID-19, based on local standard of care, will be considered a protocol-defined adverse event of special interest to be sent to the sponsor's GPSP for the purpose of timely and robust adverse event data collection.	Suspected or confirmed COVID-19 was added as an adverse event of special interest in order to manage study conduct resulting from the COVID-19 pandemic.
16. Summary of Changes to Protocol		
Section 16.2 Administrative Letter 01 Dated 10 March 2020	**Section 16.2 Administrative Letter 01 Dated 10 March 2020**	Updated to include the Administrative Letter 01.
Appendix A. Clinical Laboratories and Other Departments and Institutions		
[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	Updated as outlined in Administrative Letter 01.
[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] [redacted]	Updated as outlined in Administrative Letter 01.

Administrative Letter 01 Dated 10 March 2020

ADMINISTRATIVE LETTER 01

Study number: TV48125-CNS-30082

Clinical Study Protocol with Amendment 03

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

IND number: 106533; BLA number: 761089; EudraCT number: 2019-002053-33

10 March 2020

Dear Investigator:

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

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

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

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

Sincerely,

[redacted]

Teva Branded Pharmaceutical Products R&D, Inc.

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

Amendment 03 Dated 03 February 2020

The primary reason for this amendment is to update the sponsor's address. This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment and Written Request agreements. The amendment is considered to be substantial (ie, requires approval by competent authorities, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE (Other sections affected by this change: protocol header, Investigator Agreement, Coordinating Investigator Agreement)		
Protocol with Amendment 03 **Approval Date: 03 February 2020**	**Protocol with Amendment 03** **Approval Date: 03 February 2020**	To update for Amendment 03
Teva Branded Pharmaceutical Products R&D, Inc. **~~41 Moores Road~~** **~~Frazer, Pennsylvania 19355~~** **145 Brandywine Parkway** **West Chester, Pennsylvania 19380** **United States of America**	**Teva Branded Pharmaceutical Products R&D, Inc.** **145 Brandywine Parkway** **West Chester, Pennsylvania 19380** **United States of America**	To update the sponsor's new address.
© ~~2019~~2020 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	© 2020 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	To update for Amendment 03
3. STUDY DESIGN		
3.5. Schedule of Study Procedures and Assessments (Table 1) (Other sections affected by this change: Appendix B)		
Headache history	Headache history	Specific study procedure added for clarity to collect headache history data during screening.
Clinical laboratory tests[c,m]	Clinical laboratory tests[c,m]	To clarify that blood samples will be collected before study drug administration.
Blood samples for plasma drug concentration[c~~,p~~]	Blood samples for plasma drug concentration[c]	Correction to simplify footnotes.
Blood samples for serum ADA assessment[c~~,p~~]	Blood samples for serum ADA assessment[c]	Correction to simplify footnotes.
Injection site assessments[c]	Injection site assessments[c]	Footnote reference added to the injection site assessment row for clarity.
~~[p] Blood samples for plasma drug concentration and serum ADA determination must be collected prior to dosing as applicable.~~	-	The footnote was deleted as it was repetitive with footnote c.
4. SELECTION AND WITHDRAWAL OF PATIENTS		
4.1. Patient Inclusion Criteria		
Note: A person is considered to be not using preventive medications when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed	Note: A person is considered to be not using preventive medications when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of	This note for inclusion criterion f was updated to include onabotulinumtoxinB to coincide with it being added as a preventive migraine medication allowed for up to

Original text with changes shown	New wording	Reason/Justification for change
since the last use of Onabotulinium toxin A or B prior to screening (visit 1).	Onabotulinium toxin A or B prior to screening (visit 1).	20% of patients during the study as per Appendix C.
4.2. Patient Exclusion Criteria (Other sections affected by this change: 5.6)		
s. The patient received a live attenuated vaccine (eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine) within the 12-week period prior to screening or plans to receive a live attenuated vaccine at any time during the study and for 6 months after the last dose of IMP.	s. The patient received a live attenuated vaccine (eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine) within the 12-week period prior to screening or plans to receive a live attenuated vaccine at any time during the study and for 6 months after the last dose of IMP.	Added a clarification to describe some potentially applicable live attenuated vaccines.
7. ASSESSMENT OF SAFETY		
7.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis		
Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected hepatitis, HIV, or Lyme disease, a blood sample may be taken at screening at the discretion of the investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below (Table 4).	Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected hepatitis, HIV, or Lyme disease, a blood sample may be taken at screening at the discretion of the investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below (Table 4).	To clarify that the investigator may take a blood sample at screening in case of suspected hepatitis.
Table 4 (urinalysis column)		
~~Albumin~~	-	Albumin was removed from Table 4 as it is included in the protein measurement and will not be evaluated separately by the central laboratory.
~~Hemoglobin~~Blood	Blood	Correction as the urinalysis will specifically assess for blood in urine.
7.1.5.1. Definition of a Serious Adverse Event		
Refer to Appendix I for guidance regarding monitoring patients with elevated liver function tests. An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.	Refer to Appendix I for guidance regarding monitoring patients with elevated liver function tests. An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.	To indicate the appendix that provides the guidance regarding monitoring patients with elevated liver function tests.

