Statistical Analysis Plan

TV48125-CNS-30050

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

Phase 3

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Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: TV48125-CNS-30050

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

Statistical Analysis Plan for:

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

Amendment 02

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AMENDMENT HISTORY

The Statistical Analysis Plan for study TV48125-CNS-30050 (study protocol with amendment 01 dated 30 March 2016) has been amended and reissued as follows:

Amendment number	Date	Summary of changes	Reason for amendment
01	27 March 2017	Section 2.2.3, two exploratory efficacy endpoints to analyze the change from baseline of the weekly number of migraine days /headache days of at least moderate severity are added.	Teva Clinical decision
		Section 3.3, the definition of FAS is changed from "all patients in the ITT population who receive at least 1 dose of study drug and have at least **1** post baseline efficacy assessment on the primary endpoint" to "all patients in the ITT population who receive at least 1 dose of study drug and have at least **10** days of post baseline efficacy assessments on the primary endpoint".	Per review comments from the FDA
		Section 4.2, the baseline for calculating weekly endpoints is added.	Teva Clinical decision
		Section 4.3, Germany is removed fromTable 2, Israel and Finland are added.	Germany did not participate in the study. Israel and Finland enrolled patients.
		Section 4.4, the hierarchical testing sequence is modified.	Teva Clinical decision
		Section 4.5, the missing data handling rule is modified. The BOCF imputation is removed. The monthly efficacy variables will be prorated to 28 days if the patient has ≥10 days of e-diary data for the month. If a patient has <10 days of e-diary data for a month, the monthly number of days/hours of efficacy variables will be considered as missing.	Per review comments from the FDA
		Section 4.5, The missing data handling rule for calculating weekly efficacy variables is added. Section 4.6, the weekly window for the first month (28-days) post the first dose is defined.	Teva Clinical decision

Amendment number	Date	Summary of changes	Reason for amendment
01	27 March 2017	Section 5.3, the population for the baseline efficacy summary is changed from FAS/PP to ITT population. Section 6.1, derivation of the change from baseline of the weekly number of days of the efficacy variables is added.	Teva Clinical direction
		Section 6.2.2, the normality of the residuals from the ANCOVA model will be checked using Shapiro Wilk's normality test. If the test has a p value ≤0.001, Wilcoxon rank-sum test will be conducted as the primary analysis. Section 6.2.3.1, the BOCF sensitivity analysis is removed. The missing value handling for MMRM analysis is updated per rules in section 4.5.	Incorporation of review comments from the FDA
		Section 6.4.1.1, the analysis for weekly efficacy endpoints is added.	Teva Clinical decision
		Section 6.5, age groups of '46-65' and '>65' are consolidated as 1 group, ">45 years old"	Teva Clinical decision
02	18 May 2017	Section 6.2.2: changed test level for Shapiro-Wilk's test from 0.001 to 0.01	FDA feedback 5/18/2017

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ADA	antidrug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BUN	Blood urea nitrogen
CM	chronic migraine
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CSR	Clinical study report
ECG	electrocardiography/electrocardiogram
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
EM	episodic migraine
EOT	end of treatment (visit)
EQ-5D-5L	EuroQol-5 Dimension, 5 response level version
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GBP	global branded product
GGT	gamma-glutamyl transpeptidase
HCG	Human chorionic gonadotropin
ICH	International Conference on Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd revision
IHS	International Headache Society
INR	international normalized ratio
IRT	interactive response technology

Abbreviation	Term
ITT	intent-to-treat
LDH	lactate dehydrogenase
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model Repeated Measures
MIDAS	Migraine Disability Assessment
MSQOL	Migraine-Specific Quality of Life
NSAID	non-steroidal anti-inflammatory drug
PBO	placebo
PGIC	Patient Global Impression of Change
PHQ-2	2-item Patient Health Questionnaire
PHQ-9	9-item Patient Health Questionnaire
PT	Preferred term
RBC	red blood cell
R&D	Research and Development
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of the normal range
WBC	white blood cell
WHO Drug	World Health Organization dictionary of medical codes
WPAI (:GH)	Work Productivity and Activity Impairment (:General Health)

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PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceuticals Products R&D, Inc. study TV48125-CNS-30050, (A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study Comparing the Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of TEV-48125 Versus Placebo for the Preventive Treatment of Episodic Migraine) and was written in accordance with standard operating procedure GBP_RD_702 (Teva Pharmaceuticals Global Branded Product (GBP) Research and Development (R&D) Statistical Analysis Plan).

This Phase 3 study is being conducted to evaluate the efficacy, safety, and immunogenicity of 2 dose regimens of subcutaneous (sc) administration of TEV-48125 versus placebo for the preventive treatment of episodic migraine (EM).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) of Technical Requirements for Trials. All work planned and reported for this SAP will follow internationally accepted Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol TV48125-CNS-30050 with Amendment 01
- Case report forms (CRFs) for Study TV48125-CNS-30050.
- ICH E9 Guidance on Statistical Principles for Clinical Trials.
- ICH E3 Structure and Content of Clinical Study Reports

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails; the discrepancies will be explained in the Clinical Study Report (CSR).

1. STUDY OBJECTIVES

1.1. Primary Objectives

The primary objectives of this study are as follows:

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

1.2. Secondary Objectives

The secondary objectives of the study are as follows:

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

1.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- to demonstrate the efficacy of TEV-48125, as assessed by the decrease in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug relative to the baseline period

- to evaluate the proportion of patients reaching at least 75% reduction and total (100%) reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- to evaluate the proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug relative to the baseline period who sustain this level of response over the 12-week period after the 1st dose of study drug
- to demonstrate the efficacy of TEV-48125 in patients who previously used topiramate for migraine, but discontinued, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125 in patients who previously used onabotulinumtoxinA for migraine, but discontinued, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the number of migraine days during the 4-week period after the 2nd dose of study drug and the 4-week period after the last (3rd) dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction of the monthly average number of headache days of any severity during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 4-week period after each dose of study drug relative to the baseline period
- to evaluate the proportion of patients reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- to evaluate the proportion of patients reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients not receiving concomitant preventive migraine medications relative to the baseline period
- to demonstrate the efficacy of TEV-48125, as assessed by the reduction in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug for patients who used topiramate for migraine in the past relative to the baseline period

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

2. STUDY DESIGN

2.1. General Design and Study Schema

This is a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the safety, tolerability, and efficacy of 2 dose regimens of sc TEV-48125 and placebo in adults with EM. The study consists of a screening visit, a 28-day run-in period, and a 12-week (84-day) treatment period, including a final evaluation at week 12 (end-of-treatment [EOT] visit, approximately 4 weeks [28 days] after the final dose of study drug).

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

Patients using no more than 1 preventive medication at the time of study enrollment will be allowed to remain on the medication if the medication has at least moderate evidence of efficacy for migraine (Silberstein et al 2012). Patients should not be initiating any preventive migraine medications (presented in protocol Appendix B) at the time of the screening visit, and will not be allowed to initiate these medications after randomization. A small subgroup of patients (approximately 30%) will be allowed to use concomitant migraine preventive medications (presented in protocol Appendix A), and no changes in these medications will be allowed until the last study assessments are complete. Patients will be allowed to use acute medications to treat acute migraine attacks, as needed.

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

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

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

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

Blinded treatment will be administered sc once monthly (ie, approximately every 4 weeks) for a total of 3 doses. First treatment administration will occur at visit 2 (day 0), and additional doses will

be administered at visits 3 and 4. Final study assessments will be performed at visit 5 (EOT visit), approximately 4 weeks after administration of the 3rd and final dose of study drug.

