

Clinical Study Protocol with Amendment 01

**A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study
Comparing the Efficacy and Safety of 2 Dose Regimens of Subcutaneous
Administration of TEV-48125 Versus Placebo
for the Preventive Treatment of Episodic Migraine**

Study Number TV48125-CNS-30050

NCT02629861

Protocol with Amendment 01 Approval Date: 30 March 2016

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Comparing the Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of
TEV-48125 Versus Placebo for the Preventive Treatment of Episodic Migraine**

Phase 3

IND number: 106,533 EudraCT number: 2015-004598-34

Protocol Approval Date: 30 March 2016

Sponsor

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Sponsor's Medical Expert

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Teva Pharmaceuticals
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Sponsor's Safety Representative

[REDACTED]
[REDACTED]
ratiopharm GmbH
[REDACTED]

Confidentiality Statement

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

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AMENDMENT HISTORY

The protocol for Study TV48125-CNS-30050 (dated 21 October 2015) has been amended and reissued as follows:

Amendment 01	30 March 2016 3 patients enrolled to date
Administrative Letter 02: Suspected Anaphylaxis	01 March 2016 0 patients enrolled to date
Administrative Letter 01: Drug Administration, Patient- Reported Outcome Measures, and Laboratory Tests	22 January 2016 0 patients enrolled to date

Details about the changes and reason/justification for each change are provided in Section [17](#).



INVESTIGATOR AGREEMENT**Clinical Study Protocol with Amendment 01****Original Protocol Dated 21 October 2015****IND number: 106,533 EudraCT number: 2015-004598-34****A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study
Comparing the Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of
TEV-48125 Versus Placebo for the Preventive Treatment of Episodic Migraine****Phase 3****Principal Investigator:** _____**Title:** _____**Address of Investigational Center:** __________
_____**Tel:** _____

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

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

Principal Investigator	Signature	Date
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SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
		3. 30. 2016

COORDINATING INVESTIGATOR AGREEMENT**Clinical Study Protocol with Amendment 01****Original Protocol Dated 21 October 2015****IND number: 106,533 EudraCT number: 2015-004598-34****A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study
Comparing the Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of
TEV-48125 Versus Placebo for the Preventive Treatment of Episodic Migraine****Phase 3**

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

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

Coordinating Investigator: [REDACTED]**Title:** [REDACTED]**Address of Investigational Center:** [REDACTED]**Tel:** [REDACTED]

Coordinating Investigator	Signature	Date
[REDACTED]	[REDACTED]	March 30 / 2016

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

Central Institutional Review Board



Central Clinical Laboratory
PPD Global Central Laboratories
2 Tesseneer Drive
Highland Heights, KY 41076

Electronic Data Capture
Medidata Rave

Data Management
PRA
4130 Parklake Avenue
Suite 400
Raleigh, NC 27612

Electronic Clinical Outcome Assessment
eResearch Technology, Inc.
1818 Market Street
Philadelphia, PA 19103

Central Electrocardiogram Evaluation
eResearch Technology, Inc.
1818 Market Street
Philadelphia, PA 19103

Web and Phone Integrated Interactive Response Technology
Y-Prime

Bioanalytical Pharmacokinetics Evaluation

[REDACTED] (bioanalytical analysis)

Teva Branded Pharmaceuticals R&D, Inc.

[REDACTED] (pharmacokinetics evaluation)

Teva Branded Pharmaceuticals R&D, Inc.

Bioanalytical Immunogenicity Evaluation

[REDACTED]

Teva Branded Pharmaceuticals R&D, Inc.

Biomarker Evaluation

[REDACTED]

Teva Branded Pharmaceuticals R&D, Inc.

Pharmacogenomic and Biomarker Sample Storage

BioStorage Technologies, Inc.
2910 Fortune Circle West, Suite E
Indianapolis, IN 46241 USA

BioStorage Technologies, GmbH
Im Leuschnerpark 1b
64347 Griesheim Germany

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

[REDACTED]

[REDACTED] Teva Branded Pharmaceuticals
R&D, Inc.

Study Director

[REDACTED]

[REDACTED]

[REDACTED]

For operational issues, contact the operational leads listed below:

[REDACTED]

[REDACTED] Teva Branded Pharmaceuticals R&D, Inc.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

For serious adverse events:

Send by e-mail to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Study TV48125-CNS-30050

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of TEV-48125 Versus Placebo for the Preventive Treatment of Episodic Migraine

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

IND Number: 106,533 **EudraCT Number:** 2015-004598-34

Name of Active Ingredient: Humanized anti-calcitonin gene-related peptide (CGRP) monoclonal antibody

Name of Investigational Product: TEV-48125

Phase of Clinical Development: 3

Number of Investigational Centers Planned: Approximately 140

Countries Planned: Approximately 15

Planned Study Period: 1Q/2016 (first patient in) to 3Q/2017 (last patient last visit)

Number of Patients Planned: A total of 768 patients (256 patients per treatment group) are planned to be enrolled in this study to have 675 completers (225 completers per treatment group); a 12% drop-out rate is anticipated. Patients will be randomized 1:1:1 to the following treatment groups:

- monthly subcutaneous (sc) administration of TEV-48125 at 225 mg
- sc administration of TEV-48125 at 675 mg followed by monthly sc placebo
- monthly sc administration of placebo

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

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

Because headache consortium guidelines recommend preventive therapies for patients with EM occurring on 4 or more days per month due to the frequency of headaches and high degree of disability, patients using no more than 1 preventive medication at the time of study 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](#)). Patients on concomitant preventive medications must be on a stable dose for at least 2 months of consecutive use prior to study entry (ie, before the run-in period), without anticipated changes during the study. A list of preventive medications is presented in [Appendix A](#). The total number of patients receiving concomitant preventive medication during the study will not exceed 30% of the total sample size of the study. This subset will be randomized independently.

Primary Objectives: The primary objectives of this study are as follows:

- to demonstrate the efficacy 2 dose regimens of TEV-48125, as assessed by the decrease in the monthly average number of migraine days during 12-week period after the 1st dose of study drug relative to the baseline period
- to evaluate the safety and tolerability of 2 dose regimens TEV-48125 in the preventive treatment of EM

Secondary Objectives: The secondary objectives of the study are as follows:

- to evaluate the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days with TEV-48125 during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the number of migraine days during the 4-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period in patients not receiving concomitant migraine preventive medications at baseline
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of migraine-related disability as measured by the Migraine Disability Assessment (MIDAS) questionnaire, at 4 weeks after the last (3rd) dose of study drug relative to baseline
- to evaluate the immunogenicity of TEV-48125 and the impact of antidrug antibodies (ADAs) on efficacy and safety during 12 weeks of treatment with TEV-48125

Exploratory Objectives: The exploratory objectives of the study are as follows:

- to demonstrate the efficacy of TEV-48125, as assessed by the decrease in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug relative to the baseline period
- to evaluate the proportion of patients reaching at least 75% reduction and total (100%) reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- to evaluate the proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug relative to the baseline period who sustain this level of response over the 12-week period after the 1st dose of study drug
- to demonstrate the efficacy of TEV-48125 in patients who previously used topiramate for migraine, but discontinued, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125 in patients who previously used onabotulinumtoxinA for migraine, but discontinued, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period

- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the number of migraine days during the 4-week period after the 2nd dose of study drug and the 4-week period after the last (3rd) dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the monthly average number of headache days of any severity during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 4-week period after each dose of study drug relative to the baseline period
- to evaluate the proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- to evaluate the proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients not receiving concomitant preventive migraine medications relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used topiramate for migraine in the past relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of headache hours of any severity during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the monthly average number of days of the use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug relative to the baseline period

- to demonstrate the efficacy of TEV-48125, as assessed by a change in quality of life at 4 weeks after the last (3rd) dose of study drug relative to baseline
- to explore the correlation between pharmacokinetic parameters and drug efficacy
- to explore the relationship between genetic polymorphisms within the CGRP receptor-ligand complex (eg, CALCA, CALCB, CALCRL, CRCP, and RAMP) and migraine-associated genes (eg, PRDM16, AJAP1, TSPAN2, MEF2D, TRPM8, TGFBR2, PHACTR1, FHL5, C7orf10, MMP16, ASTN2, LRP1, APOA1BP, TBC1D7, FUT9, STAT6, ATP5B, and MTHFR) and mode-of-action-related pathways versus hypertension, migraine severity, and safety and efficacy responses
- to explore the relationship between biofluid bone, angiogenic, and inflammatory biomarkers with TEV-48125 concentrations and efficacy responses

Study Endpoints

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

Secondary Endpoints: The secondary endpoints are as follows:

- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 1st dose of the study drug
- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug in patients not receiving concomitant migraine preventive medications
- mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug

Exploratory Endpoints: The exploratory endpoints are as follows:

- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 75% reduction and total (100%) reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug in patients who used topiramate for migraine in the past

- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 2nd dose of the study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the last (3rd) dose of the study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of any severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week period after each dose of study drug
- proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients not receiving concomitant preventive migraine medications
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of any severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the Migraine-Specific Quality of Life (MSQOL) questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug

- mean change from baseline (day 0) in the health status, as measured by the EuroQol-5 Dimension, 5 response level version (EQ-5D-5L) questionnaire at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the 2-item Patient Health Questionnaire (PHQ-2) and 9-item Patient Health Questionnaire (PHQ-9), at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug
- assessment of patient satisfaction, as measured by the Patient Global Impression of Change (PGIC) scale, at 4 weeks after administration of the 1st dose of study drug, at 4 weeks after the 2nd dose of study drug, and at 4 weeks after the last (3rd) dose of study drug
- exploratory correlation of specific genetic polymorphisms and headache response, specific migraine clinical features, and adverse events to medication
- mean change from baseline in exploratory biofluid biomarkers versus treatment, migraine onset/severity, and response status (ie, responders versus nonresponders)
- correlation of exploratory biofluid biomarkers with TEV-48125 concentrations

General Design and Methodology: This is a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the safety, tolerability, and efficacy of 2 dose regimens of sc TEV-48125 and placebo.

- monthly sc administration of TEV-48125 at 225 mg
- sc administration of 675 mg of TEV-48125 at visit 2 followed by monthly sc placebo
- monthly sc administration of placebo

Randomization will be performed using electronic interactive response technology (IRT). Patients will be stratified based on gender, country, and baseline preventive migraine medication use (yes, no) to ensure balance for the covariates (treatment group, preventive medication use, country, and gender).

Blinded treatment will be administered sc once monthly (approximately every 4 weeks) for a total of 3 doses. First treatment administration will occur at visit 2 (day 0), and additional doses will be administered at visits 3 and 4. Final study assessments will be performed at visit 5 (end-of-treatment [EOT] visit), approximately 4 weeks after administration of the 3rd and final dose of study drug. Upon completion of the final study assessments, patients may enter a long-term safety and efficacy study (Study TV48125-CNS-30051), consisting of a 12-month double-blind treatment period and a 6.5-month follow-up period. In the long-term safety extension study, patients receiving active study drug in the current study will continue receiving the same treatment (ie, monthly sc TEV-48125 at 225 mg or quarterly sc TEV-48125 at 675 mg), and patients receiving placebo in the current study will be randomized in a 1:1 ratio to receive monthly sc TEV-48125 at 225 mg or quarterly sc TEV-48125 at 675 mg during the long-term safety and efficacy study. Patients who do not enroll in the long-term safety and efficacy study for any reason will be offered to enter the long-term safety extension for the purpose of evaluating ADA approximately 7.5 months (225 days [the approximate equivalent of 5 half-lives]) after receiving the last dose of study drug in this study.

Method of Blinding and Randomization: The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients 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. Kits will be identical in appearance and contain 1 prefilled syringe with active drug or placebo. Adequate kit supply for upcoming study visits will be managed by IRT and kept (refrigerated at 2°C to 8°C) on site.

This is a randomized study with stratification based on gender, country, and baseline preventive medication use (yes, no). Each patient will undergo randomization in a 1:1:1 ratio within the stratum to which he or she belongs to receive 1 of the 2 TEV-48125 dose regimens or placebo, as assigned by the IRT. The IRT will manage initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At the time of each study visit, the IRT will be queried, and site personnel will retrieve and administer a 1.5-mL volume from each syringe contained in the appropriately numbered kit(s).

The total number of patients receiving concomitant preventive medication during the study will not exceed 30% of the total sample size of the study.

Study Drug Dose, Mode of Administration, and Administration Rate: Prefilled syringes (active or placebo) will be contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Active syringes will contain 150 mg/mL of TEV-48125, and placebo syringes will contain the same vehicle and excipients as those for active injections. Each kit will contain 1 prefilled syringe.

Study drug will be administered by qualified study personnel as sc injections approximately every 4 weeks (28 days) for a total of 3 doses, as follows:

- Patients randomized to receive TEV-48125 at 225 mg will receive 225 mg of TEV-48125 as 1 active injection (225 mg/1.5 mL) and two 1.5-mL placebo injections at visit 2 and 225 mg of TEV-48125 as 1 active injection (225 mg/1.5 mL) at visits 3 and 4.
- Patients randomized to receive TEV-48125 675 mg/placebo will receive 675 mg of TEV-48125 as 3 active injections (225 mg/1.5 mL) at visit 2 and placebo as single 1.5-mL injection at visits 3 and 4.
- Patients randomized to receive placebo will receive three 1.5-mL placebo injections at visit 2 and single 1.5-mL placebo injection at visits 3 and 4.

The recommended sc injection sites follow the National Institutes of Health Patient Education Guidelines of June 2012, which are available in [Appendix C](#) and at http://www.cc.nih.gov/ccc/patient_education/pepubs/subq.pdf. The suggested sites of injection are back of upper arms, lower abdomen/belly/waistline, and front of thighs. Each of the injections at visit 2 should be given in a different location (eg, not in precisely the same place), and study staff member(s) responsible for administration of injections should inspect previous injection sites to ensure that they are free of bruising and tenderness and that proper rotation of sites is performed.

The total number of sc injections and their locations will be recorded for each dosing visit (visits 2, 3, and 4). A 1.5-mL volume from each syringe in each visit's kit(s) must be injected sc for dosing to be considered complete.

Investigational Product: TEV-48125

Reference Therapy:

Placebo: Same vehicle and excipients as those for active injection

Comparison Drug: Not applicable

Duration of Patient Participation: Patient participation will last for approximately 4 months (including a 28-day run-in period and a 12-week, double-blind treatment period); after which, patients may enter into a double-blind, long-term safety and efficacy study. Patients who do not enroll in the double-blind, long-term safety and efficacy study for any reason will be offered to enter the long-term safety extension for the purpose of evaluating ADA

approximately 7.5 months (225 days [the approximate equivalent of 5 half-lives]) after receiving the last dose of study drug in this study. Thus, patient participation for these patients will last approximately 10.5 months.

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

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

- a. Males or females aged 18 to 70 years, inclusive, with migraine onset at ≤ 50 years of age
- b. Patient signs and dates the informed consent document
- c. Patient has history of migraine (according to ICHD-3 criteria [[Classification Committee of the IHS, 2013](#)]) or clinical judgement suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥ 12 months prior to screening.
- d. Patient fulfills the following criteria for EM in prospectively collected baseline information during the 28-day run-in period:
 - headache occurring on ≥ 6 and ≤ 14 days
 - on ≥ 4 days, fulfilling any of the following:
 - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura ([Appendix D](#))
 - ICHD-3 criteria B and C for 1.2 Migraine with aura ([Appendix D](#))
 - Probable migraine (a migraine subtype where only 1 migraine criterion is missing)
 - The patient used a triptan or ergot derivative to treat an established headache
- e. Not using preventive medications (presented in [Appendix B](#)) (ie, at least 5 half-lives have passed since last use) or using no more than 1 preventive medication (presented in [Appendix A](#)) for migraine or other medical conditions (eg, propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to beginning the 28-day run-in period.
- f. Body mass index of 17.5 to 37.5 kg/m² and a total body weight between 45 and 120 kg, inclusive
- g. All patients must be of nonchildbearing potential, defined as:
 - women surgically sterile by documented complete hysterectomy, bilateral oophorectomy, or tubal ligations or confirmed to be postmenopausal (at least 1 year since last menses and follicle-stimulating hormone above 35 U/L)
 - men surgically sterile by documented vasectomyor
if of childbearing potential, patients must meet any of the following criteria:
 - Patients must simultaneously use 2 forms of highly effective contraception methods (defined in [Section 5.2](#)) with their partners during the entire study period and for 7.5 months after the last dose of study drug.
 - Sexual abstinence is only considered a **highly effective method** if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception.

- h. Female patients of childbearing potential must have negative a serum beta-human chorionic gonadotropin (β -HCG) pregnancy test at screening (confirmed by urine dipstick β -HCG pregnancy test at baseline).
- i. The patient demonstrated compliance with the electronic headache diary during the run-in period by entry of headache data on a minimum of 24 out of 28 days (~85% diary compliance).
- j. The patient is in good health as determined by a medical and psychiatric history, medical examination, 12-lead electrocardiogram (ECG), serum chemistry, hematology, coagulation, and urinalysis.
- k. The patient must be willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study period, and to return to the clinic for the follow-up evaluation, as specified in this protocol.

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

- a. Patient has received onabotulinumtoxinA (Botox[®], Allergan, Inc.) for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 4 months before screening.
- b. Patient is using medications containing opioids (including codeine) or barbiturates (including butalbital/aspirin/cafeine, butalbital/paracetamol/cafeine, or any other combination containing butalbital) on more than 4 days per month for the treatment of migraine or for any other reason.
- c. Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the following medications for treatment of EM or chronic migraine after adequate therapeutic trial defined as use for at least 3 months at accepted migraine therapeutic doses:
 - cluster A: divalproex sodium and sodium valproate
 - cluster B: flunarizine and pizotifen
 - cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine
 - cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol
- d. Patient has used an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the last 2 months prior to screening.
- e. Clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator
- f. Evidence or medical history of clinically significant psychiatric issues, including any suicide attempt in the past, or suicidal ideation with a specific plan in the past 2 years.
- g. History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism
- h. Known infection or history of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection
- i. Past or current history of cancer in the past 5 years, except for appropriately treated nonmelanoma skin carcinoma

- j. Pregnant or nursing females
- k. History of hypersensitivity reactions to injected proteins, including monoclonal antibodies
- l. Participation in a clinical study of a new chemical entity or a prescription medicine within 2 months before study drug administration or 5 half-lives, whichever is longer
- m. Any prior exposure to a monoclonal antibody targeting the CGRP pathway (AMG 334, ALD304, LY2951742, or TEV-48125)
- n. Any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator
- o. Any finding that, in the judgment of the investigator, is a clinically significant abnormality, including serum chemistry, hematology, coagulation, and urinalysis test values (abnormal tests may be repeated for confirmation)
- p. Hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) $>1.5 \times$ the upper limit of the normal range (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law at screening
- q. Serum creatinine $>1.5 \times$ the ULN, clinically significant proteinuria, or evidence of renal disease at screening
- r. History of alcohol or drug abuse during the past 2 years, or alcohol or drug dependence during the past 5 years
- s. The patient cannot participate or successfully complete the study, in the opinion of their healthcare provider or the investigator, for any of the following reasons:
 - mentally or legally incapacitated or unable to give consent for any reason
 - in custody due to an administrative or a legal decision, under guardianship, or institutionalized
 - unable to be contacted in case of emergency
 - has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study
- t. The patient is a study center or sponsor employee who is directly involved in the study or the relative of such an employee.

Measures and Time Points:

Primary Efficacy Measure and Time Point: The primary efficacy endpoint for this study will be derived from headache data (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use) collected daily using an electronic headache diary device.

Eligible patients will receive training on the use of the electronic headache diary device and will be informed of compliance requirements at screening. Patients will complete electronic headache diary entries with questions about the previous day daily, beginning on day –27 (the day after the screening visit) through the EOT/early withdrawal visit. The electronic headache diary device will allow entry of headache information for up to 48 hours after a given day.

Secondary Efficacy Measures and Time Points: Secondary efficacy endpoints will be derived from headache data (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute

migraine-specific medication use) collected daily using an electronic headache diary device. In addition, migraine-related disability will be assessed using the MIDAS, completed at time points specified in [Table 1](#).

Exploratory Efficacy Measures and Time Points: The following exploratory efficacy measures will be assessed at time points specified in [Table 1](#):

- exploratory efficacy endpoints derived from headache data (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use), which are collected daily using an electronic headache diary device
- PHQ-2/PHQ-9 (Note: Patients will first respond to the PHQ-2. They will respond to questions 3 through 9 [unique questions] of the PHQ-9 only if the PHQ-2 is positive.)
- MSQOL questionnaire
- EQ-5D-5L questionnaire
- PGIC scale
- WPAI questionnaire

Safety and Tolerability Measures and Time Points: Safety and tolerability will be assessed at time points specified in [Table 1](#) using the following measures:

- inquiries about adverse events
- inquiries about concomitant medication usage
- safety laboratory tests (serum chemistry, hematology, coagulation, and urinalysis)
- serum/urine β -HCG test (women of childbearing potential only)
- 12-lead ECGs
- vital signs measurements (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate)
- physical examinations, including body weight
- injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments
- electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

Pharmacokinetics/Biomarkers/Immunogenicity Measures and Time Points:

Pharmacokinetic Measures and Time Points: Blood samples for pharmacokinetics analysis of TEV-48125 will be collected from all patients at the time points specified in [Table 1](#) for the purpose of pharmacokinetic/pharmacodynamic relationship assessment. The pharmacodynamic parameters will be the efficacy responses.

The actual date and time of each blood sample, as well as the date and time of the last study drug dose prior to each sample, will be recorded in the case report form.

TEV-48125 plasma concentration will be measured using a validated assay.

Immunogenicity Measures and Time Points: Blood samples for immunogenicity will be collected at the time points specified in [Table 1](#).

Biomarker Measures and Time Points: Biomarker blood and urine samples will be collected from all patients at the time points specified in [Table 1](#), and a blood sample will be collected from patients who consent to pharmacogenomic analysis at visit 2 or any visit thereafter.

Allowed and Disallowed Medications Before and During the Study:

Prior Medications and Therapeutic Failures of Migraine Preventives: Details regarding excluded prior migraine preventive treatments and therapeutic failures of migraine preventives are described in the exclusion criteria.

Concomitant (Current) Therapy: Up to 30% of patients will be allowed to remain on stable doses of no more than 1 preventive migraine medication for the duration of the study provided the medication has at least moderate evidence of efficacy as defined by guidelines ([Silberstein et al 2012](#)) and presented in [Appendix A](#). Patients on preventive medication must be on a stable dose for at least 2 months of consecutive use prior to study entry. Alternatively, patients must have discontinued the preventive medication at least 5 half-lives prior to screening.

Patients will be allowed to use acute medications to treat acute migraine attacks as needed.

All concomitant medications taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All patients will be questioned about concomitant medication at each clinic visit.

Statistical Considerations:

Sample Size Rationale: A sample size of 675 randomized (ie, 225 evaluable patients completing the study per treatment group) is needed for 90% power to show a 1.6 difference in migraine days (assuming a common standard deviation [SD] of 5.2 days) at an alpha level of 0.05. Assuming a 12% discontinuation rate, 256 patients per treatment group will be randomized.

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

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

Analysis of Primary Efficacy Endpoint: The primary efficacy endpoint, the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug, will be analyzed using an analysis of covariance method. The model will include treatment, gender, country, and baseline preventive medication use as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. Ninety-five percent confidence intervals will be constructed for the least squares mean differences between each TEV-48125 group and the placebo group.

Analysis of Secondary and Exploratory Efficacy Endpoints: The same analysis used for the primary efficacy endpoint will be performed for the continuous secondary and exploratory efficacy endpoints. For the proportion of responders, defined as 50% or more reduction from baseline in the monthly average number of migraine days, Cochran-Mantel-Haenszel test will be used.