Original text with changes shown	New wording	Reason/Justification for change
APPENDIX C. PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR THE DURATION OF THE STUDY FOR UP TO 20% OF PATIENTS		
OnabotulinumtoxinA or B	OnabotulinumtoxinA or B	OnabotulinumtoxinB was added as a preventive migraine medications allowed for the duration of the study for up to 20% of patients as outlined in Appendix C.
APPENDIX I. GUIDANCE ON SAFETY MONITORING	**APPENDIX I. GUIDANCE ON SAFETY MONITORING**	Appendix I was newly added to provide guidance to the investigator on monitoring patients with elevated liver function tests.

Amendment 02 Dated 05 December 2019

The primary reason for this amendment is to update the protocol with the dose to be used for patients <45.0 kg (120 mg sc monthly) following the completion of the Phase 1 pediatric pharmacokinetic study (TV48125-CNS-10141). This update and other minor revisions do not impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment agreement. The amendment is considered to be substantial (ie, requires approval by competent authorities, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Changes to the Protocol

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

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

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

Original text with changes shown	New wording	Reason/Justification for change
pediatric migraine patients 6 to 11 years of age, inclusive (Study TV48125-CNS-10141).		
3. STUDY DESIGN		
3.1. General Study Design and Study Schematic Diagram (Other sections affected by this change: 3.2, 5.1.1.1, 5.1.3, 5.3.1, 5.4, 5.8, 9, 9.1)		
The total duration of the study is planned to be 48 months (from approximately ~~Q4 2019~~Q1 2020 to Q4 2023).	The total duration of the study is planned to be 48 months (from approximately Q1 2020 to Q4 2023).	Updated the approximate start date of the study.
• Patients weighing <45.0 kg will receive monthly sc administration of fremanezumab at ~~a dose to be confirmed after pharmacokinetic analyses and safety and tolerability results become available from the Phase 1 pharmacokinetics study (Study TV48125-CNS-10141). The sponsor will communicate the dose selection for patients <45.0 kg when it becomes available~~120 mg.	• Patients weighing <45.0 kg will receive monthly sc administration of fremanezumab at 120 mg.	Updated dose for patients <45.0 kg.
The enrollment target is approximately 418 patients in total. The goal in the 12- through 17-year-old age group is to enroll similar numbers of patients who are 12 through 14 years old and 15 through 17 years old. ~~The enrollment will start with patients weighing ≥45.0 kg. The enrollment of patients weighing <45.0 kg will commence after the dose level is finalized and approved by regulatory agencies.~~	The enrollment target is approximately 418 patients in total. The goal in the 12- through 17-year-old age group is to enroll similar numbers of patients who are 12 through 14 years old and 15 through 17 years old.	No longer applicable to study enrollment
3.5. Schedule of Study Procedures and Assessments (Other sections affected by this change: 7.9, Appendix B)		
Lifetime p~~P~~rior medication and treatment history	Lifetime prior medication and treatment history	Clarification.
p Blood samples for plasma drug concentration and serum ADA ~~concentrations~~ determination must be collected prior to dosing as applicable.	p Blood samples for plasma drug concentration and serum ADA determination must be collected prior to dosing as applicable.	Clarification.
q The C-SSRS Baseline/Screening version will be completed by the physician based on discussion with the patient/caregiver at visit 1 (screening visit), and the C-SSRS Since Last Visit version will be completed by the physician based on discussion with	q The C-SSRS Baseline/Screening version will be completed by the physician based on discussion with the patient/caregiver at visit 1 (screening visit), and the C-SSRS Since Last Visit version will be completed by the physician based on discussion	Clarified who will be completing the C-SSRS and what occurs if there is a positive finding.

