Statistical Analysis Plan

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

Study Number TV48125-CNS-30082

NCT04464707

SAP Approval Date: 20 December 2024

Statistical Analysis Plan with Amendment 02

Trial TV48125-CNS-30082 with Protocol Amendment 09

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

Phase 3

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Amendment 02 Approval Date: 20 December 2024

Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Trial No.: TV48125-CNS-30082

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

Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

Amendment: 02

Author: [redacted]

Approver: [redacted] **Date**

Approver: [redacted] **Date**

Executed signature pages are maintained separately within the Trial Master File

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AMENDMENT HISTORY

The Statistical Analysis Plan for trial TV48125-CNS-30082 (trial protocol with amendment 09 dated 24 September 2023) has been amended and reissued as follows:

Version number	Date	Summary of changes	Reason for amendment
02	20 December 2024	Throughout: SAS code removed.	Not required in SAP.
02	20 December 2024	Throughout: Remaining terminology changes (patient to participant, study to trial, study drug to IMP) and also least square mean to least squares mean.	Correction and updates for consistency with protocol amendment 09
02	20 December 2024	Throughout: < 10 changed to <10. Also e.g. change to eg, and i.e. changed to ie,	Minor formatting changes
02	20 December 2024	Throughout: SOP GBP_RD_702 changed to GSD-SOP-702	SOP title updated.
02	20 December 2024	Signature page: Approver names and titles changed	Change in personnel
02	20 December 2024	Section 2.5.2: Text amended to clarify that the SAP and any corresponding amendments will be approved before database lock and subsequent unblinding.	Amended for clarification.
02	20 December 2024	Section 4.5: Font size for the Other region countries increased.	Formatting correction
02	20 December 2024	Section 5.4: Added that MedDRA version 26.0 or higher will be used.	Added for clarification. Not previously included.
02	20 December 2024	Section 5.5: Indication categories related to migraine/headache medications updated.	Correction.
02	20 December 2024	Section 6.2: Migraine specific medications changed to acute medications	Correction
02	20 December 2024	Section 6.2: Text added to clarify that either of the criteria constitute a migraine day	Added for clarification
02	20 December 2024	Section 6.2.1: Text modified and new table 2 added in order to clarify the strategy for handling intercurrent events	FDA request
02	20 December 2024	Section 6.2.1: title updated from 'Primary Efficacy Definition' to 'Primary Estimand'. Text amended to provide a definition of the primary estimand.	Correction and clarification.

Version number	Date	Summary of changes	Reason for amendment
02	20 December 2024	Section 6.2.2: Title updated from 'Primary Efficacy Analysis' to 'Primary Analysis of the Primary Estimand'. Text describing the primary estimand moved to section 6.2.1. Clarified that region in the model is United States or Other. In addition, 'estimates' changed to 'parameters'.	Correction and clarification.
02	20 December 2024	Section 6.2.2: Shapiro Wilk's normality text removed	FDA request
02	20 December 2024	Section 6.2.2: Sentence describing the handling of intercurrent events updated.	To resolve an inconsistency in the first paragraph of this section.
02	20 December 2024	Section 6.2.3.1: 'unconstructed' amended to 'unstructured' and text provided to detail the strategy if the model does not converge. In addition, 'p-values' changed to 'nominal p-values'.	Correction and clarification.
02	20 December 2024	Section 6.2.3.1: Repeated statement added to the model code.	Previously missing
02	20 December 2024	Section 6.2.3.2: The following row added to the model: VAR TRTMI SEX PS BMU REGION WEIGHT V0 V1 V2 V3;	Previously missing
02	20 December 2024	Section 6.2.4: Text amended to clarify the subgroup analysis.	Amended for clarification
02	20 December 2024	Section 6.2.4: Title changed from 'Sub-Group Analyses' to 'Subgroup Analyses'. In addition, text added to clarify that the actual stratification will be used in the analyses.	Correction and clarification.
02	20 December 2024	Section 6.2.4: Deletion of 'participants receiving 2 preventive medications from protocol Appendix C' subgroup.	No longer required.
02	20 December 2024	Section 6.3.2: Shapiro Wilk's normality text removed	FDA request
02	20 December 2024	Section 6.3.2: Addition of age subgroup analysis of the secondary endpoints.	Not previously included. Required for Regulatory purposes
02	20 December 2024	Section 6.3.2: Text updated to state that for the logistic regression analysis, difference from placebo will also be added.	Added for clarification. Not previously included.

Version number	Date	Summary of changes	Reason for amendment
02	20 December 2024	Section 6.4.2.1: Text of 'odds ratio and p-value for the treatment comparison' changed to 'odds ratio, difference from placebo and nominal p-value for the treatment comparison'.	Correction and clarification.
02	20 December 2024	Section 7: Bulleted points changed to being numbered 1-6 and the suffix "for the TEV-48125 treatment group versus the placebo treatment group" added	Added for clarification
02	20 December 2024	Section 8.2: Duration of exposure text updated.	Addition of text to clarify the handling of participants who discontinued but were not lost to follow up.
02	20 December 2024	Section 8.6: Renumbering of tables 2 and 3 to tables 3 and 4 respectively due to insertion of new table 2 in section 6.2.1,	Due to addition of new Table 2 in Section 6.2.1.
02	20 December 2024	Section 8.8: Table 4 renumbered to table 5 due to insertion of new table 2,	Due to addition of new Table 2 in Section 6.2.1.
02	20 December 2024	Section 8.10: Indication categories related to migraine/headache medications updated.	Correction.
02	20 December 2024	Section 8.10: Sentence describing the summary of concomitant medications updated to specify that in addition to being by therapeutic class and preferred term, the summary will also be by treatment group.	Added for clarification. Not previously included,
02	20 December 2024	Section 12: Text added to state that any such analysis will be performed and reported separately	Added for clarification. Not previously included.
02	20 December 2024	Section 14: Two references added; Kenward M and Roger J, Liang K and Zeger SL.	Not previously included.
02	20 December 2024	Section 15: Subgroup analysis of 'Participants receiving 2 preventive medications from protocol Appendix C' added.	This subgroup analysis is no longer required.
02	20 December 2024	Section 15: Text added to clarify that participants from one trial site will be excluded from all analysis sets due to GCP non-compliance.	Not previously included.

Version number	Date	Summary of changes	Reason for amendment
02	20 December 2024	Appendix B: Derivation updated for migraine days and minor formatting update to headache days of at least moderate severity	For consistency with previous studies.
01	12 October 2023	Throughout: Terminology changes (patient to participant, study to trial, study drug to IMP, Fremanezumab to test IMP, placebo to placebo IMP) and modification of endpoint wording.	Consistency with protocol amendment 09.
01	12 October 2023	IMP (investigational medicinal product) added to List of Abbreviations.	Added for clarification. Not previously included.
01	12 October 2023	Section 1.2: Addition of 'To further explore efficacy and safety parameters' to the exploratory objectives.	Consistency with protocol amendment 09.
01	12 October 2023	Section 2.1: Estimated study duration changed from 48 months to 75 months.	Consistency with protocol amendment 09.
01	12 October 2023	Section 2.1: Text describing potential increase to sample size removed.	Consistency with protocol amendment 09.
01	12 October 2023	Section 2.1: Study sample size text amended.	Consistency with protocol amendment 09.
01	12 October 2023	Section 2.1: Enrollment target text updated.	Consistency with protocol amendment 09.
01	12 October 2023	Section 2.4: Sample size and enrollment target text updated.	Consistency with protocol amendment 09.
01	12 October 2023	Section 2.5.1: Text amended; there will no longer be an interim analysis performed in this trial.	Consistency with protocol amendment 09.
01	12 October 2023	Section 3.4: Modification to definition of Per-Protocol Analysis Set.	Consistency with protocol amendment 09.
01	12 October 2023	Section 4.1; post-baseline changed to postbaseline.	Consistency with other occurrences.
01	12 October 2023	Section 4.2: Text referring to calculating the change in weekly values and headache days removed	Sensitivity analyses relating to weekly values removed. Calculation of headache days not required.
01	12 October 2023	Section 4.2: Acute migraine-specific medication use changed to acute headache medication use (2 occurrences).	Correction.
01	12 October 2023	Section 4.2: NSAIDs and paracetamol added to the list of medications and migraine-specific removed.	Correction.
01	12 October 2023	Section 4.2: [redacted]	[redacted]

Version number	Date	Summary of changes	Reason for amendment
01	12 October 2023	Section 4.3: Text added to clarify that participants who have < 10 days of e-diary data will be excluded from the full analysis set.	Not previously included.
01	12 October 2023	Section 4.3: Text referring to calculating the change in weekly values removed	Sensitivity analyses relating to weekly values removed.
01	12 October 2023	Section 4.4: by-visit changed to by visit (2 occurrences).	Correction.
01	12 October 2023	Section 4.4: Clarification regarding the handling of missing dosing days.	Not previously included.
01	12 October 2023	Section 4.4: Cross-reference for Section 8.9 added.	Not previously included.
01	12 October 2023	Section 4.4: Text referring to calculating weekly visit windows.	Sensitivity analyses relating to weekly values removed.
01	12 October 2023	Section 5.3: Addition of text to highlight that there will be a demography summary table produced for each of the analysis sets.	Additional information provided.
01	12 October 2023	Section 5.3: Text referring to analysis of baseline factors removed.	No longer required.
01	12 October 2023	Section 5.5: WHO Drug changed to WHODrug.	Correction.
01	12 October 2023	Section 6.1: Text referring to weekly values removed	Sensitivity analyses relating to weekly values removed.
01	12 October 2023	Section 6.2: Inclusion of NSAIDs and paracetamol and removal of the word migraine from the list of specific medications.	Correction.
01	12 October 2023	Section 6.2.2: Removal of the word ‘each’ when referring to the estimated difference of TEV-48125 dose vs. placebo.	Correction.
01	12 October 2023	Section 6.2.2: Addition of baseline weight group as a fixed effect to the ANCOVA model and minor amendments to the example SAS code.	Minor corrections to SAS code and the addition of baseline weight group in order that the effects may be controlled for.
01	12 October 2023	Section 6.2.2: Addition of stratification factor text.	Clarification that the stratification factors (as randomized) will be used in this analysis model.