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 be described in detail in the statistical analysis plan.

Safety and Tolerability Analyses: All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to study drug (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Local tolerability findings will be listed and summarized descriptively.

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

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

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

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

Pharmacokinetic Analysis: Pharmacokinetic plasma concentration results (TEV-48125) will be tabulated descriptively at each planned sampling time point by treatment group.

Pharmacokinetic/Pharmacodynamic Analysis: The pharmacokinetic/pharmacodynamic relationship will be estimated by compartmental techniques. The pharmacokinetic parameters will be based on TEV-48125 measurements. The pharmacodynamic will be the efficacy responses.

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

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. This impact analysis will be reported separately.

Biomarker Analysis: Biomarker analysis will include logistic regression, receiver operating characteristic curves, and summary statistics. Results will be reported separately.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**Table of Abbreviations**

Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ADA	antidrug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CBC	complete blood count
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
CGRP	calcitonin gene-related peptide
CM	chronic migraine
C _{max}	maximum observed plasma drug concentration
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
DNA	deoxyribonucleic acid
ECG	electrocardiography/electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EM	episodic migraine
EOT	end of treatment (visit)
EQ-5D-5L	EuroQol-5 Dimension, 5 response level version
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration (US)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
ICH	International Conference on Harmonisation
ICHD	International Classification of Headache Disorders

Abbreviation	Term
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IHS	International Headache Society
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
iv	intravenous(ly)
IRT	interactive response technology
LSO	local safety officer
MIDAS	Migraine Disability Assessment
MSQOL	Migraine-Specific Quality of Life
NOAEL	no-observed-adverse-effect level
PBO	placebo
PEF	peak expiratory flow
PGIC	Patient Global Impression of Change
PHQ-2	2-item Patient Health Questionnaire
PHQ-9	9-item Patient Health Questionnaire
QC	quality control
RBC	red blood cell
RNA	ribonucleic acid
sc	subcutaneous(ly)
SD	standard deviation
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
t_{max}	time to maximum observed drug concentration
ULN	upper limit of the normal range
US(A)	United States (of America)
V	visit
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment

1. BACKGROUND INFORMATION

1.1. Introduction

Migraine is a prevalent condition characterized by attacks of headache and associated symptoms (such as nausea, photophobia, or phonophobia). The 2 most common forms of migraine, migraine without aura and migraine with aura, occur on less than 15 days per month and are referred to as episodic forms of migraine (ie, EM) ([Lipton et al 2007](#)). However, approximately 3% of individuals with EM evolve, in any given year, to a significantly more disabling condition called CM ([Bigal et al 2008](#), [Lipton et al 2007](#), [Scher et al 2003](#)). Individuals with CM present with headaches of any severity on 15 or more days per month and have full-blown migraine on at least 8 days per month ([Classification Committee of the International Headache Society \[IHS\], 2013](#)). A sizable proportion of individuals with CM experiences daily headaches and, therefore, faces considerable disability ([Bigal and Lipton 2008](#)).

The pathophysiology of migraine involves central and peripheral events. Activation of structures in the brainstem are involved in the modulation of sensory activity, which is impaired during migraine attacks. Chronic dysfunction in these structures predisposes migraineurs not only to migraine attacks, but to increased headache frequency ([Goadsby and Hargreaves 2008](#)). Furthermore, the activation of these structures is also associated with inflammation and protein extravasation at the level of the meningeal blood vessels, muscles and other structures innervated by the trigeminal nerve. This combination of peripheral insults (inflammation and plasma protein extravasation) with impairment of the inhibitory pain mechanisms at the level of brainstem is paramount to frequent migraines ([Goadsby et al 2002](#)).

Calcitonin gene-related peptide (CGRP) is a well-studied neuropeptide found at the centers of the migraine processes, both centrally and peripherally ([Eftekhar and Edvinsson 2010](#)). Its role in migraine pathophysiology was suggested more than 20 years ago ([Edvinsson and Goadsby 1990](#), [Goadsby et al 1990](#)). Jugular levels of CGRP are increased during migraine attacks, and intravenous (iv) CGRP administration induces migraine-like headache in most individuals with migraine ([Ashina et al 2000](#), [Hansen et al 2010](#)). Calcitonin gene-related peptide is therefore involved in the pathophysiology of migraine at all levels, peripherally (vasodilation, inflammation and protein extravasation), at the trigeminal ganglion, and inside the brain ([Ho et al 2010](#)). Inhibition of CGRP has demonstrated efficacy in the treatment of EM ([Hewitt et al 2011](#), [Ho et al 2008](#), [Olesen et al 2004](#)).

The goals of migraine treatment are to relieve pain, restore function, reduce headache frequency, and to prevent progression of EM to CM. Pharmacological interventions for the treatment of migraine include acute (symptomatic) treatments and daily preventive medications. The latter is indicated for patients with CM and may be appropriate patients with EM who have significant disability with migraine attacks (>3 days per month with headache-related disability), contraindications to triptans or other vasoactive medications, significant adverse effects from triptans, and patients with severe or prolonged attacks ([Lipton and Silberstein 2015](#)). Currently available drug therapies for preventive treatment of migraine include antiepileptic drugs, beta-blockers, triptans, antidepressants, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, serotonergic agents, calcium channel blockers, nonsteroidal anti-inflammatory drugs, opioids, and direct vascular smooth muscle relaxants. Although there

are more than 40 medications within these classes of drugs that are used with varying response rates to prevent migraine, only 5 marketed drugs are approved by the Food and Drug Administration (FDA) in the United States (US) for the preventive treatment of migraine; 4 of them are approved for the prophylaxis of migraine: propranolol, timolol maleate, divalproex sodium, and topiramate. The clinical trials ([Brandes et al 2004](#), [Klapper 1997](#), [Mathew et al 1995](#), [Nadelmann et al 1986](#), [Silberstein et al 2004](#)) that supported registration of these drugs for this indication were conducted before the establishment of CM as a single entity and generally included patients with headaches on less than 15 days per month. Only 1 medication, onabotulinumtoxinA, is approved for prophylaxis of CM ([Lipton and Silberstein 2015](#)).

TEV-48125 (also known as PF-04427429, RN307, or LBR-101) is a fully humanized immunoglobulin G (IgG) 2a/kappa monoclonal antibody derived from a murine precursor. TEV-48125 is a potent, selective CGRP binder and blocks both CGRP isoforms (α - and β -CGRP) from binding to the CGRP receptor. TEV-48125 is specific for CGRP and does not bind to the closely related family members amylin, calcitonin, or adrenomedullin peptides. Two mutations were introduced into the constant region of the TEV-48125 heavy chain to limit antibody effector functions. This loss of function prevents TEV-48125 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 pharmacokinetics and tolerability of TEV-48125 (iv doses ranging from 0.2 to 2000 mg and subcutaneous [sc] doses of 225 mg and 900 mg) has been well-characterized in the Phase 1 development program (see Section 1.3.2.1). Furthermore, the safety and effectiveness of TEV-48125 has been demonstrated in a randomized double-blind, placebo controlled Phase 2 study of 2 sc dosing regimens of TEV-48125 (monthly TEV-48125 at 900 mg or TEV-48125 at 675 mg followed by monthly TEV-48125 at 225 mg) in patients with CM and a randomized, double-blind, placebo-controlled Phase 2 study of 2 sc dosing regimens of TEV-48125 (monthly TEV-48125 at 675 or 225 mg) in patients with EM (see Section 1.3.2.2). The acceptable tolerability, long terminal elimination half-life ($t_{1/2}$, approximately 45 days) and ability to administer sc make TEV-48125 an attractive therapeutic candidate for the preventive treatment of CM and EM.

1.2. Name and Description of Investigational Product

TEV-48125 (formerly LBR-101, PF-04427429, or RN307) is a fully humanized IgG2a/kappa monoclonal antibody derived from a murine precursor. TEV-48125 is being developed for administration by the sc route. A more detailed description of the product is given in Section 3.9.

1.3. Findings from Nonclinical and Clinical Studies

1.3.1. Nonclinical Studies

In vivo pharmacology studies of TEV-48125 in animal models indicate that TEV-48125 prevented an increase in blood flow in rat paw skin and the middle meningeal artery after electrical stimulation and produced a dose-dependent inhibition of the capsaicin-induced skin flare response in cynomolgus monkey.

Safety pharmacology parameters of TEV-48125 were assessed in the pivotal toxicology studies in Sprague Dawley rats and cynomolgus monkeys and a separate cardiovascular safety pharmacology study in male cynomolgus monkeys. There were no treatment-related changes in electrocardiograms (ECGs) and heart rates in the 1- and 3-month toxicity studies, and a single iv dose of TEV-48125 at 100 mg/kg did not result in changes in cardiovascular parameters or body temperature in monkeys. Additionally, no target organ toxicity was identified. In these referenced studies, the no-observed-adverse-effect level (NOAEL) ranged from 100 to 300 mg/kg dosed either iv or sc. In a 3-month monkey study, perivascular inflammation of the ciliary artery was observed in a few animals at doses ≥ 100 mg/kg. The inflammation was suspected to be the result of immune complex formation/deposition from the monkeys' immunogenic response to the drug (TEV-48125). In the pivotal 6-month chronic toxicity study in monkeys following once-weekly sc dosing at dosage levels of up to 300 mg/kg/week, achieving high exposure throughout the study, no microscopic findings were noted in any of the organs, including the ciliary vessels of the eyes, and the NOAEL of the chronic toxicity study was determined to be the highest dose tested, 300 mg/kg/week. Thus, it is believed that in view of the low frequency (ie, observed in very few animals) and minimal severity, the finding (perivascular inflammation) that was only recorded in the 3-month toxicity study, and had been resolved during the recovery period, is an incidental finding.

The pharmacokinetics of TEV-48125 in animals (rats and monkeys) is typical of a humanized IgG2 molecule, with low mean plasma clearance, low volume of distribution at steady state, and a long $t_{1/2}$. Exposure as defined by the maximum observed plasma drug concentration (C_{max}) and the area under the plasma concentration-time curve increased linearly across doses following single and repeated once-weekly dosing. No gender differences in exposure were observed in rats or monkeys.

Additionally, pivotal reproductive and developmental toxicity studies in rabbits and rats with TEV-48125 were conducted and completed. Preliminary data suggest that weekly dosing with TEV-48125 was well tolerated and did not induce any obvious maternal toxicity at any dose level. No apparent evidence of embryo-fetal toxicity was noted in any dose group.

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

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

1.3.2. Clinical Studies

To date, TEV-48125 has been studied in 6 Phase 1 studies in healthy volunteers and 2 Phase 2b studies in migraine patients. In total, 484 subjects (118 healthy volunteers and 366 migraine patients) received at least 1 dose of TEV-48125 via iv or sc administration.

A brief summary of clinical pharmacology and clinical safety and efficacy studies of TEV-48125 follows. Further details may be found in the current Investigator's Brochure.

1.3.2.1. Clinical Pharmacology Studies

A total of 118 subjects received at least 1 dose of TEV-48125 across 6 completed Phase 1 studies at doses ranging from 0.2 through 2000 mg. Studies included 2 single-dose-escalation pharmacokinetic and pharmacodynamic studies in healthy men (Studies B0141001 and

B0141002); a 2-cohort, placebo-controlled, cross-over study to examine the acute effects administration of TEV-48125 on capsaicin flare response in healthy men (Study B0141006); a parallel-group, repeat-dose study of TEV-48125 in healthy men and women (Study B0141007); a single-dose study evaluating the safety, tolerability, and pharmacokinetics of doses up to 2000 mg administered to healthy women (Study LBR-101-008); and a single-dose study comparing the safety, tolerability, absolute bioavailability, and pharmacokinetics of sc and iv TEV-48125 in healthy men and women (Study LBR-101-011).

Based on noncompartmental analysis, TEV-48125 exposure increases with dose in an approximately dose-proportional manner from 225 to 900 mg following sc administration and over the dose range from 100 to 2000 mg following iv infusion. The C_{\max} occurred near the end of the iv infusion (median time to C_{\max} [t_{\max}] of 1 to 5 hours after the start of the infusion), and C_{\max} was prolonged as indicated by the delayed t_{\max} (median t_{\max} 96 to 108 hours postdose) after sc administration. The mean $t_{1/2}$ following sc administration was similar to that observed after iv administration for each dose level. The $t_{1/2}$ ranged from approximately 642 to 770 hours (approximately 27 to 32 days) at the 225-mg dose level, and the $t_{1/2}$ ranged from approximately 1140 to 1200 hours (approximately 48 to 50 days) at the 900-mg dose level. Absolute bioavailability of the sc dose was approximately 55%.

TEV-48125 was well tolerated with favorable safety profile. The treatment-emergent adverse events reported in the Phase 1 studies were predominantly mild to moderate in severity. A specific “pattern of adverse events” that could be associated with a dose or a dose range of TEV-48125 has not been identified, nor has a maximally tolerated dose been identified. The most common treatment-emergent adverse events reported were headache, nasopharyngitis, gastroenteritis, and back pain. There were no deaths. One serious adverse event reported as “thoracic aortic aneurysm aggravated” in an individual receiving a single iv 300-mg TEV-48125 dose resolved.

TEV-48125 does not appear to be associated with any clinically relevant patterns of change in vital signs (systolic and diastolic blood pressure, temperature and heart rate) or cardiac conduction and repolarization (P-R interval, QT interval corrected for heart rate using Bazett’s and Fridericia’s formulas) measured by frequent 12-lead ECGs. No changes in liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, and alkaline phosphatase [ALP]) or differences between TEV-48125 and placebo in hematological parameters, tests assessing renal function, electrolytes, or urinalysis has been observed in any of the Phase 1 studies.

1.3.2.2. Clinical Safety and Efficacy Studies

The safety, tolerability, and efficacy of TEV-48125 was evaluated in migraine patients in 2 Phase 2b studies. The first study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy, safety, tolerability, and pharmacokinetics of 2 doses of TEV-48125 with placebo in 264 patients with CM (Study LBR-101-021). Following a 28-day run-in period, participants were randomized and treated sc once monthly for 3 months. One active group received a 1st dose of 675 mg followed by 225 mg on the subsequent 2 months. The other active group received 900 mg per month. The mean change in headache hours relative to baseline for each TEV-48125 dose arm was significantly different from the placebo arm at 3 months (primary endpoint), and the study was

also positive at 2 and 1 months. Both doses were also superior to placebo for the secondary endpoint (decrease in the number of days with moderate or severe headache at 3 months). At the doses tested, TEV-48125 was well tolerated, and no serious treatment-related adverse events were reported. Most adverse events were mild to moderate. No safety signals were observed in the clinical laboratory tests, vital signs, physical examination, or ECGs.

The second study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy, safety, tolerability, and pharmacokinetics of 2 doses of TEV-48125 with placebo in 297 patients with EM (Study LBR-101-022). Following a 28-day run-in period, participants were randomized and treated sc once monthly for 3 months. Two active doses were tested, 225 mg given monthly for 3 months and 675 mg given monthly for 3 months. The mean change in number of migraine days at month 3 relative to baseline for both TEV-48125 dose arms was significantly different from placebo at 3 (primary endpoint), 2, and 1 months. Secondary and exploratory endpoints were also positive for the duration of the study. Both doses were well tolerated, and no serious treatment-related adverse events were reported. Most adverse events were mild to moderate and the lowest dose had a numerically lower number of adverse events relatively to placebo. No safety signals were observed in the clinical laboratory tests, vital signs, physical examination, or ECGs.

1.4. Known and Potential Risks and Benefits to Human Patients

1.4.1. Known and Potential Risks and Benefits of TEV-48125

Information regarding risks and benefits of TEV-48125 to human patients may be found in the current Investigator's Brochure.

1.4.1.1. Risks of TEV-48125

Identified risks (adverse drug reactions) of TEV-48125 include injection site erythema, administration site pain, injection site pain, injection site pruritus, injection site dermatitis, infusion-related reaction, and drug hypersensitivity. None of the identified risks are considered important risks.

Potential risks for TEV-48125 are perivascular inflammation; development of antidrug antibodies (ADAs); liver enzyme elevations; and cardiovascular consequences of CGRP inhibition, including effects on blood pressure, heart rate, or other cardiovascular parameters.

As described in Section 1.3.2.2, sc TEV-48125 has generally been well tolerated over the ranges of doses evaluated (single doses of 0.02 to 2000 mg in healthy volunteers, multiple doses of 30 to 300 mg in healthy volunteers, and multiple doses of 225 to 900 mg in migraine patients). The most common treatment-emergent adverse events were mild to moderate transient general administration site disorders/reactions. Other commonly reported treatment-emergent adverse events were headache, back pain, and upper respiratory tract infection.

1.4.1.2. Benefits of TEV-48125

As described in Section 1.3.2.2, results from Phase 2 clinical studies have demonstrated statistically significant reductions in mean headache hours after 1, 2, and 3 months of TEV-48125 treatment in patients with CM and statistically significant reductions in monthly

migraine days after 1, 2, and 3 months of TEV-48125 treatment in patients with EM. Results for several secondary/exploratory endpoints also showed TEV-48125 to be superior to placebo.

1.4.2. Overall Risk and Benefit Assessment for This Study

Based on the current safety profile and the demonstrated efficacy of the sc TEV-48125 dosage form, the overall risk and benefit assessment for this study is favorable.

1.5. Selection of Drugs and Dosages

A detailed description of study drug administration is presented in Section 5.1.

1.5.1. Justification for Dosage of Active Drug

The TEV-48125 doses and dosing regimens to be evaluated in this double-blind study were selected on the basis of animal pharmacodynamic and pharmacokinetic data, 6 pharmacokinetic/safety studies in healthy volunteers, 2 safety/efficacy study in patients with migraine, and population pharmacokinetic and pharmacokinetic/pharmacodynamic modeling and simulations.

The pharmacodynamics of TEV-48125 were examined in animal models by characterization of the ability of TEV-48125 to block CGRP functions in vivo (see Section 1.3.1). Specifically, neurogenic vasodilation by capsaicin application on the skin was used to induce a CGRP-mediated increase in vasodilation or skin blood flow in cynomolgus monkeys. In this study, TEV-48125 (dosed as a single iv bolus at 1, 10, or 100 mg/kg) produced a dose-dependent inhibition of the capsaicin-induced skin flare response. The magnitude and duration of the inhibition produced by TEV-48125 were dose-dependent, with the 10 and 100 mg/kg doses showing inhibition out to 56 days postdose. Based on body surface area conversion, these doses are equivalent to single doses of approximately 225 and 2000 mg, respectively, in patients with migraine. Therefore, the 225-mg dose was considered to be a reasonable and pragmatic choice for the lowest dose with potential for effectiveness.

Based on data from the pharmacokinetic and pharmacodynamic studies in animal models and the pharmacokinetics, safety, and tolerability of TEV-48125 from Phase 1 studies in healthy volunteers, 2 dose regimens were selected for sc administration in the Phase 2b study in patients with EM for a treatment period of 3 months. The 2 active arms were 225 and 675 mg administered monthly. The results of the Phase 2b study demonstrated that both dose regimens are effective, safe, and well tolerated by EM patients. The mean change in number of migraine days relative to baseline for both TEV-48125 dose arms were significantly different from the placebo arm at 3 months (primary endpoint), and the study was also strikingly positive at 2 months and 1 month. Although a maximum tolerated dose was not reached in the Phase 2b study, and doses up to 2000 mg were observed to be safe in healthy volunteers, it is considered best practice to select the lowest effective dose known for administration. Therefore, the lowest dose from the Phase 2b study, 225 mg TEV-48125 administered monthly, was preserved for the Phase 3 study in patients with EM. A 2nd active treatment group will receive TEV-48125 at 675 mg quarterly to examine the potential for loss of efficacy within a 3-month treatment period following a single sc administration. In a simulation, a low dose of 225 mg once in 3 months was evaluated and found to be with limited efficacy. Thus, the next supported higher dose of 675 mg was selected for this regimen.

1.5.2. Justification for Use of Placebo

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

1.6. Compliance Statement

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

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

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the applicable study staff must be familiar with the background to, and requirements of, the study and with the properties of the study drug(s) as described in the Investigator's Brochure or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Independent Ethics Committee (IEC)/Institutional Review Board (IRB), and with local authorities.

1.7. Population to be Studied and Justification

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

Because headache consortium guidelines recommend preventive therapies for patients with EM occurring on 4 or more days per month due to the frequency of headaches and high degree of disability, patients using no more than 1 preventive medication at the time of study 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](#)). Patients must be on a stable dose and regimen of the preventive medication for at least 2 months prior to study entry (ie, before the run-in period), and they cannot change the dose and regimen during the study. The total number of patients

receiving concomitant preventive medication during the study will not exceed 30% of the total sample size of the study.

Episodic migraine is a highly prevalent condition and a significant cause of disability, especially in patients with high frequency EM. Furthermore, 3% to 6% of patients with EM evolve in any given year to CM, which is significantly more disabling ([Scher et al 2003](#)). Risk factors for evolution from EM to CM include high headache frequency and the use of specific classes of acute medication, including barbiturates and opiates ([Bigal et al 2008](#)).

Aside from limiting migraine-associated disability, it is expected that effective preventive migraine medications should decrease the likelihood that a patient with EM will evolve to CM. However, available preventive medications have variable response rates and are associated adverse effects. In addition, only 4 are approved for preventive treatment of EM ([Lipton and Silberstein 2015](#), [Shamiliyan et al 2013](#)).

1.8. Location and Timing of Study

This study is planned to be conducted in approximately 15 countries, including North and South America, the European Union, and Asia Pacific, at approximately 140 centers. It is expected to start in 1Q 2016 and have a duration of approximately 21 months. Additional centers will be added, if needed. Expected duration of the study may also be extended dependent on enrollment speed and other factors.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

The study is being conducted to evaluate the efficacy, safety, and immunogenicity of TEV-48125 treatment in adult patients with EM. Results of this study may contribute to the registration of TEV-48125 for this indication.

