Statistical Analysis Plan with Amendment 01

A Multicenter, Randomized, Double-Blind, Parallel-Group Study Evaluating the Long-Term Safety, Tolerability, and Efficacy of Subcutaneous Administration of TEV 48125 for the Preventive Treatment of Migraine

Study Number TV48125-CNS-30051

NCT02638103

Statistical Analysis Plan with Amendment 01 Approval Date: 13 June 2017

Statistical Analysis Plan

TV48125-CNS-30051

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Phase 3

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **TV48125-CNS-30051**

Study Title: **A Multicenter, Randomized, Double-Blind, Parallel-Group Study Evaluating the Long Term Safety, Tolerability, and Efficacy of Subcutaneous Administration of TEV 48125 for the Preventive Treatment of Migraine**

Statistical Analysis Plan for:

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

Amendment: **01**

Author: [redacted]

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Approver: [redacted] **Date**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ADA	antidrug antibody
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 level)
FAS	full analysis set
GH	general health
HIT-6	6-item Headache Impact Test
ICH	International Conference on Harmonisation
IRT	interactive response technology
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MSQ(OL)	Migraine-Specific Quality of Life
NSAID	nonsteroidal anti-inflammatory drug
PGIC	Patient Global Impression of Change
PHQ-2	2-item Patient Health Questionnaire
PHQ-9	9-item Patient Health Questionnaire
PT	preferred term
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SD	standard deviation
SE	standard error

Abbreviation	Term
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of the normal range
VAS	visual analog scale
WHO drug	World Health Organization dictionary of medical codes
WPAI	Work Productivity and Activity Impairment

AMENDMENT HISTORY

The Statistical Analysis Plan for study TV48125-CNS-30051 (study protocol with amendment 01 dated 06 April 2016) has been amended and reissued as follows:

Amendment number	Date	Summary of changes	Reason for amendment
01	06 April 2017	Section 3.3, the definition of FAS is changed 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 e-diary efficacy assessments.	Per review comments from the FDA
		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 4.5, the missing data handling rule is modified. 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

PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for TEVA Branded Pharmaceuticals Products Research and Development, Inc. Study TV48125-CNS-30051, (A Multicenter, Randomized, Double-Blind, Parallel-Group Study Evaluating the Long-Term Safety, Tolerability, and Efficacy of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine) and was written in accordance with standard operating procedure GBP_RD_702 (Teva Pharmaceuticals Global Branded Product Research and Development SAP).

This Phase 3 study is being completed to evaluate the long-term safety, tolerability, and efficacy of subcutaneous (sc) administration of TEV-48125 in adult patients with chronic migraine (CM) or episodic migraine (EM).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted 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-30051 with Amendment 01
- case report forms (CRFs) for Study TV48125-CNS-30051
- ICH E9 Guidance on Statistical Principles for Clinical Trials
- ICH E3 Structure and Content of Clinical Study Reports (CSRs)

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 CSR.

1. STUDY OBJECTIVES

1.1. Primary Objectives

The primary objective of this study is to evaluate the long-term safety and tolerability of sc TEV-48125 in the preventive treatment of migraine.

1.2. Secondary Objectives

There are no secondary objectives.

1.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the reduction of the number of migraine days
- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the reduction in the number of headache days of at least moderate severity
- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the reduction in the number of migraine days in patients not receiving concomitant migraine preventive medications at baseline
- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the reduction in the number of headache days of at least moderate severity in patients not receiving concomitant migraine preventive medications at baseline
- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the reduction in the number of migraine days for new patients and placebo-treated rollover patients
- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the reduction in the number of headache days of at least moderate severity for new patients and placebo-treated rollover patients
- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the reduction of the number of headache days of any severity
- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the reduction of the use of any acute headache medications
- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the discontinuation of use of concomitant preventive medications
- to evaluate the efficacy of sc TEV-48125 in patients with migraine, as assessed by the reduction of migraine-related disability and change in quality of life
- to evaluate the immunogenicity of TEV-48125 and the impact of antidrug antibodies (ADAs) on clinical outcome in patients exposed to sc TEV-48125
- to explore the correlation between pharmacokinetic parameters and drug efficacy

- to explore the relationship between genetic polymorphisms within the calcitonin gene-related peptide 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 an approximately 19-month, multicenter, randomized, double-blind, parallel-group study to evaluate the long-term safety, tolerability, and efficacy of sc TEV-48125 in adult patients with migraine. For patients who complete the pivotal efficacy studies of TEV-48125 (Studies TV48125-CNS-30049 and TV48125-CNS-30050), the study will consist of a 12-month treatment period and a 6.5-month follow-up period. For patients who have not participated in a pivotal efficacy study, the study will consist of a screening visit and 28-day run-in period, a 12-month treatment period, and a 6.5-month follow-up period.

Female and male patients 18 to 70 years of age, inclusive, with CM and EM who complete the pivotal efficacy studies (Studies TV48125-CNS-30049 and TV48125-CNS-30050) and approximately 300 patients (approximately half of whom have a diagnosis of CM and half of whom have a diagnosis of EM) who have not participated in the pivotal efficacy studies may enter this long-term safety, tolerability, and efficacy study if they meet the inclusion/exclusion criteria and provide informed consent. In addition, patients who do not complete the pivotal efficacy studies and those patients who complete the pivotal efficacy studies but do not wish to continue treatment during this long-term safety, tolerability, and efficacy study may attend a follow-up visit during this study for the purpose of ADA assessment approximately 7.5 months after their last dose of study drug.

New patients (not rolling over from the pivotal efficacy studies) using up to 2 preventive medications at the time of the screening visit will be allowed to remain on the medications if the medications have at least moderate evidence of efficacy for migraine (Silberstein et al 2012) and provided that they are on stable doses for at least 2 months prior to study entry. Similarly, patients rolling over from the pivotal efficacy studies using concomitant preventive medications (up to 30% of the patients in the pivotal efficacy studies may be using no more than 1 preventive medication for migraine) will be allowed to continue taking the medication during this study. Patients will be encouraged to continue their preventive medication regimen without change for the duration of the study. If discontinuation is clinically indicated by the investigator (eg, due to no further need or safety concerns), the medication may be stopped, and the reason must be recorded. A list of preventive medications is presented in protocol Appendix A. Patients who are not using preventive medications for migraine at the time of study entry will be asked not to initiate preventive medications de novo during the safety extension study. Patients will be allowed to use acute medications to treat acute migraine attacks, as needed.

Patients who have not participated in a pivotal efficacy study will complete the informed consent process and be screened for eligibility at visit 1. Eligible patients will enter a 28-day run-in period during which they will complete daily electronic headache diary entries. 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 CM (≥15 headache days with migraine on ≥8 days) or EM with headache days on ≥4 and ≤14 days with migraine on ≥3 days and meet all other eligibility criteria (including electronic headache diary compliance criteria during the 28-day run-in period) at visit 2 will complete baseline assessments/procedures before beginning study treatment.

Patients who rollover from the pivotal efficacy studies and are eligible to participate in this study will begin this study at visit 2 after completing the informed consent process. Visit 2 may correspond with the end-of-treatment (EOT) visit (visit 5) or it may be a separate visit. For patients who begin this study on the same day as EOT visit (visit 5) for the pivotal efficacy studies, EOT visit procedures/assessments must be completed before beginning visit 2 procedures/assessments. Baseline for patients rolling over from the pivotal efficacy studies refers to the 28-day run-in period (for headache variables only) and visit 2 (day 0) of the pivotal efficacy studies.

Patients randomized to the active treatment groups in the pivotal efficacy studies who continue receiving study drug in the current study will receive the same treatment throughout the current study. Thus, patients with CM who received a loading dose of TEV-48125 at 675 mg followed by monthly sc TEV-48125 at 225 mg and patients with EM who received monthly sc TEV-48125 at 225 mg will continue receiving monthly sc TEV-48125 at 225 mg, and patients with CM or EM who received sc TEV-48125 at 675 mg once in 3 months will continue receiving quarterly sc TEV-48125 at 675 mg.

Patients with CM randomized to the placebo treatment group in the pivotal efficacy study who continue receiving study drug in the current study and patients with CM who are not rolling over from the pivotal efficacy study will be randomized at visit 2 in a 1:1 ratio to receive 1 of 2 treatments:

- sc TEV-48125 at 675 mg (loading dose) followed by 11 monthly sc doses of TEV-48125 at 225 mg
- sc TEV-48125 at 675 mg once every 3 months for 12 months for a total of 4 doses

Patients with EM randomized to the placebo treatment group in the pivotal efficacy study who continue receiving study drug in the current study and patients with EM who are not rolling over from the pivotal efficacy study will be randomized at visit 2 in a 1:1 ratio to receive 1 of 2 treatments:

- monthly sc TEV-48125 at 225 mg for 12 months
- sc TEV-48125 at 675 mg once every 3 months for 12 months for a total of 4 doses

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

First treatment administration (ie, for this study) will occur at visit 2, and additional doses will be administered at each visit (approximately every 4 weeks) through visit 13. Patients will return for the EOT visit (visit 14) approximately 4 weeks after administration of the final dose of study drug, and they will return approximately 7.5 months (225 days [the approximate equivalent of 5 half-lives]) after administration of the final dose of the study drug for collection of adverse event and concomitant medication information and samples for pharmacokinetic, immunogenicity, and biomarker analyses.

Headache information will be captured using an electronic headache diary device as follows:

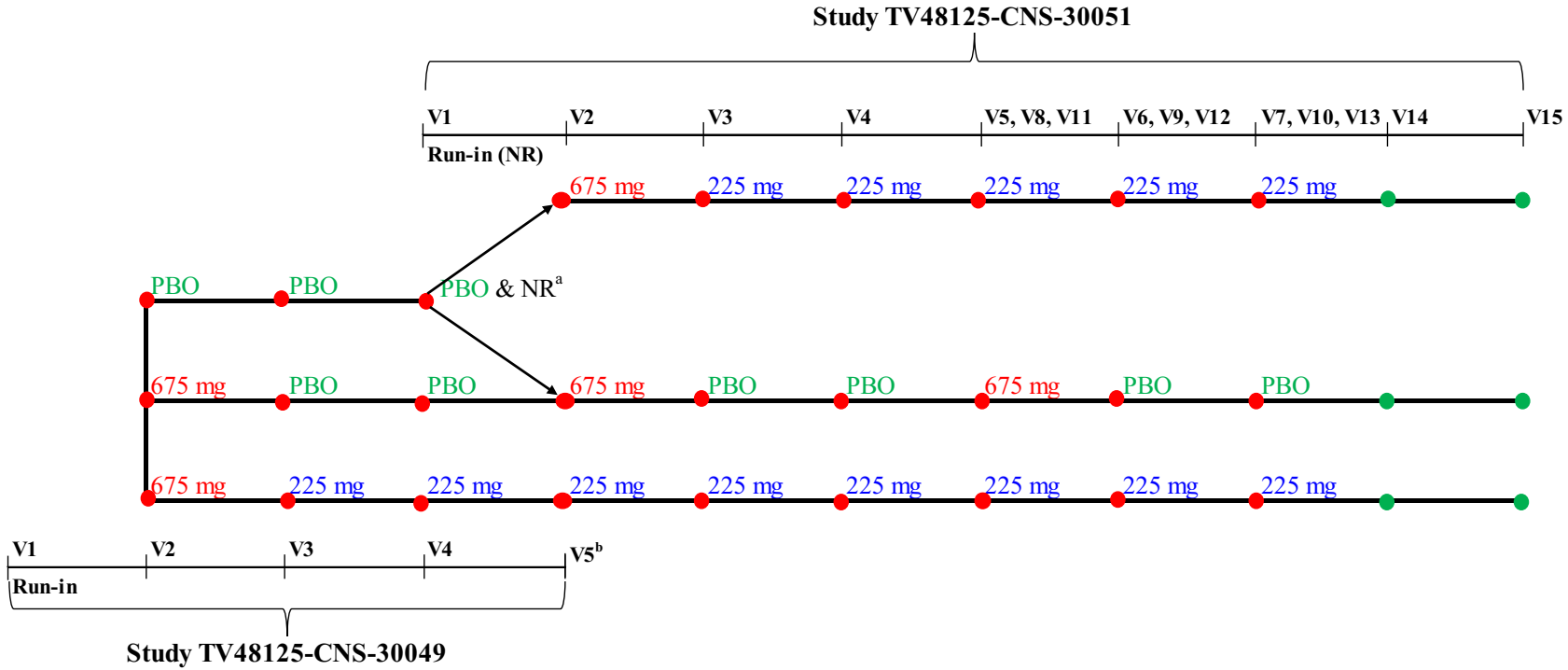
- For patients rolling over from the pivotal efficacy studies, headache information will be captured daily during the first 3 months, during the 4-week period after visit 7, and during the 4-week period after visit 13.