Version number	Date	Summary of changes	Reason for amendment
01	12 October 2023	Section 6.2.2: Addition of text regarding the assessment of the residuals from the ANCOVA model.	Clarification that in addition to ANCOVA, the Wilcoxon rank-sum test will be conducted and the most appropriate analysis selected once the normality of the residuals from the ANCOVA model have been assessed.
01	12 October 2023	Section 6.2.3.1: Addition of stratification factor text.	Clarification that the stratification factors (as randomized) will be used in this analysis model.
01	12 October 2023	Section 6.2.3.1: Addition of baseline weight group as a fixed effect to the MMRM model and minor amendments to the example SAS code.	Minor corrections to code and the addition of baseline weight group in order the effects may be controlled for.
01	12 October 2023	Section 6.2.3.1: TV48125 changed to TEV-48125.	Correction.
01	12 October 2023	Section 6.2.3.2: Added text to clarify that the Multiple Imputation method will assume a missing not at random mechanism.	Not previously included.
01	12 October 2023	Section 6.2.3.2: (X<10) text changed to (X<28).	Correction.
01	12 October 2023	Section 6.2.3.2: SAS PROC MI procedure text changed to specify that 100 complete datasets rather than 10 complete datasets will be produced.	Consistency with other studies.
01	12 October 2023	Section 6.2.3.2: Added example SAS code for the PROC MI and the PROC MIANALYZE procedures.	Not previously included.
01	12 October 2023	Section 6.2.3.2: Amended text from SAS MIANALYZE to SAS PROC MIANALYZE.	PROC previously omitted in error.
01	12 October 2023	Section 6.2.3.3: Addition of a sensitivity analysis.	Additional sensitivity analysis to assess the effect of actual rather than as randomized stratification factors in the ANCOVA model.
01	12 October 2023	Section 6.2.4: Addition of weight subgroup.	To investigate the effects of weight groups on the primary endpoint.
01	12 October 2023	Section 6.2.4: Addition of puberty status subgroup.	To investigate the effects of puberty status groups on the primary endpoint.
01	12 October 2023	Section 6.2.4: Addition of text regarding the model for the subgroup analyses.	Clarification that the subgroup analyses will be performed using a BY statement in the MODEL statement.

Version number	Date	Summary of changes	Reason for amendment
01	12 October 2023	Section 6.2.4: Deletion of 'patients receiving alternative preventive medications that belong to the same classes but are not listed in protocol Appendix C' subgroup.	No longer required.
01	12 October 2023	Section 6.3: Reformatting of subsection headings.	Correction.
01	12 October 2023	Section 6.3.2: Addition of stratification factor text (2 occurrences).	Clarification that the stratification factors (as randomized) will be used in these analysis models.
01	12 October 2023	Section 6.3.2: Weight group added as a fixed effect.	Correction.
01	12 October 2023	Section 6.3.2: Text amended since the sentence is referring to baseline preventive migraine medication use.	Correction.
01	12 October 2023	Section 6.3.2: Addition of example SAS code for the logistic regression analysis.	Example code was not previously included.
01	12 October 2023	Section 6.3.2: Additional text added regarding PedsQL psychosocial health summary score and physical health summary score.	Clarification that in addition to the PedsQL total score, also the PedsQL psychosocial health summary score and the physical health summary score will be analyzed.
01	12 October 2023	Section 6.3.2: p value changed to p-value.	Consistency with other occurrences.
01	12 October 2023	Section 6.4: Reformatting of subsection headings.	Correction.
01	12 October 2023	Section 6.4.1.1: ≥4 hours changed to ≥2 hours, ergots or triptans changed to ergots, triptans, NSAIDs or paracetamol (2 occurrences).	Correction.
01	12 October 2023	Section 6.4.1.1: Acute migraine-specific medication use changed to acute headache medication use (4 occurrences).	Correction.
01	12 October 2023	Section 6.4.1.1: Text referring to weekly values removed	Sensitivity analyses relating to weekly values removed.
01	12 October 2023	Section 6.4.1.4: Addition of baseline weight group as a fixed effect to the analysis model.	Addition of baseline weight group in order the effects may be controlled for.
01	12 October 2023	Section 6.4.1.4: Text referring to weekly efficacy values removed	Sensitivity analyses relating to weekly values removed.
01	12 October 2023	Section 6.4.1.5: Addition of stratification factor text.	Clarification that the stratification factors (as randomized) will be used in this analysis model.

Version number	Date	Summary of changes	Reason for amendment
01	12 October 2023	Section 7: p value changed to p-value.	Consistency with other occurrences.
01	12 October hours2023	Section 7: Proportion of patients developing ADAs removed from the fixed-sequence testing procedure.	Not required in the testing procedure.
01	12 October 2023	Section 8.4: Definition of adverse events of special interest amended to remove COVID-19.	Consistency with protocol amendment 09.
01	12 October 2023	Section 8.4: Added definition of adverse device effect and details of the associated listings and summary tables which will be produced.	Consistency with protocol amendment 09.
01	12 October 2023	Section 8.6: endpoint changed to Last Assessment.	Correction.
01	12 October 2023	Section 8.6, table 3: Paediatric changed to Pediatric.	Correction.
01	12 October 2023	Section 8.6, table 3: Addition of the potentially clinically significant criteria for INR.	Added for clarification. Not previously included.
01	12 October 2023	Section 8.6, table 3: Removal of one of the UNR footnotes.	UNR Footnote duplicated in error.
01	12 October 2023	Section 8.8: endpoint changed to Last Assessment.	Correction.
01	12 October 2023	Section 8.8, table 4: Paediatric changed to Pediatric.	Correction.
01	12 October 2023	Section 8.10: 'Up to 30% of patients will be allowed to remain on no more than 2 preventive migraine medications' changed to 'Approximately 30% of participants will be allowed to remain on no more than 2 preventive migraine medications (listed in protocol Appendix C).'	Consistency with protocol amendment 09.
01	12 October 2023	Section 8.10: 70% of patients changed to approximately 70% of participants.	Consistency with protocol amendment 09.
01	12 October 2023	Section 13: Planned Interim Analysis section removed.	Consistency with protocol amendment 09.
01	12 October 2023	Section 15: Section added.	Not previously included.
01	12 October 2023	Appendix B: For migraine day, removed 'EM' from title and changed Option 1, Part 1, ≥4 hours to ≥2 hours.	Correction.
01	12 October 2023	Appendix B: Headache day of at least moderate severity.	Added for clarification. Not previously included.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	antidrug antibody
AE	adverse event
ANCOVA	analysis of covariance
CM	chronic migraine
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-suicide severity rating scale
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
FAS	full analysis set
IMP	investigational medicinal product
IRT	interactive response technology
ITT	intent-to-treat
LS	least squares
MedDRA	medical dictionary for regulatory activities
MMRM	mixed-effects repeated measures model
NSAID	non-steroidal anti-inflammatory drug
PD	protocol deviations
PedMIDAS	pediatric migraine disability assessment questionnaire
PedsQL	pediatric quality of life inventory
PFS	pre-filled syringe
[redacted]	[redacted]
PT	preferred term
R&D	research and development
RTSM	randomization and trial supply management
SAP	statistical analysis plan
SAS®	statistical analysis system
sc	subcutaneous

Abbreviation	Term
SD	standard deviation
SE	standard error
SOC	system organ class
SOP	standard operating procedure
WHO	world health organization

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. Trial TV48125-CNS-30082, (A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Chronic Migraine in Pediatric Patients 6 to 17 Years of Age), and was written in accordance with GSD-SOP-702 (Statistical Analysis Plan).

The reader of this SAP is encouraged to read the trial protocol for details on the conduct of this trial, the operational aspects of clinical assessments, and the timing for completing the participation of a participant in this trial.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (eg, other endpoints). When differences exist in descriptions or explanations provided in the trial protocol and this SAP, the SAP prevails; the differences will be explained in the Clinical Study Report (CSR).

1. TRIAL OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Trial Objectives and Endpoints

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

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

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

1.2. Exploratory Objective and Endpoints

[redacted]

- [redacted]
- [redacted]
- [redacted]

2. TRIAL DESIGN

2.1. General Design

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

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

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

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

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

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

The enrollment target is approximately 278 randomized participants in total.

The trial consists of a screening visit, a 28-day baseline period, and a 12-week (84-day) treatment period, including a final evaluation at week 12 (end-of-treatment [EOT] visit, approximately 4 weeks [28 days] after the final dose of IMP).

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

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

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

for safety and ADA assessments approximately 5 months (150 days [5 half-lives]) after receiving the last dose of IMP.