Headache information will be captured daily during the entire study using an electronic headache diary device. Assessments of migraine-related disability and change in quality of life (using the MIDAS questionnaire, 2-item Patient Health Questionnaire (PHQ-2)/9-item Patient Health Questionnaire (PHQ-9), Migraine-Specific Quality of Life (MSQOL) questionnaire, EuroQol-5 Dimension, 5 response level version (EQ-5D-5L) questionnaire, Patient Global Impression of Change (PGIC) scale, and Work Productivity and Activity Impairment (WPAI) questionnaire); safety evaluations; blood draws for pharmacokinetic, immunogenicity, and biomarker analysis; and urine sampling for biomarker analysis will be performed throughout the study according to the schedule of assessments (Table 1). In addition, patients who consent to pharmacogenomic assessment will provide a blood sample for testing.

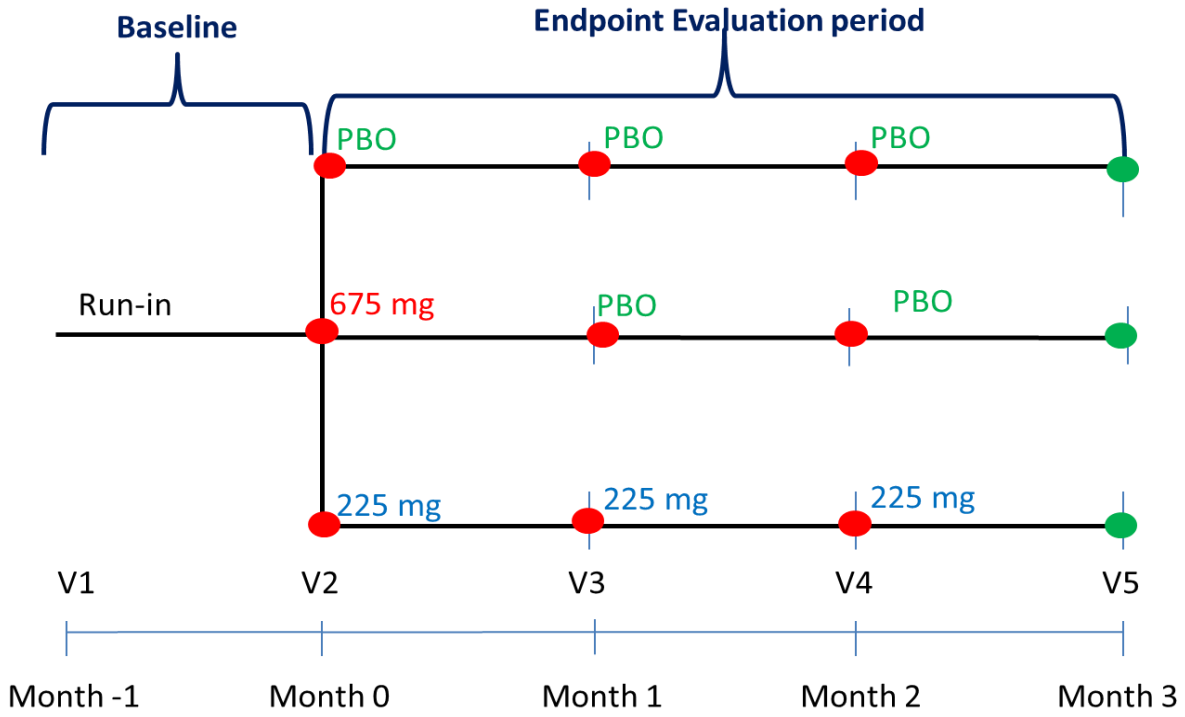
Upon completion of the final study assessments patients who complete all scheduled visits may be eligible to enter a long-term safety and efficacy study (Study TV48125-CNS-30051), consisting of a 12-month double-blind treatment period and a 6.5-month follow-up period. Patients receiving active study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

The assessments and procedures performed during each study visit are detailed in Table 1. The study schema is presented in Figure 1.

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

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

363 **Figure 1: Overall Study Schema**



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365 PBO = placebo; V = visit.
366 Note: Baseline refers to the 28-day run-in period for headache variables and visit 2 (day 0) for all other variables.

Table 1: Study Procedures and Assessments

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

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

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

[a] Height will only be obtained at screening.
[b] Procedure will be performed before other assessments (eg, blood draws and administration of questionnaires).
[c] Electrocardiograms will be performed in triplicate.
[d] Inquiries about adverse events will be made before and after study drug administration. Postdose inquiries will be made before the patient leaves the study center.
[e] Serum chemistry, hematology, coagulation, and urinalysis.
[f] Women of childbearing potential only.
[g] Postmenopausal women only.
[h] Eligible patients will be given an electronic headache diary device and will be trained in its use and compliance requirements on the day of screening.
[i] Patients will complete electronic headache diary entries about the previous day daily beginning on day -27 through the EOT/early withdrawal visit.
[j] Blood samples for plasma drug concentration determination will be collected prior to dosing at visits 2, 3, and 4.
[k] Blood samples for serum ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).
[l] A single blood sample for pharmacogenomic analysis will be collected at visit 2 or any visit thereafter from patients who consent to this procedure. A separate informed consent form for pharmacogenomic sampling must be signed by the patient.
[m] Patients will respond first to the PHQ-2. They will respond to questions 3 through 9 (unique questions) of the PHQ-9 only if PHQ-2 is positive.
[n] The eC-SSRS Baseline/Screening version will be completed at visit 2, and the eC-SSRS Since Last Visit version will be completed at all other visits.
[o] Injection sites will be assessed for erythema, induration, ecchymosis, and pain immediately and 1 hour after study drug administration. If a patient has severe injection site induration, erythema, and/or ecchymosis and/or grade 3 (severe) or grade 4 (worst possible) injection site pain at 1 hour after completion of study drug administration, the patient will be reassessed 3 hours after study drug administration and hourly thereafter until the reaction/pain is of moderate or less severity.

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

2.2. Primary and Secondary Measures and Endpoints

2.2.1. Primary Efficacy Endpoint

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

2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

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

2.2.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

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

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

- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the last (3rd) dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug
- assessment of patient satisfaction, as measured by the PGIC scale, at 4 weeks after administration of the 1st dose of study drug, at 4 weeks after the 2nd dose of study drug, and at 4 weeks after the last (3rd) dose of study drug

2.2.4. Safety and Tolerability Endpoints

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

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

2.2.5. Pharmacokinetic/Immunogenicity/Biomarker Endpoints

2.2.5.1. Pharmacokinetic Endpoints

There are no prespecified pharmacokinetic endpoints.

2.2.5.2. Immunogenicity Endpoint

There are no prespecified immunogenicity endpoints.

2.2.5.3. Biomarker Endpoints

The biomarker assessments and endpoints will be provided in a separate document by Personal Medicine and Pharmacogenomics.

2.3. Sample Size and Power Considerations

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

2.4. Randomization and Blinding

2.4.1. Randomization

Patient randomization codes will be maintained in a secure location within Teva Clinical Supply Chain. At the time of analysis, when treatment codes are needed, the Teva statistician assigned to the study will make a request to unblind and will receive the unblinded codes.

2.4.2. Blinding/Unblinding

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

The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients will be blinded to treatment assignment. A computer-generated master randomization list will be provided to drug packaging facilities. Packaging vendor(s) will package active drug and placebo into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance and contain 1 prefilled syringe with active drug or placebo. Adequate kit supply for upcoming study visits will be managed by IRT and kept (refrigerated at 2°C to 8°C) on site.

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

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

In blinded studies, for adverse events that are defined as: suspected, unexpected, serious, adverse reaction (SUSAR) (ie, reasonable possibility; see protocol Section 7.1.4), Global Patient Safety and Pharmacovigilance may independently request that the treatment code be revealed (on a case by case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct, analysis, and reporting of the data.

2.5. Sequence of Planned Analyses

2.5.1. Interim Analyses

No interim analysis is planned for this study.

2.5.2. Final Analyses and Reporting

All final, planned analyses identified in this SAP will be performed after the database lock. The study will not be unblinded until the study database lock.

3. POPULATIONS / ANALYSIS SETS

3.1. Intent-to-Treat Population

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

3.2. Safety Population

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

3.3. Full Analysis Set

The full analysis set (FAS) will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 10 days of post baseline efficacy assessments on the primary endpoint. The FAS will be used for all efficacy analysis.