- For patients not rolling over from the pivotal efficacy studies, headache information will be captured daily during the first 4 months, during the 4-week period after visit 7, and during the 4-week period after visit 13.

Assessments of migraine-related disability and change in quality of life (using the 6-item Headache Impact Test [HIT-6] test or Migraine Disability Assessment Test [MIDAS], 2-item Patient Health Questionnaire [PHQ-2]/9-item Patient Health Questionnaire [PHQ-9], Migraine-Specific Quality of Life [MSQOL] questionnaire, 5 response level EuroQol-5 Dimension [EQ-5D-5L] questionnaire, Patient Global Impression of Change [PGIC] scale, and Work Productivity and Activity Impairment [WPAI] questionnaire), safety evaluations, and collection of pharmacokinetic, immunogenicity, and biomarker samples will be performed throughout the study according to the schedules of assessments (Table 1, Table 2, and Table 3).

The study schemas for patients with CM and EM who receive study drug in the current study are presented in Figure 1 and Figure 2, respectively.

Figure 1: Study Schema for Patients with Chronic Migraine

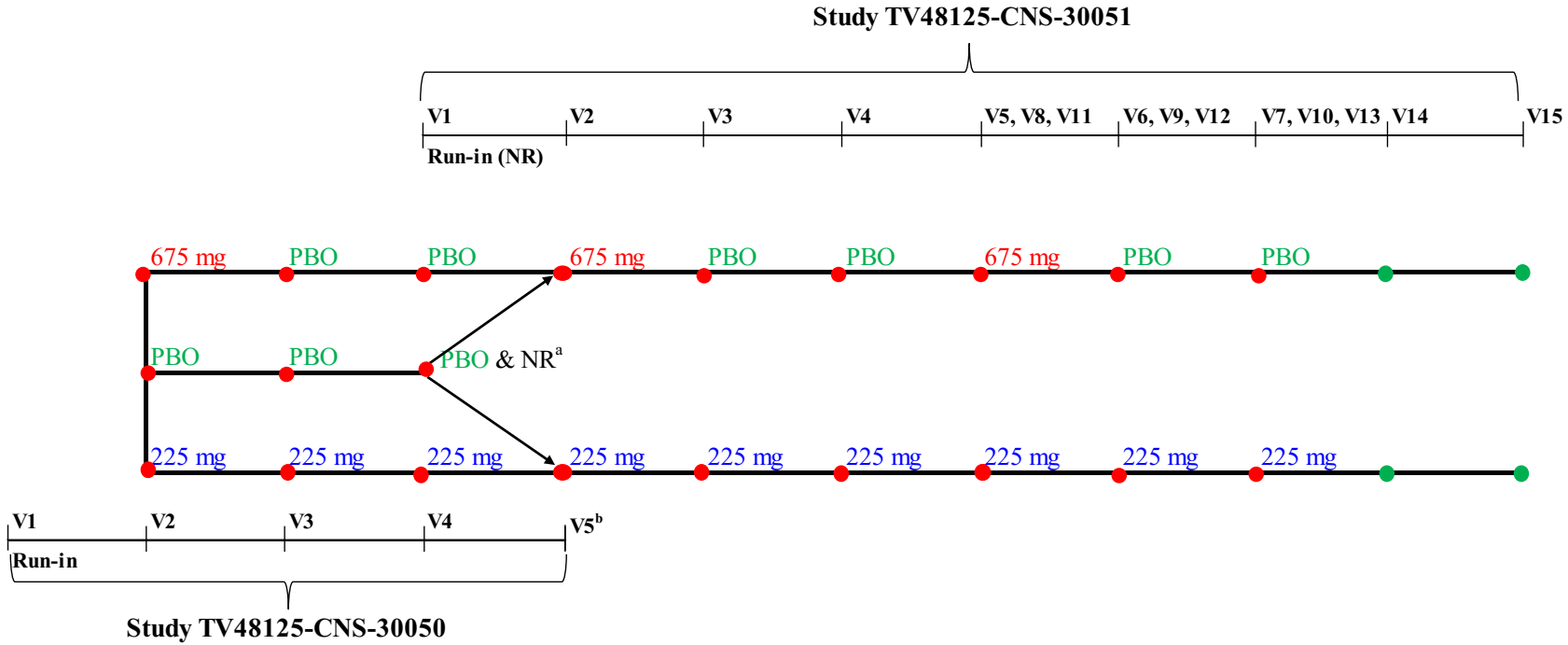


[a] Patients not rolling over from the pivotal efficacy study who meet eligibility criteria after completing a 28-day run-in period and patients rolling over from the pivotal efficacy study who received placebo will be randomized in a 1:1 ratio at visit 2 to receive a loading dose of TEV-48125 at 675 mg followed by monthly TEV-48125 at 225 mg or TEV-48125 at 675 mg quarterly.

[b] For patients who begin this study (visit 2) on the same day as the EOT visit (visit 5) of the pivotal efficacy studies, the EOT visit procedures/assessments for the pivotal efficacy study must be completed before beginning visit 2 procedures/assessments.

EOT=end-of-treatment; NR=nonrollover patients; PBO=placebo; V=visit.

Figure 2: Study Schema for Patients with Episodic Migraine



[a] Patients rolling over from the pivotal efficacy study who received placebo and patients not rolling over from the pivotal efficacy study who meet eligibility criteria after completing a 28-day run-in period will be randomized in a 1:1 ratio at visit 2 to receive quarterly TEV-48125 at 675 mg or monthly TEV-48125 at 225 mg.

[b] For patients who begin this study (visit 2) on the same day as the EOT visit (visit 5) of the pivotal efficacy study, the EOT visit procedures/assessments for the pivotal efficacy study must be completed before beginning visit 2 procedures/assessments.

EOT=end-of-treatment; NR=nonrollover patients; PBO=placebo; V=visit.

Table 1: Study Procedures and Assessments for Patients Rolling Over from the Pivotal Efficacy Studies

Study period	Pre-treatment period[a]	Treatment period													Follow-up period
Visit number	**V1**	**V2[b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	**Screening days -28 to -1**	**Dose 1 day 0 (±5 days)**	**Dose 2 day 28 (±5 days)**	**Dose 3 day 56 (±5 days)**	**Dose 4 day 84 (±5 days)**	**Dose 5 day 112 (±5 days)**	**Dose 6 day 140 (±5 days)**	**Dose 7 day 168 (±5 days)**	**Dose 8 day 196 (±5 days)**	**Dose 9 day 224 (±5 days)**	**Dose 10 day 252 (±5 days)**	**Dose 11 day 280 (±5 days)**	**Dose 12 day 308 (±5 days)**	**EOT/early withdrawal day 336 (±5 days)**	**Final visit day 533 (±15 days)**
Informed consent		X													
Inclusion and exclusion criteria		X													
Randomization[c]		X													
Full physical examination, including weight		X[d]					X	X					X	X	X
12-lead ECG[e]		X[d]												X	
Vital signs measurement[e]		X[d]	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests[f]		X[d]		X		X		X		X		X		X	
Urine β-HCG test[g]		X[d]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events[h]		X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry		X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X[k]
eC-SSRS[l]		X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide electronic headache diary device		X					X						X		
Complete electronic headache diary entries[m]		X —	—	—	X		X —	X					X —	X	

Study period	**Pre-treatment period[a]**	**Treatment period**													**Follow-up period**
Visit number	**V1**	**V2[b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	**Screening days -28 to -1**	**Dose 1 day 0 (±5 days)**	**Dose 2 day 28 (±5 days)**	**Dose 3 day 56 (±5 days)**	**Dose 4 day 84 (±5 days)**	**Dose 5 day 112 (±5 days)**	**Dose 6 day 140 (±5 days)**	**Dose 7 day 168 (±5 days)**	**Dose 8 day 196 (±5 days)**	**Dose 9 day 224 (±5 days)**	**Dose 10 day 252 (±5 days)**	**Dose 11 day 280 (±5 days)**	**Dose 12 day 308 (±5 days)**	**EOT/early withdrawal day 336 (±5 days)**	**Final visit day 533 (±15 days)**
Review electronic headache diary			X	X	X			X						X	
Return electronic headache diary device					X			X						X	
Blood samples for plasma drug concentration					X			X			X			X	X
Blood samples for serum ADA assessment[n]					X			X						X	X
Blood sample for pharmacogenomic analysis[o]		X													
Blood collection for serum, plasma, and RNA biomarker analysis								X						X	X
Urine collection for biomarker analysis								X						X	X
HIT-6[p]								X						X	
MIDAS questionnaire[q]								X						X	
PHQ-2/PHQ-9[r]								X						X	
MSQOL questionnaire								X						X	
EQ-5D-5L questionnaire								X						X	

Study period	Pre-treatment period[a]	Treatment period													Follow-up period
Visit number	V1	V2[b]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	Screening days -28 to -1	Dose 1 day 0 (±5 days)	Dose 2 day 28 (±5 days)	Dose 3 day 56 (±5 days)	Dose 4 day 84 (±5 days)	Dose 5 day 112 (±5 days)	Dose 6 day 140 (±5 days)	Dose 7 day 168 (±5 days)	Dose 8 day 196 (±5 days)	Dose 9 day 224 (±5 days)	Dose 10 day 252 (±5 days)	Dose 11 day 280 (±5 days)	Dose 12 day 308 (±5 days)	EOT/early withdrawal day 336 (±5 days)	Final visit day 533 (±15 days)
PGIC scale			X		X			X			X			X	
WPAI questionnaire								X						X	
Administer study drug injection		X	X	X	X	X	X	X	X	X	X	X	X		
Injection site assessments[s]		X	X	X	X	X	X	X	X	X	X	X	X		

[a] The pretreatment period refers to the screening visit and 28-day run-in period of the pivotal efficacy studies (Studies TV48125-CNS-30049 and TV48125-CNS-30050).
[b] Patients rolling over from the pivotal efficacy studies will begin study participation at visit 2. If visit 2 corresponds with EOT visit (visit 5) of the pivotal efficacy study, the EOT visit procedures/assessments for the pivotal efficacy study must be completed before the patient begins participation in this study, and the EOT procedures/assessments will not be repeated at visit 2. Refer to the protocols for Studies TV48125-CNS-30049 and TV48125-CNS-30050 for details regarding the EOT visit procedures/assessments.
[c] Patients who received placebo in the pivotal efficacy studies will be randomized to receive 1 of 3 TEV-48125 dose regimens (a loading dose of TEV-48125 at 675 mg followed by monthly TEV-48125 at 225 mg [CM only], monthly TEV-48125 at 225 mg, or quarterly TEV-48125 at 675 mg).
[d] Procedure/assessment will only be completed for patients who enter this study more than 30 days after completing visit 5 of the pivotal efficacy study.
[e] Procedure/assessment will be performed before other assessments (eg, blood draws and administration of questionnaires).
[f] Serum chemistry, hematology, coagulation, and urinalysis.
[g] Women of childbearing potential only.
[h] Inquiries about adverse events will be made at every visit. At visits 2 through 13, 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.
[i] The predose adverse event inquiry will only be completed for patients who begin this study on a different day from the EOT visit of the pivotal efficacy study.
[j] Procedure/assessment will only be completed for patients who begin this study on a different day from the EOT visit of the pivotal efficacy study.
[k] As appropriate, patients should be treated with standard of care following completion of the EOT/early withdrawal visit.
[l] The eC-SSRS Since Last Visit version will be completed.
[m] Patients will complete electronic headache diary entries about the previous day daily (beginning on day 1) during the first 3 months, during the 4-week period after visit 7, and during the 4-week period after visit 13.
[n] Blood samples for serum ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).
[o] A single blood sample for pharmacogenomic analysis will be collected at visit 2 of the pivotal efficacy study or any visit thereafter from patients who consent to pharmacogenomic analyses, if the sample is not obtained during their participation in Studies TV48125-CNS-30049 or TV48125-CNS-30050. A separate informed consent form for pharmacogenomic sampling must be signed by the patient.
[p] The HIT-6 will only be administered to patients with CM.