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

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

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

Original text with changes shown	New wording	Reason/Justification for change
~~• moderate headache~~ ~~• severe headache~~ ~~An 11-point numerical scale will be used for the patients to rate their headache pain intensity.~~ Each headache s~~S~~everity rating from the 11-point numerical rating scale will be mapped to mild (1 to 3), moderate (4 to 6), or severe (7 to 10) for endpoint analyses (McCaffery and Beebe 1989). Patients or parents/caregivers will also record whether photophobia, phonophobia, nausea, and vomiting are present, and they will record any migraine medications (name of drug, number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day. Diary compliance of less than 75% after the start of treatment will be recorded as a protocol deviation.	endpoint analyses (McCaffery and Beebe 1989). Patients or parents/caregivers will also record whether photophobia, phonophobia, nausea, and vomiting are present, and they will record any migraine medications (name of drug, number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day. Diary compliance of less than 75% after the start of treatment will be recorded as a protocol deviation.	
6.1.4. Pediatric Quality of Life Inventory		
For the child and adolescent self-report (8 through 18 years of age) and the parent report forms, respondents use a 5-point Likert scale to rate the item severity (0=never a problem;1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem).	For the child and adolescent self-report (8 through 18 years of age) and the parent report forms, respondents use a 5-point Likert scale to rate the item severity (0=never a problem;1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem).	Clarification.
7. ASSESSMENT OF SAFETY		
7.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis		
Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected HIV or Lyme disease, a blood sample ~~should~~may be taken at screening at the discretion of the investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below (Table 4).	Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. In case of suspected HIV or Lyme disease, a blood sample may be taken at screening at the discretion of the investigator. Baseline is screening (visit 1). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below (Table 4).	Virology sampling may be done at the discretion of the investigator.

Original text with changes shown	New wording	Reason/Justification for change
9. STATISTICS		
9.7. Safety Analysis		
Suicidal ideation and behavior will be measured using the C-SSRS. Data for patients with positive findings will be listed.	Suicidal ideation and behavior will be measured using the C-SSRS. Data for patients with positive findings will be listed.	Clarification.
9.8. Tolerability Analysis		
~~Subjective t~~Tolerability will be assessed by the following:	Tolerability will be assessed by the following:	Clarification.
15. REFERENCES		
McCaffery M, Beebe A. Pain: Clinical manual for nursing practice. St. Louis (MO): Mosby 1989. Available upon request.	McCaffery M, Beebe A. Pain: Clinical manual for nursing practice. St. Louis (MO): Mosby 1989. Available upon request.	Added in reference for the pain severity scale.
APPENDIX A CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Legal Representative of the Sponsor in the European Union (EU) and Contact Person	Legal Representative of the Sponsor in the European Union (EU) and Contact Person	Clarification.
APPENDIX B STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
• review lifetime prior medication and treatment history	• review lifetime prior medication and treatment history	Clarification.
APPENDIX C PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR THE DURATION OF THE STUDY FOR UP TO 20% OF PATIENTS	**APPENDIX C PREVENTIVE MIGRAINE MEDICATIONS ALLOWED FOR THE DURATION OF THE STUDY FOR UP TO 20% OF PATIENTS**	Clarification.
The following concomitant preventive migraine medications are allowed in up to 20% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients must have been on a stable, well-tolerated dose of this preventive medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 80% of	The following concomitant preventive migraine medications are allowed in up to 20% of patients and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Patients must have been on a stable, well-tolerated dose of this preventive medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the study. For the remaining 80% of	Clarification.