3.4. Per-Protocol Analysis Set

The per-protocol analysis set will consist of all patients who have completed the study without any violations of the inclusion/exclusion criteria or any violations or omissions of the drug administration. The efficacy analysis for the primary and secondary endpoints will be repeated for the per-protocol analysis set.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include count (n), mean, SD, standard error (SE), median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages.

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

4.2. Specification of Baseline Values

Patients will complete electronic headache diary entries daily for 28-day run-in period and enter headache information (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use) about the previous day into the electronic headache diary device. 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 baseline value for calculating change from baseline of the weekly values will be normalized to 7 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 headache hours of at least moderate severity
- total number of headache hours of any severity
- total number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) for the group of patients who use migraine-specific 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 0 before the 1st study drug administration include

- disability score, as measured by the MIDAS assessment (Appendix C)
- quality of life, as measured by the MSQOL questionnaire (Appendix D)
- health status, as measured by the EQ-5D-5L questionnaire (Appendix F)
- patient depression status, as measured by the PHQ-2 and the PHQ-9 (Appendix G)

- patient work productivity and activity impairment, as measured by the WPAI questionnaire (Appendix H)

Other baseline will be the last value prior to the 1st dose of study drug.

4.3. Region of Pooled Countries

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

Table 2: Pooled Countries by Region

Region	Country
United States	United States
Other	Japan, Czech Republic, Poland, Russia, Canada, Spain, Israel, Finland

4.4. 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 run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug for the TEV-48125 225/225/225 mg treatment group versus the placebo treatment group
2. proportion of patients reaching at least 50% reduction in monthly average number of migraine days during 12-week period after the 1st dose of study drug for the TEV-48125 225/225/225 mg treatment group versus the placebo treatment group
3. mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug for the TEV-48125 675 mg/placebo/placebo treatment group versus the placebo treatment group
4. mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 1st dose of the study drug for the TEV-48125 675 mg/placebo/placebo treatment group versus the placebo treatment group
5. proportion of patients reaching at least 50% reduction in the monthly number of migraine days during 12-week period after the 1st dose of study drug for the TEV-48125 675 mg/placebo/placebo treatment group versus the placebo treatment group
6. mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of the study drug for the TEV-48125 225/225/225 mg treatment group versus the placebo treatment group
7. mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of study drug for the TEV-48125 675 mg/placebo/placebo treatment group versus the placebo treatment group

8. mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 1st dose of the study drug for the TEV-48125 225/225/225 mg treatment group versus the placebo treatment group
9. mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug for the TEV-48125 225/225/225 mg treatment group versus the placebo treatment group
10. mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug for the TEV-48125 675 mg/placebo/placebo treatment group versus the placebo treatment group
11. mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug for the TEV-48125 225/225/225 mg treatment group versus the placebo treatment group in patients not receiving concomitant migraine preventive medications
12. mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug for the TEV-48125 675 mg/placebo/placebo treatment group versus the placebo treatment group in patients not receiving concomitant migraine preventive medications

If the resulting 2-sided p-value from the first comparison is ≤0.05, then the next comparison of interest will be interpreted inferentially at the alpha level of 0.05. This process will continue either until all comparisons of interest are interpreted inferentially or until the point at which the resulting 2-sided p value for a comparison of interest is >0.05. At the point where p>0.05, no further comparisons will be interpreted inferentially.

4.5. Handling Withdrawals and Missing Data

If a patient has ≥10 days of the e-diary data after 1st dose of the study drug, 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.

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

- If the patient 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 patient 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.

The weekly number of migraine days and headache days of at least moderate severity will be calculated for the patients' first 28 calendar days of diary data after the 1st dose of study drug. Each week is defined as 7 calendar days with week 1 counted from the 1st dose date. If a patient has missing diary days in a week, the following method will be used to handle the missing data.

- If the patient has ≥**3** days of e-diary data for a week, the weekly number of days of efficacy variables will be prorated to 7 days for that week.
- If the patient has <**3** days of e-diary data for a week, the weekly number of days of efficacy variables will be considered as missing for that week.

The handling of missing questionnaire items for the MSQOL questionnaire (Appendix D) is discussed in Appendix E: scoring instruction for MSQOL.

4.6. Study Days and Visit Windows

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

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 study drug 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 study drug 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 study on day 84 approximately.

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

The weekly (7-day) windows for calculating the weekly efficacy endpoints for the first 28 days will be determined based on the 1st dosing day. The first week is from day 1 to day 7, the second week is from day 8 to day 14, the third week is from day 15 to day 21, and the fourth week is from day 22 to day 28. Only the days between the first and the second dose will be included.

For all other by-visit summaries, 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.

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

5. STUDY POPULATION SUMMARY

5.1. General

The ITT population will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group, all TEV-48125 and overall unless otherwise noted.

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

5.2. Patient Disposition

Patients screened, screening failures, and the reasons the patients were not randomized will be summarized only for the overall group using patient counts.

Patients randomized (ie, in the ITT set), patients randomized but not treated, patients in the safety, full analysis set and per-protocol population, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Patients who withdraw from the study 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 patient signs informed consent. Patient's demographics and baseline characteristics including age, sex, country, ethnicity and race, weight, height, and body mass index, years of migraine, concomitant preventive medication use for migraine, use of topiramite or onabotulinumtoxinA for migraine in the past, and any triptans/ergots during baseline will be summarized for ITT population.

The baseline e-diary efficacy variables listed in Section 4.2, baseline MIDAS scores and MSQOL scores will be summarized by treatment group for the ITT population.

For continuous variables, treatment groups will be compared using an analysis of variance with treatment as a factor. For categorical variables, treatment groups will be compared using a Pearson's chi-square test (or Fisher's exact test if cells sizes are too small).

5.4. Medical History

All medical history abnormalities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized by system organ class (SOC) and preferred term (PT). Patients are counted only once in each SOC and only once in each PT.

5.5. Prior Medications or Therapy

All prior medications or therapy will be coded using the World Health Organization dictionary of medical codes (WHO Drug). The incidence of prior medications or therapy will be summarized using descriptive statistics by therapeutic class and PT. Patients are counted only once in each therapeutic class category, and only once in each PT category. Prior medications will include all medications taken prior to the 1st study drug treatment.

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

- preventive migraine medication
- triptans and ergots
- non-steroidal anti-inflammatory drugs (NSAIDs) for migraine/headache
- NSAIDs for reasons other than migraine/headache
- opioids for migraine/headache
- opioids for reasons other than migraine/headache
- other

5.6. Electrocardiography

Electrocardiogram findings (normal, abnormal, and missing) at baseline will be summarized using descriptive statistics.

5.7. Physical Examinations

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

5.8. Protocol Violations

Patients with at least 1 protocol violation will be summarized for each category using descriptive statistics.

5.9. Childbearing Potential

All patients must be of nonchildbearing potential as defined in protocol Section 4.1. Information related to childbearing potential will be collected and listed.

6. EFFICACY ANALYSIS

6.1. General

The efficacy data for this study consist of headache related questions responses (e.g., occurrence of headache, duration of headache in each day, maximum severity of headache, and acute migraine-specific medication use) collected daily using an electronic headache diary device.

In addition, the following questionnaires will be used for the assessments of migraine impairment, quality of life and satisfaction of treatment etc. during the study (See Table 1) for the schedule of the assessment).

- migraine disability assessment test (see Appendix C)
- migraine-specific quality of life, as measured by the MSQOL questionnaire (see Appendix D)
- health status, as measured by the EQ-5D-5L questionnaire (see Appendix F)
- patient depression status, as measured by the PHQ-2 and the PHQ-9 (see Appendix G)
- patient work productivity and activity impairment, as measured by the WPAI questionnaire (see Appendix H)
- assessment of patient satisfaction, as measured by the PGIC scale (see Appendix I)

The ***monthly average number of days or hours*** of efficacy variables (e.g. 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 study drug will be derived and normalized to **28** days equivalent using the following formula.