[q] The MIDAS questionnaire will only be administered to patients with EM.
[r] 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.
[s] Injection site assessments will be performed 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 at 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; HIT-6=6-item Headache Impact Test; 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.

Table 2: Study Procedures and Assessments for Patients Not Rolling Over from the Pivotal Efficacy Studies

Study period	**Pre-treatment period[a]**	**Treatment period**													**Follow-up period**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	**Screening days -28 to -1**	**Dose 1 day 0 (+ 5 days)**	**Dose 2 day 28 (±5 days)**	**Dose 3 day 56 (±5 days)**	**Dose 4 day 84 (±5 days)**	**Dose 5 day 112 (±5 days)**	**Dose 6 day 140 (±5 days)**	**Dose 7 day 168 (±5 days)**	**Dose 8 day 196 (±5 days)**	**Dose 9 day 224 (±5 days)**	**Dose 10 day 252 (±5 days)**	**Dose 11 day 280 (±5 days)**	**Dose 12 day 308 (±5 days)**	**EOT/early withdrawal day 336 (±5 days)**	**Final visit day 533 (±15 days)**
Informed consent	X														
Medical and psychiatric history	X														
Prior medication history	X														
Record demographic characteristics	X														
Inclusion and exclusion criteria	X	X													
Randomization[b]		X													
Physical examination, including weight/height[c]	X	X	X	X	X		X	X					X	X	X
12-lead ECG[d,e]	X	X												X	

Study period	**Pre-treatment period[a]**	**Treatment period**													**Follow-up period**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	**Screening days -28 to -1**	**Dose 1 day 0 (+ 5 days)**	**Dose 2 day 28 (±5 days)**	**Dose 3 day 56 (±5 days)**	**Dose 4 day 84 (±5 days)**	**Dose 5 day 112 (±5 days)**	**Dose 6 day 140 (±5 days)**	**Dose 7 day 168 (±5 days)**	**Dose 8 day 196 (±5 days)**	**Dose 9 day 224 (±5 days)**	**Dose 10 day 252 (±5 days)**	**Dose 11 day 280 (±5 days)**	**Dose 12 day 308 (±5 days)**	**EOT/early withdrawal day 336 (±5 days)**	**Final visit day 533 (±15 days)**
Vital signs measurement[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests[f]	X	X		X		X		X		X		X		X	
Serum β-HCG test[g]	X														
Urine β-HCG test[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	
FSH[h]	X														
Adverse events[e,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]
eC-SSRS[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide electronic headache diary device[l]	X						X						X		
Complete electronic headache diary entries[m]	X	—	—	—	X		X	X					X	X	
Review electronic headache diary		X	X	X	X			X						X	
Return electronic headache diary device					X			X						X	
Blood samples for plasma drug concentration[e]		X			X			X			X			X	X

Study period	**Pre-treatment period[a]**	**Treatment period**													**Follow-up period**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	**Screening days -28 to -1**	**Dose 1 day 0 (+ 5 days)**	**Dose 2 day 28 (±5 days)**	**Dose 3 day 56 (±5 days)**	**Dose 4 day 84 (±5 days)**	**Dose 5 day 112 (±5 days)**	**Dose 6 day 140 (±5 days)**	**Dose 7 day 168 (±5 days)**	**Dose 8 day 196 (±5 days)**	**Dose 9 day 224 (±5 days)**	**Dose 10 day 252 (±5 days)**	**Dose 11 day 280 (±5 days)**	**Dose 12 day 308 (±5 days)**	**EOT/early withdrawal day 336 (±5 days)**	**Final visit day 533 (±15 days)**
Blood samples for serum ADA assessment[n]		X			X			X						X	X
Blood sample for pharmacogenomic analysis[o]									X						
Blood collection for serum, plasma, and RNA biomarker analysis		X						X						X	X
Urine collection for biomarker analysis		X						X						X	X
HIT-6[p]		X						X						X	
MIDAS questionnaire[q]		X						X						X	
PHQ-2/PHQ-9[r]		X						X						X	
MSQOL questionnaire		X						X						X	
EQ-5D-5L questionnaire		X						X						X	
PGIC scale			X		X			X			X			X	
WPAI questionnaire		X						X						X	
Administer study drug injection		X	X	X	X	X	X	X	X	X	X	X	X		

Study period	Pre-treatment period[a]	Treatment period													Follow-up period
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	**Screening days -28 to -1**	**Dose 1 day 0 (+ 5 days)**	**Dose 2 day 28 (±5 days)**	**Dose 3 day 56 (±5 days)**	**Dose 4 day 84 (±5 days)**	**Dose 5 day 112 (±5 days)**	**Dose 6 day 140 (±5 days)**	**Dose 7 day 168 (±5 days)**	**Dose 8 day 196 (±5 days)**	**Dose 9 day 224 (±5 days)**	**Dose 10 day 252 (±5 days)**	**Dose 11 day 280 (±5 days)**	**Dose 12 day 308 (±5 days)**	**EOT/early withdrawal day 336 (±5 days)**	**Final visit day 533 (±15 days)**
Injection site assessments[s]		X	X	X	X	X	X	X	X	X	X	X	X		

[a] The pretreatment period includes the screening visit and the 28-day run-in period.
[b] Eligible patients will be randomized to receive 1 of 3 TEV-48125 dose regimens (a loading dose of TEV-48125 at 675 mg followed by monthly TEV-48125 at 225 mg [CM only], monthly TEV-48125 at 225 mg, or quarterly TEV-48125 at 675 mg).
[c] Height will only be obtained at screening.
[d] Procedure/assessment will be performed before other assessments (eg, blood draws and administration of questionnaires).
[e] Patients will return to the study center for up to 2 additional visits after any dose of study drug for blood sampling for plasma TEV-48125 concentration determination, triplicate 12-lead ECGs, and inquiries about adverse events and concomitant medications. These visits should occur during the following time periods relative to any dose of study drug: 3 to 10 days or 15 to 20 days after study drug administration.
[f] Serum chemistry, hematology, coagulation, and urinalysis.
[g] Women of childbearing potential only; a serum β-HCG test will be performed at screening, and urine β-HCG tests will be performed at subsequent visits.
[h] Postmenopausal women only.
[i] Inquiries about adverse events will be made at every visit. At visits 2 through 13, 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.
[j] As appropriate, patients should be treated with standard of care following completion of the EOT/early withdrawal visit.
[k] 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.
[l] 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.
[m] Patients will complete electronic headache diary entries about the previous day daily (beginning on day -27) during the first 4 months, during the 4-week period after visit 7, and during the 4-week period after visit 13.
[n] Blood samples for serum ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).
[o] A single blood sample for pharmacogenomic analysis will be collected at visit 2 or any other visit thereafter from patients who consent to pharmacogenomic analyses, if the sample is not obtained during their participation in Studies TV48125-CNS-30049 or TV48125-CNS-30050. A separate informed consent form for pharmacogenomic sampling must be signed by the patient.
[p] The HIT-6 will only be administered to patients with CM.
[q] The MIDAS questionnaire will only be administered to patients with EM.
[r] 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.
[s] Injection site assessments will be performed 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 at 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; HIT-6=6-item Headache Impact Test; 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.

Table 3: Study Procedures and Assessments for Patients Rolling Over from the Pivotal Efficacy Studies for Antidrug Antibody Assessment Only

	Enrollment visit	Follow-up visit
Visit number	**V2**[a]	**V16 (ADA collection)**
Procedures and assessments	**Day 0**	**Approximately 7.5 months (225±15 days) after the last dose of study drug during the pivotal efficacy study**
Informed consent	X	
Adverse events	X	X
Concomitant medication inquiry	X	X
Blood sample for serum ADA assessment		X

[a] If visit 2 corresponds with EOT visit/early withdrawal visit of the pivotal efficacy study, the EOT visit procedures/assessments for the pivotal efficacy study must be completed before the patient begins participation in this study, and the EOT procedures/assessments will not be repeated at visit 2.

ADA=antidrug antibody; EOT=end of treatment; V=visit.

2.2. Primary and Secondary Measures and Endpoints

2.2.1. Primary Efficacy Endpoint

There is no primary efficacy endpoint.

2.2.2. Secondary Efficacy Endpoints

There are no secondary efficacy endpoints.

2.2.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are as follows:

- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week periods after visits 4, 7, and 13
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week periods after visits 4, 7, and 13
- mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week periods after visits 4, 7, and 13 in patients not receiving concomitant migraine preventive medications at baseline
- mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week periods after visits 4, 7, and 13 in patients not receiving concomitant migraine preventive medications at baseline

- 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 study drug for new patients and placebo-treated rollover patients
- 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 the 1st dose of study drug for new patients and placebo-treated rollover patients
- mean change from baseline (28-day run-in period) in the number of headache days of any severity during the 4-week periods after visits 4, 7, and 13
- mean change from baseline (28-day run-in period) in the number of days of use of any acute headache medications during the 4-week periods after visits 4, 7, and 13
- proportion of patients reaching at least 50%, 75%, and total (100%) reduction in the number of headache days of at least moderate severity during the 4-week periods after visits 4, 7, and 13
- proportion of patients reaching at least 50% and 75% reduction in the number of headache days of at least moderate severity during the 4-week periods after visit 4 who sustain the same level of response during the 4-week periods after visits 7 and 13
- proportion of patients reaching at least 50%, 75%, and total (100%) reduction in the number of migraine days during the 4-week periods after visits 4, 7, and 13
- proportion of patients reaching at least 50% and 75% reduction in the number of migraine days during the 4-week periods after visit 4 who sustain the same level of response during the 4-week periods after visits 7 and 13
- proportion of patients discontinuing concomitant preventive medications during the treatment period
- mean change from baseline (day 0) in disability score in patients with CM, as measured by the HIT-6, at visits 8 and 14
- mean change from baseline (day 0) in disability score in patients with EM, as measured by the MIDAS questionnaire, at visits 8 and 14
- mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at visits 8 and 14
- mean change from baseline (day 0) in patient health status, as measured by the EQ-5D-5L questionnaire, at visits 8 and 14
- assessment of patient satisfaction, as measured by the PGIC scale at visits 3, 5, 8, 11, and 14
- mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at visits 8 and 14
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at visits 8 and 14

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
- changes from baseline in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results
- abnormal standard 12-lead electrocardiogram (ECG) findings
- changes from baseline in vital signs (pulse, systolic and diastolic blood pressure, body temperature, and respiratory rate) measurements
- abnormal physical examination findings
- abnormal local injection site tolerability findings (ie, erythema, induration, and 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

The immunogenicity endpoint is the incidence and impact of ADAs on clinical outcome after monthly sc doses of TEV-48125 and at 7.5 months after stopping treatment.