2.2. Study Objectives

2.2.1. Primary Objectives

The primary objectives of this study are as follows:

- to demonstrate the efficacy 2 dose regimens of TEV-48125, as assessed by the decrease in the monthly average number of migraine days during 12-week period after the 1st dose of study drug relative to the baseline period
- to evaluate the safety and tolerability of 2 dose regimens TEV-48125 in the preventive treatment of EM

2.2.2. Secondary Objectives

The secondary objectives of the study are as follows:

- to evaluate the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days with TEV-48125 during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the number of migraine days during the 4-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period in patients not receiving concomitant migraine preventive medications at baseline
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of migraine-related disability as measured by the Migraine Disability Assessment (MIDAS) questionnaire, at 4 weeks after the last (3rd) dose of study drug relative to baseline
- to evaluate the immunogenicity of TEV-48125 and the impact of antidrug antibodies (ADAs) on efficacy and safety during 12 weeks of treatment with TEV-48125

2.2.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- to demonstrate the efficacy of TEV-48125, as assessed by the decrease in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug relative to the baseline period
- to evaluate the proportion of patients reaching at least 75% reduction and total (100%) reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- to evaluate the proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug relative to the baseline period who sustain this level of response over the 12-week period after the 1st dose of study drug
- to demonstrate the efficacy of TEV-48125 in patients who previously used topiramate for migraine, but discontinued, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125 in patients who previously used onabotulinumtoxinA for migraine, but discontinued, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the number of migraine days during the 4-week period after the 2nd dose of study drug and the 4-week period after the last (3rd) dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the monthly average number of headache days of any severity during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 4-week period after each dose of study drug relative to the baseline period
- to evaluate the proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- to evaluate the proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the

1st dose of study drug for patients not receiving concomitant preventive migraine medications relative to the baseline period

- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used topiramate for migraine in the past relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of headache hours of any severity during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the monthly average number of days of the use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by a change in quality of life at 4 weeks after the last (3rd) dose of study drug relative to baseline
- to explore the correlation between pharmacokinetic parameters and drug efficacy
- to explore the relationship between genetic polymorphisms within the CGRP receptor-ligand complex (eg, CALCA, CALCB, CALCRL, CRCP, and RAMP) and migraine-associated genes (eg, PRDM16, AJAP1, TSPAN2, MEF2D, TRPM8, TGFBR2, PHACTR1, FHL5, C7orf10, MMP16, ASTN2, LRP1, APOA1BP, TBC1D7, FUT9, STAT6, ATP5B, and MTHFR) and mode-of-action-related pathways versus hypertension, migraine severity, and safety and efficacy responses
- to explore the relationship between biofluid bone, angiogenic, and inflammatory biomarkers with TEV-48125 concentrations and efficacy responses

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

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

2.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 1st dose of the study drug
- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug in patients not receiving concomitant migraine preventive medications
- mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug

2.3.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 75% reduction and total (100%) reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug in patients who used topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past

- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 2nd dose of the study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the last (3rd) dose of the study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of any severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week period after each dose of study drug
- proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients not receiving concomitant preventive migraine medications
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of any severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug

- mean change from baseline (day 0) in quality of life, as measured by the Migraine-Specific Quality of Life (MSQOL) questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EuroQol-5 Dimension, 5 response level version (EQ-5D-5L) questionnaire at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the 2-item Patient Health Questionnaire (PHQ-2) and 9-item Patient Health Questionnaire (PHQ-9), at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug
- assessment of patient satisfaction, as measured by the Patient Global Impression of Change (PGIC) scale, at 4 weeks after administration of the 1st dose of study drug, at 4 weeks after the 2nd dose of study drug, and at 4 weeks after the last (3rd) dose of study drug

2.3.4. Safety and Tolerability Endpoints

The safety and tolerability endpoints for this study are as follows:

- occurrence of adverse events throughout the study
- abnormal standard 12-lead ECG findings
- changes from baseline in vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate) measurements
- changes from baseline in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results
- abnormal physical examination findings
- abnormal local injection site tolerability findings (ie, erythema, induration, ecchymosis) and occurrence of injection site pain
- suicidal ideation and behavior as suggested by the electronic Columbia-Suicide Severity Scale (eC-SSRS)

2.3.5. Pharmacokinetic/Immunogenicity/Biomarker Endpoints

2.3.5.1. Pharmacokinetic Endpoints

There are no prespecified pharmacokinetic endpoints.

2.3.5.2. Immunogenicity Endpoint

There are no prespecified immunogenicity endpoints.

2.3.5.3. Biomarker Endpoints

The biomarker endpoints are as follows:

- exploratory correlation of specific genetic polymorphisms and headache response, specific migraine clinical features, and adverse events to medication
- mean change from baseline in exploratory biofluid biomarkers versus treatment, migraine onset/severity, and response status (ie, responders versus nonresponders)
- correlation of exploratory biofluid biomarkers with TEV-48125 concentrations

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the safety, tolerability, and efficacy of 2 dose regimens of sc TEV-48125 and placebo in adults with EM. The study consists of a screening visit, a 28-day run-in 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 of study drug).

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

Patients using no more than 1 preventive medication at the time of study 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](#)). Patients should not be using concomitant preventive migraine medications (presented in [Appendix B](#)) at the time of the screening visit, and will not be allowed to initiate these medications after study start. A small subgroup of patients (approximately 30%) will be allowed to use concomitant migraine preventive medications (presented in [Appendix A](#)), and no changes in these medications will be allowed until the last study assessments are complete. Patients will be allowed to use acute medications to treat acute migraine attacks as needed.

After completing the informed consent process (screening visit [visit 1]), patients will be screened for eligibility. Eligible patients will enter a 28-day run-in period. Headache information will be captured daily throughout study participation using the electronic headache diary device. After completing the run-in period, patients will be asked to return to the study center on day 0 (visit 2). Patients who have confirmed EM with headache of any type on 6 to 14 days and migraine on at least 4 days and meet all other eligibility criteria (including electronic headache diary compliance criteria during the 28-day run-in period) will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups:

- monthly sc administration of TEV-48125 at 225 mg
- sc administration of 675 mg of TEV-48125 at visit 2 followed by monthly sc placebo
- monthly sc administration of placebo

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

Randomization will be performed using electronic interactive response technology (IRT). Patients will be stratified based on gender, country, and baseline preventive migraine medication use (yes, no) to ensure balance for the covariates (treatment group, preventive migraine medication use, country, and gender). The total number of patients receiving concomitant preventive medication during the study will not exceed 30% of the total sample size of the study.

Blinded treatment will be administered sc once monthly (ie, approximately every 4 weeks) for a total of 3 doses. First treatment administration will occur at visit 2 (day 0), and additional doses will be administered at visits 3 and 4. Final study assessments will be performed at visit 5 (EOT visit), approximately 4 weeks after administration of the 3rd and final dose of study drug.

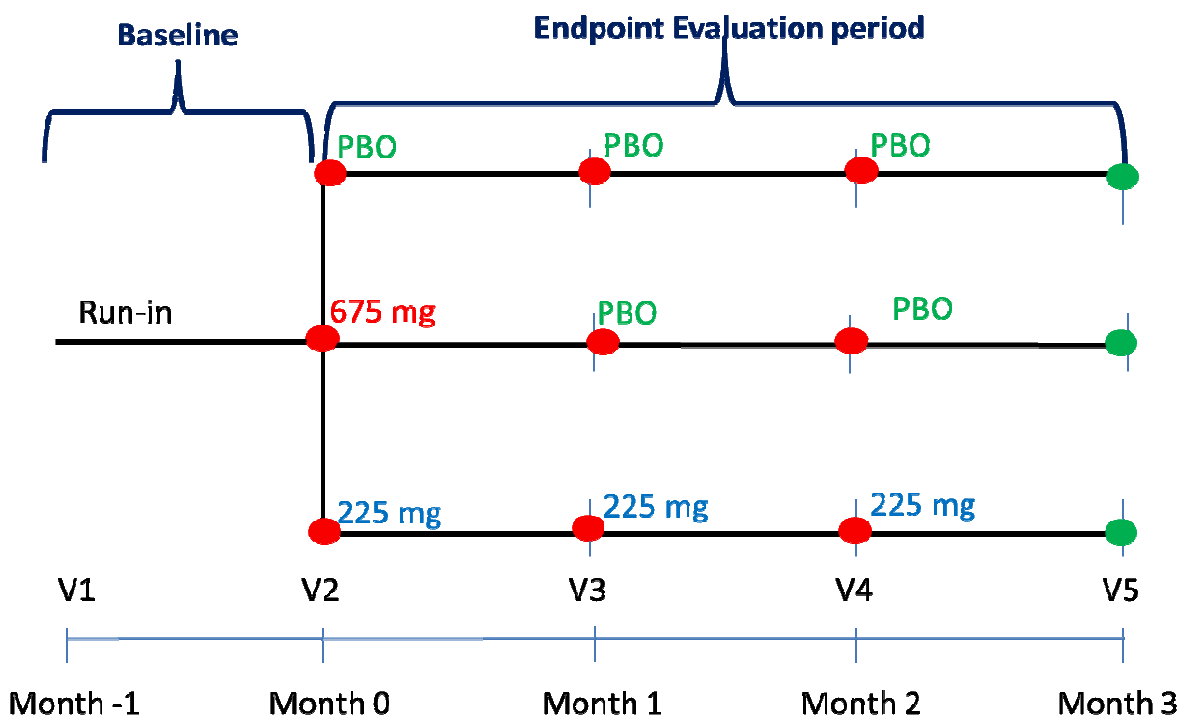
Headache information will be captured daily during the entire study using an electronic headache diary device. Assessments of migraine-related disability and change in quality of life (using the MIDAS questionnaire, PHQ-2/PHQ-9, MSQOL questionnaire, EQ-5D-5L questionnaire, and PGIC scale, and WPAI questionnaire); safety evaluations; blood draws for pharmacokinetic, immunogenicity, and biomarker analysis; and urine sampling for biomarker analysis will be performed throughout the study according to the schedule of assessments ([Table 1](#)). In addition, patients who consent to pharmacogenomic assessment will provide a blood sample for testing.

Upon completion of the final study assessments patients who complete all scheduled visits may be eligible to enter a long-term safety and efficacy study (Study TV48125-CNS-30051), consisting of a 12-month double-blind treatment period and a 6.5-month follow-up period. Patients receiving active study drug in the current study will continue receiving the same treatment (ie, monthly sc TEV-48125 at 225 mg or quarterly sc TEV-48125 at 675 mg), and patients receiving placebo in the current study will be randomized in a 1:1 ratio to receive monthly sc TEV-48125 at 225 mg or quarterly sc TEV-48125 at 675 mg during the long-term safety and efficacy study. This long-term safety and efficacy study is beyond the scope of this protocol. A separate protocol will be issued. Patients who withdraw from the study before completing the 12-week evaluation period will have EOT visit (visit 5) procedures and assessments performed on the last day they receive the study drug or as soon as possible thereafter. Those patients who do not enter the long-term safety and efficacy study for any reason will be offered to enter the long term safety extension for the purpose of evaluating ADA approximately 7.5 months (225 days [the approximate equivalent of 5 half-lives]) after administration of the last (3rd) dose of study drug in this study.

The assessments and procedures performed during each study visit are detailed in [Table 1](#) and [Section 3.14](#). The study schema is presented in [Figure 1](#).

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

A total of 768 patients are planned to be randomized in a 1:1:1 ratio (256 patients per treatment group) to receive 3 monthly sc doses of TEV-48125 at 225 mg, 1 monthly sc dose of TEV-48125 at 675 mg followed by 2 monthly sc doses of matching placebo, or 3 monthly sc doses of matching placebo.

Figure 1: Overall Study Schema

PBO=placebo; V=visit.

Note: Baseline refers to the 28-day run-in period for headache variables and visit 2 (day 0) for all other variables.

3.2. Justification for Study Design

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

The dose planned for administration at visit 2 (1st dose) for patients randomized to receive TEV-48125 at 675 mg followed by monthly sc placebo requires administration of 3×1.5 -mL injections. In order to blind the treatment arms based on both dose-volume and number of injections, each patient will receive three 1.5-mL sc injections at visit 2: three 1.5-mL sc injections of active drug, one 1.5-mL sc injection of active drug and two 1.5-mL injections of placebo, or three 1.5-mL injections of placebo. Each patient will receive a single 1.5-mL sc injection of active drug (225 mg) or placebo at visits 3 and 4 according to their randomized treatment.

3.3. Primary and Secondary Efficacy Measures and Time Points

A description of the efficacy measures is provided in Section 6.

3.3.1. Primary Efficacy Measure and Time Points

The primary efficacy endpoint for this study will be derived from headache data (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use) collected daily using an electronic headache diary device.

Eligible patients will receive training on the use of the electronic headache diary device and will be informed of compliance requirements at screening. Patients will complete electronic headache diary entries with questions about the previous day beginning on day -27 (the day after the screening visit) through the EOT/early withdrawal visit. The electronic headache diary device will allow entry of headache information for up to 48 hours after a given day.

3.3.2. Secondary Efficacy Measure and Time Points

The secondary efficacy endpoints will be derived from headache data (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use) collected daily using an electronic headache diary device. In addition, migraine-related disability will be assessed using the MIDAS questionnaire, completed at time points specified in Table 1.

3.4. Safety and Tolerability Measures and Time Points

Safety and tolerability will be assessed at time points specified in Table 1 using the following measures:

- inquiries about adverse events
- inquiries about concomitant medication usage
- safety laboratory tests (serum chemistry, hematology, coagulation, and urinalysis)
- serum/urine beta-human chorionic gonadotropin (β -HCG) test (women of childbearing potential only)
- 12-lead ECGs
- vital signs measurements (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate)
- physical examinations, including body weight
- injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments
- eC-SSRS

A description of the safety measures is provided in Section 7.

3.5. Pharmacokinetic, Biomarker, and Immunogenicity Measures and Time Points

A description of the pharmacokinetic, biomarker, and immunogenicity measures is provided in Section 8.

3.5.1. Pharmacokinetic Measures and Time Points

Blood samples for pharmacokinetics analysis of TEV-48125 will be collected from all patients at time points specified in Table 1 for the purpose of pharmacokinetic/pharmacodynamic relationship assessment. The pharmacodynamic parameters will be the efficacy responses.

The actual date and time of each blood sample, as well as the date and time of the last study drug dose prior to the sample, will be recorded in the case report form (CRF).

TEV-48125 plasma concentration will be measured using a validated assay.

3.5.2. Immunogenicity Measures and Time Points

Blood samples for immunogenicity analysis will be collected at time points specified in Table 1.

3.5.3. Biomarker Measures and Time Points

Biomarker blood and urine samples will be collected from all patients at time points specified in Table 1, and a blood sample will be collected from patients who consent to pharmacogenomic analysis at visit 2 or any visit thereafter.

3.6. Exploratory/Other Efficacy Measures and Time Points

The following exploratory efficacy measures will be assessed at time points specified in Table 1:

- exploratory efficacy endpoints derived from headache data (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use), which are collected daily using an electronic headache diary device
- PHQ-2/PHQ-9 (Note: Patients will first respond to the PHQ-2. They will respond to questions 3 through 9 [unique questions] of the PHQ-9 only if the PHQ-2 is positive.)
- MSQOL questionnaire
- EQ-5D-5L questionnaire
- PGIC scale completed
- WPAI questionnaire

3.7. Randomization and Blinding

The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients 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 drug and placebo into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance and contain 1 prefilled syringe with active drug or placebo. Adequate

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

This is a randomized study with stratification based on gender, country, and baseline preventive medication use (yes, no). Each patient will undergo randomization in a 1:1:1 ratio within the stratum to which he or she belongs to receive 1 of the 2 TEV-48125 dose regimens or placebo, as assigned by the IRT. The IRT will manage initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At the time of each study visit, the IRT will be queried, and site personnel will retrieve and administer a 1.5-mL volume from each syringe contained in the appropriately numbered kit(s).

3.8. Maintenance of Randomization and Blinding

3.8.1. Randomization

Patient randomization codes will be maintained in a secure location within Teva Global Biometrics or in a secure location with the vendor contracted to create the list. At the time of analysis, when treatment codes are needed, the Teva statistician assigned to the study will make a request to unblind and will receive the unblinded codes.

3.8.2. Blinding/Unblinding

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

For information about personnel who may be aware of treatment assignments, see Section 3.7. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events.

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

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

In blinded studies, for adverse events that are defined as: suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and

Pharmacovigilance may independently request that the treatment code be revealed (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct, analysis, and reporting of the data.

3.8.3. Data Monitoring Committee

This is not applicable.

3.9. Drugs Used in the Study

A description of administration procedures is given in Section 5.1. Additional details may also be found in the current version of the Investigator's Brochure for TEV-48125.

3.9.1. Investigational Product

TEV-48125 will be provided as a sterile, unpreserved, colorless to slightly yellow, aqueous solution for injection, supplied in a 2.25-mL prefilled syringe for single-use administration, containing 150 mg/mL in 16 ± 2.5 mM L-histidine, 0.2-mg/mL polysorbate 80, 84-mg/mL sucrose, and 0.136-mg/mL ethylenediaminetetraacetic acid (EDTA).

TEV-48125 will be administered sc at a dose of 225 mg at visit 2 (for patients randomized to both TEV-48125 dosing regimens), and TEV-48125 will be administered sc at a dose of 225 mg at visits 3 and 4 (for patients randomized to the monthly TEV-48125 at 225 mg dosing regimen). Each dose will be separated by approximately 28 days. A more detailed description of administration procedures is given in Section 5.1.

3.9.2. Placebo

Placebo will be provided as a sterile solution of 16 ± 2.5 mM L-histidine, 0.2-mg/mL polysorbate 80, 84-mg/mL sucrose, and 0.136-mg/mL EDTA, presented as 2.25 mL per syringe.

Placebo will be administered sc at visits 2, 3, and 4 (for patients randomized to the placebo treatment group) or visits 3 and 4 (for patients randomized to the TEV-48125 675 mg/placebo/placebo dosing regimen). A more detailed description of administration procedures is given in Section 5.1.

3.10. Drug Supply and Accountability

3.10.1. Drug Storage and Security

The study drug (TEV-48125 and placebo) must be stored refrigerated at 2°C to 8°C (36°F to 46°F), protected from light; the site should have a process for monitoring the drug storage temperature. TEV-48125 and placebo supplies must be kept in a secure area (eg, locked refrigerator).

3.10.2. Drug Accountability

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

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

A record of study drug accountability (ie, study drug and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies.

3.11. Duration of Patient Participation and Justification

This study will consist of a screening visit, a 28-day run-in period, and a 12-week (84-day) double-blind treatment period. Patients are expected to participate in this study for approximately 16 weeks. Patients completing this study may enroll in the double-blind, long-term safety and efficacy study (Study TV48125-CNS-30051). Those patients who do not enter the long-term safety and efficacy study for any reason will be offered to enter the long-term safety extension for the purpose of evaluating ADA approximately 7.5 months (225 days) after administration of the last (3rd) dose of study drug in this study. Thus, patient participation for these patients will last approximately 10.5 months.

See Section 12.4 for the definition of the end of the study.

The durations of the run-in and double-blind treatment periods align with Classification Committee of the IHS guidelines for controlled trials for the preventive treatment of migraine (Tfelt-Hansen et al 2012).

Patients who do not enroll in the long-term safety and efficacy study for any reason but who enter the long-term safety extension for the purpose of evaluating ADA will return approximately 7.5 months (225 days, the approximate equivalent of 5 half-lives) after the last dose of study drug. This is consistent with the 2009 FDA Guidance for Industry on Assay Development for Immunogenicity Testing of Therapeutic Proteins; a complete washout of the drug from the circulating blood is expected after approximately 7.5 months (≥ 5 half-lives), allowing a more precise evaluation of ADA.

3.12. Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (see Section 7.1.5) as they are reported from the investigational center to identify safety concerns. The study may be terminated by the sponsor at any time.

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, and adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, protocol violation or deviation as defined in Section 11.1.2, noncompliance, or adverse event). In addition, patients with abnormal hepatic laboratory values (eg, ALT, AST, ALP, gamma-glutamyl transpeptidase [GGT], total bilirubin, or international normalized ratio [INR]) may meet criteria for discontinuation from the study drug as summarized in Appendix E.

3.13. Source Data Recorded on the Case Report Form

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

Source data, including test results and/or assessments (eg, clinical laboratory, central ECG evaluation center, and electronic headache diary data) collected by other institutions outside of the study center, are sent to the investigational center where they are retained, but not entered into the CRF unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database (see Section 13.1). All data from other institutions will be available to the investigator.

The CRFs are filed in the sponsor's central file.

3.14. Study Procedures

Study procedures and assessments with their timing are summarized in Table 1. Detailed by-visit information is provided in the sections following the table. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments), Section 6.2 (safety assessments), and Section 8 (pharmacokinetic and other assessments).

Table 1: Study Procedures and Assessments

Study period	Pretreatment period (incl. screening visit and run-in period)	Double-blind treatment period			
Visit number	V1	V2	V3	V4	V5
Month number	Month -1	Month 0	Month 1	Month 2	Month 3
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	Screening days -28 to -1	Baseline dose 1 day 0 (+3 days)	Dose 2 day 28 (±3 days)	Dose 3 day 56 (±3 days)	EOT or early withdrawal day 84 (±3 days)
Informed consent	X				
Medical and psychiatric history	X				
Prior medication history	X				
Record demographic characteristics	X				
Inclusion and exclusion criteria	X	X			
Randomization		X			
Physical examination, including weight and height ^a	X	X			X
Triplicate 12-lead ECG ^{b,c}	X	X			X
Vital signs measurement ^b	X	X	X	X	X
Adverse events ^d	X	X	X	X	X
Concomitant medication inquiry	X	X	X	X	X
Clinical laboratory tests ^e	X	X	X	X	X
Serum β -HCG test ^f	X				
Urine β -HCG test ^f		X	X	X	X
FSH ^g	X				

Study period	Pretreatment period (incl. screening visit and run-in period)	Double-blind treatment period			
Visit number	V1	V2	V3	V4	V5
Month number	Month -1	Month 0	Month 1	Month 2	Month 3
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	Screening days -28 to -1	Baseline dose 1 day 0 (+3 days)	Dose 2 day 28 (±3 days)	Dose 3 day 56 (±3 days)	EOT or early withdrawal day 84 (±3 days)
Provide electronic headache diary ^h	X				
Complete electronic headache diary entries ⁱ	X				X
Review electronic headache diary		X	X	X	X
Return headache diary device					X
Blood samples for plasma drug concentration ^j		X	X	X	X
Blood samples for serum ADA assessment ^k		X	X		X
Blood sample for pharmacogenomic analysis ^l		X			
Blood collection for serum, plasma, and RNA biomarker analysis		X		X	X
Urine collection for biomarker analysis		X		X	X
MIDAS questionnaire		X			X
PHQ-2/PHQ-9 ^m		X			X
MSQOL questionnaire		X	X	X	X
EQ-5D-5L questionnaire		X			X
PGIC scale			X	X	X
WPAI questionnaire		X			X

Study period	Pretreatment period (incl. screening visit and run-in period)	Double-blind treatment period			
Visit number	V1	V2	V3	V4	V5
Month number	Month -1	Month 0	Month 1	Month 2	Month 3
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	Screening days -28 to -1	Baseline dose 1 day 0 (+3 days)	Dose 2 day 28 (±3 days)	Dose 3 day 56 (±3 days)	EOT or early withdrawal day 84 (±3 days)
eC-SSRS ^a		X	X	X	X
Administration of study drug		X	X	X	
Injection site assessments ^o		X	X	X	
Review eligibility for long-term safety study (TV48125-CNS-30051)					X

^a Height will only be obtained at screening.

^b Procedure will be performed before other assessments (eg, blood draws and administration of questionnaires).

^c Electrocardiograms will be performed in triplicate.

^d 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.

^e Serum chemistry, hematology, coagulation, and urinalysis.

^f Women of childbearing potential only.

^g Postmenopausal women only.

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

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

^j Blood samples for plasma drug concentration determination will be collected prior to dosing at visits 2, 3, and 4.

^k Blood samples for serum ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).

^l A single blood sample for pharmacogenomic analysis will be collected at visit 2 or any visit thereafter from patients who consent to this procedure. A separate informed consent form for pharmacogenomic sampling must be signed by the patient.

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

ⁿ The eC-SSRS Baseline/Screening version will be completed at visit 2, and the eC-SSRS Since Last Visit version will be completed at all other visits.

^o Injection sites will be assessed for erythema, induration, ecchymosis, and pain immediately and 1 hour after study drug administration. If a patient has severe injection site induration, erythema, and/or ecchymosis and/or grade 3 (severe) or grade 4 (worst possible) injection site pain at 1 hour after completion of study drug administration, the patient will be reassessed 3 hours after study drug administration and hourly thereafter until the reaction/pain is of moderate or less severity.

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

3.14.1. Procedures for Screening (Visit 1[Day –28])

A signed and dated informed consent form will be obtained before screening procedures commence (see Section 12.1). Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations. In addition, disease-specific assessments performed within a specified time frame before informed consent may be used for the study. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, patients who are screened will be assigned an 8-digit identification number such that all patients from each country are given consecutive identification numbers in successive order of inclusion. The first 2 digits of the screening number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the investigational center number, and the last 3 digits will be the patient number assigned at the investigator center (eg, the 3rd patient screened in the US [country 01] at center 101 would be assigned the number of 01101003). The screening number is the permanent number assigned to the patient for the duration of study.