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

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

Figure 1: Overall Trial Schematic Diagram

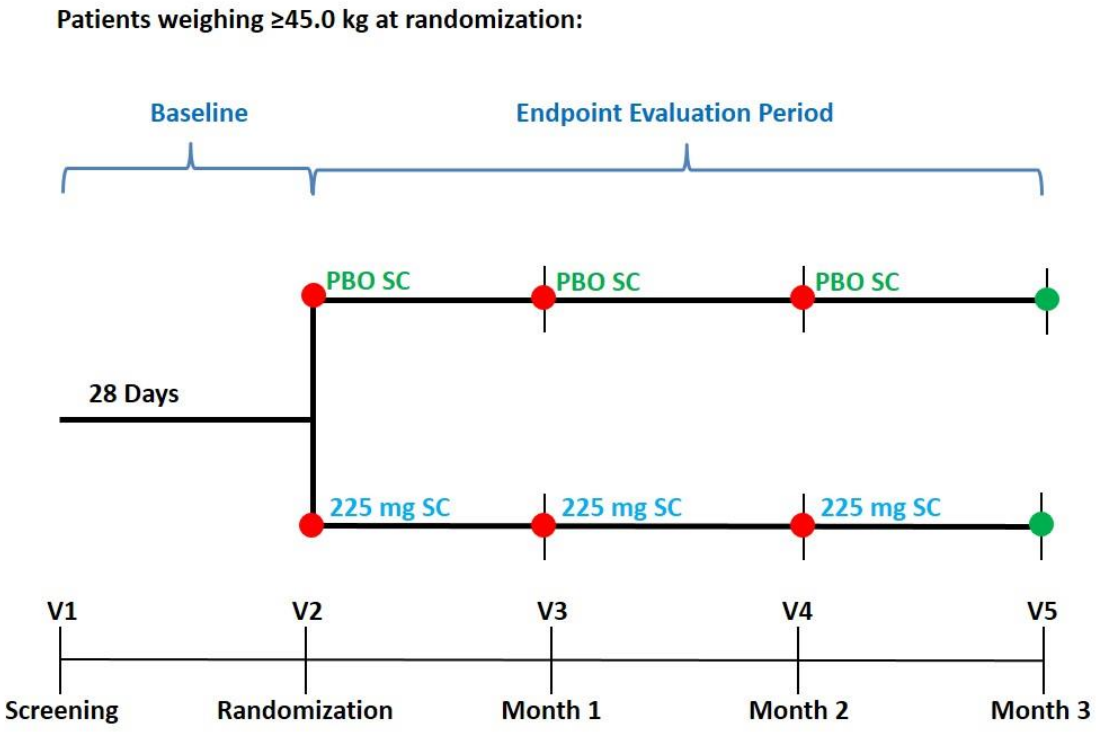
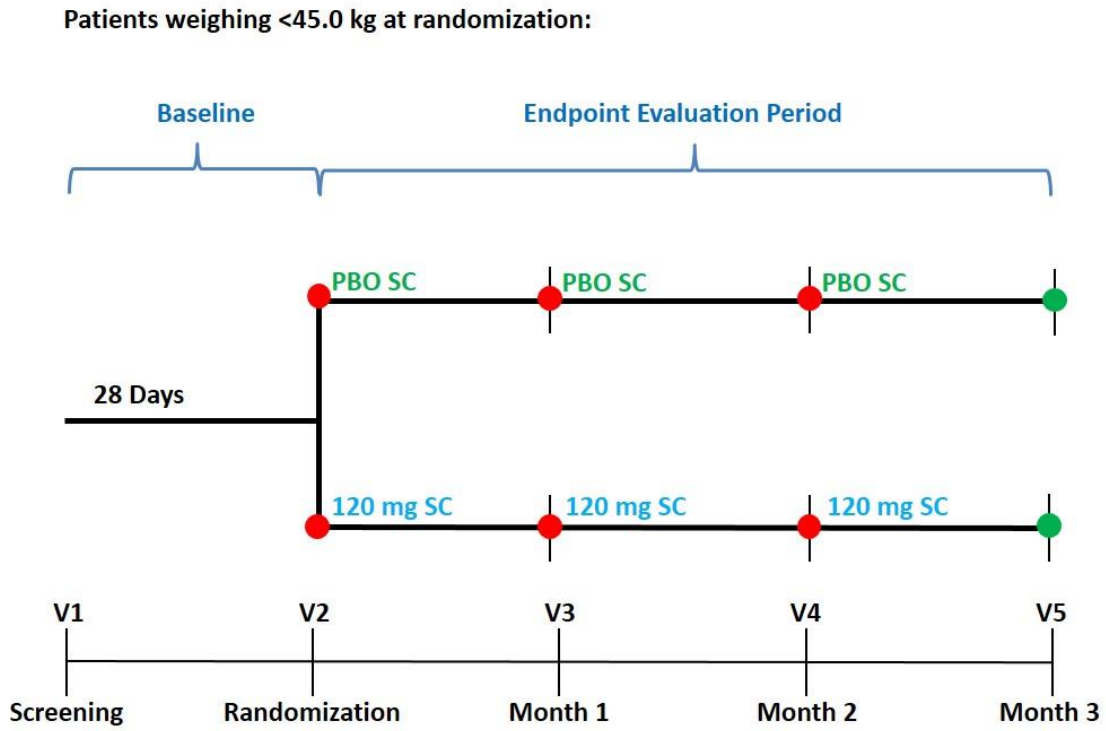


Figure 1: Overall Trial Schematic Diagram (Continued)



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

2.2. Randomization and Blinding

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

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

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

In the event of an emergency, it will be possible to determine to which treatment group and dose the participant has been allocated by accessing the Randomization and Trial Supply Management (RTSM) system. All investigational centers will be provided with details of how to access the system for code breaking at the start of the trial. The Medical Monitor or equivalent should be notified following unblinding. Any unblinding of the IMP performed by the Investigator must be recorded in the source documents.

2.3. Data Monitoring Committee

There will be no Data Monitoring Committee in this trial.

2.4. Sample Size and Power Considerations

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

The enrollment target is approximately 278 participants in total.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

There will be no interim analysis in this trial.

2.5.2. Final Analyses and Reporting

All analyses identified in this SAP will be performed after the end of trial as defined in the trial protocol. This SAP and any corresponding amendments will be approved before database lock and subsequent unblinding, in accordance with GSD-SOP-702 (Statistical Analysis Plan).

Any exploratory analyses completed to support trial analyses, which are not identified in this SAP, will be documented and reported in appendices to the CSR.

3. ANALYSIS SETS

3.1. Intent-to-Treat Analysis Set

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

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

3.2. Safety Analysis Set

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

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

3.3. Full Analysis Set

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

3.4. Per-Protocol Analysis Set

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

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. Descriptive statistics for categorical variables including participant counts, percentages and missing category will be displayed as appropriate.

Summaries of potentially clinically significant abnormal values will include all postbaseline values (including scheduled, unscheduled, and early termination visits).

4.2. Specification of Baseline Values

Participants will complete electronic headache diary entries daily for the 28-day run-in period, subjectively rating their headaches as mild, moderate, or severe and enter headache information (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute headache medication use) about the previous day into the electronic headache diary device. If the participant is unable to complete the diary themselves then a parent/caregiver will complete the diary for them. Headache severity is collected in the diary on an 11-point numerical rating scale where mild is defined as a rating of 1-3, moderate as 4-6 and severe as 7-10. If the run-in period is greater or less than 28 days, the baseline values for calculating the change from baseline of the monthly values of the efficacy variables will be normalized to **28** days.

The efficacy baseline values during the 28-day run-in period derived from the e-diary include

- total number of migraine days
- total headache days of at least moderate severity
- total number of days of use of any acute headache medication
- total headache days of any severity
- total number of days of use of acute headache medications (triptans and ergot compounds, NSAIDs or paracetamol) for the group of participants who use acute headache medications at baseline
- total number of days with nausea or vomiting
- total number of days with photophobia and phonophobia

Other efficacy baseline values that will be measured on day 1 before the 1st IMP administration include

- disability score, as measured by the PedMIDAS assessment (Appendix C)
- quality of life, as measured by the PedsQL questionnaire (Appendix D)

Otherwise, baseline value will be the last non-missing value prior to the 1st dose of IMP, unless otherwise noted.

4.3. Handling Withdrawals and Missing Data

If a participant has ≥10 days of the e-diary data after 1st dose of IMP, his/her monthly average number of days/hours of efficacy variables ***during the 12-week period*** or monthly number of days/hours of efficacy variables ***during the 4-week period*** will be prorated to **28** days. Participants who have <10 days/hours of diary data will be excluded from the full analysis set.

Multiple imputation (MI) method will be applied on the primary variable as sensitivity analyses. The methods will be described in detail in Section 6.2.3.

A participant's monthly number of days/hours of efficacy variables ***during the 4-week period*** after each dose of IMP will be calculated for months 1, 2, and 3. If a participant has missing diary days in a month, the following method will be used to handle the missing data.

- If the participant has 10 or more days of e-diary data for a month, the monthly number of days/hours of efficacy variables will be prorated to **28** days for that month.
- If the participant has less than 10 days of e-diary data for a month, the monthly number of days/hours of efficacy variables will be considered as missing.

4.4. Trial Days and Visits

Trial days will be numbered relative to the 1st day of IMP administration. The start of treatment (visit 2 or day 1) is defined as the date on which a participant takes the 1st dose of IMP, as recorded on the IMP administration CRF. Days will be numbered relative to IMP start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the start of IMP and day –1 being the day before the start of IMP).