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

There are no statistical considerations for this sample size. A total of 1842 patients (867 patients from Study TV48125-CNS-30049, 675 patients from Study TV48125-30050, and approximately 300 patients who did not participate in the pivotal efficacy studies) are planned for enrollment, and a 30% drop-out rate is anticipated.

2.4. Randomization and Blinding

2.4.1. Randomization

This is a randomized study with patients being stratified by gender, country, and preventive medication use at baseline (yes, no) during the pivotal efficacy studies or during this study if they are not rolling over from the pivotal efficacy study.

Patients rolling over from the pivotal efficacy studies who were randomized to the active treatment groups will continue receiving the same treatment throughout the study. Patients rolling over from the pivotal efficacy studies who received placebo and new patients will be randomly assigned in a 1:1 ratio to receive quarterly TEV-48125 at 675 mg or monthly TEV-48125 at 225 mg (Note: Patients with CM will receive a 675-mg loading dosing at visit 2 and TEV-48125 at 225 mg at each subsequent visit.).

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

In order to blind the treatment groups based on both dose-volume and number of injections, each patient will receive three 1.5 mL sc injections (three 1.5 mL sc injections of active drug, one 1.5 mL sc injection of active drug and two 1.5 mL injections of placebo, or three 1.5 mL injections of placebo) at visits 2, 5, 8, and 11 and 1 injection at all other visits as detailed in the Table 1 and Table 2.

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

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

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

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

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 & 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

In support of a biologics license application (BLA), a cut-off date will be determined for this study and all data accumulated up to the cut-off date will be analyzed. An interim CSR will be prepared on the interim data.

2.5.2. Final Analyses and Reporting

All final, planned analyses identified in this SAP will be performed after the database lock.

3. POPULATIONS /ANALYSIS SETS

3.1. Intent to Treat Population

The intent-to-treat (ITT) population will include all patients who are randomized in this study for long-term safety evaluation, regardless if they receive study treatment or not. In this population, treatment will be assigned based on the treatment to which patients are randomized (see Section 2.4.1 for the details of the patients randomization), 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 TEV-48125 in this study. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they are randomized.

3.3. Full Analysis Set

The full analysis set (FAS) will include all patients in the safety population and have at least 10 days of efficacy assessments by e-diary post the 1st injection for this study.

3.4. Antidrug Antibody Only Analysis Set

The ADA only analysis set will include all patients rolling over from the pivotal efficacy studies for ADA assessment only.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include count (n), mean, standard deviation (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 postbaseline values (including scheduled, unscheduled, and early termination visits).

Endpoint for safety analyses and summaries is the last observed postbaseline data (see Section 4.6 for the definition).

4.2. Specification of Baseline Values

For the patients rolling over from the pivotal efficacy studies, their baseline values will be the baseline values from the pivotal studies.

Eligible new patients will enter a 28-day run-in period during which they will complete daily electronic headache diary entries. The efficacy baseline values are based on the run-in period data. If the run-in period is greater than 28 days, the baseline values will be normalized to **28**-day.

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

- total number of migraine days
- total headache days of at least moderate severity
- total headache days of any severity
- total number of days of use of any acute headache medication
- total number of headache hours of at least moderate severity
- total number of headache hours of any severity
- 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 include

- disability score in patients with CM, as measured by the HIT-6 (Appendix C)
- disability score in patients with EM, as measured by the MIDAS questionnaire (Appendix D)
- quality of life, as measured by the MSQOL questionnaire (Appendix E)
- health status, as measured by the EQ-5D-5L questionnaire (Appendix G)
- patient depression status, as measured by the PHQ-2 and the PHQ-9 (Appendix I)

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

For safety data, new patient's baseline values will be the last values prior to the 1st dose of study drug.

4.3. Region of Pooled Countries

The countries will be pooled to 2 regions as Table 4 for the analysis.

Table 4: The Region of Pooled Countries

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

4.4. Multiple Comparisons and Multiplicity

No inferential analysis will be performed in this study.

4.5. Handling Withdrawals and Missing Data

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, 3, 6 and 12. If a patient has missing diary days when calculating the monthly variables, the following method will be used to handle the missing data.

- If a patient has ≥10 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 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 for that month.

The missing questionnaire items handling for the MSQOL questionnaire (Appendix E) is discussed in Appendix F: 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 receives the 1st dose of study drug, as recorded on the study drug diary. The 1st day for the patients rolling over from the pivotal efficacy studies will be the day when they receive the 1st dose of study drug after finishing their procedures/assessments for the pivotal study EOT visit (Figure 1 and Figure 2). Days will be numbered relative to study 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 for the new patients is defined as day -28 to -1 before the 1st injection on day 1. Treatment is from the visit 2 to visit 14 or the EOT visit. 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, and so on.

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

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, their safety 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 (ie, randomized population) will be used for all study population summaries unless otherwise noted. Summaries of the efficacy endpoints will be presented by treatment group and overall for CM and EM patients respectively, and total unless otherwise noted. Summaries of the safety endpoints will be presented by treatment group and overall for combined EM and CM patients.

The FAS will be used for all efficacy analyses. Summaries for the FAS population will be presented by treatment group, new patients and placebo-treated rollover patients, active rollover patients, and overall for CM and EM patients.

The safety population will be used for all safety analyses. Summaries for safety population will be presented by treatment group (loading dose of TEV 48125 at 675 mg followed by monthly TEV-48125 at 225 mg, monthly TEV-48125 at 225 mg, and quarterly TEV-48125 at 675 mg) and overall. EM and CM patients will be combined for the safety analysis.

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.

For the rollover patients, their baseline data refer to the baseline in the pivotal studies.

5.2. Patient Disposition

Patients screened, screening failures, and the reasons of the patients not randomized will be summarized only for the newly enrolled patients using patient counts.

The numbers of patients randomized (ITT population), patients randomized but not treated, patients in the safety population, and FAS, patients who completed the study, and patients who discontinued from the study will be summarized using descriptive statistics by indication (EM or CM) and overall for new randomized patients and rollover patients separately. The number of patients discontinued from the study will also be summarized using descriptive statistics by reasons for withdrawal. The denominator for calculating the percentages will be the number of patients in ITT population.

The disposition table will also be presented by treatment group, new patients and placebo-treated rollover patients, TEV-48125-treated rollover patients, and overall for CM and EM patients respectively for ITT population.

5.3. Demographics and Baseline Characteristics

The demographics and baseline characteristics including age, sex, race, ethnicity, country, region, weight, height, 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 the ITT population, FAS, safety population and ADA analysis set.

The baseline e-diary efficacy variables listed in Section 4.2, and the baseline scores for the assessments of migraine impairment and quality of life including HIT-6 for CM patients, MIDAS for EM patients, MSQOL, EQ-5D-5L measurements, PHQ-9, and WPAI will be summarized.

5.4. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. The incidence of medical history 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

For the rollover patients, their prior medications refer to the medication before they took the 1st study drugs in the pivotal studies.

All prior medications or therapy will be coded using the World Health Organization dictionary of medical codes (WHO Drug) version 01 March 2015. 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 first study drug treatment.

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

- triptans and ergots
- nonsteroidal 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. 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.

5.7. Electrocardiography

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

5.8. 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 FAS will be used for all efficacy analyses. The patients with CM and patients with EM will be summarized separately for their efficacy endpoints. The descriptive statistics will be presented by treatment group and visits/months for new patients and placebo-treated rollover patients, TEV-48125-treated rollover patients, and overall under the same treatment, unless otherwise specified.

Efficacy endpoints will be derived from headache related question responses (eg, occurrence of headache, duration of headache in each day, maximum severity of headache, and acute migraine-specific medication use etc. Appendix A) collected daily using an electronic headache diary device for month 1, 2, 3, 6 and 12.

Following the Classification Committee of the International Headache Society guidelines (Silberstein et al 2008), headache days of at least moderate severity for both CM and EM patients will be defined for the purpose of this study as a calendar day (0:00 to 23:59) when 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 an acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration

Migraine day is endorsed based on the same criteria as described in the pivotal studies. For CM patients, a migraine day is endorsed when at least 1 of the following situations occur:

- a calendar day (0:00 to 23:59) demonstrating ≥4 consecutive hours of a headache meeting criteria for migraine with or without aura
- a calendar day (0:00 to 23:59) demonstrating ≥4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion is missing
- a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds)

For EM patients, a migraine day is endorsed when at least 1 of the following situations occur:

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

The derivation logic is presented in Appendix B.

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 and Table 2 for the schedules of the assessments).

- assessment of headache impact in patients with CM using the HIT-6 (Appendix C)
- assessment of headache-related disability based on lost days of activity in 3 domains (work, household work, and nonwork) over the previous 3 months in patients with EM using the MIDAS (Appendix D)
- quality of life, as measured by the MSQOL questionnaire (Appendix E)
- health status, as measured by the EQ-5D-5L questionnaire (Appendix G)
- assessment of patient satisfaction, as measured by the PGIC scale, at 4 weeks after administration of the 1st dose, 3rd dose, 6th dose, 9th dose, and last (12th) dose of study drug (Appendix H)
- patient depression status, as measured by the PHQ-2 and the 9-item PHQ-9 (Appendix I)
- patient work productivity and activity impairment, as measured by the WPAI questionnaire (Appendix J)

The ***monthly average*** number of days of efficacy variables ***during a 4-week period*** after each dose at visits 2, 3, 4, 7, and 13 will be derived and normalized to **28** days equivalent for month 1, 2, 3, 6 and 12, respectively, using the following formula, where the monthly data separated by each visit will be used.

$$\frac{\sum Days\ of\ efficacy\ variable\ during\ the\ 4\ week\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 4\ week\ period} \times 28 \quad (1)$$

The ***baseline values*** for the patients rolling over from the pivotal Studies TV48125-CNS-30049 and TV48125-CNS-30050 will be carried forward. The ***baseline value*** for the eligible new randomized patients will be calculated using all data collected in the run-in period, ie,

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

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

$$\frac{baseline\ value - postbaseline\ value}{baseline\ value} \times 100\% \quad (3)$$

where the postbaseline value in the equation is calculated by formula (1) for the variables ***during the 4-week period*** after each dose at visits 2, 3, 4, 7, and 13 for months 1, 2, 3, 6, and 12, respectively.

6.2. Primary Efficacy Variable(s) and Analysis

There is no primary efficacy endpoint and analysis.

6.3. Secondary Efficacy Variable(s) and Analysis

There are no secondary efficacy endpoints.

6.4. Exploratory Efficacy Variables and Analysis

The exploratory efficacy endpoints are listed in Section 2.2.3.

6.4.1. Variable Definition

6.4.1.1. Headache Diary Data

The exploratory efficacy variables derived from the headache e-diary data include mean change from baseline in the monthly average number of migraine days, headache days of at least moderate severity, headache days of any severity, days of use of any acute headache medications, headache hours of at least moderate severity, headache hours of any severity, days with nausea or vomiting, days with photophobia and phonophobia ***during the 4-week periods*** after visits 2, 3, 4, 7, and 13 for months 1, 2, 3, 6, and 12. The change from baseline is calculated as $\boldsymbol{postbaseline\ value - baseline\ value}$, where the postbaseline values are derived using formula (1) in Section 6.1 and the baseline values are carried forward from the pivotal studies or calculated using formula (2) inSection 6.1 for new patients

If a patient has missing days of entries in the e-diary for a month, his/her monthly average number of days of study variables ***during the 4-week period*** for that month will be handled as discussed in Section 4.5.