After confirmation of study eligibility, patients will be screen failed or randomized into Study TV48125-CNS-30049 (ie, patients with CM) or the current study (ie, patients with EM). For randomized patients, an enrollment number will be assigned consisting of the 8-digit screening number and the last 2 digits of the assigned protocol (ie, 49 for Study TV48125-CNS-30049 or 50 for the current study; in the example above, the enrollment number would be 01101003-50 for this study).

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

The screening visit (visit 1) will take place approximately 28 days before the baseline visit. The following procedures will be performed at visit 1:

- Obtain written informed consent before any other study-related procedures are performed.
- Record demographic characteristic including race.
- Review inclusion/exclusion criteria.
- Review medical and psychiatric history.
- Review medication history.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform triplicate 12-lead ECGs.
- Perform a physical examination, including height and weight. Body mass index will be calculated from the screening height and weight.
- Perform clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis).

- Perform serum β -HCG test (women of childbearing potential only).
- Perform FSH test (postmenopausal women only).

Patients who meet inclusion/exclusion criteria will be given an electronic headache diary device and trained on its use and compliance requirements.

3.14.2. Procedures Before Study Drug Treatment

3.14.2.1. 28-Day Run-In Period (Days –28 Through –1)

Patients will complete electronic headache diary entries daily beginning on day –27. Patients will enter headache information (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use) about the previous day into the electronic headache diary device. Refer to Section 6.1 for additional details.

3.14.2.2. Baseline (Visit 2 [Day 0 (± 3 Days)])

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

The following procedures will be performed at visit 2 before study drug administration:

- Review inclusion/exclusion criteria.
- Review headache diary.
- Review study compliance.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform triplicate 12-lead ECGs.
- Perform a physical examination (including weight).
- Inquire about adverse events.
- Inquire about/review concomitant medications.
- Perform clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis).
- Perform urine β -HCG test (women of childbearing potential only).
- Obtain a 4-mL blood sample for plasma TEV-48125 concentration determination.
- Obtain a 5-mL blood sample for serum ADA assessment.
- Obtain a 5-mL urine sample for biomarker analysis.
- Obtain an 18.5-mL blood sample (6 mL each for serum and plasma and 6.5 mL for ribonucleic acid [RNA]) for serum, plasma, and RNA biomarker analysis.
- Complete the eC-SSRS Baseline/Screening version.

- Administer the MIDAS questionnaire, MSQOL questionnaire, EQ-5D-5L questionnaire, WPAI questionnaire, and PHQ-2/PHQ-9 (Note: Patients will respond first to the PHQ-2. They will respond to questions 3 through 9 [unique questions] of the PHQ-9 only if the PHQ-2 is positive.)

In addition, a 6-mL blood sample for pharmacogenomics (deoxyribonucleic acid [DNA]) may be obtained from patients who consent to pharmacogenomics analysis.

A patient who does not meet study entry criteria on the basis of results of baseline assessments and is not randomized in the study will not be considered for screening again.

Patients who continue to meet the inclusion/exclusion criteria will be assigned a permanent unique randomization number generated by the IRT. This assigned number will be entered into the CRF.

3.14.3. Procedures During Study Drug Treatment

3.14.3.1. Double-Blind Treatment Period (Visits 2 Through 5 [Day 0 Through Day 84 ±3 Days])

Each day during the double-blind treatment period, patients will enter headache information (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use) about the previous day into the electronic headache diary device. Refer to Section 6.1 for additional details.

3.14.3.1.1. Visit 2 (Day 0 [± 3 Days]/Dose 1)

Patients will receive a single sc TEV-48125 at 675 or 225 mg or sc placebo after completing baseline procedures/assessments. The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately and 1 hour after study drug administration. Additional assessments may be performed based on the severity of any observed injection site reaction. See Section 7.9 for additional details.
- Inquire about postdose adverse events before the patient leaves the study center.

3.14.3.1.2. Visits 3 and 4 (Day 28 [±3 Days]/Dose 2 and Day 56 [±3 Days]/Dose 3)

The following procedures/assessments will be performed before study drug administration at visits 3 and 4:

- Review headache diary.
- Review study compliance.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Inquire about adverse events.
- Inquire about/review concomitant medications.

- Perform clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis).
- Perform urine β -HCG test (women of childbearing potential only).
- Obtain a 4-mL blood sample for plasma TEV-48125 concentration determination.
- Obtain a 5-mL blood sample for serum ADA assessment (visit 3 only).
- Obtain a 5-mL urine sample for biomarker analysis (visit 4 only).
- Obtain an 18.5-mL blood sample (6 mL each for serum and plasma and 6.5 mL for RNA) for serum, plasma, and RNA biomarker analysis (visit 4 only).
- Complete the eC-SSRS Since Last Visit version.
- Administer the MSQOL questionnaire and the PGIC scale.

In addition, a single 6-mL blood sample for pharmacogenomics (DNA) may be obtained from patients who consent to pharmacogenomics analysis at visit 3 or visit 4 if the sample is not obtained at visit 2.

Patients will receive a sc TEV-48125 at 225 mg or sc placebo after completing predose procedures/assessments. The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately and 1 hour after study drug administration. Additional assessments may be performed based on the severity of any observed injection site reaction. See Section 7.9 for additional details.
- Inquire about postdose adverse events before the patient leaves the study center.

3.14.3.1.3. End-of-Treatment Visit (Visit 5 [Day 84 (\pm 3 Days)])

The following procedures/assessments will be performed at the EOT visit (visit 5):

- Review headache diary. (Note: Patients will return the electronic headache diary device at the EOT visit.)
- Review study compliance.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).
- Perform triplicate 12-lead ECGs.
- Perform physical examination (including weight).
- Inquire about adverse events.
- Inquire about/review concomitant medications.
- Perform clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis).
- Perform a urine β -HCG test (women of childbearing potential only).
- Obtain a 4-mL blood sample for plasma TEV-48125 concentration determination.

- Obtain a 5-mL blood sample for serum ADA assessment.
- Obtain a 5-mL urine sample for biomarker analysis.
- Obtain an 18.5-mL blood sample (6 mL each for serum and plasma and 6.5 mL for RNA) for serum, plasma, and RNA biomarker analysis.
- Complete eC-SSRS Since Last Visit version.
- Administer the MIDAS questionnaire, MSQOL questionnaire, EQ-5D-5L questionnaire, PGIC scale, WPAI questionnaire, and PHQ-2/PHQ-9. (Note: Patients will respond first to the PHQ-2. They will respond to questions 3 through 9 [unique questions] of the PHQ-9 only if the PHQ-2 is positive.)

In addition, a single 6-mL blood sample for pharmacogenomics (DNA) may be obtained from patients who consent to pharmacogenomics analysis if the sample is not obtained at an earlier visit.

3.14.4. Procedures After Study Drug Treatment

Patients who participate in the study in compliance with the protocol for the entire double-blind treatment period (ie, through visit 5) will be considered to have completed the study. See Section 12.4 for the definition of the end of the study. Patients who complete the double-blind treatment period may enter the 12-month double-blind, long-term safety and efficacy study (Study TV48125-CNS-30051). For these patients, final evaluations for the current study will be performed at the EOT visit (visit 5).

Patients who withdraw from the study should have final evaluations (EOT/early withdrawal visit) performed on the last day they receive the study drug or as soon as possible thereafter. Procedures for patients who withdraw prematurely from the study are described in Section 4.4. All protocol-specified evaluations should be performed at the early withdrawal visit (see Table 1).

Patients who do not enroll in the double-blind, long-term safety and efficacy study for any reason will be offered to enter the long term safety extension for the purpose of evaluating ADA approximately 7.5 months (225 days [the approximate equivalent of 5 half-lives]) after administration of the final dose of study drug in this study.

3.14.5. Unscheduled Visits

An unscheduled visit may be performed at any time during the study, at the patient's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

Procedures performed during unscheduled visits include the following:

- Review headache diary.
- Review study compliance.
- Perform vital signs measurements (including systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate).

- Inquire about adverse events.
- Inquire about/review concomitant medications.

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

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study eligibility criteria to allow patients to enter a study are not granted by Teva (see Section 11.1.2).

4.1. Patient Inclusion Criteria

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

- a. Males or females aged 18 to 70 years, inclusive, with migraine onset at ≤ 50 years of age
- b. Patient signs and dates the informed consent document.
- c. Patient has history of migraine (according to ICHD-3 criteria [[Classification Committee of the IHS, 2013](#)]) or clinical judgement suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥ 12 months prior to screening.
- d. Patient fulfills the following criteria for EM in prospectively collected baseline information during the 28-day run-in period:
 - headache occurring on ≥ 6 and ≤ 14 days
 - on ≥ 4 days, fulfilling any of the following:
 - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura ([Appendix D](#))
 - ICHD-3 criteria B and C for 1.2 Migraine with aura ([Appendix D](#))
 - Probable migraine (a migraine subtype where only 1 migraine criterion is missing)
 - The patient used a triptan or ergot derivative to treat an established headache.
- e. Not using preventive medications (presented in [Appendix B](#)) (ie, at least 5 half-lives have passed since last use) or using no more than 1 preventive medication (presented in [Appendix A](#)) for migraine or other medical conditions (eg, propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to beginning the 28-day run-in period.
- f. Body mass index of 17.5 to 37.5 kg/m² and a total body weight between 45 and 120 kg, inclusive
- g. All patients must be of nonchildbearing potential, defined as:
 - women surgically sterile by documented complete hysterectomy, bilateral oophorectomy, or bitubal ligations or confirmed to be postmenopausal (at least 1 year since last menses and follicle-stimulating hormone [FSH] above 35 U/L)
 - men surgically sterile by documented vasectomy

or

if of childbearing potential, patients must meet any of the following criteria:

- Patients must simultaneously use 2 forms of highly effective contraception methods (defined in Section 5.2) with their partners during the entire study period and for 7.5 months after the last dose of study drug.
 - Sexual abstinence is only considered a **highly effective method** if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception.
- h. Female patients of childbearing potential must have a negative serum β -HCG pregnancy test at screening (confirmed by urine dipstick β -HCG pregnancy test at baseline).
 - i. The patient demonstrated compliance with the electronic headache diary during the run-in period by entry of headache data on a minimum of 24 out of 28 days (~85% diary compliance).
 - j. The patient is in good health as determined by a medical and psychiatric history, medical examination, 12-lead ECG, serum chemistry, hematology, coagulation, and urinalysis.
 - k. The patient must be willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study period, and to return to the clinic for the follow-up evaluation as specified in this protocol.

4.2. Patient Exclusion Criteria

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

- a. Patient has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 4 months before screening.
- b. Patient is using medications containing opioids (including codeine) or barbiturates (including butalbital/aspirin/caffeine, butalbital/paracetamol/caffeine, or any other combination containing butalbital) on more than 4 days per month for the treatment of migraine or for any other reason.
- c. Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the following medications for treatment of EM or CM after adequate therapeutic trial defined as use for at least 3 months at accepted migraine therapeutic doses:
 - cluster A: divalproex sodium and sodium valproate
 - cluster B: flunarizine and pizotifen

- cluster C : amitriptyline, nortriptyline, venlafaxine, and duloxetine
- cluster D : atenolol, nadolol, metoprolol, propranolol, and timolol
- d. Patient has used an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the last 2 months prior to screening
- e. Clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator
- f. Evidence or medical history of clinically significant psychiatric issues, including any suicide attempt in the past, or suicidal ideation with a specific plan in the past 2 years
- g. History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events) such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism
- h. Known infection or history of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection
- i. Past or current history of cancer in the past 5 years, except for appropriately treated nonmelanoma skin carcinoma
- j. Pregnant or nursing females
- k. History of hypersensitivity reactions to injected proteins, including monoclonal antibodies
- l. Participation in a clinical study of a new chemical entity or a prescription medicine within 2 months before study drug administration or 5 half-lives, whichever is longer
- m. Any prior exposure to a monoclonal antibody targeting the CGRP pathway (AMG 334, ALD304, LY2951742, or TEV-48125)
- n. Any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator
- o. Any finding that, in the judgment of the investigator, is a clinically significant abnormality, including serum chemistry, hematology, coagulation, and urinalysis test values (abnormal tests may be repeated for confirmation)
- p. Hepatic enzymes (ALT, AST, and ALP) more than 1.5× the upper limit of the normal range (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law at screening
- q. Serum creatinine >1.5 × the ULN, clinically significant proteinuria (urine dipstick +4), or evidence of renal disease at screening
- r. History of alcohol or drug abuse during the past 2 years, or alcohol or drug dependence during the past 5 years

- s. The patient cannot participate or successfully complete the study, in the opinion of their healthcare provider or the investigator, for any of the following reasons:
 - mentally or legally incapacitated or unable to give consent for any reason
 - in custody due to an administrative or a legal decision, under guardianship, or institutionalized
 - unable to be contacted in case of emergency
 - has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study
- t. The patient is a study center or sponsor employee who is directly involved in the study or the relative of such an employee

4.3. Justification for Key Inclusion and Exclusion Criteria

The inclusion and exclusion criteria select for patients who meet ICHD-3 revision criteria for EM ([Classification Committee of the IHS, 2013](#)). Because headache consortium guidelines recommend preventive therapies for patients with EM occurring on 4 or more days per month due to the frequency of headaches and the high degree of disability, Inclusion Criterion e allows for the use of 1 concomitant preventive medication for migraine.

4.4. Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the patient, or in the event of lack of cooperation. In addition, a patient may be withdrawn from the study as described in Sections 3.8, 3.12, 3.14.4, 5.4, and 7.1.7.

Should a patient decide to withdraw after administration of study drug, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given as to why the patient is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from study drug treatment and the reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a potentially clinically significant abnormal laboratory test result, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event or test result must be recorded on the source documentation and transcribed onto the CRF.

All protocol-specified procedures/assessments should be performed at the EOT/early withdrawal visit (see Table 1). Patients who withdraw from the study will be offered to enter the long-term

safety extension for the purpose of evaluating ADA approximately 7.5 months (225 days [the approximate equivalent of 5 half-lives]) after their last dose of study drug in this study. A patient should only be designated as lost to follow up if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

5. TREATMENT OF PATIENTS

5.1. Drugs Administered During the Study

Following the baseline assessments, eligible patients will be randomly assigned with stratification based on gender, country, and baseline use of preventive migraine medication (yes, no) to receive monthly TEV-48125 at 225 mg, TEV-48125 at 675 mg followed by monthly placebo, or monthly placebo.

Study drug will be administered by qualified study personnel as sc injections approximately every 28 days for a total of 3 doses, as follows:

- Patients randomized to receive monthly TEV-48125 at 225 mg will receive 225 mg of TEV-48125 as 1 active injection (225 mg/1.5 mL) and two 1.5-mL placebo injections at visit 2 and 225 mg of TEV-48125 as 1 active injection (225 mg/1.5 mL) at visits 3 and 4.
- Patients randomized to receive TEV-48125 at 675 mg/placebo/placebo will receive 675 mg of TEV-48125 as 3 active injections (225 mg/1.5 mL) at visit 2 and placebo as a single 1.5-mL injection at visits 3 and 4.
- Patients randomized to receive placebo will receive three 1.5-mL placebo injections at visit 2 and a single 1.5-mL placebo injection at visits 3 and 4.

The 4-week (28-day) period will be determined relative to the planned dosing day provided the patient returns to the study center within the tolerance window (± 3 days). If the patient returns to the study center more than 3 days late, then the 4-week period will be determined from the actual dosing day rather than the planned dosing day.

Individual, uniquely numbered visit kits containing 1 prefilled syringe with a staked 27 G $\frac{1}{2}$ " needle will be provided.

At the time of each study visit, the IRT will be queried, and site personnel will retrieve and administer 1.5 mL from each syringe contained in the appropriately numbered kit(s).

Recommended sc injection sites follow the National Institutes of Health Patient Education Guidelines of June 2012, which are available in [Appendix C](http://www.cc.nih.gov/ccc/patient_education/pepubs/subq.pdf) of this document and in this website: http://www.cc.nih.gov/ccc/patient_education/pepubs/subq.pdf. The suggested sites of injection are back of upper arms, lower abdomen/belly/waistline, and front of thighs. Each of the injections at visit 2 should be given in a different location (eg, not in precisely the same place), and study staff member(s) responsible for administration of injections should inspect previous injection sites to ensure that they are free of bruising and tenderness and that proper rotation of sites is performed.

Study drug should be removed from the refrigerator and allowed to equilibrate at room temperature for 15 to 30 minutes before study drug administration.

A 1.5-mL volume from each syringe in each visit's kit(s) must be injected sc for dosing to be considered complete. The total number of sc injections and their locations will be recorded for each dosing visit (visits 2, 3, and 4).

5.2. Restrictions

Medications prohibited before and/or during the study are described in Section 5.3 and the exclusion criteria (Section 4.2). Restrictions in regard to pregnancy and required laboratory values are provided in the inclusion and exclusion criteria (Section 4.1 and Section 4.2, respectively). Restrictions in regard to sexual activity are also detailed in the inclusion and exclusion criteria (Section 4.1 and Section 4.2, respectively), and highly effective contraception methods are reviewed below.

Highly effective contraception methods include the following hormonal and other methods of birth control:

- combined (estrogen and gestagen) oral contraceptives, hormone implants, hormone rings, contraceptive patch, and hormone injectables initiated at least 7 days before study drug administration
- intrauterine device in place for a period of at least 2 months before study drug administration
- barrier methods of contraception: condoms with spermicide for males, diaphragm with spermicide for females, and portio cap with spermicide for females
- vasectomy for male partners of female patients

There were no additional restrictions in this study.

In addition, male patients may not donate sperm for the duration of the study and for 7.5 months after discontinuation of study drug.

5.3. Prior and Concomitant Therapy or Medication

Any prior or concomitant therapy, medication, or procedure that a patient has had within 6 months before study drug administration and up to the end of the study period will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. In addition, migraine preventive medication that a patient took within 2 years before study drug administration will be recorded on the CRF. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary.

5.3.1. Prior Medications and Therapeutic Failures of Migraine Preventives:

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

5.3.2. Concomitant Therapies and Medications

Up to 30% of patients will be allowed to remain on stable doses of no more than 1 preventive migraine medication for the duration of the study provided the medication has at least moderate evidence of efficacy as defined by guidelines ([Silberstein et al 2012](#)) and presented in [Appendix A](#). Patients on preventive medication must be on a stable dose for at least 2 months of consecutive use prior to study entry. Alternatively, patients must have discontinued the preventive medication at least 5 half-lives prior to screening. Preventive migraine medications disallowed for at least 70% of patients for the duration of the study are presented in [Appendix B](#).

Patients will be allowed to use acute medication to treat acute migraine attacks, as needed.

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

5.4. Procedures for Monitoring Patient Compliance

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

5.5. Total Blood Volume

The total volume of blood to be collected for each patient in this study is approximately 140.5 mL, as detailed in [Table 2](#).

Table 2: Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume
Serum chemistry and pregnancy ^a	6	5	30
Hematology	3	5	15
FSH ^b	3	1	3
Pharmacokinetics	4	4	16
ADA	5	3	15
Biomarker	18.5 ^c	3	55.5
Pharmacogenomic ^d	6	1	6
Total	--	22	140.5

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

^b Postmenopausal women only.

^c For each 18.5-mL sample, individual volumes will be 6 mL each for serum and plasma and 6.5 mL for RNA.

^d For patients who consent to pharmacogenomic testing.

ADA=antidrug antibody; FSH=follicle-stimulating hormone; RNA=ribonucleic acid.

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Measure and Justification

The primary efficacy endpoint (and secondary and exploratory efficacy endpoints as well) will be derived from headache variables collected daily using an electronic headache diary device. Eligible patients will receive comprehensive training from site personnel on the use of the electronic headache diary device. Site personnel will also instruct patients on the requirement for timely and daily completion of the electronic diary.

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

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

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

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

- mild headache
- moderate headache
- severe headache

Patients will also record whether photophobia, phonophobia, nausea, and vomiting are present, and they will record any migraine medications (name of drug, number of tablets/capsules, and the dose in milligrams per tablet/capsule) taken on each day.

6.2. Migraine Disability Assessment

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

Patients will complete the MIDAS questionnaire at baseline (visit 2) and the EOT visit (visit 5).

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

The PHQ is a 9-item questionnaire with each item corresponding to 1 criterion of the Diagnostic and Statistical Manual for Mental Disorders 4th edition diagnostic criteria for major depressive disorder. Each of the items is scored on a scale of 0 (“not at all”), 1 (“several days”), 2 (“more than half the days”), and 3 (“nearly every day”) based on the frequency of symptoms during the past 2 weeks ([Spitzer et al 1999](#)). The PHQ-2 was developed from the PHQ-9 to rapidly screen for depression and consists of the first 2 questions from the PHQ-9. The PHQ-2 and the PHQ-9 are validated measures for detecting and monitoring depression, anxiety, and somatization ([Kroenke et al 2010](#)).

Patients will complete the PHQ-2 at baseline (visit 2) and the EOT visit (visit 5). If the PHQ-2 is positive (ie, a score of ≥ 3), patients will complete questions 3 through 9 (unique questions) of the PHQ-9.

6.4. Migraine-Specific Quality of Life Questionnaire

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

Patients will complete the MSQOL at baseline (visit 2), visits 3 and 4, and the EOT visit (visit 5).

6.5. EuroQol-5 Dimension Questionnaire

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

Patients will complete the EQ-5D-5L at baseline (visit 2) and the EOT visit (visit 5).

6.6. Patient Global Impression of Change Scale

The PGIC scale is a validated generic tool for assessment of overall change in the severity of illness following treatment. Patients will rate how they describe the change (if any) that their migraine/headaches have had in their general quality of life and health status since beginning the treatment in this study on a 7-point scale where 1=no change (or condition has got worse);

2=almost the same, hardly any change at all; 3=a little better, but no noticeable change; 4=somewhat better, but the change has not made any real difference; 5=moderately better, and a slight but noticeable change; 6=better, and a definite improvement that has made a real and worthwhile difference; and 7=a great deal better, and a considerable improvement that has made all the difference.

Patients will complete the PGIC scale before study drug administration at visits 3 and 4 and at the EOT visit (visit 5).

6.7. Work Productivity and Activity Impairment Questionnaire

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

Patients will complete the WPAI questionnaire at baseline (visit 2) and at the EOT visit (visit 5).

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings (including body weight measurements), eC-SSRS scores, local injection site assessments, and concomitant medication usage.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after the clinical study patient has signed the informed consent form should be recorded and reported as an adverse event.

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

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

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event.)
- drug interactions
- events occurring during diagnostic procedures of this study or during any follow-up period of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study drug are not considered adverse events.)
- all events of possible drug-induced liver injury with hyperbilirubinemia (defined as AST or ALT ≥ 3 times the ULN, plus either total bilirubin ≥ 2 times the ULN or INR

>1.5) or Hy’s Law events require immediate study treatment cessation and reporting as a serious adverse event. Refer to [Appendix E](#) for guidance regarding monitoring patients with elevated liver function tests.

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

7.1.2. Recording and Reporting Adverse Events

For adverse event recording, the study period is defined for each patient as the time period from signature of the informed consent form through completion of visit 5 or the early withdrawal visit for patients who withdraw from the study for any reason. Adverse events will be collected at each visit via adverse event inquiry.

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

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

The clinical course of each adverse event will be monitored at suitable intervals until it resolves, stabilizes, or returns to baseline; until the patient is referred for continued care to a another health care professional; or until a determination of a cause unrelated to the study drug or study procedure is made.