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

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 study drug 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, i.e.,

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

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 ***baseline values*** for calculating the change from baseline of the weekly number of days of the efficacy variables will use all data collected in the run-in period and be calculated as

$$\frac{\sum Days\ of\ efficacy\ variable\ during\ the\ run-in\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ run-in\ period} \times 7 \quad (5)$$

The ***weekly number of days*** of efficacy variables (e.g., days of headache with at least moderate severity, migraine days) for each week during the 4-week period after the 1st dose of study drug will be derived and normalized to **7** days equivalent using the following formula.

$$\frac{\sum Days\ of\ efficacy\ variable\ during\ the\ 7\ days\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 7\ days\ period} \times 7 \quad (6)$$

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

The primary and secondary endpoints analysis listed in Section 4.4 will be repeated for the per-protocol analysis set.

6.2. Primary Efficacy Variable(s) and Analysis

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

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

The derivation logic is presented in Appendix B.

6.2.1. Variable Definition

The primary efficacy variable is the change from baseline in the monthly average number of migraine days ***during the 12-week period*** after the 1st dose of study drug. The baseline values will be derived using formula (3). The postbaseline values will be derived using formula (1), and ***the change*** is calculated as $\boldsymbol{postbaseline\ value - baseline\ value}$.

6.2.2. Primary Analysis

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 estimates 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 each TEV-48125 dose vs. placebo will be tested following the pre-specified fixed sequence as specified in Section 4.4.

An analysis of covariance (ANCOVA) method will be applied for the primary analysis. The model will include treatment, sex, region (Table 2) , and baseline preventive migraine medication use (yes/no) as fixed effects; the baseline number of migraine days and years since onset of migraine as covariates. The least square (LS) means for the treatment groups, LS mean and corresponding 95% confidence intervals for the treatment differences (TEV-48125 – placebo), and associated p-value will be provided.

The following sample SAS code pertains to the primary efficacy analysis.

```
ODS OUTPUT DIFFS=XXX LSMEANS=XXX TESTS3=XXX;
PROC MIXED DATA=XXX;
    CLASS TREAT SEX BMU REGION;
    MODEL CHG=BASE YOD BMU SEX TREAT REGION/S;
    LSMEANS TREAT/PDIFF CL ALPHA=0.05;
RUN;
```

The normality of the residuals from the ANCOVA model will be checked using Shapiro Wilk's normality test. In case that the Shapiro Wilk's test has a p value ≤0.01, Wilcoxon rank-sum test will be conducted as the primary analysis using SAS procedure NPAR1WAY for each active treatment group and placebo group. P value based on normal approximation from this procedure will be selected for the treatment comparison. The ANCOVA analysis will be performed as a supportive analysis.

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 patient'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 patient 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 4.5.

The MMRM model will include baseline value, treatment, sex, region, baseline preventive migraine medication use (yes/no), years since onset of migraines, month and treatment-by-month interaction as fixed effects, and patient in the repeated statement as a random effect. The unconstructed covariance structure will be used for the repeated observations within a patient. LS means for the treatment groups, LS means for the treatment differences (TEV-48125 - placebo), and corresponding 95% confidence intervals and associated p-values will be calculated by month and for the overall treatment period.

The following SAS code pertains to the MMRM analysis.

```
ODS OUTPUT DIFFS=XXX LSMEANS=XXX TESTS3=XXX;
PROC MIXED DATA=XXX METHOD=REML;
    CLASS USUBJID MONTH TREAT SEX BMU REGION;
    MODEL CHG=BASE YOD BMU SEX TREAT MONTH TREAT*MONTH/S;
    REPEATED MONTH/SUBJECT=USUBJID TYPE=UN R;
    LSMEANS TREAT TREAT*MONTH/PDIFF CL ALPHA=0.05;
RUN;
```

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

6.2.3.2. Analysis with Multiple Imputation Method

Multiple imputation (MI) method will be applied to impute the monthly missing data. The data will be processed by the following steps.

- If a patient has partial e-diary data for a month, ie, <10 days of data, that month value will be considered missing before the MI procedure.
- For the patients in the active treatment group 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 patients
- Run SAS PROC MI procedure to create 10 complete datasets.
- Within each imputed data set, for a patient who has partial, say X days (X<10) , 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 study drug will be the average of month 1, month 2 and month 3 values.

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 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.

6.3. Secondary Efficacy Variables and Analysis

The secondary efficacy endpoints are as follows:

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

6.3.1. Variable Definition

6.3.1.1. Electronic Headache Diary Data

The change from baseline in the monthly average number of days of secondary efficacy variables (e.g. migraine days, days of use of any acute headache medications etc.) ***during the 12-week period*** after the 1st dose of study drug 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 study drug will be calculated by formula (4) in Section 6.1. The patient is considered as a responder if the percent reduction is 50% or more. If a patient is early discontinued from the study, he/she will be counted as a non-responder.

The change from baseline (run-in period) in the number of migraine days ***during the 4-week period*** after the 1st dose of study drug will be derived similar to the primary endpoint using only the 1st month diary data.

6.3.1.2. Migraine Disability Assessment (MIDAS)

The MIDAS questionnaire is a 5-item instrument developed to assess headache-related disability based on lost days of activity in 3 domains (work, household work, and nonwork) over the previous 3 months. Patients will complete the MIDAS questionnaire at baseline (visit 2) and the EOT visit (visit 5). The total score, ie, the sum of the first 5 questions, is used for grading of disability, with scores of 0 to 5, 6 to 10, 11 to 20, and ≥21 interpreted as disability grades 1 (little or no disability), 2 (mild disability), 3 (moderate disability), and 4 (severe disability), respectively.

6.3.2. Analysis of Secondary Efficacy Variables

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, region, and baseline preventive migraine medication use (yes/no) as fixed effects; the baseline values and years since onset of migraines as covariates. 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.

If a patient has less than 10 days of e-diary data entries after the 1st dose of study drug, the missing data handling method for the primary variable discussed in Section 6.2.1 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 study drug.

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

LS means for the treatment groups, LS mean 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.

Cochran Mantel-Haenszel test stratified by baseline preventive migraine medication use (yes/no) will be used for analyzing the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug. The SAS Proc FREQ will be used to carry out this analysis.

The change from baseline values in the MIDAS total scores will be analyzed using the same ANCOVA method as described above.

Patients not receiving concomitant preventive medication constitute the sub-population who don't take any preventive migraine medications listed in APPENDIX B of the protocol during the study, ie, with baseline preventive migraine medication use = No.

For all relevant secondary endpoints, the normality of the residuals from each ANCOVA model will be checked using Shapiro Wilk's normality test. In case that the Shapiro Wilk's test has a p value ≤ 0.01, Wilcoxon rank-sum test will be conducted as the primary analysis. The ANCOVA analysis will be considered as a supportive analysis.

6.4. Exploratory Efficacy Variables and Analysis

The exploratory efficacy endpoints are described in Section 2.2.3.

6.4.1. Variable Definition

6.4.1.1. Electronic Headache Diary Data

A headache day of at least moderate severity will be defined as a calendar day (00:00 to 23:59) where the patient reports:

- a day with headache pain that lasts ≥4 hours with a peak severity of at least moderate severity

  or

- a day when the patient used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration

The percent reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug will be calculated by formula (4) in Section 6.1. The patient 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 patients 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 study drug. If a patient is early discontinued from the study, 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 patient has 50% reduction or more in month 1, he/she will be considered responder during the 4-week period after 1st dose of study drug. In addition if the patient 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 study drug for this patient. 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 ≥4 hours of any severity or a day when the patient used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration.

The change from baseline in the monthly average number of days or hours of exploratory efficacy variables (e.g. days with at least moderate severity, days with any severity, total hours of headache with at least moderate severity, total hours of headache with any severity, days of use of migraine-specific acute medications, days with nausea or vomiting, days with photophobia and phonophobia etc.) ***during the 12-week period*** after the 1st dose of study drug 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 derived using

formula (3) and (1) respectively, and ***the change*** is calculated as ***postbaseline value – baseline value***.