The 4-week (28-day) visit windows for the e-diary based efficacy endpoints will be determined based on the actual dosing day. The run-in phase is defined as day -28 to -1 before the 1st injection on day 1. Treatment phase including month 1, 2 and 3 is from the beginning of the 1st injection of IMP to visit 5/day 84 or the end of treatment visit. The 3-month visit windows are separated by each dosing date/time. Month 1 is from the date/time of the 1st dose of IMP administration on day 1 to the date/time just before the 2nd dose. Month 2 is from the date/time of the 2nd dose to the date/time just before the 3rd dose. Month 3 is from the date/time of the 3rd dose to the end of the trial on day 84 approximately. If the Month 2 or Month 3 dosing day is missed, then the dosing day is considered to be previous dosing day +28 days.

Throughout this document, all by month efficacy summaries for the headache data will refer to these visit windows.

For all other by visit summaries, except for triplicate ECG assessments (see Section 8.9 for further details), if there are multiple assessments at a postbaseline visit then the last non-missing assessment at that visit will be used for the summary. This includes assessments at the scheduled and unscheduled visits.

Last Assessment for analyses and summaries is the last observed postbaseline data. For participants who withdraw from the trial, data at the early termination visit will be excluded from the by-visit summaries but will be included in the endpoint summaries.

4.5. Region of Pooled Countries

The countries will be pooled to 2 regions as described below in Table 1 for analysis purpose.

Table 1: Pooled Countries by Region

Region	Country
United States	United States
Other	Poland, Canada, Spain, Israel, Finland, Germany, Italy, The Netherlands

5. TRIAL POPULATION

5.1. General

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

For continuous variables, descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be provided. For categorical variables, participant counts and percentages will be provided. Categories for missing data will be presented if necessary.

5.2. Participant Disposition

Participants screened, screening failures, and the reasons the participants were not randomized will be summarized only for the overall group using participant counts.

Participants randomized (ie, in the ITT set), participants randomized but not treated, participants in the safety analysis set, full analysis set and per-protocol analysis set, participants who complete the trial, and participants who withdraw from the trial will be summarized using descriptive statistics. Participants who withdraw from the trial will also be summarized using descriptive statistics by reason for withdrawal. The denominator for calculating the percentages will be the number of ITT population.

5.3. Demographics and Baseline Characteristics

The demographic data including date of birth (or year of birth), sex, country, ethnicity, and race will be collected at the screening after the participant signs informed consent. Participants' demographics and baseline characteristics including age, age in categories, sex, country, ethnicity and race, race by subgroups, region, body weight, body weight in categories, height, body mass index, years of migraine, migraine with aura, time since initial migraine diagnosis (years), protocol version, concomitant preventive medication use for migraine and any triptans/ergots during baseline will be summarized for ITT population. The demographic characteristics will be summarized for each of the analysis sets.

The baseline e-diary efficacy variables, baseline PedMIDAS scores and PedsQL scores will be summarized by treatment group for the ITT population.

5.4. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher. The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term (PT). Participants are counted only once in each PT and SOC category. Summaries will be presented by treatment group and for all participants.

5.5. Prior Therapy and Medication

Any prior therapy, medication, or procedure a participant has had before IMP administration will be recorded on the CRF. Trade name or INN, indication, and dosage will be recorded. The

sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHODrug).

The incidence of prior therapies and medications will be summarized using descriptive statistics by therapeutic class and PT. Participants are counted only once in each therapeutic class category, and only once in each PT category. Prior therapies and medications will include all medications taken and therapies administered before the 1st day of IMP administration.

The subset of prior medications will be summarized for the following categories.

- Medication from Appendix C for migraine/headache
- Medication from Appendix C for other reason than Migraine/Headache
- Migraine/headache prevention medication not from Appendix C
- NSAIDs for migraine/headache
- NSAIDs for other reason than migraine/headache
- Triptan for migraine/headache
- Triptan for other reason than migraine/headache
- Ergot for migraine/headache
- Ergot for other reason than migraine/headache
- Medication used for symptoms during migraine attack other than pain
- Other

5.6. Electrocardiography

Electrocardiogram findings by Investigator (normal, abnormal not clinically significant and abnormal clinically significant) and by Cardiologist (normal, abnormal) overall and at last visit will be summarized.

5.7. Physical Examinations

Physical examinations results will be listed. Participants with at least 1 abnormal finding (overall) and abnormal findings for each category will be summarized.

5.8. Childbearing Potential and Methods of Contraception

All participants must be of non-childbearing potential or be using highly effective contraception as defined in the protocol. Information related to childbearing potential will be collected and listed.

Methods of contraception will be collected and this data will be listed.

5.9. Trial Protocol Violations

Protocol deviations (PD) will be collected and reviewed by the trial team prior to database lock and will be provided in a data listing. Participants with at least 1 important protocol deviation will be summarized for each category using descriptive statistics.

6. EFFICACY ANALYSIS

6.1. General

The primary efficacy endpoint (and some secondary and exploratory efficacy endpoints) will be derived from headache variables collected daily using an electronic headache diary device.

On each day, the participant or parent/caregiver will be asked to record diary data for the previous 24-hour period. Participants or parents/caregivers who report headache on the previous day will answer questions about the headache (ie, the number of hours with headache, headache severity, presence of associated symptoms, and use of acute migraine medications).

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

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

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

In addition to the headache diary device, the following questionnaires will be used for the assessments of migraine impairment, quality of life and satisfaction of treatment etc. during the trial.

- migraine disability assessment, as measured by the PedMIDAS questionnaire (Appendix C)
- quality of life, as measured by the PedsQL questionnaire (Appendix D)
- [redacted] (Appendix E)

The ***monthly average number of days or hours*** of efficacy variables (eg, migraine days, days of headache with at least moderate severity, days of headache with any severity, total hours of headache with any severity, total hours of headache with at least moderate severity, days of use of any acute headache medications, days with nausea or vomiting, days with photophobia and phonophobia etc.) ***during the 12-week period*** after the 1st dose of IMP will be derived and normalized to **28** days equivalent using the following formula.

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

The ***monthly number of days or hours*** of efficacy variables ***during a 4-week period*** after each dose will be derived and normalized to **28** days equivalent using the following formula, where monthly data separated by each visit of IMP dosing will be used.

$$\frac{\sum Days\ or\ hours\ of\ efficacy\ variable\ during\ the\ 4\ week\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 4\ week\ period} \times 28 \quad (2)$$

The ***baseline values*** will be calculated using all data collected in the run-in period, ie,

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

The ***percentage of reduction*** in the monthly average number of an efficacy variable will be calculated as

$$\frac{baseline\ value - postbaseline\ value}{baseline\ value} \times 100\% \quad (4)$$

where the baseline value is calculated by formula (3) and the postbaseline value in the equation is calculated by formula (1) for the variables ***during the 12-week period*** or by formula (2) for the variables ***during the 4-week period*** after each dose for months 1, 2 and 3.

The FAS will be used for all efficacy analyses unless otherwise specified. Summaries will be presented by treatment group as randomized (test IMP or placebo IMP), unless otherwise noted. Descriptive statistics for all efficacy data will be presented by month or visit as appropriate and over 12-week period.

The primary and secondary endpoints analysis will be repeated for the per-protocol analysis set.

6.2. Primary Efficacy Endpoint and Analysis

A migraine day will be defined as a calendar day (00:00 to 23:59) where the participant reports either of the following:

- A calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of a headache that is accompanied by ≥1 migraine symptom(s)
- A calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with acute headache medications (NSAIDs, paracetamol or triptans and ergot compounds)

The derivation logic is presented in Appendix B.

6.2.1. Primary Estimand

For the primary efficacy objective, the following estimand attributes will be employed:

a. **Treatment**: monthly sc administration of fremanezumab or matching placebo.

b. **Population**: male or female participants between the ages of 6 to 17 years (inclusive) with a clinical history of recurrent headache consistent with the diagnosis of migraine for at least 6 months before screening and a history of ≥15 headache days per month on average during the 3 months prior to screening.

c. **Endpoint**: change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP.

d. **Population-level summary**: difference between the fremanezumab group and the placebo group for the mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP.

The treatment policy strategy will be applied for any intercurrent events including concomitant medication and treatment noncompliance, meaning all observed participant data will be used for assessing the primary estimand regardless of any intercurrent events. The potential intercurrent events and the strategies used to handle them are listed in Table 2

Table 2: Intercurrent Event Strategies

Intercurrent Event	Strategy	Analysis
Concomitant medication noncompliance	Treatment policy	Measurements after intercurrent event will be included in analysis
Treatment noncompliance	Treatment policy	Measurements after intercurrent event will be included in analysis
All other events and protocol deviations	Treatment policy	Measurements after intercurrent event will be included in analysis

As described in Section 4.3 and Section 6.1, if a participant has ≥10 days of e-diary data after 1st dose of IMP, his/her monthly average number of days/hours of efficacy variables during the 12-week period will be prorated to 28 days. Participants who have <10 days of e-diary data will be excluded from the full analysis set.

6.2.2. Primary Analysis of the Primary Estimand

The hypothesis testing for the primary analysis is

$$H_o : \delta_1 = \delta_2 \quad vs \quad H_a : \delta_1 \neq \delta_2$$

where δ_1 and δ_2 are the parameters of mean change from baseline in the monthly average number of migraine days for the TEV-48125 treatment group and the placebo group respectively. The estimated difference of TEV-48125 dose vs. placebo will be tested following the pre-specified fixed sequence as specified in Section **7**.