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

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

7.1.3. Severity of an Adverse Event

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

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Study Drug

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

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 study drug.	<p>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:</p> <ul style="list-style-type: none"> • It does not follow a reasonable temporal sequence from the administration of the study drug. • It could readily have been produced by the patient’s clinical state, environmental, or toxic factors or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the study drug. • It does not reappear or worsen when the study drug 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 study drug administration cannot be ruled out with certainty.	<p>The relationship of an adverse event may be considered “reasonable possibility” if at least 2 of the following apply:</p> <ul style="list-style-type: none"> • It follows a reasonable temporal sequence from administration of the study drug. • It cannot be reasonably explained by the known characteristics of the patient’s clinical state, environmental, or toxic factors or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the study drug, yet a drug relationship clearly exists. • It follows a known pattern of response to the study drug.

7.1.5. Serious Adverse Events**7.1.5.1. Definition of a Serious Adverse Event**

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

- death
- a life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurs); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission and/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 prior to study entry will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study
- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

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

7.1.5.2. Expectedness

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

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

For the purpose of SUSAR reporting, the version of the reference safety information document at the moment of the occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event**7.1.5.3.1. Investigator Responsibility**

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during the defined study period, regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended. Serious adverse events occurring in a patient after the defined study period should be reported to the sponsor if the investigator becomes aware of them.

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

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

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

Additional information may include the following:

- age and sex of patient
- date of 1st dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant therapy (including doses, routes, 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 is related to study drug)
 - autopsy findings (if available)

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

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

For all countries, the sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences form/extensible markup language file to the LSO and/or CRO for local submission to the regulatory authorities, IEC/IRBs, and investigators, according to regulations. The investigator is responsible for ensuring that the IRB/IEC is also informed of the event, in accordance with local regulations.

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

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

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TEV-48125 and the appropriate regulatory authorities (and IEC/IRB, if appropriate).

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

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing current study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TEV-48125

7.1.6. Protocol-Defined Adverse Events of Special Interest

The following are considered protocol-defined adverse events to be sent to the sponsor's Global Patient Safety and Pharmacovigilance Department for evaluation: ophthalmic adverse events of at least moderate severity, events of possible drug-induced liver injury (AST or ALT $\geq 3 \times$ the

ULN, total bilirubin $\geq 2 \times$ the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions. Severe 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](#) [also see [Appendix F](#)]). In the event of suspected anaphylaxis, vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator.

The process for reporting a protocol-defined adverse event is the same as that for reporting a serious adverse event (see Section [7.1.5.3](#)). Protocol-defined adverse events for reporting to Pharmacovigilance Department can be either serious or nonserious according to the criteria outlined in Section [7.1.5](#).

7.1.7. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study or from study drug at any time, at the discretion of the investigator. If a patient is withdrawn because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time.

The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the clinical project physician/clinical leader as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study or study drug for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal is 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 requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be the need to take a prohibited medication, not the adverse event.

7.1.8. Overdose of Study Drug

Any dose of study drug (whether the investigational product or placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. When the identification of the study drug must be known, the investigator must follow the procedures outlined in Section [3.8](#).

7.1.9. Protocol Deviations Because of an Adverse Event

If a patient 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 patient safety, the investigator or other physician in attendance must contact the individual identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Pregnancy

All pregnancies of women participating in the study that occur during the study, or within 7.5 months after the last administration of TEV-48125, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the LSO and/or CRO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 7.1.5.3).

Any female patient becoming pregnant during the study will discontinue the study drug. All patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after termination from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

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

For pregnancies of partners of men participating in the study, the Teva Pharmacovigilance Department will determine the procedure to appropriately follow up after notification as described above. All partners who become pregnant and provide appropriate consent to the Teva Pharmacovigilance Department will be monitored to the completion or termination of the pregnancy.

7.3. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be interpreted by the investigator as belonging to 1 of the following categories:

- abnormal but not a clinically significant worsening from baseline
- abnormal and a clinically significant worsening from baseline

A laboratory test result that has significantly worsened (according to medical judgment) from the baseline result will be recorded on the source documentation, transcribed onto the CRF as an adverse event, and monitored as described in Section 7.1.2. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with study drug, or medical treatment or further diagnostic work-up.

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](#). Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below.

7.3.1. Serum Chemistry

The following serum chemistry tests will be performed:

- calcium
- phosphorus
- sodium
- potassium
- chloride
- carbon dioxide
- magnesium
- glucose
- blood urea nitrogen
- creatinine
- ALT
- AST
- total bilirubin
- direct bilirubin
- indirect bilirubin (calculated)
- lactate dehydrogenase
- GGT
- ALP
- albumin
- creatine phosphokinase
- total protein

7.3.2. Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- red blood cell (RBC) count

- RBC indices
 - mean corpuscular volume
 - mean corpuscular hemoglobin concentration
 - RBC distribution width
- platelet count
- white blood cell (WBC) count and differential count (absolute values and percentages)
 - neutrophils
 - lymphocytes
 - eosinophils
 - monocytes
 - basophils

7.3.3. Coagulation

The following coagulation tests will be performed:

- prothrombin time
- partial thromboplastin time
- INR

7.3.4. Urinalysis

Urinalysis will include testing for the following:

- color and appearance
- specific gravity
- pH
- blood (hemoglobin)
- glucose
- albumin
- protein
- ketones
- leukocyte esterase
- nitrite
- direct bilirubin

- microscopic
 - bacteria
 - RBCs
 - WBCs
 - casts
 - crystals

7.3.5. Other Clinical Laboratory Tests

7.3.5.1. Human Chorionic Gonadotropin Tests

Serum β -HCG tests will be performed for women of childbearing potential at screening (visit 1), and urine β -HCG tests will be performed for women of childbearing potential at visits 2 through 5. Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.3.5.2. Follicle-Stimulating Hormone Tests

Postmenopausal women will have an FSH test at screening (visit 1).

7.4. Vital Signs

Vital signs (pulse, systolic and diastolic blood pressure, body temperature, and respiratory rate) will be measured before other assessments (eg, blood draws and administration of questionnaires) at the time points detailed in Table 1.

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

In addition, potentially clinically significant values may be predefined by the sponsor for selected vital signs (see Section 9.7.2) and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan).

7.5. Electrocardiography

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

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 7.1.2.

7.6. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit only) and weight will be performed at the time points detailed in Table 1.

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 7.1.2.

7.7. Electronic Columbia-Suicide Severity Rating Scale

The eC-SSRS will be used to assess the patient’s suicidal ideation (severity and intensity) and behavior (Posner et al 2011). The eC-SSRS Baseline/Screening version will be completed by the patient at visit 2, and the eC-SSRS Since Last Visit version will be completed by the patient at all other time points, as described in Table 1. Any positive findings on the eC-SSRS Since Last Visit version requires evaluation by a physician or doctoral-level psychologist.

7.8. Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of prohibited medications are found in Section 5.3.

7.9. Immunogenicity

Blood samples for serum ADA assessment will be collected at visits 2, 3, and the EOT/early withdrawal visit. Only the samples from TEV-48125-treated patients will be analyzed for ADA. Blood samples for ADA assessment will also be collected upon observation of any severe

hypersensitivity reaction (eg, anaphylaxis). See [Appendix F](#) for the clinical criteria for diagnosing anaphylaxis. Bioanalytical personnel should be made aware of any anaphylaxis occurrence as soon as possible in case an anti-TEV-48125 immunoglobulin E assay is required.

7.10. Injection Site Assessments

Injection site assessments will be performed immediately and 1 hour after administration of each dose of study drug ([Table 1](#)). The injection site(s) will be assessed for erythema, induration, ecchymosis, and pain, and severity will be graded according to the following criteria:

- Injection-site erythema, injection-site induration, and injection-site ecchymosis will be graded according to measurements: absent, 5 mm to ≤ 50 mm (mild), >50 to ≤ 100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.
- Injection-site pain will be measured as summarized in [Table 3](#).

Table 3: Severity of Pain Scale for Injection Site Assessments

Grade	Assessments
0	No pain
1	Mild
2	Moderate
3	Severe
4	Worst possible

If a patient has severe injection site induration, erythema, and/or ecchymosis and/or grade 3 (severe) or grade 4 (worst possible) injection site pain at 1 hour after completion of study drug administration, the patient will be reassessed at 3 hours after study drug administration and hourly thereafter until the reaction/pain is of moderate or less severity.

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

Injection site reactions will also be recorded as adverse events as described in [Section 7.1](#).

7.11. Methods and Timing of Assessing, Recording, and Analyzing Safety Data

All adverse events will be reviewed on a periodic basis by the clinical project physician/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for TEV-48125) as interim/preliminary safety databases become available. Safety data will additionally be evaluated periodically and ad hoc (if necessary) in the Product Safety Group.

Methods and timing of assessing safety data are discussed in [Section 3.14](#). Procedures for recording safety data are discussed in [Section 13.1](#) and methods of analyses are discussed in [Section 9.7.2](#).

8. ASSESSMENT OF PHARMACOKINETICS/ BIOMARKERS/ IMMUNOGENICITY

8.1. Pharmacokinetic Variables

Sampling for pharmacokinetics will be sparse. Thus, the TEV-48125 pharmacokinetic samples will be analyzed using a population pharmacokinetic approach and will be reported separately to the clinical study report.

Samples from patients who receive active study drug will be analyzed for TEV-48125 using a validated method. Samples from patients who receive placebo will not be analyzed.

8.1.1. Specimen Sampling and Handling

Blood samples (4 mL) will be collected via venipuncture or indwelling catheter at the time points detailed in [Table 1](#) for plasma concentration measurements of TEV-48125.

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

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

Labels for samples should include study number, patient number, period, nominal collection time, set (A or B), and indication that they are pharmacokinetic samples. Samples will be stored at a temperature within the range of -70°C ±20°C in an upright position until they are shipped to the central laboratory.

8.1.2. Shipment and Analysis of Samples

Plasma samples for all patients will be shipped frozen on dry ice from the investigational center to the central laboratory, where they will be stored until shipment to the sponsor or its designee for analysis.

- Set A samples will be transported (frozen) with a temperature data logger, by next-day courier, to the central laboratory.
- Set B samples will either be sent to the same laboratory as that for set A on a subsequent day, by next-day courier, or be retained at the investigational center until the study is completed and the clinical study report has been issued (unless shipment to another facility is requested by the sponsor).

Samples will be analyzed using a validated method. Timing of the initiation of sample analysis will be determined by the Teva Pharmaceuticals bioanalytical representative responsible for the bioanalysis. Refer to the laboratory manual for additional details.

8.2. Immunogenicity Testing

8.2.1. Blood Sampling and Handling

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

Blood samples (5 mL) will be collected via venipuncture or indwelling catheter at the time points detailed in [Table 1](#) for immunogenicity testing.

For serum collection, samples will be collected into Vacutainer tubes containing no anticoagulant, and allowed to set at room temperature less than 30 minutes to allow for serum separation to occur. Samples will then be centrifuged (1500g, approximately 10 minutes, 2°C to 6°C). If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Other measures should be taken as appropriate to prevent samples from heating significantly during centrifugation. Separated serum will be transferred in approximately equal portions into 2 labeled, 2-mL polypropylene tubes (sets A and B).

Sample labels should include study number, patient number, period, nominal collection time, set (A or B), and indication that they are ADA samples. Serum samples will be stored at a temperature within the range of $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$ in an upright position until they are shipped to the central laboratory.

8.2.2. Shipment and Analysis of Samples

Serum samples for all patients will be shipped frozen on dry ice from the investigational center to the central laboratory, where they will be stored until shipment to the sponsor or its designee for analysis.

- Set A samples will be transported (frozen) with a temperature data logger, by next-day courier, to the central laboratory.
- Set B samples will either be sent to the same laboratory as that for set A on a subsequent day, by next-day courier, or be retained at the investigational center until the study is completed and the clinical study report has been issued (unless shipment to another facility is requested by the sponsor).

Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the Teva Pharmaceuticals department representative responsible for the bioanalysis. Refer to the laboratory manual for additional details.

8.3. Assessment of Exploratory Biofluid Biomarkers

Biomarkers are defined as biological substances that monitor physiological effects, assess drug activity, and predict clinical outcome, safety, and response to therapy.

Calcitonin gene-related peptide-containing nerve fibers are prevalent in bone tissue and have been hypothesized to be important in the regulation of bone metabolism, response to bone injury, and the perception of bone pain. In vitro, CGRP is anabolic to osteoblasts and can inhibit maturation to osteoclasts. Preclinical studies suggest CGRP antagonism may have benefit in osteoarthritis ([Benschop et al 2014](#)) and bone-related pain. In the current study, exploratory

analysis may be conducted on blood (serum, plasma, and RNA) and urine biomarkers, extracellular matrix turnover, bone formation, and bone resorption.

In preclinical models, CGRP can promote angiogenesis in ischemia, capsaicin-induced synovitis, and neovascularization of tumors. Exploratory analysis will be conducted on endothelial/angiogenic markers to determine if TEV-48125 alters angiogenic markers.

Calcitonin gene-related peptide is known to act directly on macrophage and dendritic cells by inhibiting them from producing inflammatory cytokines and presenting antigens to T cells. It has been hypothesized that CGRP may act as a regulator of the innate immune response. Exploratory analysis will be conducted on inflammatory endpoints in blood to examine effects of TEV-48125 in patients with migraine.

Based on the known biology of CGRP's mechanism of action, biomarker assessment will potentially include markers of bone remodeling, inflammation, and angiogenesis. Multiplex immunoassay panels will be applied to measure changes in urine, serum, plasma, and RNA biomarkers.

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

8.3.1. Pharmacogenomic Assessment

A blood sample (6 mL) will be collected from each patient who signs the separate informed consent form for pharmacogenomic assessment during this study. Pharmacogenomic assessment potentially includes the association analysis of both known and unknown DNA and RNA genetic variations. In the current study, known CGRP and migraine-associated genes will be examined to determine their association with clinical treatment responses to study drug and their potential to be markers predictive of migraine severity and progression (eg, efficacy, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features). The current list of genes with polymorphisms associated with either CGRP target engagement or migraine mechanism of action includes CALCA, CALCB, CALCRL, CRCP, RAMP, PRDM16, AJAP1, TSPAN2, MEF2D, TRPM8, TGFBR2, PHACTR1, FHL5, C7orf10, MMP16, ASTN2, LRP1, APOA1BP, TBC1D7, FUT9, STAT6, ATP5B, and MTHFR ([Anttila et al 2013](#)). The final list of genes that may be investigated may be edited at a later time before the analysis to allow updating with new scientific information. Genetic analysis could also include sequencing of the whole genome and/or RNA transcripts, if required.

Pharmacogenomic assessment will be performed based on study results. Samples will be used for investigations related to headache, indications where CGRP pathways are implicated, and indications that may be associated with the risk of headache or those that are common comorbidities associated with headache and/or response to study drug or related investigational drugs.

8.3.2. Specimen Sampling and Handling

Blood samples (a total of 18.5 mL; 6 mL each for plasma and serum and 6.5 mL for RNA [PAXgene]) will be collected via venipuncture or indwelling catheter at the time points detailed in [Table 1](#) for serum, plasma, and RNA biomarker measures. Urine will be collected in parallel with blood collection. In addition, a 6-mL whole blood sample will be collected at baseline for

DNA. Details for processing and handling of each type of biomarker sample will be outlined in the laboratory manual.

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

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

8.3.3. Shipment and Analysis of Samples

Biomarker samples for serum, plasma, RNA, and urine will be stored at -70°C and sent to the central laboratory on dry ice, per instructions in the laboratory manual. Sample labels should include study number, patient randomization number, visit code, collection date and time, and indication that they are biomarker samples. Shipments should be made as specified in laboratory manual. An electronic file containing sample demographics will be e-mailed to the respective biomarker laboratory and the sponsor's biomarker representative for each shipment.

Following DNA extractions of whole blood, the samples will be stored at -70°C and labeled with a new code (ie, double coding), so that genomic data will not be recorded with a patient number. Data will be kept confidential and stored separately.

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

8.4. Methods and Timing of Assessing, Recording, and Analyzing Clinical Pharmacology Data

Methods and timing of assessing clinical pharmacology data are discussed in Section 3.14. Procedures for recording clinical pharmacology data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.5.4.

9. STATISTICS

This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled parallel-group study to assess the efficacy and safety of 2 dose regimens of sc administration of TEV-48125 compared with placebo for preventive treatment of EM. Eligible patients will be randomized in a 1:1:1 ratio to receive monthly TEV-48125 at 225 mg, TEV-48125 at 675 mg followed by monthly placebo, or monthly placebo. Randomization will be stratified by gender, country, and baseline preventive medication use (yes, no).

9.1. Sample Size and Power Considerations

A total of 768 patients are planned to be randomized in this study to have 675 completers (225 completers per treatment group); a 12% drop-out rate is anticipated. A sample size of 675 patients (ie, 225 evaluable patients completing the study per treatment group) will provide 90% power to detect a 1.6 difference in migraine days between an active arm and placebo arm at an alpha level of 0.05, assuming a common standard deviation (SD) of 5.2 days.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients are randomized, regardless of which treatment they actually received.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they are randomized.

9.2.3. Full Analysis Set

The full analysis set (FAS) will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 1 postbaseline efficacy assessment on the primary endpoint.

9.2.4. Additional Analysis Sets

The per-protocol population will consist of all patients who have completed the study without any violations of the inclusion/exclusion criteria or any violations or omissions of the drug administration.

9.3. Data Handling Conventions

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

9.4. Study Population

The ITT analysis set (see Section 9.2) will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group and for all patients.

9.4.1. Patient Disposition

Data from patients screened, patients screened but not randomized and reason not randomized, patients who are randomized (ie, in the ITT set), patients randomized but not treated, patients in the safety and other analysis sets, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.4.2. Demographic and Baseline Characteristics

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

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

9.5. Efficacy Analysis

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

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

9.5.1. Primary Endpoint

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

9.5.2. Secondary Endpoints

The secondary efficacy endpoints are as follows:

- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 1st dose of the study drug
- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug in patients not receiving concomitant migraine preventive medications
- mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug

9.5.3. Exploratory Endpoints

The exploratory efficacy endpoints are as follows:

- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 75% reduction and total (100%) reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug in patients who used topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 2nd dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the last (3rd) dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of any severity during the 12-week period after the 1st dose of study drug

- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week period after each dose of study drug
- proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients not receiving concomitant preventive migraine medications
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of any severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the last (3rd) dose of study drug

- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug
- assessment of patient satisfaction, as measured by the PGIC scale, at 4 weeks after administration of the 1st dose of study drug, at 4 weeks after the 2nd dose of study drug, and at 4 weeks after the last (3rd) dose of study drug

9.5.4. Planned Method of Analysis

The FAS (see Section 9.2.3) will be used for all efficacy analyses. Summaries will be presented by treatment group.

9.5.4.1. Primary Efficacy Analysis

The primary efficacy endpoint, the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug, will be analyzed using an analysis of covariance method. The model will include treatment, gender, country, and baseline preventive medication use as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. Ninety-five percent confidence intervals will be constructed for the least squares mean differences between each TEV-48125 group and the placebo group. A hierarchical procedure will be used to control type 1 error rate.

9.5.4.2. Sensitivity Analysis

Sensitivity analysis may be conducted to explore the impact of missing data in the primary efficacy analysis.

9.5.4.3. Secondary Efficacy Analysis

The same analysis used for the primary efficacy endpoint will be performed for the secondary efficacy endpoints. For the proportion of responders defined as 50% or more reduction from baseline in the monthly average number of migraine days, Cochran-Mantel-Haenszel test will be used.

9.5.4.4. Exploratory Efficacy Analysis

The same analyses used for the primary and secondary efficacy endpoints will be performed for the exploratory efficacy endpoints, as appropriate.

9.6. Multiple Comparisons and Multiplicity

A fixed-sequence (hierarchical) testing procedure will be implemented to control the type 1 error rate at 0.05. The sequence of comparisons will be described in detail in the statistical analysis plan.

9.7. Safety and Tolerability Endpoints and Analysis

Safety and tolerability analyses will be performed on the safety analysis set.

9.7.1. Safety and Tolerability Endpoints

The safety and tolerability endpoints for this study are as follows:

- occurrence of adverse events throughout the study
- abnormal standard 12-lead ECG findings
- changes from baseline in vital signs (systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate) measurements
- changes from baseline in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results
- abnormal physical examination findings
- abnormal local injection site tolerability findings (ie, erythema, induration, ecchymosis) and occurrence of injection site pain
- suicidal ideation and behavior as suggested by the eC-SSRS

Safety and tolerability measures and time points are provided in [Table 1](#).

9.7.2. Safety Analysis

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

Injection site erythema, induration, ecchymosis, and pain will be assessed as described in Section 7.9, and findings will be listed and summarized.

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

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

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

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

9.8. Pharmacokinetic Analysis

Pharmacokinetic plasma concentration results (TEV-48125) will be tabulated descriptively at each planned sampling time point by treatment group.

9.9. Biomarker Analysis

Biomarker analysis will include logistic regression, receiver operating characteristic curves, and summary statistics. Results will be reported separately.

9.10. Pharmacokinetic/Pharmacodynamic Analysis

The pharmacokinetic/pharmacodynamic relationship will be estimated by compartmental techniques. The pharmacokinetic parameters will be based on TEV-48125 measurements. The pharmacodynamic measures will be the efficacy responses.

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

9.11. 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. This impact analysis will be reported separately.

9.12. Planned Interim Analysis

No interim analysis is planned for this study.

9.13. Reporting Deviations from the Statistical Plan

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

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, diary data, protocol-required worksheets, and CRFs that are used as the source (see Section [3.13](#)).

The investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments and Protocol Deviations and Violations

11.1.1. Protocol Amendments

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

11.1.2. Protocol Violations

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

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

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

11.2. Information to Study Personnel

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

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring that they comply with the protocol. Additional information will be

made available during the study when new staff members become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3. Study Monitoring

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

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

The study monitor(s) will contact the investigator and visit the investigational center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, including specific electronic source documentation [see Section 3.13]) relating to the study 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 study, the study 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 study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits and/or provided in follow-up written communication.

11.4. Clinical Product Complaints

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

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the site with more or less than the designated number of units inside)
- incorrect packaging or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor (or both)

- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the Product Complaint Form provided by Teva and emailing it to

████████████████████ within 48 hours of becoming aware of the issue.

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

11.4.1. Product Complaint Information Needed from the Investigational Center

In the event that the Product Complaint Form cannot be completed, the investigator will obtain the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- patient number, bottle, and kit numbers (if applicable)
- 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 (yes, no)
- date and name of person receiving the complaint

Note: Reporting a complaint must not be delayed because 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.

11.4.2. Handling the Study Drug at the Investigational Center

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

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

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality

problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

11.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event, the protocol should be followed.

11.4.4. Documenting a Product Complaint

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

11.5. Audit and Inspection

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

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

12. ETHICS

Details of compliance with regulatory guidances and applicable laws are provided in Section [1.6](#).

12.1. Informed Consent

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

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

Patients will be asked to sign a separate informed consent form if they agree to provide blood samples for pharmacogenomic assessment.

12.2. Health Authorities and Independent Ethics Committees/Institutional Review Boards

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

12.3. Confidentiality Regarding Study Patients

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

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of the Clinical Study

The end of the study is defined as the date the last patient attends the EOT/early withdrawal visit. For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

12.5. Registration of the Clinical Study

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

13. DATA HANDLING, DATA QUALITY CONTROL, AND RECORD KEEPING

13.1. Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. 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.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, or ePRO Tablet), the results will be sent to the investigational center, where they will be retained but not entered into the CRF, unless otherwise specified in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database. Laboratory test results will not be entered into the CRF, unless otherwise noted in the protocol. All data from other sources will be available to the investigators.

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

13.2. Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality control (QC), will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data QC, will be described in a data management plan.