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td>patients, these medications are not allowed for migraine or for any other indications.</td><td>patients, these medications are not allowed for migraine or for any other indications.</td><td></td></tr>
<tr><td colspan="3">APPENDIX I TOTAL BLOOD VOLUME</td></tr>
<tr><td>
<table>
<tr><th>Type of samples</th><th>Volume per sample (mL)</th><th>Total number of samples</th><th>Total volume (mL)</th></tr>
<tr><td>Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)</td><td>10</td><td>3</td><td>30</td></tr>
<tr><td>Pharmacokinetics</td><td>2</td><td>3</td><td>6</td></tr>
<tr><td>ADA</td><td>4</td><td>3</td><td>12</td></tr>
<tr><td><s>Virology (hepatitis, HIV, Lyme disease, and tuberculosis)</s></td><td><s>18</s></td><td><s>1</s></td><td><s>18</s></td></tr>
<tr><td>Total</td><td></td><td></td><td><s>66</s>48</td></tr>
</table>
ADA=antidrug antibody; β-HCG=beta-human chorionic gonadotropin<s>; HIV=human immunodeficiency virus</s>.
</td><td>
<table>
<tr><th>Type of samples</th><th>Volume per sample (mL)</th><th>Total number of samples</th><th>Total volume (mL)</th></tr>
<tr><td>Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)</td><td>10</td><td>3</td><td>30</td></tr>
<tr><td>Pharmacokinetics</td><td>2</td><td>3</td><td>6</td></tr>
<tr><td>ADA</td><td>4</td><td>3</td><td>12</td></tr>
<tr><td>Total</td><td></td><td></td><td>48</td></tr>
</table>
ADA=antidrug antibody; β-HCG=beta-human chorionic gonadotropin.
</td><td>Updated blood samples to remove virology testing. Virology blood sampling will be done at the discretion of the investigator.</td></tr>
</table>

Amendment 01 Dated 21 June 2019

The primary reasons for this amendment are to improve the feasibility of the diary compliance requirement, clarify the exclusion criterion for nerve stimulation or device, and clarify the timing of injection site reaction assessment. None of these revisions impact the study design, and the amended protocol remains consistent with the United States FDA Special Protocol Assessment agreement. The amendment is considered to be substantial (ie, requires approval by competent authorities, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Changes to the Protocol

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

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE (Other sections affected by this change: Investigator Agreement, Coordinating Investigator Agreement)		
EudraCT number: ~~<TBD>~~2019-002053-33	EudraCT number: 2019-002053-33	This change was made to provide the EudraCT number.
Teva Branded Pharmaceutical Products R&D, Inc. ~~145 Brandywine Parkway~~ ~~West Chester, PA 19380~~ 41 Moores Road Frazer, Pennsylvania 19355 United States of America	Teva Branded Pharmaceutical Products R&D, Inc. 41 Moores Road Frazer, Pennsylvania 19355 United States of America	This change was made to update the addresses for the Sponsor.
SELECTION AND WITHDRAWAL OF PATIENTS		
Section 4.1		
i. The patient/caregiver has demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of ~~24~~21 out of 28 days (approximately ~~85~~75% diary compliance).	i. The patient/caregiver has demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum of 21 out of 28 days (approximately 75% diary compliance).	This change was made to harmonize the required diary compliance during the baseline and treatment periods across the 3 Phase 3 pediatric protocols. The change will not impact data quality or accuracy.
(Not applicable)	n. The patient has received all recommended age-appropriate vaccines according to local standard of care and schedule.	This inclusion criterion was added to protect study participants from preventable childhood illnesses in accordance with current medical recommendations for pediatric patients and to help prevent the spread of communicable infections to others at the investigational site.
Section 4.2		
(Not applicable)	b. The patient has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine during the 2 months prior to the day of the screening visit.	This exclusion criterion was added to decrease the chances that previous nonpharmacologic treatments would confound the assessment of safety and efficacy of fremanezumab.
(Not applicable)	s. The patient received a live attenuated vaccine within the 12-week period prior to screening or plans to receive a live attenuated vaccine at any time during the study and for 6 months after the last dose of IMP.	This exclusion criterion was added to avoid an immune response elicited by administration of a live attenuated vaccine that could interfere with the accurate

Original text with changes shown	New wording	Reason/Justification for change
		assessment of efficacy and safety of fremanezumab.
ASSESSMENT OF SAFETY		
Section 7.8		
Injection site assessments will be performed ~~immediately and 1 hour~~ after administration of each dose of study drug and before patients leave the investigational site.	Injection site assessments will be performed after administration of each dose of study drug and before patients leave the investigational site.	This change was made to clarify the procedure for assessment of local tolerability and pain.
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Appendix A		
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	This change was made to add details for the Sponsor's Authorized Representative.
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Tel: [redacted]	[redacted] Tel: [redacted]	This change was made to add details for the Legal Representative of the Sponsor in the European Union.
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted]	This change was made to add details for the Sponsor's Medical Expert.
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted]	[redacted]	This change was made to add details for the Coordinating Investigator.