The percent reduction in the monthly average number of migraine days ***during the 4-week period*** after each dose at visits 2, 3, 4, 7, and 13 for months 1, 2, 3, 6, and 12 will be calculated by formula (3) 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 4-week period for months 1, 2, 3, 6 and 12. If a patient is early discontinued from the study, he/she will be counted as a non-responder.

If a patient has 50% reduction or more in monthly average number of migraine days during month 3, he/she will be considered a responder during the 4-week period after visit 4. In addition if the patient also has 50% reduction or more during the 4-week periods after visits 7 and 13, he/she is a responder for months 6 and 12, respectively, and the level of effect is sustained after visits 7 and 13. Similar definition will be applied to calculate the proportion of patients reaching at least 75% (and 100%) reduction in the number of migraine days during the 4-week period after visits 4, 7, and 13 for whom this level of effect is sustained through month 12. The proportion of patients reaching at least 50%, 75% and 100% reduction in the number of headache days of at least moderate severity during the 4-week period after visits 4, 7, and 13 for whom this level of effect is sustained throughout the 12-month period after visits 4, 7, and 13 will be derived similarly.

6.4.1.2. Patients Discontinuing Concomitant Preventive Medications during the Treatment Period

If a patient used preventive migraine medication at baseline, stopped the medicine during the treatment period and did not resume the medcation through the EOT visit, he/she will be counted as a patient discontinuing concomitant preventive medication during the treatment.

6.4.1.3. Six-Item Headache Impact Test

Migraine-related disability for CM patients will be assessed using the HIT-6 (see Appendix C) completed at the time points specified in Table 1 and Table 2 to measure the impact headaches having on his/her ability to function on the job, at school, at home, and in social situations. Each question is answered on the scale ranging with the following response options: 6 points (never), 8 points (rarely), 10 points (sometimes), 11 points (very often), and 13 points (always). The total score is obtained from summation of the 6 question points. The HIT-6 total score ranges between 36 and 78, with larger scores reflecting greater impact. If one or more items are missing, then the total score is missing.

6.4.1.4. Migraine Disability Assessment Questionnaire

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

Patients with EM will complete the MIDAS questionnaire at time points specified in Table 1 and Table 2.

6.4.1.5. Migraine Specific Quality of Life

The 14-item MSQOL (Appendix E) questionnaire is designed to measure how migraines affect and/or limit daily functioning across 3 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, 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 from a 0 to 100 scale such that higher scores indicate better health-related quality of life. Appendix F provides the scoring instructions on how to rescale the raw score to the scales that will be used for the analysis.

Patients will complete the MSQOL at time points specified in Table 1 and Table 2.

6.4.1.6. EuroQol-5 Dimension Questionnaire

The EQ-5D-5L questionnaire (Appendix G) is a standardized questionnaire that assesses overall state of health. The EQ-5D consists of 2 parts. In Part 1, patients rate their health state in 5

domains: mobility, self-care, usual activities, pain/discomfort, and mood, using a scale of 1 to 5 where 1=no problems, 2=slight problems,3=moderate problems, 4=severe problems, and 5=extreme problems. In Part 2, patients rate their health state on a 100 mm visual analog scale (VAS); a rating of 0 represents the worst imaginable health state, and a rating of 100 represents the best imaginable health state.

Patients will complete the EQ-5D-5L at the time points specified in in Table 1 and Table 2.

6.4.1.7. Patient Global Impression of Change Scale

The PGIC scale (Appendix H) 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 1=no change (or condition got worse); 2=almost the same, hardly any change at all; 3=a little better, but no noticeable change; 4=somewhat better, but the change has not made any real difference; 5=moderately better, and a slight but noticeable change; 6=better, and a definite improvement that has made a real and worthwhile difference; and 7=a great deal better, and a considerable improvement that has made all the difference.

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.

Patients will complete the PGIC scale at time points specified in Table 1 and Table 2.

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

The PHQ (Appendix I) 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") to 3 ("nearly every day") based on the frequency of symptoms (Spitzer et al 1999). The PHQ-2 was developed from the PHQ-9 to rapidly screen for depression. 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 time points specified in Table 1 and Table 2. If the PHQ-2 is positive (ie, a score ≥3), patients will complete questions 3 through 9 [unique questions] of the PHQ-9. If the PHQ-2 is negative (ie, a score <3), the scores for the questions 3 through 9 are imputed '0'.

6.4.1.9. Work Productivity and Activity Impairment Questionnaire

The generic version of the WPAI:general health (GH) (Appendix J) questionnaire measures the overall effect of health on productivity at work and daily activities. The specific health problems version of the WPAI questionnaire allows investigators to attribute productivity and activity impairment issues to specific health conditions.

After the employment status of a respondent is identified, 3 open-ended questions are asked concerning (1) hours absent from work due to health problems (or specific condition), (2) hours absent from work due to other reasons, and (3) hours actually worked. Two additional questions are included that ask about the impact of health on productivity, 1 concerning productivity at

work and the other concerning daily activities outside of work. The response format of each item of the WPAI questionnaire consists of an 11-point scale ranging from 0 (no impairment) to 10 (complete impairment) (Reilly et al 1993).

The following scores will be derived based on the WPAI: GH questionnaire. Multiply scores by 100 to express in percentages.

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

Patients will complete the WPAI questionnaire at time points specified in Table 1 and Table 2.

6.4.2. Efficacy Analysis

No statistical testing will be applied on the exploratory efficacy analysis.

6.4.2.1. Electronic Headache Diary Data

The exploratory variables listed below will be summarized by visit/month. The summary statistics of the change from baseline and 95% confidence interval of the means will be presented.

- total number of migraine days
- total headache days of at least moderate severity
- total headache days of any severity
- total number of days of use of any acute headache medication
- total number of headache hours of at least moderate severity
- total number of headache hours of any severity
- total number of days with nausea or vomiting
- total number of days with photophobia and phonophobia

The means ± SEs of monthly change from baseline values of number of migraine days, headache days of at least moderate severity, headache days of any severity, and days of use of any acute headache medication will be plotted by month for each treatment group.

The number (%) of patients who reach at least 50%, 75%, and total (100%) reduction in the number of migraine days (and headache days of at least moderate severity) during the 4-week period after visits 2, 3, 4, 7, and 13 will be presented by visits/months. The 95% confidence interval of the responder rate by normal approximation will be presented.

The number (%) of patients who reach at least 50%, 75%, and total (100%) reduction in the number of migraine days (and headache days of at least moderate severity) during the 4-week

period after visits 4 and sustain the same level of response during the 4 week periods after visits 7 and 13 will be presented by visits/months.

6.4.2.2. Patients Discontinuing Concomitant Preventive Medications during the Treatment Period

The proportion of patients discontinuing concomitant preventive medications during the treatment period for those who used concomitant preventive migraine medications will be summarized.

6.4.2.3. Six-Item Headache Impact Test

Summary of the HIT-6 total score will be presented for CM patients by their treatment group and visits/months. The summary and 95% confidence interval of the change from baseline will also be presented by visits/months.

6.4.2.4. Migraine Disability Assessment Questionnaire

The total MIDAS score and change from baseline score will be summarized for EM patients by their treatment group and visits/months. The 95% confidence interval of the change from baseline will also be presented.

The number (%) of patients in each disability grade will be summarized by visits/months.

6.4.2.5. Migraine-Specific Quality of Life Questionnaire

The transformed scores for the 3 domains (ie, Role Function-Restrictive, Role Function-Preventive and Emotional Function) and the rescaled raw dimention score of MSQOL will be summarized by visits/months. The 95% confidence interval of the change from baseline will also be presented.

6.4.2.6. EuroQol-5 Dimension Questionnaire

The number (%) of patients rating their scale of 1 to 5 for the 5 domains of EQ-5D-5L will be presented by visits/months. The VAS and the change from baseline with 95% confidence interval of the VAS will be summarized by visits/months.

6.4.2.7. Patient Global Impression of Change Scale

The number (%) of patients rating their scale of 1 to 7 of the change in the severity of illness following treatment and their dichotomous scale of “Yes” or “No” rated by PGIC assessments will be presented by visits/months.

6.4.2.8. Patient Health Questionnaire

The change from baseline in total PHQ-9 score and 95% confidence interval will be summarized by visits/months.

6.4.2.9. Work Productivity and Activity Impairment Questionnaire

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 summarized by visits/months.

6.4.3. Subgroup Analysis

The mean change from baseline in the number of migraine days and headache days of at least moderated severity during the 4-week periods will be summarized for the following subgroup population of the patients.

- patients who are receiving any concomitant migraine preventive medications at baseline
- patients who are not receiving any concomitant migraine preventive medications at baseline
- patients who used topiramate for migraine in the past
- patients who used onabotulinumtoxinA for migraine in the past

The means ± SE of monthly change from baseline values of number of migraine days and headache days of at least moderate severity will be plotted by month for subgroup of patients who are receiving or not receiving any concomitant migraine preventive medications for each treatment group.

7. SAFETY ANALYSIS

7.1. General

The safety population will be used for all safety analyses. The CM and EM patients will be combined if they receive the same treatment. Summaries will be presented by treatment group (loading dose of TEV-48125 at 675 mg followed by monthly TEV-48125 at 225 mg, monthly TEV-48125 at 225 mg, and quarterly TEV-48125 at 675 mg) as actually received and overall. In addition, the patients with CM and patients with EM will be summarized separately for their safety endpoints. The descriptive statistics will be presented by treatment group and visits/months for new patients and placebo-treated rollover patients, TEV-48125-treated rollover patients, and overall under the same treatment, unless otherwise specified.

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

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

Safety and tolerability measures and time points are provided in Table 1 (patients rolling over from the pivotal efficacy studies), Table 2 (patients not rolling over from the pivotal efficacy studies), and Table 3 (patients rolling over from the pivotal efficacy studies for ADA assessment only).

Adverse events collected for the ADA only analysis population will be listed separately.

7.2. Study Drug Administration

Patients rolling over from the pivotal efficacy studies who were randomized to the active treatment groups will continue receiving the same treatment (ie, monthly TEV-48125 at 225 mg or quarterly TEV-48125 at 675 mg) throughout this long-term safety and efficacy study. Patients rolling over from the pivotal efficacy studies who received placebo and the new patients will be randomly assigned in a 1:1 ratio using IRT as follows:

- Patients with CM will receive sc TEV-48125 at 675 mg (loading dose) followed by 11 monthly sc doses of TEV-48125 at 225 mg or sc TEV-48125 at 675 mg once every 3 months for 12 months for a total of 4 doses.
- Patients with EM will receive monthly sc TEV-48125 at 225 mg for 12 months or sc TEV-48125 at 675 mg once every 3 months for 12 months for a total of 4 doses

Study drug will be administered as sc injections approximately every 4 weeks (28 days).

In order to maintain the study blind, all patients will receive 3 injections at visits 2, 5, 8, and 11 and 1 injection at all other visits as detailed in Table 5.