Case report forms 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 study. 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 study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

13.3. Archiving of Case Report Forms and Source Documents

13.3.1. Sponsor Responsibilities

The sponsor will have final responsibility for the processing and QC of the data. Data management oversight will be carried out as described in the sponsor's SOPs for clinical studies.

Day-to-day data management tasks for this study are delegated to a CRO, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities. The original CRFs will be archived by the sponsor. Center-specific CRFs will be provided to the respective investigational centers for archiving.

13.3.2. Investigator Responsibilities

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

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

The investigator will retain all records related to the study until the CRO or sponsor sends written notification that records may be destroyed. If, after 10 years from study completion, or earlier (in the case of the investigative center closing or going out of business), the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least sixty 60 days before any planned disposition of study records. Upon receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

14. FINANCING AND INSURANCE

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

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

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

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

15. REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements and regulations for registration and posting of results.

The sponsor is responsible for the preparation of a clinical study report, in cooperation with the coordinating investigator. The final report is signed by the sponsor and, if applicable, by the coordinating investigator.

When the sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the coordinating investigator for comments and suggestions. An endorsement of the final report will be sought from the coordinating investigator.

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 primary publication from this study will report the results of the study in accordance with the current “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. Authorship will be restricted to parties who have editorial or conceptual input to protocol design, collection of data and/or analysis, interpretation of data, and manuscript preparation.

Authorship will be based on meeting all of the following 4 criteria:

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

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

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

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17. SUMMARY OF CHANGES TO PROTOCOL TV48125-CNS-30049**17.1. Amendment 01 Dated 30 March 2016**









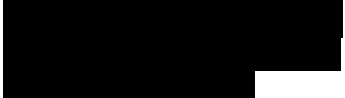
The primary reasons for this amendment are as follows:

- To incorporate required revisions based on health authority input from the European Medicines Agency, FDA, and Pharmaceuticals and Medical Devices Agency.
- To provide clarifying language for the inclusion and exclusion criteria.
- To clarify allowed and disallowed preventive medications
- To revise protocol-defined adverse events of special interest, and to add clinical criteria for diagnosing anaphylaxis
- To update and/or clarify versions of certain exploratory endpoints, including the EQ-5D (now -5L) and PGIC, respectively.

This revision is considered to be substantial by the sponsor's Authorized Representative. Other nonsubstantial revisions have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect to a significant degree the safety or rights (physical or mental integrity) of the patients in the clinical study or the scientific value of the clinical study.

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

Table 4: Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE (Other section affected by this change: Clinical Study Personnel Contact Information)		
Monitors NCGS, Inc. 65 Society 288 Meeting Street Suite 400 Charleston, South Carolina 29401 United States	Monitors NCGS, Inc. 288 Meeting Street Suite 400 Charleston, South Carolina 29401 United States	Update was made to the address of the monitors.
Authorized Representative  Teva Branded Pharmaceutical Products R&D, Inc.  Teva Branded Pharmaceutical Products R&D, Inc.	Authorized Representative  Teva Branded Pharmaceutical Products R&D, Inc.	This reflects a change in responsibilities at Teva, Inc.
Sponsor's Medical Expert  Teva Pharmaceuticals 	Sponsor's Medical Expert  Teva Pharmaceuticals 	This reflects a change in responsibilities at Teva, Inc. and a minor correction to the department name.
		Minor change was made in the representative's title and department name.

© 2015 2016 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	© 2016 Teva Branded Pharmaceutical Products R&D, Inc. All rights reserved.	Administrative change.
Amendment history was added.		Administrative change.
Signature pages were updated according to most the recent template.		Administrative change.

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
<p>Bioanalytical Pharmacokinetics Evaluation [REDACTED] (bioanalytical analysis) [REDACTED] Teva Branded Pharmaceuticals R&D, Inc.</p> <p>Bioanalytical Immunogenicity Evaluation [REDACTED] Teva Branded Pharmaceuticals R&D, Inc.</p> <p>Biomarker Evaluation [REDACTED] Teva Branded Pharmaceuticals R&D, Inc.</p>	<p>Bioanalytical Pharmacokinetics Evaluation [REDACTED] Teva Branded Pharmaceuticals R&D, Inc.</p> <p>Bioanalytical Immunogenicity Evaluation [REDACTED] Teva Branded Pharmaceuticals R&D, Inc.</p> <p>Biomarker Evaluation [REDACTED] Teva Branded Pharmaceuticals R&D, Inc.</p>	<p>This change was made to update the personnel responsible for the applicable evaluations and their titles, as applicable.</p>
<p>Pharmacogenomic and Biomarker Sample Storage BioStorage Technologies, Inc. 2910 Fortune Circle West, Suite E Indianapolis, IN 46241 USA</p> <p>BioStorage Technologies, GmbH Im Leuschnerpark 1b 64347 Griesheim, Germany</p>	<p>Pharmacogenomic and Biomarker Storage BioStorage Technologies, Inc. 2910 Fortune Circle West, Suite E Indianapolis, IN 46241 USA</p> <p>BioStorage Technologies, GmbH Im Leuschnerpark 1b 64347 Griesheim, Germany</p>	<p>Available vendor information was added.</p>

CLINICAL STUDY PROTOCOL SYNOPSIS		
Study Drug Dose, Mode of Administration, and Administration Rate		
Prefilled syringes (active or placebo) will be contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Active syringes will contain 150 mg/mL of TEV-48125, and placebo syringes will contain the same vehicle and excipients as those for active injections. Each kit will contain 1 prefilled syringe. All study drugs will be administered by a qualified clinic staff member separate from the staff member(s) responsible for collecting safety and efficacy information from the patients.	Prefilled syringes (active or placebo) will be contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Active syringes will contain 150 mg/mL of TEV-48125, and placebo syringes will contain the same vehicle and excipients as those for active injections. Each kit will contain 1 prefilled syringe.	The requirement for administration of study drugs by a qualified clinic staff member separate from the staff member(s) responsible for collecting safety and efficacy information from the patients was removed.
1 BACKGROUND INFORMATION		
1.1 Introduction (Other sections affected by this change: Section 16)		
However, approximately 3% to 6% of individuals with EM evolve, in any given year, to a significantly more disabling condition called chronic migraine (CM) (Bigal et al 2008, Lipton et al 2007, Scher et al 2003). Individuals with CM present with headaches of any severity on 15 or more days per month and have full-blown migraine on at least 8 days per month (Classification Committee of the IHS, 2013). A sizable proportion of individuals with CM experiences daily headaches and, therefore, faces considerable disability (Bigal and Lipton 2008). [...] Calcitonin gene-related peptide (CGRP) is a well-studied neuropeptide found at the centers of the migraine processes, both centrally and peripherally (Eftekhari and Edvinsson 2010, Olesen 2011).	However, approximately 3% of individuals with EM evolve, in any given year, to a significantly more disabling condition called chronic migraine (CM) (Bigal et al 2008, Lipton et al 2007, Scher et al 2003). Individuals with CM present with headaches of any severity on 15 or more days per month and have full-blown migraine on at least 8 days per month (Classification Committee of the IHS, 2013). A sizable proportion of individuals with CM experiences daily headaches and, therefore, faces considerable disability (Bigal and Lipton 2008). [...] Calcitonin gene-related peptide (CGRP) is a well-studied neuropeptide found at the centers of the migraine processes, both centrally and peripherally (Eftekhari and Edvinsson 2010).	Update/correction of information and associated literature on evolution of EM to CM was made. Revision of other select literature cited was made here and throughout the document.
Although there are more than 40 medications within	Although there are more than 40 medications within	Update/correction was made

<p>these classes of drugs that are used with varying response rates to prevent migraine, only 5 marketed drugs are approved by the Food and Drug Administration (FDA) in the United States (US) for the preventive treatment of migraine; 4 of them are approved for the prophylaxis of migraine: propranolol, timolol maleate, divalproex sodium, and topiramate. The clinical trials (Brandes et al 2004, Klapper 1997, Mathew et al 1995, Nadelmann et al 1986, Silberstein et al 2004) that supported registration of these drugs for this indication were conducted before the establishment of CM as a single entity and generally included patients with headaches on less than 15 days per month. 4 (propranolol [Inderal[®]; Akrimax Pharmaceuticals], timolol [Blocadren[®]; Merck & Co, Inc.], divalproex sodium [Depakote[®]; AbbVie, Inc.], and topiramate [Topamax[®]; Janssen]) are approved by the United States Food and Drug Administration (FDA) for the prevention or prophylaxis of EM and only 1 (onabotulinumtoxinA [Botox[®]; Allergan, Inc.]) is approved for the prevention of CM Only 1 medication, onabotulinumtoxinA, is approved for prophylaxis of CM (Lipton and Silberstein 2015). Notably, despite evidence suggesting that inhibition of CGRP is effective as a preventive migraine treatment, no available treatment directly targets CGRP.</p>	<p>these classes of drugs that are used with varying response rates to prevent migraine, only 5 marketed drugs are approved by the Food and Drug Administration (FDA) in the United States (US) for the preventive treatment of migraine; 4 of them are approved for the prophylaxis of migraine: propranolol, timolol maleate, divalproex sodium, and topiramate. The clinical studies (Brandes et al 2004, Klapper 1997, Mathew et al 1995, Nadelmann et al 1986, Silberstein et al 2004) that supported registration of these drugs for this indication were conducted before the establishment of CM as a single entity and generally included patients with headaches on less than 15 days per month. Only 1 medication, onabotulinumtoxinA, is approved for prophylaxis of CM (Lipton and Silberstein 2015).</p>	<p>regarding approved drugs for preventive treatment of migraine and associated literature.</p>
<p>1.3.1 Nonclinical Studies</p>		
<p>In vivo pharmacology studies of TEV-48125 in animal models indicate that TEV-48125 prevented an increase in blood flow in rat paw skin and the middle meningeal artery after electrical stimulation and produced a dose-dependent inhibition of the capsaicin-induced skin flare</p>	<p>In vivo pharmacology studies of TEV-48125 in animal models indicate that TEV-48125 prevented an increase in blood flow in rat paw skin and the middle meningeal artery after electrical stimulation and produced a dose-dependent inhibition of the capsaicin-induced skin flare response in cynomolgus</p>	<p>Text was updated with the latest relevant information available from the nonclinical studies.</p>

<p>response in cynomolgus monkey.</p> <p>[...]</p> <p>The inflammation was consideredsuspected to be the result of immune complex formation/deposition from the monkeys' immunogenic response to the drug (TEV-48125) and was not considered to be clinically relevant. In the pivotal 6-month chronic toxicity study in monkeys following once-weekly sc dosing at dosage levels of up to 300 mg/kg/week, achieving high exposure throughout the study, no microscopic findings were noted in any of the organs, including the ciliary vessels of the eyes, and the NOAEL of the chronic toxicity study was determined to be the highest dose tested, 300 mg/kg/week. Thus, it is believed that in view of the low frequency (ie, observed in very few animals) and minimal severity, the finding (perivascular inflammation) that was only recorded in the 3-month toxicity study, and had been resolved during the recovery period, is an incidental finding.</p> <p>The pharmacokinetics of TEV-48125 in animals (rats and monkeys) is typical of a humanized IgG2 molecule, with low mean plasma clearance, low volume of distribution at steady state, and a long t_{1/2}. Exposure as defined by the maximum observed plasma drug concentration (C_{max}) and the area under the plasma concentration-time curve increased linearly across doses following single and repeated once-weekly dosing. No gender differences in exposure were observed in rats or monkeys.</p> <p>Additionally, pivotal reproductive and developmental toxicity studies in animalsrabbits and rats with TEV-48125 were conducted. The in-life portion was</p>	<p>monkey.</p> <p>[...]</p> <p>The inflammation was suspected to be the result of immune complex formation/deposition from the monkeys' immunogenic response to the drug (TEV-48125). In the pivotal 6-month chronic toxicity study in monkeys following once-weekly sc dosing at dosage levels of up to 300 mg/kg/week, achieving high exposure throughout the study, no microscopic findings were noted in any of the organs, including the ciliary vessels of the eyes, and the NOAEL of the chronic toxicity study was determined to be the highest dose tested, 300 mg/kg/week. Thus, it is believed that in view of the low frequency (ie, observed in very few animals) and minimal severity, the finding (perivascular inflammation) that was only recorded in the 3-month toxicity study, and had been resolved during the recovery period, is an incidental finding.</p> <p>The pharmacokinetics of TEV-48125 in animals (rats and monkeys) is typical of a humanized IgG2 molecule, with low mean plasma clearance, low volume of distribution at steady state, and a long t_{1/2}. Exposure as defined by the maximum observed plasma drug concentration (C_{max}) and the area under the plasma concentration-time curve increased linearly across doses following single and repeated once-weekly dosing. No gender differences in exposure were observed in rats or monkeys.</p> <p>Additionally, pivotal reproductive and developmental toxicity studies in rabbits and rats with TEV-48125 were conducted and completed.</p>	
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and completed, and evaluation is ongoing.		
1.8 Location and Timing of Study (Other sections affected by this change: Synopsis)		
This study is planned to be conducted ...at approximately 130 140 centers.	This study is planned to be conducted ...at approximately 140 centers.	The number of study centers was expanded.
2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES		
2.2.2 Secondary Objectives (Other sections affected by this change: Synopsis and Sections 2.3.2 and 9.5.2)		
<p>The secondary objectives of this study are as follows:</p> <ul style="list-style-type: none"> to evaluate the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days with TEV-48125 during the 12-week period after the 1st dose of study drug relative to the baseline period <p>[...]</p> <ul style="list-style-type: none"> to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period in patients not receiving concomitant migraine preventive medications at baseline <p>[...]</p> <ul style="list-style-type: none"> to evaluate the incidenceimmunogenicity of TEV-48125 and the impact of antidrug antibodies (ADAs) on efficacy and tolerabilitysafety during 12 weeks of treatment with TEV-48125 relative to placebo 	<p>The secondary objectives of this study are as follows:</p> <ul style="list-style-type: none"> to evaluate the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days with TEV-48125 during the 12-week period after the 1st dose of study drug relative to the baseline period <p>[...]</p> <ul style="list-style-type: none"> to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug relative to the baseline period in patients not receiving concomitant migraine preventive medications <ul style="list-style-type: none"> to evaluate the immunogenicity of TEV-48125 and the impact of antidrug antibodies (ADAs) on efficacy and safety during 12 weeks of treatment with TEV-48125 	<p>Two secondary objectives were revised for clarity and correctness.</p> <p>A secondary objective was added for patients not receiving concomitant medications at baseline.</p> <p>For all secondary objectives, corresponding changes were made to the associated endpoints.</p>
2.2.3 Exploratory Objectives (Other sections affected by this change: Synopsis and Sections 2.3.3 and 9.5.3)		
The exploratory objectives of the study are as	The exploratory objectives of the study are as	Two related objectives (responder

<p>follows:</p> <ul style="list-style-type: none"> • to demonstrate the efficacy of TEV-48125, as assessed by the decrease in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug relative to the baseline period • to evaluate the proportion of patients reaching at least 75% reduction and total (100%) reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug • to evaluate the proportion of patients reaching total (100%) reduction in the number of migraine days during the 12-week period after the 1st dose of study drug • to evaluate the proportion of patients reaching at least 50% reduction and at least 75%, or 100% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug relative to the baseline period who sustain this level of response over the 12-week period after the 1st dose of study drug • to demonstrate the efficacy of TEV-48125 in patients who previously used topiramate for migraine, but discontinued, as assessed by the reduction in of the monthly average number of headachemigraine days of at least moderate severity during the 12-week period after the 1st dose of study drug relative to the baseline period • to demonstrate the efficacy of TEV-48125 in patients who previously used topiramate onabotulinumtoxinA for migraine, but 	<p>follows:</p> <ul style="list-style-type: none"> • to demonstrate the efficacy of TEV-48125, as assessed by the decrease in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug relative to the baseline period • to evaluate the proportion of patients reaching at least 75% reduction and total (100%) reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug • to evaluate the proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug relative to the baseline period who sustain this level of response over the 12-week period after the 1st dose of study drug • to demonstrate the efficacy of TEV-48125 in patients who previously used topiramate for migraine, but discontinued, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period • to demonstrate the efficacy of TEV-48125 in patients who previously used onabotulinumtoxinA for migraine, but discontinued, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period 	<p>analysis) were combined.</p> <p>Several objectives were added for improved alignment across migraine studies.</p> <p>Several minor editorial changes were made.</p> <p>For all exploratory objectives, corresponding changes were made to the associated endpoints.</p>
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<p>discontinued, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period</p> <p>[...]</p> <ul style="list-style-type: none"> • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 4-week period after each dose of study drug • to evaluate the proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug • to evaluate the proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients not receiving concomitant preventive migraine medications • to demonstrate the efficacy of TEV-48125, 	<p>[...]</p> <ul style="list-style-type: none"> • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 4-week period after each dose of study drug • to evaluate the proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug • to evaluate the proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients not receiving concomitant preventive migraine medications • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used topiramate for migraine in the past • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of 	
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<p>as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used topiramate for migraine in the past</p> <ul style="list-style-type: none"> • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of headache hours of any severity during the 12-week period after the 1st dose of study drug • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of study drug <p>[...]</p> <ul style="list-style-type: none"> • to explore the relationship between genetic polymorphisms within the CGRP receptor-ligand complex (eg, CALCA, CALCB, CALCRL, CRCP, and RAMP) and migraine-associated genes (eg, PRDM16, AJAP1, TSPAN2, MEF2D, TRPM8, TGFBR2, PHACTR1, FHL5, C7orf10, MMP16, ASTN2, LRP1, APOA1BP, TBC1D7, FUT9, STAT6, ATP5B, and MTHFR) and mode-of-action-related pathways versus hypertension, migraine severity, and safety 	<p>headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used onabotulinumtoxinA for migraine in the past</p> <ul style="list-style-type: none"> • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of headache hours of any severity during the 12-week period after the 1st dose of study drug • to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of study drug <p>[...]</p> <ul style="list-style-type: none"> • to explore the relationship between genetic polymorphisms within the CGRP receptor-ligand complex (eg, CALCA, CALCB, CALCRL, CRCP, and RAMP) and migraine-associated genes (eg, PRDM16, AJAP1, TSPAN2, MEF2D, TRPM8, TGFBR2, PHACTR1, FHL5, C7orf10, MMP16, ASTN2, LRP1, APOA1BP, TBC1D7, FUT9, STAT6, ATP5B, and MTHFR) and mode-of-action-related pathways versus hypertension, migraine severity, and safety and efficacy responses 	
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and efficacy responses		
2.3.3 Exploratory Efficacy Endpoints (Other sections affected by this change: Synopsis, List of Abbreviations, and Sections 3.1, 3.6, 3.14 [Table 1], 3.14.2.2, 3.14.3.1.3, 6.5, and 9.5.3)		
<ul style="list-style-type: none"> mean change from baseline (day 0) in the health status, as measured by the EuroQol-5 Dimension, 5 response level version (EQ-5D-5L) questionnaire at 4 weeks after administration of the last (3rd) dose of study drug 	<ul style="list-style-type: none"> mean change from baseline (day 0) in the health status, as measured by the EuroQol-5 Dimension, 5 response level version (EQ-5D-5L) questionnaire at 4 weeks after administration of the last (3rd) dose of study drug 	This change reflects the update to the 5-level version instead of the 3-level version of the EQ-5D (5 responses).
2.3.4 Safety and Tolerability Endpoints (Other sections affected by this change: Synopsis and Section 3.4)		
changes from baseline in vital signs (systolic and diastolic blood pressure, pulse, oral temperature, and respiratory rate) measurements	changes from baseline in vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate) measurements	“Oral” was removed to allow temperature to be measured using other methods (eg, under arm).
3.1 General Design and Study Schema (Other sections affected by this change: Synopsis and Sections 3.14.1, 3.14.2.2, and 5.3.2)		
If Patients are should not be using concomitant preventive migraine medications (presented in Appendix B) before enrolling in the study (ie, signing of the informed consent form) at the time of the screening visit, they and will not be allowed to initiate these medications after study start.	Patients should not be using concomitant preventive migraine medications (presented in Appendix B) at the time of the screening visit and will not be allowed to initiate these medications after study start.	An error was corrected. In this study, enrollment is considered to occur at the time of randomization rather than at the time of consent form signature.
3.7 Randomization and Blinding (Other sections affected by this change: Synopsis and Sections 3.1, 5.1, and 9)		
This study is a randomized study with stratification based on gender, country, and baseline preventive medication use (yes, no).	This is a randomized study with stratification based on gender, country, and baseline preventive medication use (yes, no).	Clarification was made regarding a stratification factor.

3.8.2 Blinding/Unblinding		
Pharmacokinetic data may be assessed during the study. For patients who have pharmacokinetic sample bioanalysis and/or data analysis conducted, the individuals responsible for sample bioanalysis and other responsible personnel will know who received each TEV 48125 dose regimen and who received placebo during the study (of those patients only). Personnel responsible for bioanalysis will be provided with the randomization code in order to facilitate the analysis. However, the personnel responsible for bioanalysis and pharmacokinetic data analysis will not have access to clinical safety and efficacy data and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to an individual patient's concentration data).	Pharmacokinetic data may be assessed during the study. Personnel responsible for bioanalysis will be provided with the randomization code in order to facilitate the analysis. However, the personnel responsible for bioanalysis will not have access to clinical safety and efficacy data and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to an individual patient's concentration data).	The blinding criteria and procedures with respect to pharmacokinetic data were updated.
3.11 Duration of Patient Participation and Justification		
This is consistent with the 2009 FDA Guidance for Industry on Assay Development for Immunogenicity Testing of Therapeutic Proteins; a complete washout of the antibody drug from the circulating blood is expected after approximately 7.5 months (≥ 5 half-lives), allowing a more precise evaluation of ADA.	This is consistent with the 2009 FDA Guidance for Industry on Assay Development for Immunogenicity Testing of Therapeutic Proteins; a complete washout of the drug from the circulating blood is expected after approximately 7.5 months (≥ 5 half-lives), allowing a more precise evaluation of ADA	An error was corrected.
3.14 Study Procedures, Table 1 (Other sections affected by this change: Sections 3.14.3.1.2, 3.14.3.1.3, and 7.3.5.1)		
Serum/ urine β -HCG test ^f Urine β -HCG test ^f ^f Women of childbearing potential only; a serum β-HCG test will be performed at screening, and urine β-HCG tests will be performed at subsequent visits.	Serum β -HCG test ^f Urine β -HCG test ^f ^f Women of childbearing potential only.	The footnote describing serum and urine β -HCG tests was simplified, and the rows for these tests were placed on 2 separate rows in Table 1 for ease of reference to time points.