The change from baseline in the monthly number of days or hours of exploratory efficacy variables (e.g. days of headache with at least moderate severity, days of headache with any severity, total hours of headache with at least moderate severity, total hours of headache with any severity, days of use of migraine-specific acute medications, days with nausea or vomiting, days with photophobia and phonophobia etc.) ***during the 4 week period*** after the each dose of study drug will be calculated using formula (2) using the month 1, month 2 and month 3 diary data respectively.

The change from baseline in weekly number of headache days of at least moderate severity or migraine days for week 1 (Day 1-7), week 2 (Day 8-14), week 3 (Day15-21) and week 4 (Day 22-28) after the 1st dose of study drug will be derived using the 1st 28-day diary data. The baseline values and the postbaseline values will be derived using formula (5) and (6) in Section 6.2.1 respectively, and ***the change*** is calculated as ***postbaseline value – baseline value***.

6.4.1.2. Migraine-Specific Quality of Life

The 14-item MSQOL (see Appendix D) questionnaire is designed to measure how migraines affect and/or limit daily functioning across three domains: Role Function-Restrictive domain comprising 7 items assessing how migraines limit one's daily social and work-related activities; Role Function-Preventive domain comprising 4 items assessing how migraines prevent these activities, and Emotional Function domain comprising 3 items assessing the emotions associated with migraines. Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale such that higher scores indicate better quality of life. Appendix E provides the scoring instructions on how to rescale the raw score to the scales that will be used for analysis.

6.4.1.3. EuroQol-5 Dimension Questionnaire

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

6.4.1.4. Patient Health Questionnaire

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

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

6.4.1.5. Work Productivity and Activity Impairment Questionnaire: General Health V2.0

The generic version of the WPAI: General Health (GH) (Appendix H) questionnaire measures the overall effect of health on productivity at work and daily activities. The specific health problems version of the WPAI questionnaire allows investigators to attribute productivity and activity impairment issues to specific health conditions. This assessment will be done at baseline (visit 2) and the EOT visit (visit 5).

The following scores (in percentages) will be derived based on the WPAI:GH questionnaire.

- percent work item missed due to health: $\frac{Q2}{Q2+Q4}$x100
- percent impairment while working due to health: $\frac{Q5}{10}$ x100
- percent overall work impairment due to health: $\{\frac{Q2}{Q2+Q4}+\left[\left(1-\frac{Q2}{Q2+Q4}\right)\times\frac{Q5}{10}\right]\}$x100
- percent activity impairment due to health: $\frac{Q6}{10}$x100

6.4.1.6. Patient's Global Impression of Change

The PGIC scale (Appendix I) is a validated generic tool for assessment of overall change in the severity of illness following treatment. Patients will rate how they feel now compared with how they felt before receiving study drug on a 7-point scale where 0 is "No change" and 7 is "A great deal better".

Based on the PGIC assessment, a dichotomous scale of " Yes" or "No" will be derived. A favorable change is score of 5-7 = 'Yes', which means there is significant improvement with the treatment. If the response is 1-4 = 'No', it is considered no significant change.

6.4.2. Exploratory Efficacy Analysis

6.4.2.1. Electronic Headache Diary Data

Cochran Mantel-Haenszel test stratified by baseline preventive migraine medication use (yes/no) will be implemented for analyzing the responder type of exploratory efficacy endpoints. The SAS Proc FREQ will be used to carry out this analysis.

An ANCOVA method defined in Section 6.2.2 and an MMRM model defined Section 6.2.3.1 will be implemented for the following exploratory endpoints analysis.

- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of any severity during the 12-week period after the 1st dose of study drug

- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of any severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of the study
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug

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 endpoints by week after the 1st dose of study drug.

- mean change from baseline in the weekly number of headache days of at least moderate severity
- mean change from baseline in the weekly number of migraine days

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 week.

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

6.4.2.2. Migraine-Specific Quality of Life

The transformed scores for the three domains (i.e., Role Function-Restrictive, Role Function-Preventive and Emotional Function) of MSQOL will be derived for baseline (visit 2), visit 3, visit 4, and visit 5. The change from baseline values after the 3rd injection will be analyzed by ANCOVA method as described in Section 6.2.2 and MMRM method as described in Section 6.2.3.1.

6.4.2.3. EuroQol-5 Dimension Questionnaire

The number and percentage of patients rating their scale of 1 to 5 for the 5 domains will be presented before and after treatment. The change from baseline values on the visual analogue scale will be analyzed using the same ANCOVA method as described in Section 6.2.2.

6.4.2.4. Patient Health Questionnaire

The change from baseline in total PHQ-9 score will be analyzed using the same ANCOVA method as described in Section 6.2.2.

6.4.2.5. Work Productivity and Activity Impairment Questionnaire : General Health V2.0

For the patients who are currently employed, their scores of

- percent work item missed due to health

- percent impairment while working due to health
- percent overall work impairment due to health
- percent activity impairment due to health

will be analyzed using the same ANCOVA method as described in Section 6.2.2 .

6.4.2.6. Patient's Global Impression of Change Scale

The percentage of patients' dichotomous scale of " Yes" or "No" rated by PGIC assessments at 4-week after each dose will be analyzed by Cochran Mantel-Haenszel test stratified by baseline preventive migraine medication use (yes/no) as described in Section 6.3.2.

6.5. Subgroup Analysis

The primary analysis with ANCOVA method defined in Section 6.2.2 and MMRM method defined in Section 6.2.3.1 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.

- patients receiving or not receiving any concomitant preventive treatment at baseline
- patients who used topiramate for migraine in the past
- patients who used onabotulinumtoxinA for migraine in the past
- patients in different age groups (18-45, >45 years old)
- patients in different race groups (caucasian, non-caucasian)
- patients by sex

7. SAFETY ANALYSIS

7.1. General

The safety population will be used for all safety analyses. Summaries will be presented by treatment group and all TV48125 as actually received unless specified otherwise.

7.2. Study Drug Administration

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

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

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

Duration of treatment (days treated) is the number of days on treatment based on the 1st study drug administration day and end of treatment (EOT) visit day/early withdrawal day (EOT visit day – first day of study drug + 1). For subjects who are lost to follow-up, the EOT date is defined as the last study drug administration date +27.

Number (%) of patient 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.

7.3. Adverse Events

All adverse events will be coded using the MedDRA version 18.1.

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

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

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, events of possible drug-induced liver injury (AST or ALT $\geq 3 \times$ the ULN, total bilirubin $\geq 2 \times$ the ULN or INR >1.5), or Hy's Law events, as well anaphylaxis and hypersensitivity reactions. Hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious

Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al, 2006). 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 events determined by the investigator to be treatment-related adverse events (overall and by severity), serious adverse events, adverse events causing discontinuation from the study, non-serious treatment emergent adverse events and prior to treatment adverse events. Additionally, the injection site reactions recorded as adverse events and protocol defined adverse events 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 patient 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 study drug and adverse events with missing relationship to study drug. 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, serious adverse events, adverse events leading to discontinuation, injection site related adverse event, and protocol defined adverse events will be presented. All information pertaining to adverse events noted during the study 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 patient number and treatment group will be presented.

7.4. Injection Site Assessments

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

- Injection-site erythema, injection-site induration, and injection-site ecchymosis will be graded according to measurements: absent, 5 mm to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe).

Injection-site pain will be measured as summarized in Table 3.

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

Number (%) of patients having injections and their post injection assessments for erythema, induration, ecchymosis, and pain of each grade will be summarized by visits and timepoints for each treatment group.

Table 3: Severity of Pain Scale for Injection Site Assessments

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

To differentiate between assessments at active treatment (TEV 48125) injection sites and placebo injection sites for subjects who receive 225 mg TEV 48125 (1 active, 2 placebo injections) at visit 2, summaries for these treatments will be presented by treatment type (TEV-48125 or placebo). Subjects are only counted once for each treatment type, and if multiple sites with the same treatment type (TEV-48125 or placebo) present with different severities, the most severe reaction will be summarized.