An analysis of covariance (ANCOVA) method will be applied for the primary analysis. The model will include treatment, sex, puberty status, region (United States or Other (Table 1)), weight category (<45.0kg or ≥45 kg) and baseline preventive migraine medication use (yes/no) as fixed effects and the baseline number of migraine days as a covariate. The stratification factors (as randomized) will be used in the model. The least squares (LS) means for the treatment groups, LS means and corresponding 95% confidence intervals for the treatment differences (TEV-48125 – placebo), and associated p-value will be provided.

A hierarchical procedure will be used to control Type 1 error rate, as described in Section 7.

6.2.3. Sensitivity Analysis

6.2.3.1. MMRM Analysis

A mixed-effects repeated measures (MMRM) analysis model will be implemented to estimate the mean change from baseline in the monthly average number of migraine days for the overall 3 months treatment period and by each month to support the primary analysis.

Each participant's monthly number of migraine days ***during the 4-week period*** for month 1, month 2 and month 3 will be calculated by formula (2) in Section 6.1 based on the e-diary responses for that month. If a participant is early terminated or has intermittent missing days and has less than 10 days of e-diary entries for a month, that month's value will be considered as missing as described in Section 4.3.

The MMRM model will include baseline value, treatment, puberty status, sex, region, weight category (<45.0 kg or ≥45.0 kg), baseline preventive migraine medication use (yes/no), month and treatment-by-month interaction as fixed effects, and participant in the repeated statement as a random effect. The stratification factors (as randomized) will be used in the model. The unstructured covariance structure will be used for the repeated observations within a participant. If the model does not converge, then simpler covariance structures with fewer parameters will be used in the following order (stopping at the first converging structure); heterogeneous Toeplitz, Toeplitz, or compound symmetry with a robust sandwich estimator (Liang and Zeger, 1986). For a model based estimator of the covariance (ie, unstructured, heterogeneous Toeplitz, or Toeplitz) for making inferences between treatment groups, especially at a particular visit, the Kenward-Roger degrees of freedom will be employed (Kenward and Roger, 1997).

LS means for the treatment groups, LS means for the treatment differences (TEV48125-48125 - placebo), and corresponding 95% confidence intervals and associated p-values will be calculated by month and for the overall treatment period.

The LS means ±SE of monthly change from baseline values estimated by MMRM will be plotted by month for each treatment group.

A supplementary analysis using the ITT population will also be carried out for the primary efficacy endpoint.

A further supplementary analysis will be performed by week for the first month after baseline to support the primary analysis. The change from baseline (run-in period) in the number of migraine days ***during the 4-week period*** after the 1st dose of IMP will be derived similar to the primary endpoint using only the 1st month diary data.

6.2.3.2. Analysis with Multiple Imputation Method

Multiple imputation (MI) method will be applied to impute the monthly missing data assuming a missing not at random (MNAR) mechanism. The data will be processed by the following steps.

If a participant has partial e-diary data for a month, ie, <10 days of data, that month's value will be considered missing before the MI procedure.

For the participants in the active treatment groups who are early terminated with reasons of adverse event or lack of efficacy, they will be assigned to placebo group so their missing values will be imputed using data from the placebo treated participants.

Run SAS PROC MI procedure to create 100 complete datasets.

Within each imputed data set, for a participant who has partial, say X days (X<28), e-diary data in a month, the monthly value will be replaced by

$$\sum(oberseved\ migraine\ days\ ) + (28 - X) * imputed\ value/28$$

The monthly average number of migraine days ***during the 12-week period*** after the 1st dose of IMP will be the average of month 1, month 2 and month 3 values.

SAS PROC MIANALYZE procedure will be used to find the average number of migraine days during the 12-week period for both treatment groups. It will find the mean and standard errors of both the average number of migraine days and the change from baseline over the 100 datasets.

Each dataset will be analyzed using the same ANCOVA model as described in Section 6.2.2. The LS means and standard errors from each analysis will be output to a SAS data set. SAS PROC MIANALYZE procedure will be used to generate the final LS means (±SE) for the treatment groups and the treatment differences (TEV-48125 – placebo) as well as p-values associated with treatment differences. The 95% confidence intervals for the treatment differences will also be constructed.

The output dataset will contain the estimate of the mean difference and the standard error of the estimate from each of the 100 datasets. SAS procedure, PROC MIANALYZE, will be used to generate an overall p-value and 95% CI for the treatment difference.

6.2.3.3. ANCOVA Analysis

The ANCOVA analysis defined in Section 6.2.2 will be repeated as a sensitivity analysis using the actual stratification factors in the model.

6.2.4. Subgroup Analyses

The ANCOVA method will also be applied to the following subgroups for the change from baseline values in the number of migraine days and the monthly average number of headache days of at least moderate severity.

- participants receiving or not receiving any concomitant preventive treatment at baseline
- participants in different race groups (caucasian, non-caucasian)
- participants by age group (6-11 years, 12-17 years)
- participants by weight group
- participants by puberty status
- participants by sex
- participants by region

The model to be used in exploring the consistency of a treatment effect (ie, TEV-48125 – placebo) across the subgroup levels will have treatment, subgroup, and treatment-by-subgroup interaction as fixed effects, and a baseline covariate that corresponds to the respective endpoint (ie, response variable in the model). For ease of modeling purposes, a comparable cell means

parameterization will be used. Hence when assessing the treatment effect for change from baseline in number of migraine days in the age subgroup, the model will have treatment, age, and treatment-by-age interaction as fixed effects, and baseline number of migraine days as a covariate. Likewise, when assessing the treatment effect for change from baseline in number of migraine days in the weight subgroup, the model will have treatment, weight, and treatment-by weight interaction as fixed effects, and baseline number of migraine days as a covariate. For the by month analyses, MMRM will be performed in a similar manner in which the within subject covariance structure is the same as in Section 6.2.3.1. Actual rather than 'as randomized' stratification values will be used.

The estimated treatment effects at each subgroup level will be based on the least squares means treatment difference at each subgroup level and their corresponding two-sided 95% confidence intervals obtained from each of the respective models. Since there is a continuous covariate in each of these subgroup analyses, the least squares means will need to be adjusted to a common overall baseline value.

The results from the subgroup analysis will be displayed graphically using a forest plot.

6.3. Secondary Efficacy Endpoints and Analysis

The secondary efficacy endpoints are as follows:

- mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP
- proportion of participants reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of IMP
- mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of IMP
- mean change from baseline (day 1) in migraine-related disability score, as measured by the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire, at 12 weeks after administration of the first dose of IMP
- mean change from baseline (day 1) in quality of life, as measured by the Pediatric Quality of Life Inventory (PedsQL), at 12 weeks after administration of the first dose of IMP
- proportion of participants developing ADAs throughout the trial. The impact of ADAs on safety and efficacy will be analyzed if the number of ADA-positive participants allows.

6.3.1. Definition

6.3.1.1. Electronic Headache Diary Data

The change from baseline in the monthly average number of days of secondary efficacy variables (eg, migraine days, headache days of at least moderate severity, days of use of any acute headache medications etc.) ***during the 12-week period*** after the 1st dose of IMP will be derived

similar to the primary variables using the e-diary data collected through the corresponding headache diary questions (Appendix A). The baseline values and the postbaseline values will be calculated using formula (3) and (1) respectively. ***The change*** is calculated as ***postbaseline value – baseline value***.

The percent reduction in the monthly average number of migraine days ***during the 12-week period*** after the 1st dose of IMP will be calculated by formula (4) in Section 6.1. The participant is considered as a responder if the percent reduction is 50% or more. If a participant is early discontinued from the trial, he/she will be counted as a non-responder.

6.3.1.2. Migraine Disability Assessment (PedMIDAS)

The PedMIDAS questionnaire is a 6-item instrument developed to assess headache-related disability which can be self-administered by the participant or administered by a caregiver. It has been validated in participants aged 4 through 18 years and includes questions related to the impact of headache on school performance, disability at home (eg, inability to do chores or homework), and social/sport functioning. The PedMIDAS questionnaire is completed at baseline (visit 2) and the EOT visit (visit 5). The total score, ie, the sum of the 1st 6 questions, is used for grading of disability, with scores of 0 to 10, 11 to 30, 31 to 50, and >50 interpreted as disability grades 1 (little or no disability), 2 (mild disability), 3 (moderate disability), and 4 (severe disability), respectively.

6.3.1.3. Migraine-Specific Quality of Life

The Pediatric Quality of Life Inventory (PedsQL) 4.0 is a brief 23-item health-related quality of life instrument that evaluates quality of life in 4 areas of functioning: physical, emotional, social, and school functioning. The PedsQL 4.0 has 4 age ranges: toddlers (2 through 4 years), young child (5 through 7 years), child (8 through 12 years), and adolescent (13 through 18 years). This trial will use the young child, child, and adolescent formats. The PedsQL 4.0 asks respondents to indicate how much of a problem each item has been during the past month. For the child and adolescent self-report (8 through 18 years of age) and the parent report forms, respondents use a 5-point Likert scale to rate the item severity (0=never a problem;1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem). For younger children (5 through 7 years of age), a simplified 3-point Likert scale, anchored with a happy and a sad face, is used (0=not at all a problem; 2=sometimes a problem; 4=a lot of a problem) to increase further the developmental sensitivity of the measure. The PedsQL 4.0 yields a total quality of life score and 2 summary scores: Physical Health Summary Score and Psychosocial Health Summary Score. To obtain scores, items are reverse scored, transformed to a 0 through 100 scale (0=100, 1=75, 2=50, 3=25, 4=0), and averaged; total scores near 0 indicate lower quality of life, while scores approaching 100 indicate higher quality of life. The PedsQL version that will be used for the participant for the duration of the trial will be based on the age of the participant at visit 2 and will not change during the course of the trial.