Original text with changes shown	New wording	Reason/Justification for change
[redacted] Tel: [redacted]	[redacted] Tel: [redacted]	
~~<Name, Degree, Company, Function, Phone, Fax, Cell, Email>~~ [redacted] Teva Pharmaceutical Industries Ltd. Tel: [redacted] Cell: [redacted]	[redacted] Teva Pharmaceutical Industries Ltd. Tel: [redacted] Cell: [redacted]	This change was made to add details for the Sponsor's Representative of Global Patient Safety and Pharmacovigilance.
~~<Name of Company>~~ICON	ICON plc South County Business Park Leopardstown, Dublin 18, Ireland	This change was made to add the name and contact information of the Contract Research Organization.
~~<Name of Company>~~Icon Laboratories 123 Smith Street Farmingdale, NY 11735 United States Icon Laboratories South County Business Park Leopardstown, Dublin 18, Ireland	Icon Laboratories 123 Smith Street Farmingdale, NY 11735 United States Icon Laboratories South County Business Park Leopardstown, Dublin 18, Ireland	This change was made to add the name and contact information of the Central Clinical Laboratories.
~~<Name of Company>~~ eResearch Technology, Inc 1818 Market Street #1000 Philadelphia, PA 19103 United States	eResearch Technology, Inc 1818 Market Street #1000 Philadelphia, PA 19103 United States	This change was made to add the name and contact information of the Central Electrocardiogram Evaluation site.
~~<Name of Company>~~ PAREXEL International Corp. 195 West Street Waltham, MA 02451 Tel: [redacted]	PAREXEL International Corp. 195 West Street Waltham, MA 02451 Tel: [redacted]	This change was made to add the name and contact information of the Randomization and Trial Supply Management (RTSM) vendor.
TOTAL BLOOD VOLUME		
Appendix I (Other sections affected by this change: Section 5.10)		
(Not applicable)	Virology (hepatitis, HIV, Lyme disease, and tuberculosis)	Added virology testing to Total Blood Volume table in order to align with exclusion criterion e: The patient has an ongoing infection, known history of HIV infection, tuberculosis, Lyme disease, or hepatitis.
(Not applicable)	Virology (hepatitis, HIV, Lyme disease, and tuberculosis) 18 | 1 | 18	Total blood draws were adjusted to reflect the addition of virology testing.

Original text with changes shown				New wording				Reason/Justification for change
Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)	~~7.5~~ 10	3	~~22.5~~ 30	Clinical laboratory (serum chemistry, including β-HCG test, hematology, coagulation)	10	3	30	Blood draw volumes were adjusted to include β-HCG testing.
Total			**~~44.5~~ ~~55~~66**	**Total**			**66**	Total blood draws were updated to reflect the new total based on blood draw adjustments.

13.4. Financial Disclosure

A separate clinical trial agreement, including a trial budget, will be signed between each Principal Investigator/institution and the Sponsor (or the CRO designated by the Sponsor) before the IMP is delivered.

The participants in this clinical trial 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 participant had not taken part in the clinical trial.

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

For covered clinical trials (see 21CFR Part 54), the Investigator will provide the Sponsor with financial information required to complete FDA 3454 form. Each Investigator will notify the Sponsor of any relevant changes during the conduct of the trial and for 1 year after the trial has been completed.

13.5. Recruitment Strategy

Recruitment will be conducted by the sites. Where needed recruitment strategies may include site outreach and encouragement, and employment of recruitment vendors. More details can be found in the Project Recruitment Strategy Plan.

13.6. Dissemination of Clinical Trial Data

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical trial will be registered on clinical trial registries if applicable.

13.7. 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 trial 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.

Further details pertaining to publications and review periods are described in the clinical trial agreement with the Investigator/institution.

The Sponsor will comply with the requirements for publication of trial results: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials 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.

No patent applications based on the results of the trial 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.