7.5. Deaths

If any patient dies during the study all relevant information will be discussed in the patient's narratives included in CSR.

7.6. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1 using the central laboratory. Specific laboratory tests to be performed are listed below in Table 4.

Table 4: Clinical Laboratory Test

Serum Chemistry	Hematology	Coagulation	Urinalysis

• calcium
• phosphorus
• sodium
• potassium
• chloride
• carbon dioxide
• magnesium
• glucose
• blood urea nitrogen
• creatinine
• ALT
• AST
• total bilirubin
• direct bilirubin
• lactate dehydrogenase
• GGT
• ALP
• albumin
• creatine phosphokinase
• total protein
	• hemoglobin
	• hematocrit
	• RBC count
	• RBC indices
	  - mean corpuscular volume
	  - mean corpuscular hemoglobin concentration
	  - RBC distribution width
	• platelet count
	• WBC count and differential count (absolute values and percentages)
	  - neutrophils
	  - lymphocytes
	  - eosinophils
	  - monocytes
	  - basophils
		• prothrombin time
		• partial thromboplastin time
		• INR
			• color and appearance
			• specific gravity
			• pH
			• blood (hemoglobin)
			• glucose
			• albumin
			• protein
			• ketones
			• leukocyte esterase
			• nitrite
			• direct bilirubin
			• microscopic
			  - bacteria
			  - RBCs
			  - WBCs
			  - casts
			  - crystals

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma- glutamyl transpeptidase; INR=international normalized ratio; RBC=red blood cell; WBC=white 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 endpoint will be summarized using patient counts. Listings of all individual patients' laboratory test results will be presented.

The incidence of potentially clinically significant abnormal results will be summarized using descriptive statistics with the criteria specified in Table 5. The potentially clinically significant abnormal laboratory values will include all postbaseline values (including scheduled, unscheduled, and early termination visits) for the summaries. Listings of patients who have potentially clinically significant abnormal laboratory data will be presented.

Table 5: Criteria for Potentially Clinically Significant Laboratory Values

Test		Criterion value
Serum chemistry		
ALT		≥3x ULN
AST		≥3x ULN
ALP		≥3x ULN
GGT		≥3x ULN
LDH		≥3x ULN
BUN		≥10.71 mmol/L
Creatinine		≥177 μmol/L
Uric acid	Men	≥625 μmol/L
	Women	≥506 μmol/L
Bilirubin (total)		≥34.2 μmol/L
Hematology		
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L
Hemoglobin	Men	≤115 g/L
	Women	≤95 g/L
WBC counts		≤3 x 10^9/L ≥20 x 10^9/L
Eosinophils		≥10%
ANC		≤1 x 10^9/L
Platelet counts		≤75 x 10^9/L ≥700 x 10^9/L
Urinalysis		
HGB		≥2 unit increase from baseline
Glucose		≥2 unit increase from baseline
Ketones		≥2 unit increase from baseline
Total protein		≥2 unit increase from baseline

ULN=upper limit of normal range.
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 women of childbearing potential at screening (visit 1), and urine β-HCG tests will be performed for women of childbearing potential at visits 2 through 5. Positive pregnancy test results will be listed.

7.7. Vital Signs

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

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 endpoint 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 6 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: i.e., 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 6: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥15
	≤50 bpm	Decrease of ≥15
Systolic blood pressure	≥180 mm Hg	Increase of ≥20
	≤90 mm Hg	Decrease of ≥20
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15
	≤50 mm Hg	Decrease of ≥15
Respiratory rate	<10 breaths/min	
Body temperature	≥38.3°C	Change of ≥1.1°C

bpm=beats per minute

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

7.8. Electrocardiography

Twelve-lead ECGs will be conducted before other assessments (eg, blood draws and administration of questionnaires) at the time points detailed in Table 1.

The ECGs 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.

Shifts (normal and abnormal) from baseline to the endpoint will be summarized using patient counts and percentages. ECG variables results and changes from baseline to EOT/EOS will be summarized using descriptive statistics.

7.9. Physical Examinations

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

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

Abnormal physical examination findings will be listed.

7.10. Electronic Columbia-Suicide Severity Rating Scale

The electronic columbia-suicide severity rating scale (eC-SSRS) will be used to assess the patient's suicidal ideation (severity and intensity) and behavior (Posner et al 2011). The eC-SSRS 'Baseline/Screening version' will be completed by the patient at visit 2, and the eC-SSRS 'Since Last Visit version' will be completed by the patient at all other time points, as described in Table 1.

Any positive findings on the eC-SSRS 'Since Last Visit version' require evaluation by a physician or doctoral-level psychologist.

Patients having positive findings will be listed.

7.11. Concomitant Therapy or Medication

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

The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients 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.

- migraine/headache preventive medication
- opioids for reasons other than migraine/headache
- opioids for migraine/headache
- triptans and ergots
- NSAIDs for reasons other than migraine/headache
- NSAIDs for migraine/headache
- other

8. PHARMACOKINETIC ANALYSIS

There are no prespecified pharmacokinetic endpoints.

Summary of plasma concentration of the study drug will be based on the safety population and will be presented by visit for each of the active treatment groups (samples from patients who received placebo will not be analyzed). The plasma concentration will be listed by active treatments, scheduled visits and timepoints.

9. BIOMARKER ANALYSIS

The biomarker analysis is not included in this SAP. A separate planned analysis will be conducted.

10. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS®.

11. CHANGES TO PROTOCOL SPECIFIED ANALYSES

The FAS definition is modified per the FDA feedback. The original definition was “all patients in the ITT population who receive at least 1 dose of study drug and have at least **1** post baseline efficacy assessment on the primary endpoint”. The modified definition is “all patients in the ITT population who receive at least 1 dose of study drug and have at least **10** days of post baseline efficacy assessments on the primary endpoint”.

The first 4-week efficacy data for at least moderate severity headache days and migraine days will be explored by week using descriptive method and MMRM method.

12. REFERENCES

Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):629-808.

Kroenke K, Spitzer RL, Williams JB, Löwe B. The Patient Health Questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. Gen Hosp Psychiatry 2010;32(4):345-59.

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.

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

Silberstein S, Holland S, Freitag F, Dodick DW, Argoff C, Ashma E. Evidence-based guideline update: pharmacologic treatment of episodic migraine prevention in adults. Neurology 2012;78:1337-45.

Spitzer RL, Kroenke K, Williams JB. Validation and utility of self-report version of PRIME MD: the PHQ primary care study. Primary care evaluation of metal disorders. Patient health questionnaire. JAMA 1999;282(18):1737-44.

APPENDIX A. E-DIARY QUESTIONNAIRE

	The following questions are referring to yesterday (00:00 - 23:59)
A1	Did you experience a headache of any severity yesterday?
A2	Did you have at least four (4) consecutive hours of headache yesterday?
A3	Did you have at least two (2) consecutive hours of headache yesterday?
A4	What was the greatest severity that your headache reached yesterday at anytime?
A5	How many total hours did you have a headache(s) of any severity yesterday?
A6	How many total hours did you have a headache(s) of moderate or severe intensity yesterday?

	The following questions are referring to yesterday (00:00 - 23:59) AT THE TIME WHEN YOUR HEADCAHE REACHED THE WORST SEVERITY
B1	Was it worse on one side of the head than on the other, and/or limited to one side of the head?
B2	Was it pounding, pulsating, or throbbing?
B3	Was it made worse by routine activities such as walking or climbing stairs?
B4	Did you have nausea, or get sick to your stomach?
B5	Did light bother you more than when you didn't have a headache (did you experience photophobia)?
B6	Did sounds bother you more than when you didn't have a headache (did you experience phonophobia)?
	The following questions are referring to yesterday (00:00 - 23:59)
B7	Did you experience something like seeing spots, stars, lines, flashing lights, zigzag lines, or "heat waves" around the time of your headache? (This is different from "light bothers you")
B8	Did you have feelings such as numbness or tingling in any part of your body or face around the time of your headache?
B9	Did you experience something like seeing spots, stars, lines, flashing lights, zigzag lines, or "heat waves" similar to those you may have seen when you have a headache? (This is different from "light bothers you")
B10	Did you have feelings such as numbness or tingling in any part of your body or face, similar to what you may have felt when you have a headache?