Table 5: Study Drug Administration by Treatment Group and Visit

Treatment group in this study	Visit 2	Visits 5, 8, and 11	Visits 3, 4, 6, 7, 9, 10, 12, and 13
Loading dose of TEV-48125 at 675 mg followed by monthly TEV-48125 at 225 mg	3 active injections (225 mg/1.5 mL)	1 active injection (225 mg/1.5 mL) and two 1.5-mL placebo injections	1 active injection (225 mg/1.5 mL)
Monthly TEV-48125 at 225 mg	1 active injection (225 mg/1.5 mL) and two 1.5-mL placebo injections	1 active injection (225 mg/1.5 mL) and two 1.5-mL placebo injections	1 active injection (225 mg/1.5 mL)
Quarterly TEV-48125 at 675 mg	3 active injections (225 mg/1.5 mL)	3 active injections (225 mg/1.5 mL)	one 1.5-mL placebo injection

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

Number (%) of patients receiving ≥1 dose, ≥2 doses, ≥3 doses, and so on will be summarized using descriptive statistics by treatment group. Duration of treatment (days) and number of doses 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 for this study through the follow-up visit (approximately 7.5 months after the final dose of study drug). Adverse events will be collected at each visit via adverse event inquiry. The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF.

The following are considered protocol-defined adverse events to be sent to the sponsor's Global Patient Safety and Pharmacovigilance Department for evaluation: ophthalmic adverse events of at least moderate severity, events of possible drug-induced liver injury (aspartate aminotransferase or alanine aminotransferase ≥3 × the upper limit of the normal range [ULN], total bilirubin ≥2 × the ULN or international normalized ratio >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions. Severe hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al 2006). In the event of suspected anaphylaxis, vital signs, including oxygen saturation and respiration rate, will be measured.

Summaries by treatment group and overall 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, protocol-defined 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 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 events, 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 PTs 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 (see Table 1 and Table 2). The injection site(s) will be assessed for erythema, induration, ecchymosis, and pain, and severity will be graded according to the following criteria:

- Injection-site erythema, injection-site induration, and injection-site ecchymosis will be graded according to measurements: absent, 5 mm to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.
- Injection-site pain will be graded as: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe, 4 = worst possible.

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

Number (%) of patients having injections at each visit and their post injection assessments for erythema, induration, ecchymosis, and pain of each grade will be summarized by visit and timepoint for each treatment group. If a patient has multiple sites with different severities, the most severe reaction will be summarized.

To differentiate between assessments at active treatment (TEV-48125) injection sites and placebo injection sites for subjects who receive combined injections of TEV-48125 225 mg and

placebo at the same dose, ie, loading dose of TEV-48125 at 675 mg followed by monthly TEV-48125 at 225 mg, and 225 mg TEV-48125 (1 active, 2 placebo injections) at visit 2, 5, 8, and 11, summaries will be presented by treatment type (TEV-48125 or placebo) within each treatment group. 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.

To compare the post injection site assessment between the active TEV-48125 injections and placebo injections, the total number of injections for both active and placebo type will be counted. The number (%) of injection sites fell into different grade of severity will be presented by visits/months.

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 and Table 2 using the central laboratory. Specific laboratory tests to be performed are listed below in Table 6.

Table 6: 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 • indirect bilirubin (calculated) • 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

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.

The incidence of potentially clinically significant abnormal results will be summarized using descriptive statistics with the criteria specified in Table 7. 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 7: Criteria for Potentially Clinically Significant Laboratory Values

Test		Criterion value
Serum chemistry		
ALT		≥3 × ULN
AST		≥3 × ULN
ALP		≥3 × ULN
GGT		≥3 × ULN
Lactate dehydrogenase		≥3 × ULN
Blood urea nitrogen		≥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 × 10^9/L or ≥20 × 10^9/L
Eosinophils		≥10%
Absolute neutrophil counts		≤1 × 10^9/L
Platelet counts		≤75 × 10^9/L or ≥700 × 10^9/L
Urinalysis		
Blood (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

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transpeptidase; HGB=hemoglobin; INR=international normalized ratio; ULN=upper limit of normal range; WBC=white blood cell

Serum beta-human chorionic gonadotropin (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 and Table 2 .

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

Table 8: Criteria for Potentially Clinically Significant Vital Signs

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

A listing for 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 and Table 2.

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 end of treatment will be summarized using patient counts and percentages. For overall, the worst post baseline finding (the abnormal finding if there are both normal and abnormal findings) for the patient will be summarized. Electrocardiogram variables results and changes from baseline to each visit and endpoint 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 and Table 2.

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 (eC-SSRS)

The eC-SSRS will be used to assess the patient's suicidal ideation (severity and intensity) and behavior (Posner et al 2011). The eC-SSRS Baseline/Screening version will be completed by the patient at visit 2, and the eC-SSRS Since Last Visit version will be completed by the patient at all other time points, as described in Table 1 and Table 2. Any positive findings on the eC-SSRS Since Last Visit version requires 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 Drug. The concomitant medication will include all medications taken after the first study drug administration up to the end of the study.

The incidence of concomitant medications 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.

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

- 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 indication and active treatment groups. The plasma concentration will be listed by indication, active treatments, scheduled visits, and time points.

9. BIOMARKER ANALYSIS

The biomarker analysis is not included in this SAP. A separate report will be provided.

10. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The pharmacokinetic/pharmacodynamic relationship will be estimated and reported separately.

11. IMMUNOGENECITY ANALYSIS

The analysis of immunogenicity data is not included in this SAP. A separate report will be provided.

12. STATISTICAL SOFTWARE

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

13. CHANGES TO PROTOCOL SPECIFIED ANALYSES

Not applicable.

14. REFERENCES

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.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmaco Economics 1993;4(5):353-65.

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. J Allergy Clin Immunol 2006;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.

Silberstein S, Tfelt-Hansen P, Dodick DQ, Limmroth V, Lipton RB, Pascual J, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia 2008;28:484-95.

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

Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. Cephalalgia 1999a Mar;19(2):74,107-14.

Stewart WF, Lipton RB, Whyte J, Dowson A, Kolodner K, Liberman JN, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology 1999b;53(5):988-94.

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 yesterady?
A3	Did you have at least two (2) consecutive hours of headache yesterady?
A4	What was the greatest severity that your headache reached yesterady 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 headcahe/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 yesterady?
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 headche?
E8	Overall, how interested were you in doing daily activities yesterday?

APPENDIX B. LOGICS FOR ENDPOINTS DERIVATION

headache day of at least moderate severity ***Primary endpoint CM***		
OPTION 1		
1	**A1**	YES
2	**A2**	YES
3	**A4**	Moderate or Severe
OPTION 2		
1	**A1**	YES
2	**C0**	YES
3	**C1**	YES
4	**C1**	ERGOT OR TRIPTAN
OPTION 3		
1	**A1**	YES
2	**C0**	YES
3	**D1**	YES
4	**D1**	ERGOT OR TRIPTAN

CM migraine day: 1 of the following 5 options

OPTION 1

Part 1	1	**A1**	YES
	2	**A2**	YES
		AND	
		TWO OF THE FOLLOWING	
Part 2	1	**A4**	Mod-S
	2	**B1**	YES
	3	**B2**	YES
	4	**B3**	YES
		AND	
		ONE OF THE FOLLOWING	
Part 3	1	**B4**	YES
	2	**B5**	YES
		AND	
		B6	YES

OPTION 2

1	**A1**	YES
2	**C0**	YES
3	**C1**	YES
4	C1	ERGOT OR TRIPTAN

OPTION 3

1	**A1**	YES
2	**C0**	YES
3	**D1**	YES
4	**D1**	ERGOT OR TRIPTAN

OPTION 4

1	**A1**	YES
	AND	
	ONE OF THE FOLLOWING	
1	**B7**	YES
	OR	
2	**B8**	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

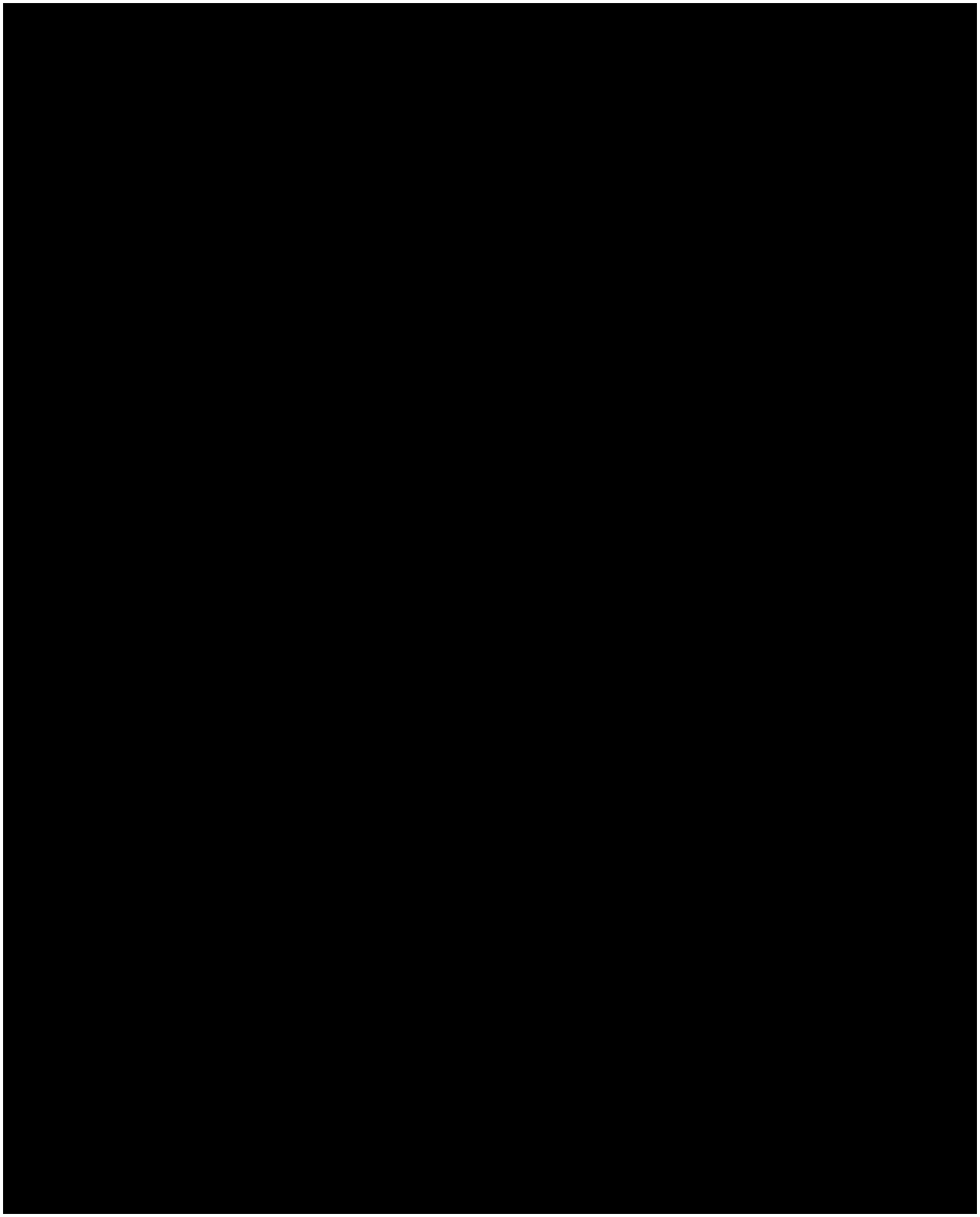
	EM migraine day: 1 of the following 5 options						
		OPTION 1				OPTION 2	
Part 1	**1**	**A1**	YES		**1**	**A1**	YES
	2*	**A2 or A3**	YES		**2**	**C0**	YES
		AND			**3**	**C1**	YES
					4	C1	ERGOT OR TRIPTAN
		TWO OF THE FOLLOWING				OPTION 3	
Part 2	**1**	**A4**	Mod-S				
	2	**B1**	YES		**1**	**A1**	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'.