13.8. Preventive Migraine Medications for Any Condition Allowed for the Duration of the Trial

The chronic use of 2 of the following concomitant medications is allowed in approximately 35% of participants, and should be entered in electronic case report form (eCRF) pages specific for migraine preventive medication. Participants using no more than 2 of the following migraine preventive medications for any condition at the time of trial enrollment will be allowed to remain on the medication. Participants must have been on a stable, well-tolerated dose of this medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the trial. For the remaining approximately 65% of participants, these medications are not allowed for migraine or for any other indications. PRN use of the following medications are allowed during the course of the trial for any indications and do not have to have established dosing regimens. PRN use of these medications should be reported in the eCRF as concomitant medications. Participants should be trained and should not report PRN use of these medications in the electronic headache diary. PRN use is defined as any treatment regimen outside of the prescribing information or local treatment guidelines. Participants will be allowed PRN use of acute medications to treat acute migraine attacks, as needed, with the exception of regular use of medications containing opioids and barbiturates.

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

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

Adapted from O'Brien et al 2015 and Lewis and Winner 2006.

13.9. Trial Procedures and Assessments by Visit

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

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

- obtain written informed consent from parent(s) or legal guardian(s) and assent (according to local regulations) from each participant before any trial-related procedures are performed
- inform participants of trial restrictions and compliance requirements
- review medical and psychiatric history
- review headache history
- review lifetime prior medication and treatment history
- review demographic characteristics
- review inclusion and exclusion criteria
- full physical examination (including height, weight, and body mass index)
- triplicate 12-lead ECG
- vital signs measurements
- review adverse events
- review concomitant medications
- clinical laboratory tests

- serum β-HCG and urine pregnancy tests (only female participants who are postmenarchal or ≥12 years of age); inquire and record start / stop date of menstrual period
- provide electronic headache diary device and instructions
- administer C-SSRS

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

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

- review inclusion and exclusion criteria
- full physical examination (including height, weight, and body mass index)
- assessment of puberty status (Tanner staging scale) by participant's self-report or by physical examination
- assign randomization number and enter into CRF
- triplicate 12-lead ECG
- vital signs measurements
- review adverse events
- review concomitant medications
- urine β-HCG pregnancy test (only female participants who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period
- review electronic headache diary
- collect blood samples for plasma drug concentration and serum ADA prior to dosing
- administer C-SSRS
- administer PedMIDAS questionnaire
- administer PedsQL
- administer IMP
- assess injection site

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

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

- triplicate 12-lead ECG
- vital signs measurements
- review adverse events
- review concomitant medications
- clinical laboratory tests - **visit 3 only**

- collect blood samples for plasma drug concentration and serum ADA prior to dosing - **visit 3 only**
- urine β-HCG pregnancy test (only female participants who are postmenarchal or ≥12 years of age); inquire and record start/stop date of menstrual period
- review electronic headache diary
- administer C-SSRS
- administer PedsQL
- administer IMP
- assess injection site

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

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

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

5. **Unscheduled Visits**

An unscheduled procedure or visit may be performed at any time during the trial at the participant's request or as deemed necessary by the Investigator.

Unscheduled procedures may include the following:

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

Other procedures may be performed at the discretion of the Investigator, who may consult with the Sponsor.

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

14. APPENDIX: GLOSSARY OF TERMS

Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ADAs	antidrug antibodies
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
BLA	Biological License Application
BP	blood pressure
CBC	complete blood count
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CGRP	calcitonin gene-related peptide
CH	cluster headache
CIOMS	Council for International Organizations of Medical Sciences
CM	chronic migraine
COVID-19	coronavirus disease 2019
CRF	case report form (refers to any media used to collect trial data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EM	episodic migraine
EMA	European Medicines Agency
EOT	end-of-treatment
EU	European Union
EudraCT	European Clinical Trials
FAS	full analysis set

Abbreviation	Term
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
Global PV	Global Pharmacovigilance
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd revision
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgG2	immunoglobulin G2
IHS	International Headache Society
IMP	investigational medicinal product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous
LSO	local safety officer
mAb	monoclonal antibody
n	number
NDA	New Drug Application
NIH	National Institutes of Health
PedMIDAS	Pediatric Migraine Disability Assessment
PedsQL	Pediatric Quality of Life Inventory
PEF	peak expiratory flow
PFS	pre-filled syringe
[redacted]	[redacted]
PPTH	persistent posttraumatic headache
PRN	as-needed (use)

Abbreviation	Term
Q	quarter
RBC	red blood cell
RSI	Reference Safety Information
sc	subcutaneous
SD	standard deviation
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US or USA	United States or United States of America

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