C0	Did you take any medications yesterday for your headache/migraine?
C1	Were any of the following Medications taken yesterday?
	Local list of Triptans, Ergots and Opioid combinations, Presented in groups of 5 per screen, with Yes / No option to answer.
	For the following questions please do not consider any medications you listed in the above questions.
D1	Did you use any other prescription medications (i.e. opioids) in an effort to get relief from your headache/migraine?
D5	Did you use any other over the counter medications in an effort to get relief from your headache/migraine?
E1	Did you have problems falling sleep last night?
E2	Which of the following situations best describe your work/school performance yesterday, when you did not have a headache?
E3	What would better describe in general, how did you feel yesterday?
E4	How much of the time yesterday did you find it difficult to concentrate on what you needed to do?
E5	On average, how much of the time yesterday were you very tired, asleep, or feeling drained?
E6	Which of the following situations best describe your ability to perform household chores yesterday, when you did not have a headache?
E7	How engaged were you with your partner's or children's activities yesterday, when you didn't have a headache?
E8	Overall, how interested were you in doing daily activities yesterday?

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APPENDIX B. LOGICS FOR ENDPOINTS DERIVATION

		EM migraine day: 1 of the following 5 options					
		OPTION 1				OPTION 2	
Part 1	1	A1	YES	1	A1		YES
	2*	A2 or A3	YES	2	C0		YES
		AND		3	C1		YES
				4	C1		ERGOT OR TRIPTAN
		TWO OF THE FOLLOWING			OPTION 3		
Part 2	1	A4	Mod-S				
	2	B1	YES	1	A1		YES
	3	B2	YES	2	C0		YES
	4	B3	YES	3	D1		YES
		AND		4	D1		ERGOT OR TRIPTAN
		ONE OF THE FOLLOWING			OPTION 4		
Part 3	1	B4	YES				
				1	A1		YES
	2	B5	YES		AND		ONE OF THE FOLLOWING
		AND		1	B7		YES
		B6	YES	2	B8		YES

* For eligibility evaluation, replace A2 or A3 = YES with A2='YES'.

OPTION 5: PROBABLE MIGRAINE			
If **Part 1** and **Part 2** met, **Part 3** needs ONLY one of the following:			
Part 3		**B5**	YES
		B6	YES
If **Part 1** and **Part 3** met, **Part 2** needs ONLY one of the following:			
Part 2	**1**	**A4**	Mod-S
	2	**B1**	YES
	3	**B2**	YES
	4	**B3**	YES
If **Part 2** and **Part 3** met, **Part 1** needs ONLY the following:			
Part 1	**1**	**A1**	YES

APPENDIX C. THE MIGRAINE DISABILITY ASSESSMENT

The MIDAS (Migraine Disability Assessment) questionnaire was put together to help you measure the impact your headaches have on your life. The information on this questionnaire is also helpful for your primary care provider to determine the level of pain and disability caused by your headaches and to find the best treatment for you.

INSTRUCTIONS:

Please answer the following questions about ALL of the headaches you have had over the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months.

_____ 1. On how many days in the last 3 months did you miss work or school because of your headaches?

_____ 2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

_____ 3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

_____ 4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

_____ 5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

_____ Total (Questions 1-5)

_____ A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)
B. On a scale of 0 - 10, on average how painful were these headaches? (where 0 = no pain at all, and 10 = pain as bad as it can be.)

Scoring: *After you have filled out this questionnaire, add the total number of days from questions 1-5 (ignore A and B)*

MIDAS Grade	Definition	MIDAS Score
I	Little or no disability	0-5
II	Mild disability	6-10
III	Moderate disability	11-20
IV	Severe disability	21+

Please give the completed form to your clinician.

This survey was developed by Richard B. Lipton, MD, Professor of Neurology, Albert Einstein College of Medicine, New York, NY, and Walter F. Stewart, MPH, PhD, Associate Professor of Epidemiology, Johns Hopkins University, Baltimore, MD.

APPENDIX D. MIGRAINE-SPECIFIC QUALITY OF LIFE QUESTIONNAIRE (MSQ) (VERSION 2.1)

While answering the following questions, please think about ***all migraine attacks*** you may have had ***in the past 4 weeks***.

1. In the past 4 weeks, how often have migraines **interfered** with how well you dealt with family, friends and others who are close to you? (Select only **one** response.)

   $_1$❑ None of the time
   $_2$❑ A little bit of the time
   $_3$❑ Some of the time
   $_4$❑ A good bit of the time
   $_5$❑ Most of the time
   $_6$❑ All of the time

2. In the past 4 weeks, how often have migraines **interfered** with your leisure time activities, such as reading or exercising? (Select only **one** response.)

   $_1$❑ None of the time
   $_2$❑ A little bit of the time
   $_3$❑ Some of the time
   $_4$❑ A good bit of the time
   $_5$❑ Most of the time
   $_6$❑ All of the time

3. In the past 4 weeks, how often have you had **difficulty** in performing work or daily activities because of migraine symptoms? (Select only **one** response.)

   $_1$❑ None of the time
   $_2$❑ A little bit of the time
   $_3$❑ Some of the time
   $_4$❑ A good bit of the time
   $_5$❑ Most of the time
   $_6$❑ All of the time

4. In the past 4 weeks, how often did migraines **keep you** from getting as much done at work or at home? (Select only **one** response.)

$_1$❑ None of the time
$_2$❑ A little bit of the time
$_3$❑ Some of the time
$_4$❑ A good bit of the time
$_5$❑ Most of the time
$_6$❑ All of the time

5. In the past 4 weeks, how often did migraines **limit** your ability to concentrate on work or daily activities? (Select only **one** response.)

$_1$❑ None of the time
$_2$❑ A little bit of the time
$_3$❑ Some of the time
$_4$❑ A good bit of the time
$_5$❑ Most of the time
$_6$❑ All of the time

6. In the past 4 weeks, how often have migraines **left you too tired** to do work or daily activities? (Select only **one** response.)

$_1$❑ None of the time
$_2$❑ A little bit of the time
$_3$❑ Some of the time
$_4$❑ A good bit of the time
$_5$❑ Most of the time
$_6$❑ All of the time

7. In the past 4 weeks, how often have migraines **limited** the number of days you have felt energetic? (Select only **one** response.)

$_1$❑ None of the time
$_2$❑ A little bit of the time
$_3$❑ Some of the time
$_4$❑ A good bit of the time
$_5$❑ Most of the time
$_6$❑ All of the time

8. In the past 4 weeks, how often have you had to **cancel** work or daily activities because you had a migraine? (Select only **one** response.)

$_1$❑ None of the time
$_2$❑ A little bit of the time
$_3$❑ Some of the time
$_4$❑ A good bit of the time
$_5$❑ Most of the time
$_6$❑ All of the time

9. In the past 4 weeks, how often did you **need help** in handling routine tasks such as every day household chores, doing necessary business, shopping, or caring for others, when you had a migraine? (Select only **one** response.)

$_1$❑ None of the time
$_2$❑ A little bit of the time
$_3$❑ Some of the time
$_4$❑ A good bit of the time
$_5$❑ Most of the time
$_6$❑ All of the time

10. In the past 4 weeks, how often did you have to **stop** work or daily activities to deal with migraine symptoms? (Select only **one** response.)

$_1$❑ None of the time
$_2$❑ A little bit of the time
$_3$❑ Some of the time
$_4$❑ A good bit of the time
$_5$❑ Most of the time
$_6$❑ All of the time

11. In the past 4 weeks, how often were you **not able to go** to social activities such as parties, dinner with friends, because you had a migraine? (Select only **one** response.)