6.3.2. Analysis

An ANCOVA method, which is similar to the primary analysis setup, will be used for the analysis of the mean change from baseline in the monthly average number of days of secondary efficacy variables ***during the 12-week period*** derived from headache diary data. The model will include treatment, sex, puberty status, region, weight category (<45.0 kg or ≥45.0 kg), and

baseline preventive migraine medication use (yes/no) as fixed effects and the baseline values as a covariate. The stratification factors (as randomized) will be used in the model. The LS means for the treatment groups, LS means and 95% confidence intervals for the treatment differences (TEV-48125 – placebo), and associated p-values will be provided.

Participants not receiving concomitant preventive medication constitute the sub-population who don't take any preventive migraine medications listed in the protocol, ie, with baseline preventive migraine medication use = no.

If a participant has less than 10 days of e-diary data entries after the 1st dose of IMP, the missing data handling method for the primary variable discussed in Section 4.3 will be applied for the monthly average number of days of secondary efficacy variables ***during the 12-week period***.

Similar to the sensitivity analysis for the primary efficacy variable described in Section 6.2.3.1 an MMRM model will be implemented to estimate the mean change from baseline for the following endpoint by month and for overall 3 months after the 1st dose of IMP.

- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications

LS means for the treatment groups, LS means and corresponding 95% confidence intervals for the treatment differences (TEV-48125 – placebo), and associated p-values will be calculated by month and for the overall treatment period.

The LS means ±SE of e-diary efficacy variables estimated by MMRM will be plotted by month for each treatment group.

For the proportion of responders, defined as at least 50% reduction from baseline in the monthly average number of migraine days, a logistic regression model will be used with the following factors: treatment, sex, region, puberty status, weight category (<45.0 kg or ≥45.0 kg), preventive medication use at baseline (yes/no) and baseline number of migraine days. The stratification factors (as randomized) will be used in the model. The odds ratio, 95% confidence interval for the odds ratio, difference from placebo and p-value for the treatment comparison will be presented.

The change from baseline values in the PedMIDAS total score and in the PedsQL psychosocial health summary score, physical health summary score and total scores will be analyzed using the same ANCOVA method as described above.

The proportion of participants positive for ADAs throughout the trial will be summarized.

For each of the secondary endpoints, the specified method of summary/analysis will also be performed for the following subgroups:

- participants by age group (6-11 years, 12-17 years)

6.4. Other Efficacy Endpoints

[redacted]

[redacted]

6.4.1. Definition

6.4.1.1. Electronic Headache Diary Data

For the purpose of this trial, a headache day of at least moderate severity will be defined as a calendar day (00:00 to 23:59) where the participant reports either of the following:

- headache pain that lasts ≥2 hours with a peak severity of at least moderate severity
- the participant used acute headache medication (NSAIDs, paracetamol, triptans or ergots) to treat a headache of any severity or duration

The derivation logic is presented in Appendix B.

The percent reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP will be calculated by formula (4) in Section 6.1. The participant is considered as a responder reaching 50%, 75% or 100% reduction if his/her percent reduction is 50% or more, 75% or more, or 100% respectively. Similar definition will be applied to calculate the proportion of participants reaching at least 50%, 75% or 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 IMP. If a participant is discontinued early from the trial, he/she will be counted as a non-responder.

The percent reduction in the monthly number of migraine days during the 4-week period after each dose for months 1, 2, and 3 will be calculated by formula (4) where the postbaseline value will be the number of headache days of at least moderate severity prorated to 28 days for month 1, month 2, and month 3, respectively. If the participant has 50% reduction or more in month 1, he/she will be considered responder during the 4-week period after 1st dose of IMP. In addition, if the participant also has 50% reduction or more in month 2 and 3, he/she is a responder for months 2 and 3, and the level of effect is sustained throughout the 12-week period after the 1st dose of IMP for this participant. Similar definition will be applied to calculate the proportion of sustained responders reaching at least 75% reduction. The proportion of sustained responders reaching at least 50% and 75% reduction in the number of headache days of at least moderate severity will be derived similarly.

The headache day of any severity will be defined as a calendar day (00:00 to 23:59) with headache pain that lasts ≥2 hours of any severity or a day when the participant used acute headache medication (triptans, ergots, NSAIDs or paracetamol) to treat a headache of any severity or duration.

[redacted]

The change from baseline (run-in period) in the number of headache days of at least moderate severity days ***during the 4-week period*** after the 1st dose of IMP will be derived similar to the primary endpoint using only the 1st month diary data.

6.4.1.2. [redacted]

[redacted]

6.4.2. Exploratory Efficacy Analysis

6.4.2.1. Electronic Headache Diary Data

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]

6.4.2.2. [redacted]

[redacted]

7. 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 as follows:

1. mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of IMP for the TEV-48125 treatment group versus the placebo treatment group
2. mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP for the TEV-48125 treatment group versus the placebo treatment group
3. proportion of participants reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of IMP for the TEV-48125 treatment group versus the placebo treatment group
4. mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of IMP for the TEV-48125 treatment group versus the placebo treatment group
5. mean change from baseline (day 1) in migraine-related disability score, as measured by the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire, at 12 weeks after administration of the first dose of IMP for the TEV-48125 treatment group versus the placebo treatment group
6. mean change from baseline (day 1) in quality of life, as measured by the Pediatric Quality of Life Inventory (PedsQL), at 12 weeks after administration of the first dose of IMP for the TEV-48125 treatment group versus the placebo treatment group

If the resulting 2-sided p-value from the 1st comparison is $\leq$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.

8. SAFETY ANALYSIS

8.1. General

The safety population will be used for all safety analyses. Summaries will be presented by treatment group (TEV-48125 225 mg, TEV-48125 120 mg and placebo). TEV-48125 will be presented as actually received unless specified otherwise. A total column will also be provided.

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, participant counts and percentages will be provided.

Missing values will be reported as missing and no imputation will be undertaken.

8.2. Duration of Exposure to IMP

Duration of treatment (days treated) is the number of days on treatment based on the 1st IMP administration day and end of treatment (EOT) visit day (EOT visit day – 1st day of IMP + 1). For participants who completed trial, EOT date is estimated as the date of visit 5. For participants who did not complete the trial and were not lost to follow-up, their EOT date is estimated as the date of trial discontinuation. For participants who did not complete trial, EOT date is estimated as the date of the last dose of IMP +27.

Number (%) of participants receiving 1 dose, 2 doses, and 3 doses will be summarized using descriptive statistics by treatment group. Duration of treatment (days) will also be summarized using descriptive statistics for each treatment group.

8.3. IMP Compliance

Not applicable.

8.4. Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

For adverse event recording, the trial period is defined for each participant as the time period from signature of the informed consent form through completion of visit 5 or the early withdrawal visit for participants who withdraw from the trial for any reason.

Adverse events will be collected at each visit via adverse event inquiry.

The following are considered protocol-defined adverse events of special interest to be sent to the Sponsor's Pharmacovigilance Department for evaluation: ophthalmic related adverse events of at least moderate severity and severe hypersensitivity or anaphylactic reactions.

An adverse device effect is an adverse event related to the use of an investigational medical device or combination product. The full definition is provided in the trial protocol.

Events of possible drug-induced liver injury (AST or ALT ≥3 × the ULN, total bilirubin ≥2 × the ULN), or Hy's Law events, as well anaphylaxis and hypersensitivity reactions will be assessed. 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). In the event of suspected anaphylaxis, vital signs, including oxygen saturation and respiration rate, will be measured.

Summaries by treatment group will be presented for treatment emergent adverse events (overall and by severity), treatment emergent adverse device effects, treatment emergent adverse events determined by the investigator to be treatment-related adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (and/or PFS) (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, serious adverse device effects, protocol-defined adverse events of special interest, adverse events causing discontinuation from the trial, adverse device effects causing discontinuation from the trial, non-serious treatment emergent adverse events and prior to treatment adverse events. Additionally, the injection site reactions recorded as adverse events requiring concomitant or special treatment given and protocol defined adverse events of special interest will be summarized by treatment group separately.

The incidence of adverse event will be summarized using descriptive statistics by SOC, PT, and severity of the adverse event. Each participant will be counted only once within a SOC or a PT by using the adverse events with the highest severity within each category. Treatment-related adverse event summaries will include adverse events related to IMP and adverse events with missing relationship to IMP. Adverse events with the missing flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non-serious adverse events.

Listings for deaths, adverse events, adverse device effects, serious adverse events, serious adverse device effects, serious adverse events additional information, adverse events leading to discontinuation, adverse device effects leading to discontinuation, injection site related adverse event requiring concomitant or additional treatment given and protocol defined adverse events of special interest will be presented. All information pertaining to adverse events noted during the trial will be listed by subject, detailing verbatim given by the investigator, PT, SOC, date of onset, date of resolution, severity, and relationship to treatment. The onset of adverse events will also be shown relative (in number of days) to the 1st day of treatment. In addition, MedDRA dictionary terms for adverse event descriptions, and adverse event preferred terms by participant number and treatment group will be presented.

All adverse events summary tables will be split by the subgroups of 6-11 years, 12-17 years and overall.

8.5. Deaths

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

8.6. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed using the central laboratory at the time points detailed in the trial protocol. Specific laboratory tests to be performed are listed below in Table 3.