3.14 Study Procedures, Table 1 (Related to the change in Section 7.1.6 described below; Other sections affected by this change: Sections 3.14.2.2, 3.14.3.1.2, and 3.14.3.1.3)		
<p>Blood samples for serum ADA concentrationassessment^k</p> <p>^k Blood samples for serum ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).</p>	<p>Blood samples for serum ADA assessment^k</p> <p>^k Blood samples for serum ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).</p>	<p>These additional blood sample collections are related to the designation of anaphylaxis and severe hypersensitivity reactions as adverse events of special interest in this amendment.</p> <p>“Concentration” and “assay” were changed to “assessment” throughout the document for consistency of verbiage.” Please check if this should also be added here.</p>
3.14 Study Procedures, Table 1		
<p>Blood sample for pharmacogenomic analysis^l</p> <p>^l A single blood sample for pharmacogenomic analysis will be collected at visit 2 or any visit thereafter from patients who consent to this procedure. A separate informed consent form for pharmacogenomic sampling must be signed by the patient.</p>	<p>Blood sample for pharmacogenomic analysis^l</p> <p>^l A single blood sample for pharmacogenomic analysis will be collected at visit 2 or any visit thereafter from patients who consent to this procedure. A separate informed consent form for pharmacogenomic sampling must be signed by the patient.</p>	<p>Details of this sampling were moved to a footnote and revised to emphasize that a separate ICF is required.</p>
3.14 Study Procedures, Table 1 (Other sections affected by this change: Section 7.5)		
<p>^c Electrocardiograms will be performed in triplicate, with approximately 1 minute between recordings.</p>	<p>^c Electrocardiograms will be performed in triplicate.</p>	<p>Specification for approximately 1 minute interval between recordings was removed, as it was deemed unnecessary.</p>

3.14.1 Procedures for Screening (Visit 1 [Day –28])		
The first 2 digits of the screening number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the investigational center number, and the last 3 digits will be the patient number assigned at the investigator center (eg, the 3 rd patient screened in Italy the US [country 01] at center 101 would be assigned the number of 01101003).	The first 2 digits of the screening number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the investigational center number, and the last 3 digits will be the patient number assigned at the investigator center (eg, the 3 rd patient screened in the US [country 01] at center 101 would be assigned the number of 01101003).	Country 01 is the US.
4 SELECTION AND WITHDRAWAL OF PATIENTS		
4.1 Patient Inclusion Criteria (Other sections affected by this change: Synopsis)		
<p>d. [...]</p> <ul style="list-style-type: none"> on ≥ 4 days, fulfilling any of the following: <ul style="list-style-type: none"> ICHHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix ED) ICHHD-3 criteria B and C for 1.2 Migraine with aura (Appendix ED) Probable migraine (a migraine subtype where only 1 migraine criterion is missing) [...] <p>e. Not using preventive medications (presented in Appendix B) (ie, at least 5 half-lives have passed since last use) or using no more than 1 preventive medication (presented in Appendix A medications) for migraine or other medical conditions (eg, topiramate) for migraine or other medical conditions (eg, propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to</p>	<p>d. [...]</p> <ul style="list-style-type: none"> on ≥ 4 days, fulfilling any of the following: <ul style="list-style-type: none"> ICHHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix D) ICHHD-3 criteria B and C for 1.2 Migraine with aura (Appendix D) Probable migraine (a migraine subtype where only 1 migraine criterion is missing) [...] <p>e. Not using preventive medications (presented in Appendix B) (ie, at least 5 half-lives have passed since last use) or using no more than 1 preventive medication (presented in Appendix A) for migraine or other medical conditions (eg, propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to beginning the 28 day run-in period.</p> <p>f. Body mass index of 17.5 to 37.5 kg/m² and a total body weight between 45 and 120 kg, inclusive</p>	<p>A criterion of a probable migraine was added to further define the patient population.</p> <p>Allowed/disallowed preventive medication was clarified.</p> <p>Upper boundary of the total body weight was expanded up to 120 kg. This limit was used in Phase 2 studies; no associated safety signals were detected.</p> <p>Contraception criteria were updated and clarified to comply with the current Teva standards.</p> <p>Language regarding the timing of the serum β-HCG pregnancy testing was clarified.</p>

<p>beginning the 28 day run-in period. A list of preventive medications is presented in Appendix A.</p> <p>f. Body mass index of 17.5 to 37.5 kg/m² and a total body weight between 45 and 115120 kg, inclusive</p> <p>g. [...] if of childbearing potential, patients must meet any of the following criteria: [...]</p> <ul style="list-style-type: none"> – Sexual abstinence is only considered a <u>highly effective method</u> if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception. – Patients will remain abstinent throughout the study in the context of the preferred and usual lifestyle. Declaration of abstinence for the duration of the study and withdrawal are not acceptable methods of contraception. – Patients have sexual preference that precludes the possibility of pregnancy. <p>h. Female patients of childbearing potential must have sa negative serum β-HCG pregnancy test prior to randomization at screening (confirmed by urine dipstick β-HCG pregnancy test at baseline).</p>	<p>g. [...] if of childbearing potential, patients must meet any of the following criteria: [...]</p> <ul style="list-style-type: none"> – Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception. <p>h. Female patients of childbearing potential must have a negative serum β-HCG pregnancy test at screening-(confirmed by urine dipstick β-HCG pregnancy test at baseline).</p>	
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4.2 Patient Exclusion Criteria (Other sections affected by this change: Synopsis)		
<p>b. Patient is using medications containing opioids (including codeine) or barbiturates (including butalbital/aspirin/caffeine [Fiorinal®, Actavis plc], butalbital/paracetamol/caffeine [Fioricet®, Cardinal Health], or any other combination containing butalbital) on more than 4 days per month for the treatment of migraine or for any other reason.</p> <p>c. Patients who are taking migraine preventative treatment at the time of screening and Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the following medications for treatment of EM or CM after adequate therapeutic trial defined as use for at least 3 months at accepted migraine therapeutic doses:</p> <ul style="list-style-type: none"> – cluster A: divalproex sodium and sodium valproate – cluster B: topiramate flunarizine and pizotifen – cluster C : amitriptyline, nortriptyline, and venlafaxine, and duloxetine – [...] <p>f. Evidence or medical history of clinically significant psychiatric issues, including major depression, panic disorder, or generalized anxiety disorder any suicide attempt in the past or suicidal ideation with a specific plan in the past 2 years, at the discretion of the investigator</p> <p>[...]</p> <p>j. Past or current history of cancer in the past 5 years, except for appropriately treated nonmelanoma skin carcinoma in the last 5 years</p> <p>[...]</p>	<p>b. Patient is using medications containing opioids (including codeine) or barbiturates (including butalbital/aspirin/caffeine, butalbital/paracetamol/caffeine, or any other combination containing butalbital) on more than 4 days per month for the treatment of migraine or for any other reason.</p> <p>c. Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the following medications for treatment of EM or CM after adequate therapeutic trial defined as use for at least 3 months at accepted migraine therapeutic doses:</p> <ul style="list-style-type: none"> – cluster A: divalproex sodium and sodium valproate – cluster B: flunarizine and pizotifen – cluster C : amitriptyline, nortriptyline, venlafaxine, and duloxetine – [...] <p>f. Evidence or medical history of clinically significant psychiatric issues, including any suicide attempt in the past or suicidal ideation with a specific plan in the past 2 years</p> <p>[...]</p> <p>j. Past or current history of cancer in the past 5 years, except for appropriately treated nonmelanoma skin carcinoma</p> <p>[...]</p> <p>r. History of alcohol or drug abuse during the past 2 years, or alcohol or drug dependence during the past 5 years</p> <p>s. The patient cannot participate or successfully complete the study, in the opinion of their</p>	<p>References to drug brand names have been removed.</p> <p>Exclusion criterion related to prior migraine medication use was updated in line with clinical practice.</p> <p>Editorial change was made to the prior history of cancer criterion.</p> <p>Minor editorial changes were also made to other exclusion criteria (not shown)</p> <p>Psychiatric history criterion was updated to specifically address suicidal ideation or behavior within the last 6 months.</p> <p>History of alcohol and drug abuse and dependence criterion was modified to align with Teva's current practice.</p> <p>Language was updated to reflect commonly used terminology.</p>

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<p>r. Lifetime History of alcohol or drug abuse during the past 2 years, or alcohol or drug dependence during the past 5 years</p> <p>s. The patient cannot participate or successfully complete the study, in the opinion of their healthcare provider or the investigator, for any of the following reasons:</p> <ul style="list-style-type: none"> – [...] – in custody due to an administrative or a legal decision, under tutelage guardianship, or being admitted to a sanitarium or social institution institutionalized 	<p>healthcare provider or the investigator, for any of the following reasons:</p> <ul style="list-style-type: none"> – [...] – in custody due to an administrative or a legal decision, under guardianship, or or institutionalized 	
<p>5.2 Restrictions</p>		
<p>Highly effective contraception methods include the following hormonal and other methods of birth control:</p> <ul style="list-style-type: none"> • combined (estrogen and gestagen) oral contraceptives, hormone implants, hormone rings, contraceptive patch, and hormone injectables initiated at least 7 days before study drug administration • hormone-containing intrauterine device in place for a period of at least 2 months before study drug administration • [...] <p>There were no additional restrictions in this study.</p> <p>In addition, male patients may not donate sperm for the duration of the study and for 7.5 months after discontinuation of study drug.</p>	<p>Highly effective contraception methods include the following hormonal and other methods of birth control:</p> <ul style="list-style-type: none"> • combined (estrogen and gestagen) oral contraceptives, hormone implants, hormone rings, contraceptive patch, and hormone injectables initiated at least 7 days before study drug administration • intrauterine device in place for a period of at least 2 months before study drug administration • [...] <p>There were no additional restrictions in this study.</p> <p>In addition, male patients may not donate sperm for the duration of the study and for 7.5 months after discontinuation of study drug.</p>	<p>Contraception criteria were updated.</p>

5.3 Prior and Concomitant Therapy or Medication		
Any prior or concomitant therapy, medication, or procedure (ie, procedures for the treatment of migraine [eg, nerve blocks]) that a patient has had within 6 months before study drug administration and up to the end of the study period will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. In addition, migraine preventive medication that a patient took within 2 years before study drug administration will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded.	Any prior or concomitant therapy, medication, or procedure that a patient has had within 6 months before study drug administration and up to the end of the study period will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. In addition, migraine preventive medication that a patient took within 2 years before study drug administration will be recorded on the CRF.	Parenthetical clarification was considered to be limiting and was therefore removed. Process clarification was added.

5.3.2 Concomitant Therapy : Therapies and Medications (Other sections affected by this change: Synopsis, Sections 3.1 and 4.1, and Appendix A)		
<p>Up to 30% of patients will be allowed to remain on stable doses of no more than 1 preventive migraine medication for the duration of the study provided the medication has at least moderate evidence of efficacy as defined by guidelines (Silberstein et al 2012) and presented in Appendix A. Patients on preventive medication must be on a stable dose for at least 2 months of consecutive use prior to study entry.</p> <p>Alternatively, patients must have discontinued the preventive medication at least 5 half-lives prior to screening. Preventive migraine medications disallowed for at least 70% of patients for the duration of the study are presented in Appendix B.</p> <p>Patients will be allowed to use acute medications to treat acute migraine attacks, as needed, with the exception of medications containing opioids and barbiturates, which cannot be used more than 4 times per month prior to study entry.</p> <p>Use of concomitant therapies for indications other than migraine prevention is allowed throughout the course of the study, provided they are not effective for migraine or they meet the criteria for permitted concomitant preventive medication.</p> <p>All concomitant medications taken during the study...</p>	<p>Up to 30% of patients will be allowed to remain on stable doses of no more than 1 preventive migraine medication for the duration of the study provided the medication has at least moderate evidence of efficacy as defined by guidelines (Silberstein et al 2012) and presented in Appendix A. Patients on preventive medication must be on a stable dose for at least 2 months of consecutive use prior to study entry.</p> <p>Alternatively, patients must have discontinued the preventive medication at least 5 half-lives prior to screening. Preventive migraine medications disallowed for at least 70% of patients for the duration of the study are presented in Appendix B.</p> <p>Patients will be allowed to use acute medications to treat acute migraines attacks, as needed.</p> <p>All concomitant medications taken during the study...</p>	<p>The title of this section was updated.</p> <p>It was specified that up to 30% of patients could remain on stable doses of 1 preventive migraine medication.</p> <p>An alternative option was provided for patients to discontinue preventive medication at least 5 half-lives prior to screening.</p> <p>Provision regarding the use of medications containing opioids and barbiturates was removed, as it was redundant with exclusion criterion b.</p> <p>Provision regarding the use of other concomitant medications was removed to further align with current approach.</p> <p>A clarification was made. In this study, acute medications can be used to treat acute migraine attacks.</p>
5.5 Total Blood Volume, Table 2		

<p>^c For each 18.5-mL sample, individual volumes will be 6 mL each for serum and plasma and 6.5 mL for RNA.</p> <p>^d For patients who consent to pharmacogenomic testing.</p>	<p>^c For each 18.5-mL sample, individual volumes will be 6 mL each for serum and plasma and 6.5 mL for RNA.</p> <p>^d For patients who consent to pharmacogenomic testing.</p>	<p>A footnote was added for consistency with the blood volumes described throughout the protocol.</p>
6 ASSESSMENT OF EFFICACY		
6.3 Two-Item Patient Health Questionnaire/9-Item Patient Health Questionnaire (Other sections affected by this change: Synopsis and Sections 3.6, 3.14 [Table 1], 3.14.2.2, and 3.14.3.1.3)		
<p>Each of the items is scored on a scale of 0 (“not at all”), 1 (“several days”), 2 (“more than half the days”), and 3 (“nearly every day”) based on the frequency of symptoms during the past 2 weeks (Spitzer et al 1999). The PHQ-2 was developed from the PHQ-9 to rapidly screen for depression and consists of the first 2 questions from the PHQ-9. [...]</p> <p>If the PHQ-2 is positive (ie, a score of ≥ 3), patients will complete questions 3 through 9 (unique questions) of the PHQ-9.</p>	<p>Each of the items is scored on a scale of 0 (“not at all”), 1 (“several days”), 2 (“more than half the days”), and 3 (“nearly every day”) based on the frequency of symptoms during the past 2 weeks (Spitzer et al 1999). The PHQ-2 was developed from the PHQ-9 to rapidly screen for depression and consists of the first 2 questions from the PHQ-9. [...]</p> <p>If the PHQ-2 is positive (ie, a score of ≥ 3), patients will complete questions 3 through 9 (unique questions) of the PHQ-9.</p>	<p>Time period for symptom frequency in the PHQ was specified.</p> <p>Update/correction was made indicating that patients will only complete the unique portions of the PHQ-9 after a positive PHQ-2 score.</p>
6.6 Patient Global Impression of Change Scale		
<p>The PGIC scale is a validated generic tool for assessment of overall change in the severity of illness following treatment. Patients will rate how they feel now compared with how they felt before receiving study drug on a 7-point scale where 3 is “very much worse,” 0 is “no change,” and 3 is “very much improved.” Patients will rate how they describe the change (if any) that their migraine/headaches have had in their general quality of life and health status since beginning the treatment in this study on a 7-point scale where 1=no change (or condition has got worse); 2=almost the same, hardly any change at all; 3=a little better, but no</p>	<p>The PGIC scale is a validated generic tool for assessment of overall change in the severity of illness following treatment. Patients will rate how they describe the change (if any) that their migraine/headaches have had in their general quality of life and health status since beginning the treatment in this study on a 7-point scale where 1=no change (or condition has got worse); 2=almost the same, hardly any change at all; 3=a little better, but no noticeable change; 4=somewhat better, but the change has not made any real difference; 5=moderately better, and a slight but noticeable change; 6=better, and a definite improvement that</p>	<p>Correction was made regarding PGIC scale numbering and descriptors.</p>

noticeable change; 4=somewhat better, but the change has not made any real difference; 5=moderately better, and a slight but noticeable change; 6=better, and a definite improvement that has made a real and worthwhile difference; and 7=a great deal better, and a considerable improvement that has made all the difference.	has made a real and worthwhile difference; and 7=a great deal better, and a considerable improvement that has made all the difference.	
7 ASSESSMENT OF SAFETY		
7.1.6 Protocol Defined Adverse Events of Special Interest (Other sections affected by this change: Appendices [Appendix F added], Section 3.14 [Table 1], and Section 16)		
<p>7.1.6 Protocol-Defined Adverse Events of Special Interest</p> <p>The following are considered protocol-defined adverse events to be sent to the sponsor’s Global Patient Safety and Pharmacovigilance Department for evaluation: ophthalmic related adverse events of at least moderate severity, events of possible drug-induced liver injury (AST or ALT $\geq 3 \times$ the ULN, total bilirubin $\geq 2 \times$ the ULN or INR > 1.5), or Hy’s Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions. Severe 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 [also see Appendix F]). In the event of suspected anaphylaxis, vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator.</p> <p>The process for reporting a protocol-defined adverse event is the same as that for reporting a</p>	<p>7.1.6 Protocol-Defined Adverse Events of Special Interest</p> <p>The following are considered protocol-defined adverse events to be sent to the sponsor’s Global Patient Safety and Pharmacovigilance Department for evaluation: ophthalmic adverse events of at least moderate severity, events of possible drug-induced liver injury (AST or ALT $\geq 3 \times$ the ULN, total bilirubin $\geq 2 \times$ the ULN or INR > 1.5), Hy’s Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions. Severe 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 [also see Appendix F]). In the event of suspected anaphylaxis, vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator.</p> <p>The process for reporting a protocol-defined adverse event is the same as that for reporting a serious</p>	<p>The title of this section was updated, adding the word “Special”.</p> <p>Adverse events of special interest were updated to include anaphylaxis and severe hypersensitivity reactions.</p> <p>Relatedly, Appendix F (clinical criteria for diagnosing anaphylaxis) was added.</p>

serious adverse event (see Section 7.1.5.3).	adverse event (see Section 7.1.5.3).	
7.3.1 Serum Chemistry (Other sections affected by this change: Sections 7.1.1, 7.1.6, 7.3.4. and Appendix E)		
<p>The following serum chemistry tests will be performed:</p> <ul style="list-style-type: none"> • [...] • total bilirubin • direct bilirubin • indirect bilirubin (calculated) • lactate dehydrogenase • [...] 	<p>The following serum chemistry tests will be performed:</p> <ul style="list-style-type: none"> • [...] • total bilirubin • direct bilirubin • indirect bilirubin (calculated) • lactate dehydrogenase • [...] 	<p>Total and direct bilirubin tests will be conducted at all visits that have chemistry laboratory assessments. Previously, direct bilirubin collection was triggered only under certain conditions.</p> <p>Relatedly, editorial changes were made throughout the protocol to clarify when total or direct (or both) bilirubin was being referred to.</p>
7.3.2 Hematology		
<p>The following hematology tests will be performed:</p> <ul style="list-style-type: none"> • [...] • white blood cell (WBC) count and differential count (absolute values and percentages) <ul style="list-style-type: none"> – neutrophils – lymphocytes – eosinophils – monocytes – basophils – atypical lymphocytes 	<p>The following hematology tests will be performed:</p> <ul style="list-style-type: none"> • [...] • white blood cell (WBC) count and differential count (absolute values and percentages) <ul style="list-style-type: none"> – neutrophils – lymphocytes – eosinophils – monocytes – basophils 	<p>A hematology test that was determined not to be needed was removed.</p>

7.4 Vital Signs		
In addition, potentially clinically significant values may be predefined by the sponsor for selected vital signs (see Section 9.7.2) and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan).	In addition, potentially clinically significant values may be predefined by the sponsor for selected vital signs (see Section 9.7.2) and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan).	This language was added to align with Teva’s standard practices.
7.9 Immunogenicity		
7.9. Injection Site Assessments Immunogenicity Blood samples for serum ADA assessment will be collected at visits 2, 3, and the EOT/early withdrawal visit. Only the samples from TEV-48125-treated patients will be analyzed for ADA. Blood samples for ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). See Appendix F for the clinical criteria for diagnosing anaphylaxis. Bioanalytical personnel should be made aware of any anaphylaxis occurrence as soon as possible in case an anti-TEV-48125 immunoglobulin E assay is required. 7.10. Injection Site Assessments	7.9. Immunogenicity Blood samples for serum ADA assessment will be collected at visits 2, 3, and the EOT/early withdrawal visit. Only the samples from TEV-48125-treated patients will be analyzed for ADA. Blood samples for ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). See Appendix F for the clinical criteria for diagnosing anaphylaxis. Bioanalytical personnel should be made aware of any anaphylaxis occurrence as soon as possible in case an anti-TEV-48125 immunoglobulin E assay is required. 7.10. Injection Site Assessments	A dedicated immunogenicity subsection was added for clarity and completeness; it includes anaphylaxis-related text according to the change to Section 7.1.6 (above).
8 ASSESSMENT OF PHARMACOKINETICS/ BIOMARKERS/ IMMUNOGENICITY		
8.1.1 Specimen Sampling and Handling (Other sections affected by this change: Section 8.2.1)		
Blood samples will be centrifuged (1500g, ~10 minutes, 02°C to 56°C) between 5 minutes and 1 hour after sampling...Separated plasma will be transferred in approximately equal portions into 2 opaque , labeled, 2-mL polypropylene tubes (sets A and B).	Blood samples will be centrifuged (1500g, ~10 minutes, 2°C to 6°C) between 5 minutes and 1 hour after sampling...Separated plasma will be transferred in approximately equal portions into 2 labeled, 2-mL polypropylene tubes (sets A and B).	Procedures for plasma and serum collection were updated.

8.2.2 Shipment and Analysis of Samples		
Serum samples for all patients will be shipped frozen on dry ice from the investigational center to the central laboratory	Serum samples for all patients will be shipped frozen on dry ice from the investigational center to the central laboratory	Shipping requirements for serum were clarified and aligned with those for plasma (Section 8.1.2).
8.3 Assessment of Exploratory Biofluid Biomarkers (Other sections affected by this change: Synopsis and Sections 3.14 [Table 1], 3.14.2.2, 3.14.3.1.2, 3.14.3.1.3, 5.5 [Table 2], 8.3.2, and 9.9)		
In the current study, exploratory analysis may be conducted on blood (serum, plasma, and RNA) and urine biomarkers for extracellular matrix turnover, bone formation, and bone resorption. [...] Validated in Multiplex immunoassay panels will be applied to measure changes in urine, serum, and plasma markers, and RNA biomarkers.	In the current study, exploratory analysis may be conducted on blood (serum, plasma, and RNA) and urine biomarkers for extracellular matrix turnover, bone formation, and bone resorption. [...] Multiplex immunoassay panels will be applied to measure changes in urine, serum, plasma, and RNA biomarkers.	Clarification was made for internal consistency throughout the protocol specifying that serum, plasma, and RNA would be collected from blood. The blood volume required for each separate biomarker assessment is now reiterated in Table 2. Statement regarding the assays being validated was removed to allow for operational flexibility.
9 STATISTICS		
9.2.4 Additional Analysis Sets		
The per-protocol population will consist of all patients who have completed the study without any violations of the inclusion/ exclusion criteria or any violations or omissions of the drug administration.	The per-protocol population will consist of all patients who have completed the study without any violations of the inclusion/exclusion criteria or any violations or omissions of the drug administration.	An error was corrected.
9.4.1 Patient Disposition		
Data from patients screened; patients screened but not randomized and reason not randomized; patients who are randomized (ie, in the ITT set); patients randomized but not treated; patients in the ITT , safety, and other analysis sets; patients who complete the study; and patients who withdraw from the study will be summarized using descriptive statistics.	Data from patients screened, patients screened but not randomized and reason not randomized, patients who are randomized (ie, in the ITT set), patients randomized but not treated, patients in the safety and other analysis sets; patients who complete the study; and patients who withdraw from the study will be summarized using descriptive statistics.	Editorial changes were made.