$_1$❑ None of the time
$_2$❑ A little bit of the time
$_3$❑ Some of the time
$_4$❑ A good bit of the time
$_5$❑ Most of the time
$_6$❑ All of the time

12. In the past 4 weeks, how often have you **felt** fed up or frustrated because of your migraines? (Select only **one** response.)

$_1$❑ None of the time
$_2$❑ A little bit of the time
$_3$❑ Some of the time
$_4$❑ A good bit of the time
$_5$❑ Most of the time
$_6$❑ All of the time

13. In the past 4 weeks, how often have you **felt** like you were a burden on others because of your migraines? (Select only **one** response.)

1❑ None of the time
2❑ A little bit of the time
3❑ Some of the time
4❑ A good bit of the time
5❑ Most of the time
6❑ All of the time

14. In the past 4 weeks, how often have you been **afraid** of letting others down because of your migraines? (Select only **one** response.)

1❑ None of the time
2❑ A little bit of the time
3❑ Some of the time
4❑ A good bit of the time
5❑ Most of the time
6❑ All of the time

APPENDIX E. SCORING INSTRUCTIONS FOR MSQ (VERSION 2.1)

MSQ (Version 2.1) is a 14-item self-administered questionnaire. Patients are asked to provide responses to each item using a standard six-point Likert type scale. The specific items which make up each dimension are presented in Appendix D.

Scoring

Each of the three MSQ dimensions is scored independently. For each dimension, a higher score indicates a better health status. The 14 MSQ items used in scoring are worded with a negative perspective, therefore must be recoded before the dimension scores are calculated.

The scoring of the MSQ is completed in 3 steps:

1. Recoding of MSQ items (final item value assignment)
2. Computation of raw dimension scores
3. Transformation of raw dimension scores to a 0 to 100 scale

Final item value assignment

The precoded and final item values for each MSQ item response is shown in Table 1. All item values range from 1 to 6.

How to handle missing values

In the event that responses on one or more items within a dimension are missing, a missing item value may be estimated using the average of the other items within the same dimension.

The general rule of thumb for handling missing data similar to the SF-36 Health Survey is applied. If a respondent answered at least half of the items in a multi-item scale (or half plus one in the case of scales with an odd number of items), a missing item value can be estimated. Therefore, when the number of missing items is fewer than or equal to 3 for the Role Function-Restrictive, fewer than or equal to 2 for the Role Function-Preventive, and fewer than or equal to 1 for the Emotional Function dimension, the value of missing item(s) can be estimated using the average of the other completed items within the same dimension.

For example, if a respondent leaves one item (e.g. item 4) within the 7-item Role Function-Restrictive dimension blank, substitute the respondent's average score across the six completed Role Function-Restrictive items (e.g. item 1, 2, 3, 5, 6, 7) for that one item.

It is important to note that the psychometric properties of the MSQ dimension are based on the assumption that all items within the dimendion are answered. Therefore, when the number of missing responses exceeds the limits as noted above, a dimension score may not be estimated and should be considered as missing.

Raw score computation

Once a final item value has been assigned to each item, a raw score can be computed for each MSQ dimension. The raw score for each dimension is simply the algebraic sum of the final item value for all items in that dimension. The range of each raw dimension score is shown in Table 2.

Transformation of dimension scores

After the raw score for each MSQ dimension is computed, the each score is transformed to a 0 to 100 scale. The transformation formula for each dimension is provided in Table 2. The transformation process allows each dimension score to reflect the percentage of the total possible score achieved (since 100 equal the highest score).

Scoring checks

The following scoring checks are recommended to ensure accuracy in data entry and processing:

1) After recoding items to their final item values, inspect the frequency distribution to verify all item values are within the range of 1 to 6.
2) Inspect frequency distributions for raw scores and transformed scores to verify that all scores are within the expected ranges.

Table 1 Precoded and final item values for MSQ item responses

Item No.	Response categories	Precoded items value	Final item value
1-14	None of the time	1	6
	A little bit of the time	2	5
	Some of the time	3	4
	A good bit of the time	4	3
	Most of the time	5	2
	All of the time	6	1

Table 2 Raw score and transformation formula for each MSQ dimension

MSQ dimension	Item No.	Raw score range	Transformation formula
Role Function - Restrictive	1-7	7 to 42	$\frac{(raw\ score - 7) \times 100}{35}$
Role Function - Preventive	8-11	4 to 24	$\frac{(raw\ score - 4) \times 100}{20}$
Emotional Function	12-14	3 to 18	$\frac{(raw\ score - 3) \times 100}{15}$

APPENDIX F. EQ-5D-5L AND EQ VAS

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

Self-Care

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

Pain/Discomfort

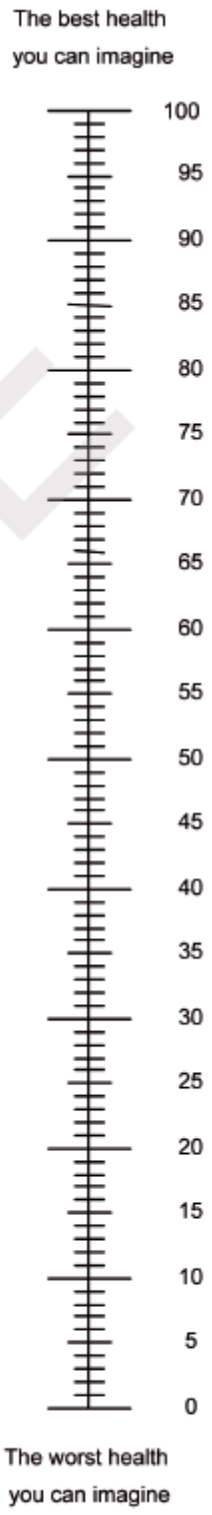
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



1594

APPENDIX G. PATIENT HEALTH QUESTIONNAIRE (PHQ-2) AND (PHQ-9)

Screening for Depression

Quick Screen
A quick way of screening patients for depression is to ask patients to respond the first two questions of PHQ-9:
Over the last 2 weeks, how often have you been bothered by any of the following problems? Give answers as 0 to 3, using this scale: 0=Not at all; 1=Several days; 2=More than half the days; 3=Nearly every day
1. Little interest or pleasure in doing things? ***2. Feeling down, depressed or hopeless?*** If the total score of the patient's response to ***both*** questions is <3, the screen is negative. If the total score is ≥3, PHQ-2 is positive and the patient will complete questions 3 through 9 (unique questions) of the PHQ-9.

1602

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING ___*0*___ + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

1603

APPENDIX H. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: GENERAL HEALTH V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES

   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

APPENDIX I. PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE

Date _____ Patient Name _____ Date of Birth_____

Chief Complaint (Presenting Problem): _____

Since beginning treatment at this clinic, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS, and OVERALL QUALITY OF LIFE, related to your painful condition? Please circle the number below, that matches your degree of change since beginning care at this clinic for the above stated chief complaint.

No change	Almost the same	A little better	Somewhat better	Moderately better	Better	A great deal better
1	2	3	4	5	6	7

Explanation:

1 = No change (or condition has got worse)

2 = Almost the same, hardly any change at all

3 = A little better, but no noticeable change

4 = Somewhat better, but the change has not made any real difference

5 = Moderately better, and a slight but noticeable change

6 = Better, and a definite improvement that has made a real and worthwhile difference

7 = A great deal better, and a considerable improvement that has made all the difference

Patient's signature: X _____

Do not write in this box - FOR OFFICE USE ONLY.

NOTE TO HEALTH CARE PROVIDER

A significant, favorable change is a score of 5- 7

No significant change is a 1-4 response.

Note, this is a dichotomous scale (5-7 = yes; 1-4 = no).

A 2-point change is significant from their last reported score.

Reference: Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of Manipulative Physiological Therapeutics (IMPT) 2004;27:26-35.