Table 3: Clinical Laboratory Tests

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

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

Laboratory tests results and changes from baseline for chemistry, hematology, urinalysis, and coagulation laboratory tests will be summarized by visits for each treatment group using descriptive statistics. Shifts (below, within, and above the normal range) from baseline to each visit and Last Assessment will be summarized using participant counts. Listings of all individual participants' laboratory test results will be presented.

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

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the Investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event. The incidence of potentially clinically significant abnormal results will be summarized using descriptive statistics with the criteria specified in Table 4. The potentially clinically significant abnormal laboratory values will include all postbaseline values (including scheduled, unscheduled, and early termination visits) for the summaries. Listings of participants who have potentially clinically significant abnormal laboratory data will be presented.

Table 4: Criteria for Potentially Clinically Significant Laboratory Values

Test		Pediatric 6-11 Years Criterion Value	Pediatric 12-17 Years Criterion Value
Serum chemistry			
ALT		≥ 2x ULN	≥ 2x ULN
AST		≥ 2x ULN	≥ 2x ULN
ALP		≥ 3x ULN	≥ 3x ULN
GGT		≥ 3x ULN	≥ 3x ULN
LDH		≥ 2x ULN	≥ 2x ULN
BUN		≥ 9.0 mmol/L	≥ 9.0 mmol/L
Creatinine		≥ 100 μmol/L	≥ 150 μmol/L
Bilirubin (total)		≥34.2 μmol/L	≥34.2 μmol/L
Hematology			
Hematocrit	Males	< 0.30 L/L	< 0.32 L/L
	Females	< 0.30 L/L	< 0.31 L/L
Hemoglobin	Males	≤ 100 g/L	≤ 110 g/L
	Females	≤ 100 g/L	≤ 100 g/L
WBC counts		≤ 3 x 10^9/L ≥ 20 x 10^9/L	≤ 3 x 10^9/L ≥ 20 x 10^9/L
Eosinophils		≥10%	≥10%
ANC		≤1 x 10^9/L	≤1 x 10^9/L
Platelet counts		≤ 75 x 10^9/L ≥ 700 x 10^9/L	≤ 75 x 10^9/L ≥ 700 x 10^9/L
Urinalysis			
HGB		≥2 unit increase from baseline	≥2 unit increase from baseline
Glucose		≥2 unit increase from baseline	≥2 unit increase from baseline
Ketones		≥2 unit increase from baseline	≥2 unit increase from baseline
Total protein		≥2 unit increase from baseline	≥2 unit increase from baseline
Coagulation			
INR		>1.5	>1.5

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma- glutamyl transpeptidase; HGB=hemoglobin; INR=international normalized ratio; LDH=lactate dehydrogenase; RBC=red blood cell; ULN=upper limit of normal range; WBC=white blood cell

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

8.7. Physical Examinations

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

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 and recorded on the CRF.

8.8. Vital Signs

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

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.

Vital signs values and changes from baseline to each visit and Last Assessment will be summarized using descriptive statistics. The incidence of potentially clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics.

Table 5 specifies the criteria for identifying vital signs as potentially clinically significant abnormal. Note that in order to be identified as potentially clinically significant abnormal, a value would need to meet both conditions below: ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change from baseline column. The potentially clinically significant abnormal vital signs values will include all postbaseline values (including scheduled, unscheduled, and early termination visits) for the summaries.

Table 5: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Pediatric 6-11 Years Criterion Value	Pediatric 12-17 Years Criterion Value	Change relative to baseline
Pulse	≥ 140 bpm	≥ 120 bpm	Increase of ≥ 15
	≤ 60 bpm	≤ 50 bpm	Decrease of ≥ 15
Systolic blood pressure	≥ 135 mm Hg	≥ 150 mm Hg	Increase of ≥ 20
	≤ 80 mm Hg	≤ 85 mm Hg	Decrease of ≥ 20
Diastolic blood pressure	≥ 93 mm Hg	≥ 100 mm Hg	Increase of ≥15

Vital Sign	Pediatric 6-11 Years Criterion Value	Pediatric 12-17 Years Criterion Value	Change relative to baseline
	≤ 37 mm Hg	≤ 44 mm Hg	Decrease of ≥15
Respiratory rate	<15 breaths/min	<10 breaths/min	
Body temperature	≥ 38.3°C	≥ 38.3°C	Change of ≥1.1°C

bpm=beats per minute

A listing for potentially clinically significant abnormal vital signs will be presented.

8.9. Electrocardiography

ECGs will be performed in triplicate, with approximately 1 minute between recordings. The average of the recorded measurements will be calculated for each visit.

Any ECG finding that is judged by the Investigator as a potentially clinically significant change (worsening) compared with the baseline value will be considered an adverse event.

For ECG variables, the mean of recorded results from last three measurements at a visit will be calculated. The mean results and mean changes from baseline to each visit in the treatment period and Last Assessment (see Section 4.4) will be summarized using descriptive statistics. Baseline is determined based on the last set of observed data before the administration of the 1st dose of the IMP.

For ECG findings, the worst value of recorded from last three findings at a visit will be used for analysis. Baseline ECG findings and shifts (normal, abnormal not clinically significant, and abnormal clinically significant) from baseline to each visit in the treatment period, Overall (worst value for a participant), and the Last Assessment (worst value of recorded findings from the last visit) will be summarized using participant counts.

8.10. Concomitant Medications or Therapies

Approximately 30% of participants will be allowed to remain on no more than 2 preventive migraine medications (listed in protocol Appendix C), provided the medication is recognized to have at least moderate evidence of efficacy or is commonly used. Participants must have been on a stable, well-tolerated dose of this preventive medication for at least 2 months prior to screening (visit 1) and would be expected to remain on this medication for the duration of the trial. For the remaining approximately 70% of participants, these medications are not allowed for migraine or for any other indications.

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

All concomitant medications will be coded using the WHO dictionary of medical codes. The concomitant medication will include all medications taken after the 1st IMP administration.

The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term for each treatment group. Participants are counted only once in each therapeutic class category, and only once in each preferred term category.

The subset of concomitant pain medication and medication or therapy for migraine/headache will be summarized by the following indication categories.

- Medication from Appendix C for migraine/headache
- Medication from Appendix C for other reason than Migraine/Headache
- Migraine/headache prevention medication not from Appendix C
- NSAIDs for migraine/headache
- NSAIDs for other reason than migraine/headache
- Triptan for migraine/headache
- Triptan for other reason than migraine/headache
- Ergot for migraine/headache
- Ergot for other reason than migraine/headache
- Medication used for symptoms during migraine attack other than pain
- Other

8.11. Columbia Suicide Severity Rating Scale (C-SSRS)

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

9. TOLERABILITY VARIABLES AND ANALYSIS

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

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

Tolerability will be assessed by the following:

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

Local tolerability findings will be listed and summarized descriptively.

10. PHARMACOKINETIC ANALYSIS

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

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

11. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

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

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

12. IMMUNOGENICITY ANALYSIS

The impact of ADAs on safety and efficacy will be analyzed if the number of ADA-positive participants allows. If performed, this analysis will be reported separately.

13. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

14. REFERENCES

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

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15. CHANGES TO ANALYSES SPECIFIED IN THE TRIAL PROTOCOL

The subgroup analysis of 'participants receiving alternative preventive medications that belong to the same classes but are not listed in protocol Appendix C' specified in the protocol will not be performed, as it is not required.

The subgroup analysis of 'participants receiving 2 preventive medications from protocol Appendix C' will not be performed, as it is not required.

Participants from site [redacted] will be excluded from all analysis sets due to GCP non-compliance. The site has been terminated from continuous participation in the trial.

APPENDIX A. E-DIARY QUESTIONNAIRE

	The following questions are referring to yesterday (00:00 - 23:59)
A1	Did you have a headache yesterday?
A2	Did your headache last for 2 hours or more yesterday?
A3	On a scale of 0-10, how painful was your headache yesterday?
A4	Was your headache pain worse on one side (left or right) of your head yesterday?
A5	Was your head pain throbbing, pounding, or beating like a drum yesterday?
A6	Was your headache worse by doing simple activities like walking, bending or going up the stairs yesterday?
A7	Did you have stomach ache, feel sick to your stomach or did you throw up yesterday?
A8	Did light bother you or did you want to be in a dark room yesterday?
A9	Did sounds bother you or did you want to be alone in a quiet room yesterday?

	The following questions are referring to the day before yesterday (00:00 - 23:59)
A10	Did you have a headache the day before yesterday?
A11	Did your headache last for 2 hours or more the day before yesterday?
A12	On a scale of 0-10, how painful was your headache the day before yesterday?
A13	Was your headache pain worse on one side (left or right) of your head the day before yesterday?
A14	Was your head pain throbbing, pounding, or beating like a drum the day before yesterday?
A15	Was your headache worse by doing simple activities like walking, bending or going up the stairs the day before yesterday?
A16	Did you have stomach ache, feel sick to your stomach or did you throw up the day before yesterday?
A17	Did light bother you or did you want to be in a dark room the day before yesterday
A18	Did sounds bother you or did you want to be alone in a quiet room the day before yesterday?

	The following questions are referring to the time DURING/BEFORE your headache yesterday (00:00 - 23:59)
B1	Think about the time **during** your headache yesterday. Did you have trouble seeing normally or did you see spots, stars, wavy lines, or flashes?
B2	Think about the time **before** your headache started yesterday. Did you notice any of the usual signs that a headache is coming? This could include seeing spots, stars, wavy lines, or flashes, having trouble speaking, feeling dizzy or having tingling, numbness or weakness in your arms or legs.
B3	Did you take a nap or go to sleep earlier than usual because of your headache yesterday?
B4	Did you take any medicine for your headache yesterday?
B5	What medicine did you take?
B6	How many doses of this medicine did you take?