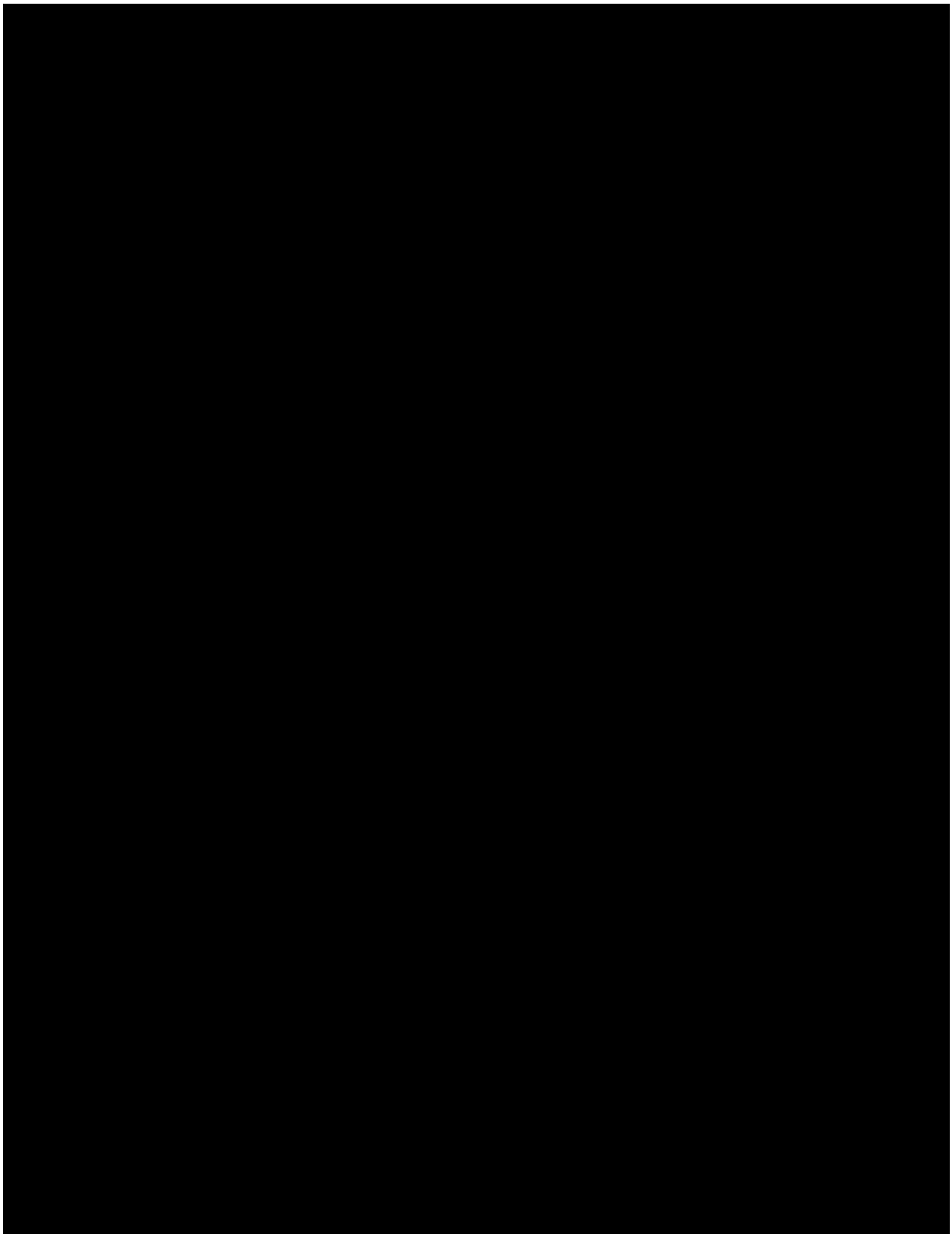
OPTION 5: PROBABLE MIGRAINE			
If **Part 1** and **Part 2** met, **Part 3** needs ONLY one of the following:			
Part 3		**B5**	YES
		B6	YES
If **Part 1** and **Part 3** met, **Part 2** needs ONLY one of the following:			
Part 2	**1**	**A4**	Mod-S