9.6 Multiple Comparisons and Multiplicity (Other sections affected by this change: Synopsis, Section 9.5.4.1)		
<p>A fixed-sequence (hierarchical) testing procedure will be implemented to control the type 1 error rate at 0.05. The sequence of comparisons will be as follows: described in detail in the statistical analysis plan.</p> <ol style="list-style-type: none"> 1. mean change from baseline (28 day run in period) in the monthly average number of migraine days during the 12 week period after the 1st dose of study drug for the TEV 48125 225/225/225 mg treatment group versus the placebo treatment group 2. proportion of patients reaching at least 50% reduction in monthly average number of migraine days during 12 week period after the 1st dose of study drug for the TEV 48125 225/225/225 mg treatment group versus the placebo treatment group 3. mean change from baseline (28 day run in period) in the monthly average number of migraine days during the 12 week period after the 1st dose of study drug for the TEV 48125 675 mg/placebo/placebo treatment group versus the placebo treatment group 4. mean change from baseline (28 day run in period) in the monthly average number of days of use of any acute headache medications during the 12 week period after the 1st dose of the study drug for the TEV 48125 225/225/225 mg treatment group versus the placebo treatment group 5. mean change from baseline (28 day run in period) in the number of migraine days during the 4 week period after the 1st dose of 	<p>A fixed-sequence (hierarchical) testing procedure will be implemented to control the type 1 error rate at 0.05. The sequence of comparisons will be described in detail in the statistical analysis plan.</p>	<p>The text was updated to reflect that the hierarchical testing procedure will not be finalized/available until the statistical analysis plan has been completed.</p>

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<p>the study drug for the TEV 48125 675 mg/placebo/placebo treatment group versus the placebo treatment group</p> <p>6. mean change from baseline (28 day run in period) in the number of migraine days during the 4 week period after the 1st dose of the study drug for the TEV 48125 225/225/225 mg treatment group versus the placebo treatment group</p> <p>7. proportion of patients reaching at least 50% reduction in the monthly number of migraine days during 12 week period after the 1st dose of study drug for the TEV 48125 675 mg/placebo/placebo treatment group versus the placebo treatment group</p> <p>8. mean change from baseline (28 day run in period) in the monthly average number of days of use of any acute headache medications during the 12 week period after the 1st dose of study drug for the TEV 48125 675 mg/placebo/placebo treatment group versus the placebo treatment group</p> <p>9. mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug for the TEV 48125 675 mg/placebo/placebo treatment group versus the placebo treatment group</p> <p>10. mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug for the TEV 48125 225/225/225 mg treatment group versus the placebo treatment group</p>		
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<p>If the resulting 2-sided p-value from the first comparison is ≤ 0.05, then the next comparison of interest will be interpreted inferentially at the alpha level of 0.05. This process will continue either until all comparisons of interest are interpreted inferentially or until the point at which the resulting 2-sided p-value for a comparison of interest is > 0.05. At the point where $p > 0.05$, no further comparisons will be interpreted inferentially.</p>		
<p>9.11 Immunogenicity Analysis (Other sections affected by this change: Synopsis)</p>		
<p>This impact analysis will be reported separately.</p>	<p>This impact analysis will be reported separately.</p>	<p>Clarification was added.</p>
<p>11 QUALITY CONTROL AND QUALITY ASSURANCE</p>		
<p>11.1.1 Protocol Amendments</p>		
<p>No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and national and local competent authorities, (as applicable), except when necessary to address immediate safety concerns to the patients, or when the change involves only nonsubstantial logistics or administration. Each investigator The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.</p>	<p>No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients, or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.</p>	<p>Updates were made to align with the latest Teva practices.</p>
<p>11.1.2 Protocol Violations</p>		
<p>A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations, referred to as protocol violations, are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may</p>	<p>Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the subjects of the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol violations may include nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective</p>	<p>Updates were made to align with the latest Teva practices.</p>

<p>significantly affect a patient's rights, safety, or well-being. Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the subjects of the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol violations include enrolling patients in violation of key eligibility criteria designed to ensure a specific subject population, failing to collect data necessary to interpret primary endpoints, Protocol violations may include nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; use of prohibited medications, GCP noncompliance, or any other deviations that may have an impact on the processes put in place for the care and safety of the patients or compromise the scientific value of the trial.</p> <p>Protocol violations will be identified and recorded by investigational center personnel onin the CRF. All protocol violations will be reported to the responsible IEC/IRB, as required.</p> <p>When a protocol violation is reported, the sponsor will determine whether to discontinue the patient from the study or permit the patient to continue in the study, with documented approval from the medical representativeexpert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.</p> <p>Deviations from Changes in the inclusion/ and exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol eligibilityinclusion and exclusion criteria was entered into a study, they must immediately</p>	<p>variable criteria, or GCP guidelines; noncompliance to study drug administration; use of prohibited medications. Protocol violations will be identified and recorded by investigational center personnel in the CRF. All protocol violations will be reported to the responsible IEC/IRB, as required.</p> <p>When a protocol violation is reported, the sponsor will determine whether to discontinue the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.</p> <p>Changes in the inclusion and exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered into a study, they must immediately inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken; but the violation will be recorded.</p>	
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<p>inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken; but the violation will be recorded. If such patient is still participating in the study, a determination will be made by the sponsor and the investigator as to whether it is in the best interest of the patient to continue in the study.</p>		
<p>APPENDIX A PREVENTIVE MEDICATIONS ALLOWED FOR THE DURATION OF THE STUDY</p>		
<p>Preventive migraine medications allowed for up to 30% of patients for the duration of the study specifically include the following (only if they were previously prescribed for migraine or for another indication if used at an approved dose for migraine prophylaxis):</p> <ul style="list-style-type: none"> • beta-blockers: atenolol, propranolol, metoprolol, nadolol, and timolol • calcium channel blocker/benzocycloheptene: verapamil, flunarizine and pizotifen • tricyclic-antidepressants: amitriptyline, venlafaxine, nortriptyline, and duloxetine • serotonin norepinephrine reuptake inhibitor: venlafaxine • triptans: frovatriptan, naratriptan, and zolmitriptan if they were used as preventive medications for the treatment of menstrual migraine. (Note: They cannot be used daily for the preventive treatment of migraine.) • anti-epileptic medications: topiramate, valproate, and divalproate 	<p>Preventive migraine medications allowed for up to 30% of patients for the duration of the study specifically include the following (if they were previously prescribed for migraine or for another indication):</p> <ul style="list-style-type: none"> • beta-blockers: atenolol, propranolol, metoprolol, nadolol, and timolol • calcium channel blocker/benzocycloheptene: flunarizine and pizotifen • antidepressants: amitriptyline, venlafaxine, nortriptyline, and duloxetine • anti-epileptic medications: topiramate, valproate, and divalproate 	<p>Appendix A was updated to reflect the most recent list of preventive medications allowed for the duration of the study.</p>
<p>APPENDIX B. DISALLOWED MEDICATIONS FOR THE DURATION OF THE STUDY</p>		
<p>Preventive migraine medications/treatments</p>	<p>Preventive migraine medications disallowed for at</p>	<p>A new Appendix B was added to</p>

<p>disallowed for at least 70% of patients for the duration of the study specifically include the following:</p> <ul style="list-style-type: none"> • beta-blockers: atenolol, propranolol, metoprolol, nadolol, and timolol • calcium channel blocker/benzocycloheptene: flunarizine and pizotifen • antidepressants: amitriptyline, venlafaxine, nortriptyline, and duloxetine • anti-epileptic medications: topiramate, valproate, carbamazepine, and divalproate • angiotensin receptor blocker: candesartan and lisinopril • onabotulinimtoxinA: botox • triptans/ergots: used as preventive therapy for migraine • NSAIDs: used as preventive therapy for migraine or on a daily basis for other indications • devices for migraine prophylaxis • nerve blocks in the head and neck <p>Any of the listed medications are allowed if given as topical or eye drops.</p> <p>Other medications in the same classes but not included in this list are allowed.</p>	<p>least 70% of patients for the duration of the study specifically include the following:</p> <ul style="list-style-type: none"> • beta-blockers: atenolol, propranolol, metoprolol, nadolol, and timolol • calcium channel blocker/benzocycloheptene: flunarizine and pizotifen • antidepressants: amitriptyline, venlafaxine, nortriptyline, and duloxetine • anti-epileptic medications: topiramate, valproate, carbamazepine, and divalproate • angiotensin receptor blocker: candesartan and lisinopril • onabotulinimtoxinA: botox • triptans/ergots: used as preventive therapies for migraine • NSAIDs: used as preventive therapy for migraine or on a daily basis for other indications • devices for migraine prophylaxis • nerve blocks in the head and neck <p>Any of the listed medications are allowed if given as topical or eye drops.</p> <p>Other medications in the same classes but not included in this list are allowed.</p>	<p>show the most recent list of preventive medications disallowed for the duration of the study. The numbering of all subsequent appendices shifted.</p>
<p>APPENDIX F. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS</p>		
<p>Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:</p> <p>a. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal</p>	<p>Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:</p> <p>a. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal</p>	<p>Appendix F was added to provide the criteria for diagnosis of anaphylaxis.</p>

<p>tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING</p> <ul style="list-style-type: none"> – Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia) – Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence) <p>b. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):</p> <ul style="list-style-type: none"> – 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) <p>c. Reduced BP after exposure to known allergen for that subject (minutes to several hours):</p> <ul style="list-style-type: none"> – Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP – Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline <p>Source: Modified from Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the</p>	<p>tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING</p> <ul style="list-style-type: none"> – Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia) – Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence) <p>b. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):</p> <ul style="list-style-type: none"> – 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) <p>c. Reduced BP after exposure to known allergen for that subject (minutes to several hours):</p> <ul style="list-style-type: none"> – Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP – Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline <p>Source: Modified from Sampson HA, Munoz-</p>	
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definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium.[reprint in Ann Emerg Med 2006 Apr;47(4):373-80; PMID:16546624]. J Allergy Clin Immunol 2006 Feb;117(2):391-7.	Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium.[reprint in Ann Emerg Med 2006 Apr;47(4):373-80; PMID:16546624]. J Allergy Clin Immunol 2006 Feb;117(2):391-7.	
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17.2. Administrative Letter Dated 01 March 2016

1 March 2016

Re: Administrative Change #2 to the following protocols:

TV48125-CNS-30049 dated 21 October 2015

TV48125-CNS-30050 dated 21 October 2015

TV48125-CNS-30051 dated 02 November 2015

The purpose of this administrative letter is to provide guidance regarding the evaluation of suspected anaphylaxis during the execution of these studies as well as make a correction to a change in Administrative Letter #1. This information should take immediate effect and the language will be added to the next protocol amendments.

7.1.6 Protocol-Defined Adverse Events of Special Interest:

In addition to ophthalmic adverse events and possible drug-induced liver injury or Hy's Law events, the following protocol-defined adverse events of special interest should result in notification of the sponsor's Pharmacovigilance (PhV) department for evaluation: suspected anaphylaxis and severe hypersensitivity reactions. At this time, there have not been any cases of suspected anaphylaxis with TEV-48125. However, treatment of patients with therapeutic protein products or peptides may result in immune responses of varying clinical relevance, ranging from antibody responses with no apparent clinical manifestations to life-threatening reactions. Suspected anaphylaxis will be monitored in these studies using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al, 2006):

The diagnosis of anaphylaxis is based on the following three clinical criteria, with anaphylaxis considered as highly likely when one of these criteria is fulfilled:

- a. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
 - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
 - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
- b. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (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 patient (minutes to several hours):
 - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

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

If a case of suspected anaphylaxis is identified based on one of the three criteria above, please contact Teva's Pharmacovigilance (PhV) department within 24 hours.

After this language has been added to the protocol amendments, the Electronic Data Capture (EDC) system will also be updated to collect data associated with suspected anaphylaxis. As with all study-related data, thorough source documentation should be maintained to support the EDC data.

The Study Drug Dose, Mode of Administration and Administration Rate

Please note that the following clarification from Administrative Letter #1 dated 22 January 2016 should refer to all three protocols TV48125-CNS-30049/50/51 rather than just TV48125-CNS-30049 as noted:

The Study Drug Dose, Mode of Administration and Administration Rate section of the synopsis currently notes that "All study drugs will be administered by a qualified clinic staff member separate from the staff member(s) responsible for collecting safety and efficacy information from the patients." A 'separate staff member' is not required. Drug may be administered by any qualified clinic staff member. This language will be updated in the next protocol amendment.

If you have any questions, please contact your CRA or the Teva [REDACTED]

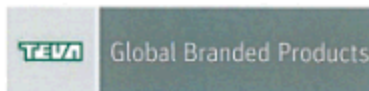
[REDACTED] or [REDACTED]

Sincerely,

[REDACTED]

Teva Pharmaceuticals

17.3. Administrative Letter Dated 22 January 2016



22 January 2016

Re: Administrative Change to the following protocols:

TV48125-CNS-30049 dated 21 October 2015

TV48125-CNS-30050 dated 21 October 2015

TV48125-CNS-30051 dated 02 November 2015

The purpose of this administrative letter is to clarify the following sections of the protocols:

The Study Drug Dose, Mode of Administration and Administration Rate- Protocol TV48125-CNS-30049 only:

The Study Drug Dose, Mode of Administration and Administration Rate section of the synopsis currently notes that "All study drugs will be administered by a qualified clinic staff member separate from the staff member(s) responsible for collecting safety and efficacy information from the patients." A 'separate staff member' is not required. Drug may be administered by any qualified clinic staff member. This language will be updated in the next protocol amendment.

6.5 EuroQol-5 Dimension Questionnaire- Protocols TV48125-CNS-30049/50/51:

The current protocol notes using a scale of 1 to 3. However, we are using the EQ5D-5L, which is a rating scale of 1 to 5 where 1=no problems, 2=slight problems, 3=moderate problems, 4= severe problems, 5=extreme problems. The database reflects the correct questionnaire and responses. This language will be updated in the next protocol amendment.

6.6 Patient Global Impression of Change Scale- Protocols TV48125-CNS-30049/50/51:

The current protocol notes that the 7-point scale is from -3 to 3. However, the 7-point rating scale is from 1 ("no change (it got worse)") to 7 ("a great deal better"). The database reflects the correct responses. This language will be updated in the next protocol amendment.

7.3 Clinical Laboratory Tests- Protocol TV48125-CNS-30049/50/51:

The current protocol notes that atypical lymphocytes will be analyzed, but this will not be performed. Additionally, direct and indirect bilirubin will be performed on the chemistry sample at all visits where a chemistry panel is specified. These changes will not affect the blood volume required from the patient. This language will be updated in the next protocol amendment.

If you have any questions, please contact your CRA or the Teva

[REDACTED]

or

[REDACTED]

Sincerely yours,

[REDACTED]

APPENDIX A. PREVENTIVE MEDICATIONS ALLOWED FOR THE DURATION OF THE STUDY

Preventive migraine medications allowed for up to 30% of patients for the duration of the study specifically include the following (if they were previously prescribed for migraine or for another indication):

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

APPENDIX B. DISALLOWED MEDICATIONS FOR THE DURATION OF THE STUDY

Preventive migraine medications/treatments disallowed for at least 70% of patients for the duration of the study specifically include the following:

- beta-blockers: atenolol, propranolol, metoprolol, nadolol, and timolol
- calcium channel blocker/benzocycloheptene: flunarizine and pizotifen
- antidepressants: amitriptyline, venlafaxine, nortriptyline, and duloxetine
- anti-epileptic medications: topiramate, valproate, carbamazepine, and divalproate
- angiotensin receptor blocker: candesartan and lisinopril
- onabotulinumtoxinA: botox
- triptans/ergots: used as preventive therapies for migraine
- NSAIDs: used as preventive therapy for migraine or on a daily basis for other indications
- devices for migraine prophylaxis
- nerve blocks in the head and neck

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

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

**APPENDIX C. NATIONAL INSTITUTES OF HEALTH PATIENT
EDUCATION GUIDELINES OF JUNE 2012**

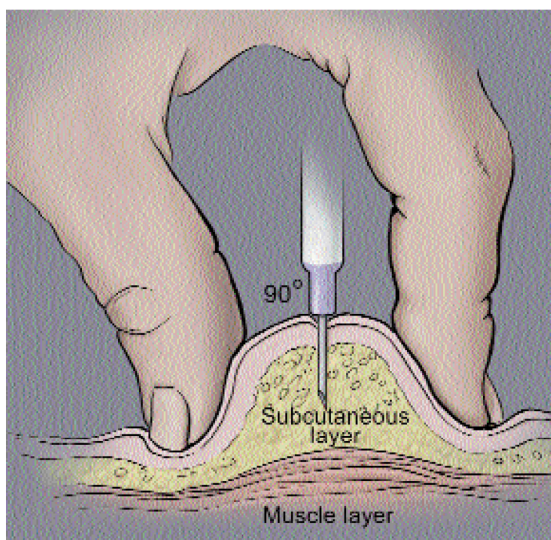
Patient Education

Clinical Center
NATIONAL INSTITUTES OF HEALTH

Giving a subcutaneous injection

What is a subcutaneous injection?

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



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

Why are subcutaneous injections given?

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

Preparing to give medication

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

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

Medication

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

Syringe or pen and needle

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

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

Drawing up medication

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

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

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

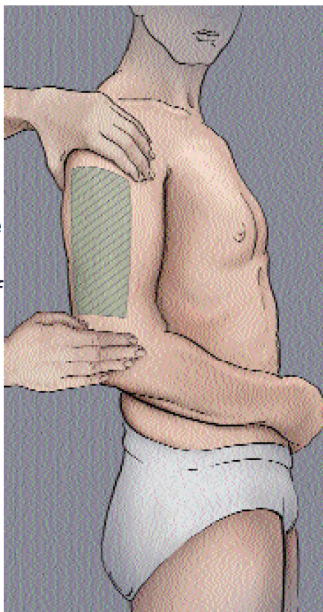
Note: It is important to eliminate large air bubbles because they take up space needed for the medication, and they may cause pain or discomfort when injected.
16. After removing the bubbles, check the dose of medication in the syringe to be sure you have drawn up the correct amount.

If using a pen, skip steps 5 to 16. Do the following:
 - a. Attach needle to pen by cleaning the top with alcohol and screwing on the needle.
 - b. Dial in your prime volume (usually 0.02 mL) using the manufacturer’s directions.
 - c. With pen needle pointed up, push the injection button completely. You should see a drop or stream of liquid. If you do not, repeat priming steps until this occurs.
 - d. Dial in prescribed dose of medication.
17. After the medication is correctly drawn up, carefully replace the needle cap to prevent contamination.

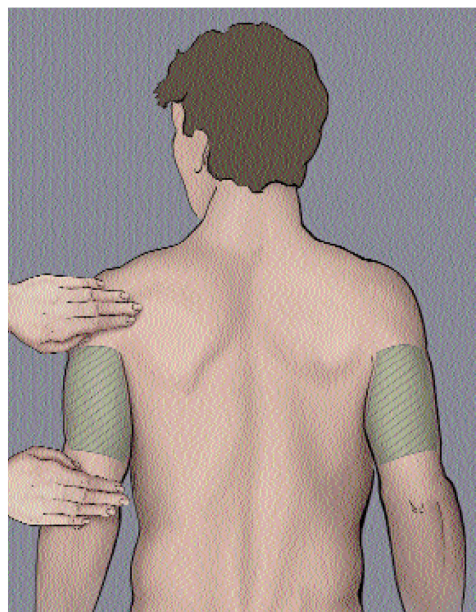
Locating injection sites

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

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

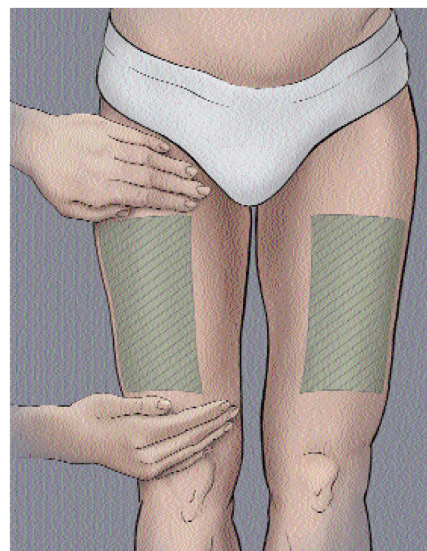


Injection sites on the side of the arm.



Injection sites on the back of the arm.

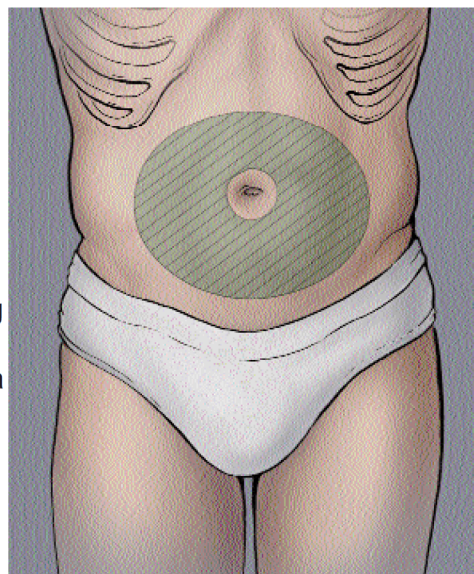
2. To locate injection sites on the thighs, sit down, place your hand above the knee, and draw an imaginary line above it. Place your hand at the uppermost part of the thigh and draw an imaginary line below your hand. Draw an imaginary line down the outer side of the leg and down the center front of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



Injection sites on the front of the thigh.

Rotating injection sites

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



Injection sites on the abdomen

Preparing the skin

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

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

Giving the injection

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

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

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

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

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

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

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

7. As the needle is pulled out of the skin, gently press a 2 x 2 gauze onto the needle insertion site. Pressure over the site while removing the needle prevents skin from pulling back, which may be uncomfortable. The gauze also helps seal the punctured tissue and prevents leakage.
8. If instructed to do so, press or rub the site for a few seconds.
9. It is not serious if you notice blood at the site after the needle is removed. You may have nicked a surface blood vessel when you injected, and blood is following the needle track out to the surface. Simply press the site with a 2 x 2

gauze pad. Also, a small amount of clear fluid may appear at the site. This may be medication that is following the needle track to the surface. Again, apply pressure using a 2 x 2 gauze pad.

If using a pen:

Untwist needle on the pen and safely dispose the needle. Replace pen cap and store as instructed.

Safe needle disposal

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

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

Medication
Dose
Schedule
Primary Nurse
Phone
Physician
Phone

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

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

National Institutes of Health Clinical Center
Bethesda, MD 20892

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

6/2012



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APPENDIX D. ICHD-3 DIAGNOSTIC CRITERIA

For further details, refer to [Classification Committee of the IHS, 2013](#).

1.1 Migraine without Aura

- a. at least 5 attacks fulfilling criteria B through D
- b. headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)
- c. headache has at least 2 of the following 4 characteristics:
 - unilateral location
 - pulsating quality
 - moderate or severe pain intensity
 - aggravation by, or causing avoidance of, routine physical activity (eg, walking or climbing stairs)
- d. during headache, at least 1 of the following:
 - nausea and/or vomiting
 - photophobia and phonophobia
- e. not better accounted for by another ICHD-3 diagnosis

1.2 Migraine with Aura

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

APPENDIX E. GUIDANCE ON SAFETY MONITORING

Guidance on Monitoring Patients with Elevated Liver Function Tests

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

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

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

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

Confirmation is required prior to study drug discontinuation in cases of elevation of either ALT or AST $\geq 3\times$ ULN (Note: In cases of elevation of ALT or AST $\geq 8\times$ the ULN, no confirmation is required prior to study drug 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 and direct 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 patient regarding symptoms.

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

- the baseline value was within the normal range and ALT or AST is still $\geq 3\times$ the ULN
- the baseline value was above the ULN and ALT or AST is $\geq 2\times$ the baseline value

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

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

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

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

- Alanine aminotransferase, AST, GGT, ALP, total 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 ($\geq 3\times$ the ULN in case baseline was within the normal range or $\geq 2\times$ the ULN in case the baseline value was above ULN but still $<5\times$ the ULN) persist further, the patient will be followed according to the investigator's discretion, but a blood sample for ALT, AST, GGT, ALP, and total and direct bilirubin should be sent to the central laboratory at least once a month.

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

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

- Alanine aminotransferase, AST, GGT, ALP, total 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 $\geq 8\times$ the ULN

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

- The study drug 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 study drug will be discontinued immediately:

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

Follow-Up of Liver Enzymes After Stopping Rules Are Met

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

APPENDIX F. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

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

- a. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **AND AT LEAST ONE OF THE FOLLOWING**
 - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
 - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
- b. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):
 - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
- c. Reduced BP after exposure to known allergen for that subject (minutes to several hours):
 - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

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