	The following questions are referring to the time DURING/BEFORE your headache on the day before yesterday (00:00 - 23:59)
B7	Think about the time **during** your headache the day before yesterday. Did you have trouble seeing normally or did you see spots, stars, wavy lines, or flashes?
B8	Think about the time **before** your headache started the day before yesterday. Did you notice any of the usual signs that a headache is coming? This could include seeing spots, stars, wavy lines, or flashes, having trouble speaking, feeling dizzy or having tingling, numbness or weakness in your arms or legs.
B9	Did you take a nap or go to sleep earlier than usual because of your headache the day before yesterday?
B10	Did you take any medicine for your headache the day before yesterday?
B11	What medicine did you take?
B12	How many doses of this medicine did you take?

	The following questions are referring to yesterday (00:00 - 23:59)
C0	Even if you did not have a headache, did you feel fine yesterday?
C1	Even if you did not have a headache, did you sleep well yesterday?
C2	Even if you did not have a headache, did you eat normally yesterday?
C3	Even if you did not have a headache, did you miss any school time yesterday?
C4	Even if you did not have a headache, did you avoid playing any sports yesterday?
C5	Even if you did not have a headache, did you avoid watching television or movies yesterday?
C6	Even if you did not have a headache, did you avoid playing video games yesterday?
C7	Even if you did not have a headache, did you avoid reading yesterday?
C8	Even if you did not have a headache, did you avoid any other activities yesterday because of how your headache makes you feel or because of concern that you might have a headache?

	The following questions are referring to the day before yesterday (00:00 - 23:59)
C9	Even if you did not have a headache, did you feel fine the day before yesterday?
C10	Even if you did not have a headache, did you sleep well the day before yesterday?
C11	Even if you did not have a headache, did you eat normally the day before yesterday?
C12	Even if you did not have a headache, did you miss any school time the day before yesterday?
C13	Even if you did not have a headache, did you avoid playing any sports the day before yesterday?
C14	Even if you did not have a headache, did you avoid watching television or movies the day before yesterday?
C15	Even if you did not have a headache, did you avoid playing video games the day before yesterday?
C16	Even if you did not have a headache, did you avoid reading the day before yesterday?
C17	Even if you did not have a headache, did you avoid any other activities the day before yesterday because of how your headache makes you feel or because of concern that you might have a headache?

APPENDIX B. LOGICS FOR ENDPOINTS DERIVATION

Migraine day: 1 of the following 3 options							
		OPTION 1				OPTION 2	
Part 1	**1**	**A1 / A10**	YES		**1**	**A1 / A10**	YES
	2	**A2 / A11**	YES		**2**	**B4 / B10**	YES
		AND			**3**	**B5 / B11**	ERGOT OR TRIPTAN OR NSAID OR PARACETAMOL
		TWO OF THE FOLLOWING				OPTION 3	
Part 2	**1**	**A3 / A12**	>=4				
	2	**A4 / A13**	YES		**1**	**A1 / A10**	YES
	3	**A5 / A14**	YES			***AND***	
	4	**A6 / A15**	YES			**ONE OF THE FOLLOWING**	
		AND			**1**	**B1 / B7**	YES
		ONE OF THE FOLLOWING			2	**B2 / B8**	YES
Part 3	**1**	**A7 / A16**	YES				
	2	**A8 / A17**	YES				
		AND					
		A9 / A18	YES				

Headache day of at least moderate severity: 1 of the following 2 options		
OPTION 1		
1	**A2 / A11**	YES
2	**A3 / A12**	Moderate (headache severity 4 to 6) or Severe (headache severity 7 to 10)
OPTION 2		
1	**B4 / B10**	YES
2	**B5 / B11**	ERGOT OR TRIPTAN OR NSAID OR PARACETAMOL

APPENDIX C. PEDMIDAS QUESTIONNAIRE

PedMIDAS was developed to assess migraine disability in pediatric and adolescent participants. It has been tested and validated for ages 4 to 18 and mirrors the use of the adult MIDAS that Stewart and Lipton developed for adults age 20 to 50 (Stewart and Lipton 2001). It is intended to be self-administered by the participant and their parent. It can be completed in collaboration, but the answers need to be confirmed with the participant. Its implementation and design are straightforward.

The 1st 3 PedMIDAS questions relate to the impact of headache on school performance. Caution needs to be taken to minimize duplication of days (ie, don't count a half day missed both as a full day missed and a half day missed). This is stated in the directions and in the questions, but occasionally needs to be checked.

The 4th question concerns disability at home. Occasionally it needs to be clarified that it only counts as a missed day due to headaches if the activity was expected on that day (ie, homework was not completed due to headaches for the day, not just delayed OR the chores aren't done for other reasons). This usually is not a problem for teenagers to understand and has lesser impact on the pediatric group. The final 2 questions relate to social / sports function and rarely are a problem for the children to answer − they easily remember the days they missed out on fun events.

The score is a simple composite of the total of 6 questions. If a range is provided, use the high end of the range or ask the family to provide a single number − both methods show equal validity. If the answer is blank or is a phrase (ie, "few" or "couple"), they need to be asked to provide a number. The frequency and severity questions are not scored but obtained for clinical reference.

The PedMIDAS questionnaire is as follows:

The following questions try to assess how much the headaches are affecting day-to-day activity. Your answers should be based on the last three months. There are no "right" or "wrong" answers so please put down your best guess.

1. How many full school days of school were missed in the last 3 months due to headaches? _____

2. How many partial days of school were missed in the last 3 months due to headaches (do not include full days counted in the first question)? _____

3. How many days in the last 3 months did you function at less than half your ability in school because of a headache (do not include days counted in the first two questions)? _____

4. How many days were you not able to do things at home (i.e., chores, homework, etc.) due to a headache? _____

5. How many days did you not participate in other activities due to headaches (i.e., play, go out, sports, etc.)? _____

6. How many days did you participate in these activities, but functioned at less than half your ability (do not include days counted in the 5th question)? _____

The PedMIDAS grading scale is as follows:

PedMIDAS Score Range	**Disability Grade**
0 to 10	Little to none
11 to 30	Mild
31 to 50	Moderate
Greater than 50	Severe

APPENDIX D. PEDSQL QUESTIONNAIRE

The PedsQL™ Measurement Model is a modular approach to measuring health-related quality of life (HRQOL) in healthy children and adolescents and those with acute and chronic health conditions. The PedsQL 4.0 has 4 age ranges: toddlers (2 through 4 years), young child (5 through 7 years), child (8 through 12 years), and adolescent (13 through 18 years). This trial uses the young child, child, and adolescent formats. The 23-item PedsQL™ Generic Core Scales were designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning. The 4 Multidimensional Scales and 3 Summary Scores are:

Generic Core Scale Scores:	Summary Scores:
Physical Functioning (8 items)	Total Scale Score (23 items)
Emotional Functioning (5 items)	Physical Health Summary Score (8 items)
Social Functioning (5 items)	Psychosocial Health Summary Score (15 items)
School Functioning (5 items)	

On the PedsQL™ **Generic Core Scales**, for ease of interpretability, items are reversed scored and linearly transformed to a 0-100 scale, so that higher scores indicate better HRQOL (Health-Related Quality of Life). To reverse score, transform the 0-4 scale items to 0-100 as follows: 0 (“Never”) = 100, 1 (“Almost Never”) = 75, 2 (“Sometimes”) = 50, 3 (“Often”) = 25, 4 (“Almost Always”) = 0.

To create **Scale Scores**, the mean is computed as the sum of the items over the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the Scale Score should not be computed. Imputing the mean of the completed items in a scale when 50% or more are completed is generally the most unbiased and precise method. To do this, count the number of missing values in the scale (call it nmiss). Next, sum the item scores and divide by the number of items in the scale minus nmiss.

To create the **Psychosocial Health Summary Score**, the mean is computed as the sum of the items over the number of items answered in the generic core scale scores of Emotional, Social and School Functioning. The **Physical Health Summary Score** is the same as the Physical Functioning Scale Score. The **Total Scale Score** is the mean of all items.

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

APPENDIX E. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

NOTE TO FILE

TV48125-CNS-30082: Migraine Day Definition Discrepancy

From: [redacted]

Protocol: TV48125-CNS-30082

Date Originated: 29-May-2025

Date Issue was identified: 18-Mar-2025

Topic: Migraine Day Definition Discrepancy

Description: In reviewing the documentation for TV48125-CNS-30082, a discrepancy was identified in the definition of a migraine day between the main body of the Statistical Analysis Plan with Amendment 02 (SAP; dated: 20 December 2024) and its Appendix B.

The main body of the SAP defines a migraine day as a headache lasting ≥2 hours and accompanied by ≥1 migraine symptom(s).

In contrast, Appendix B of the SAP provides a more detailed and stringent definition requiring multiple symptoms. Specifically, Appendix B defines a migraine day as one where the participant has a headache lasting ≥2 hours plus at least two of the following: at least moderate severity, unilateral location, throbbing/pounding quality, and difficulty with usual activities, plus one of the following: photophobia and phonophobia, or nausea/vomiting.

The trial analysis was conducted using the definition outlined in Appendix B, which reflects a stricter threshold of ≥2 migraine-related symptoms. This is noted here for clarity and transparency.

This discrepancy is not anticipated to impact the trial's results or conclusions.

Study statistician:

Signed by:

Signature and date

Director, Statistics:

Signed by:

Signature and da'e