	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

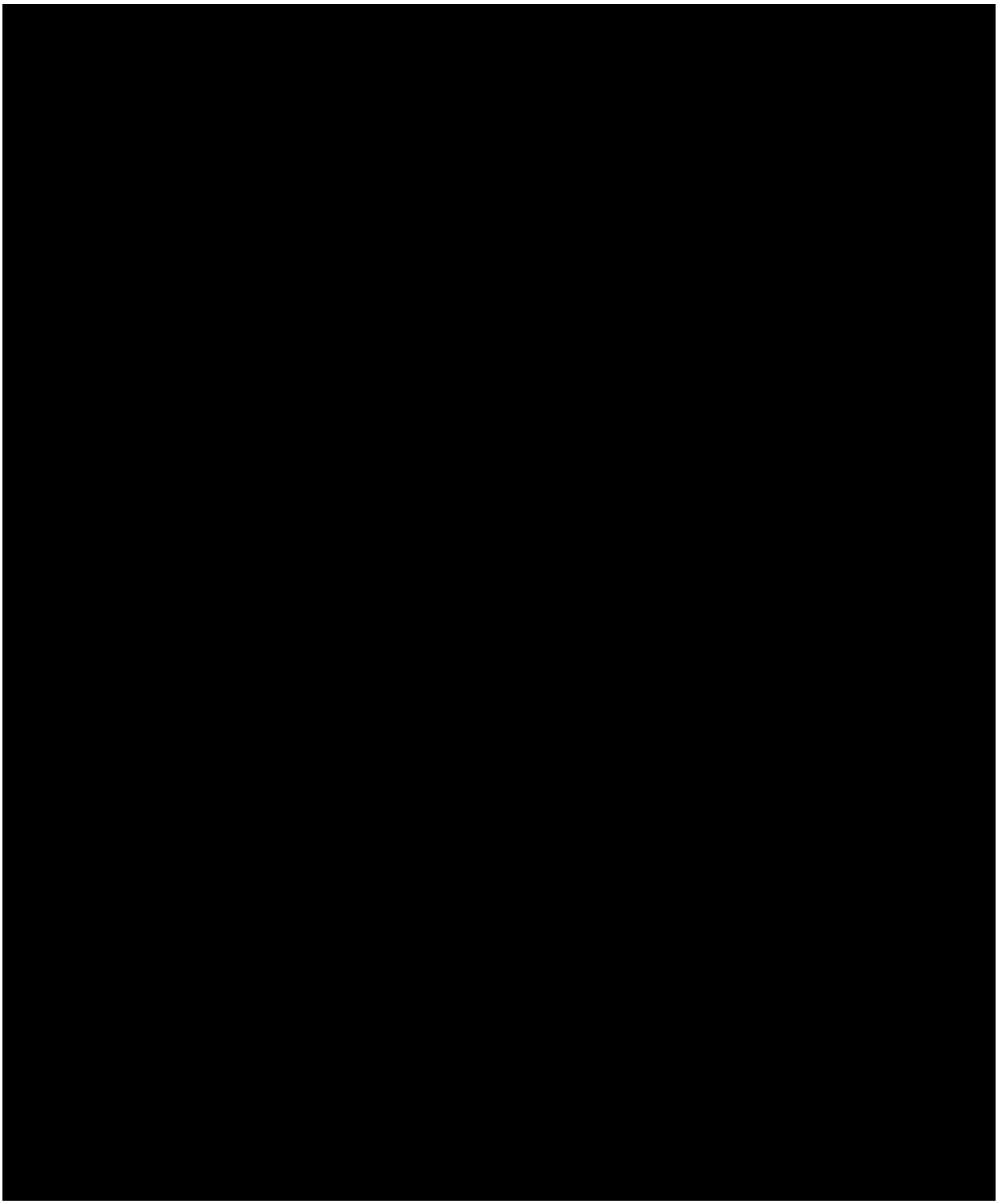
APPENDIX C. HIT-6™ HEADACHE IMPACT TEST

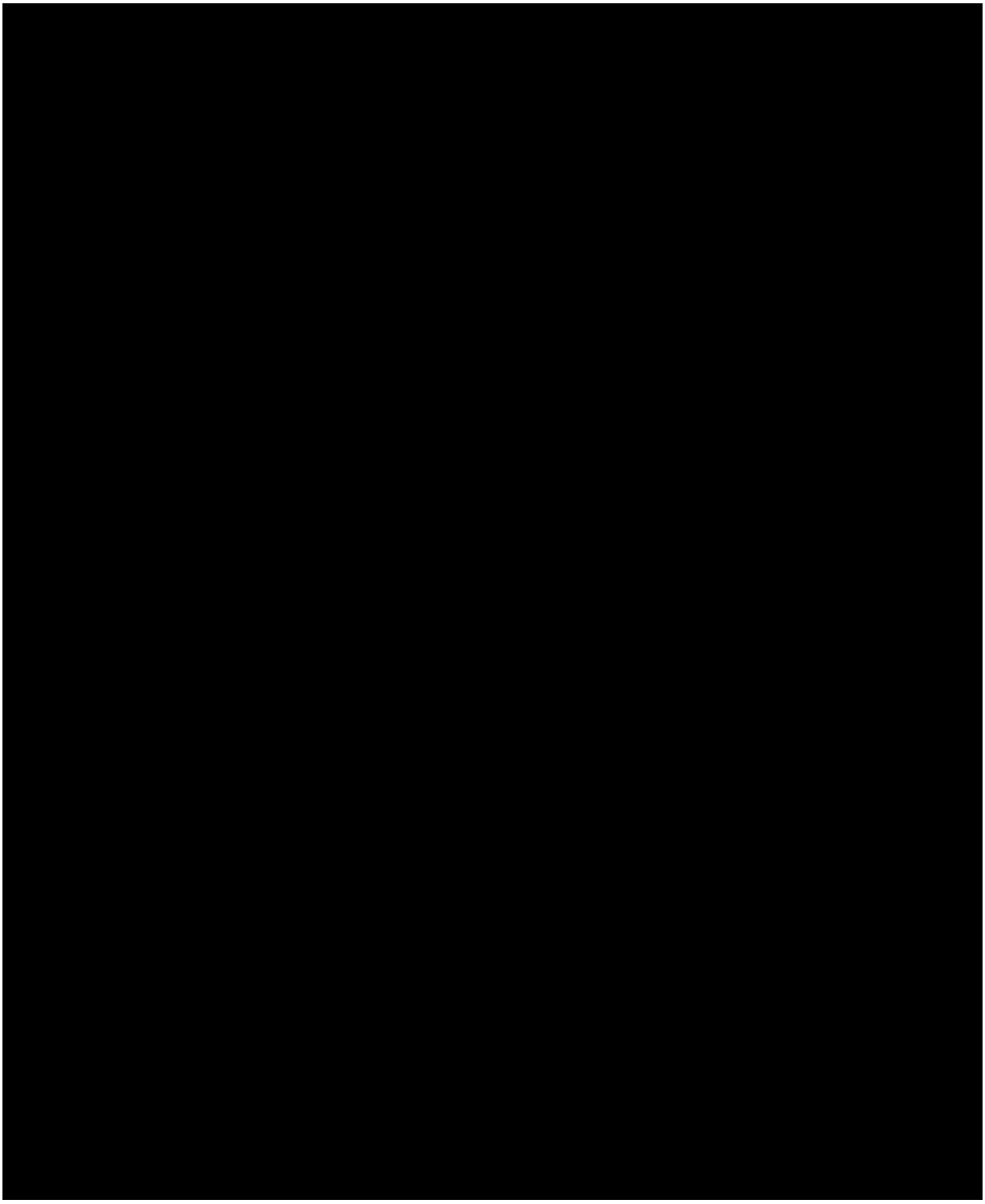


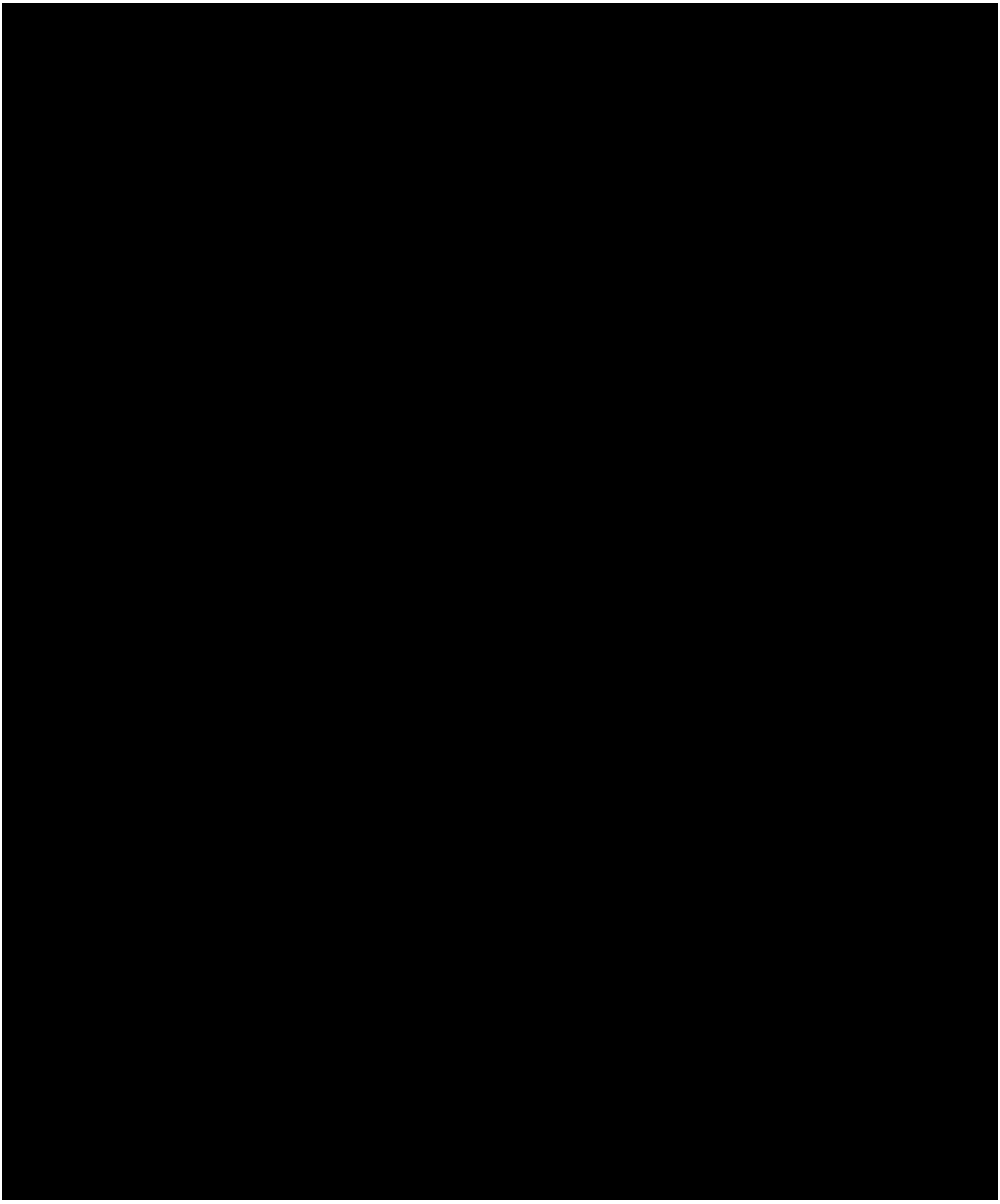
APPENDIX D. THE MIGRAINE DISABILITY ASSESSMENT TEST

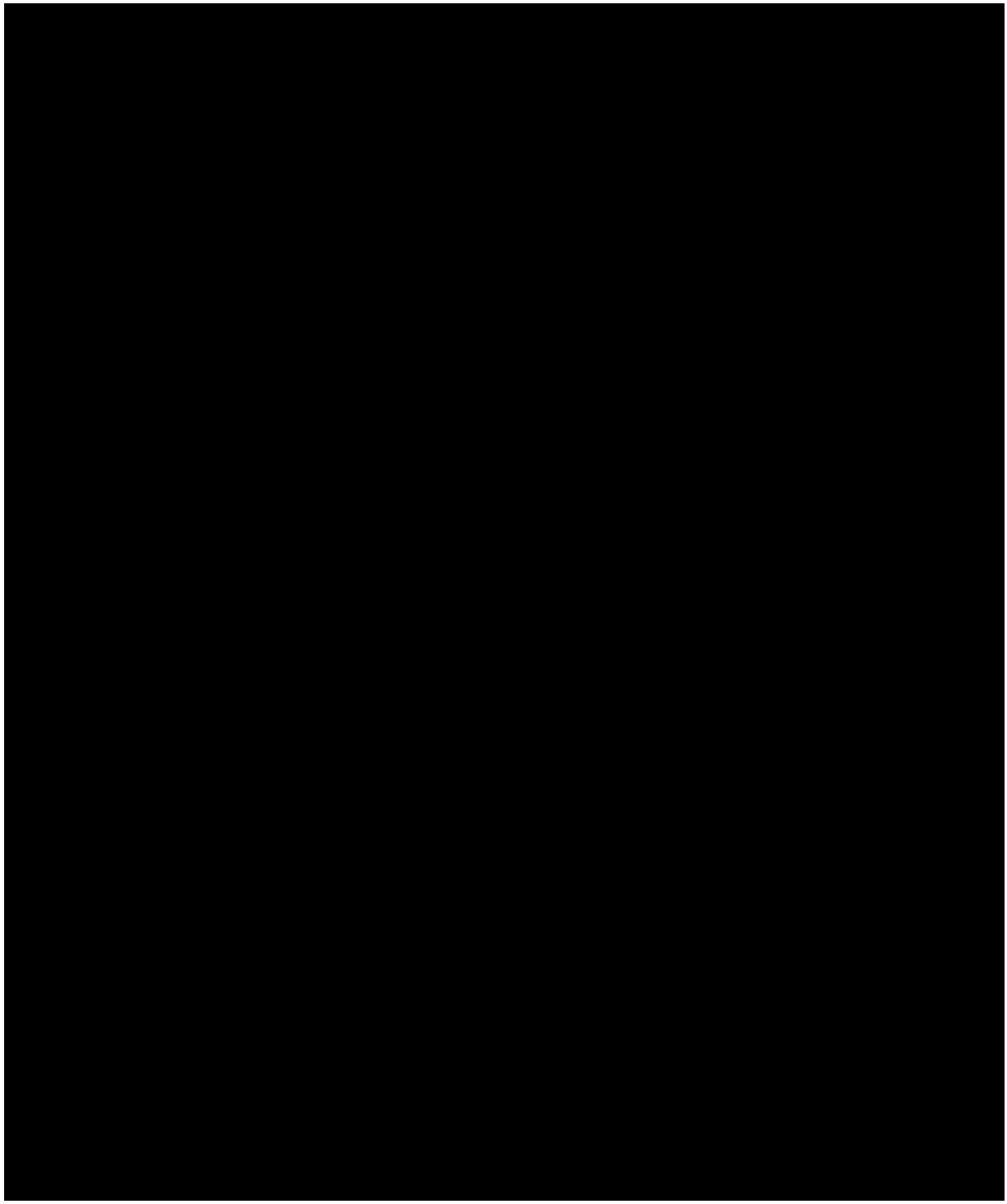


APPENDIX E. MIGRAINE SPECIFIC QUALITY OF LIFE QUESTIONNAIRE (MSQ) (VERSION 2.1)

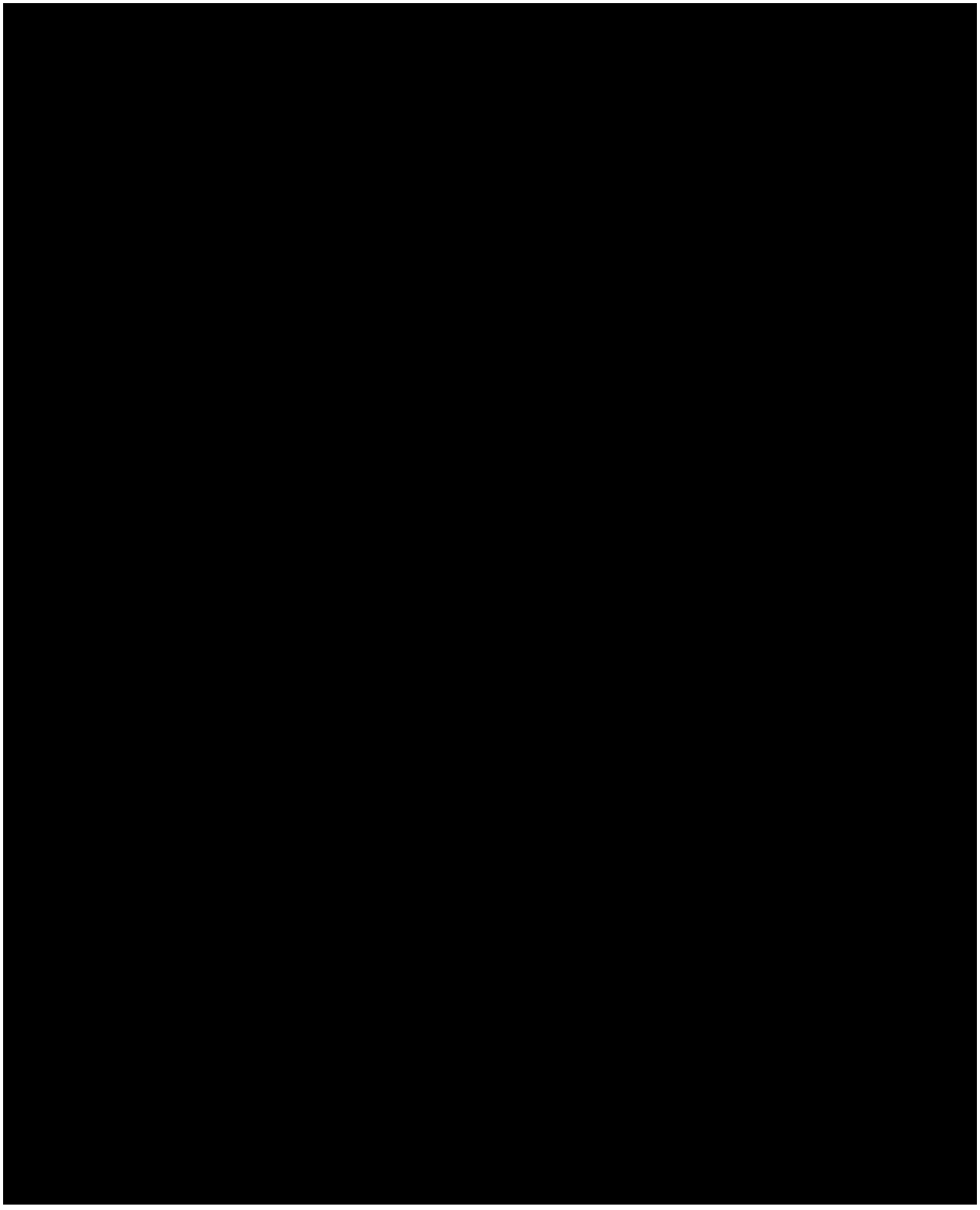


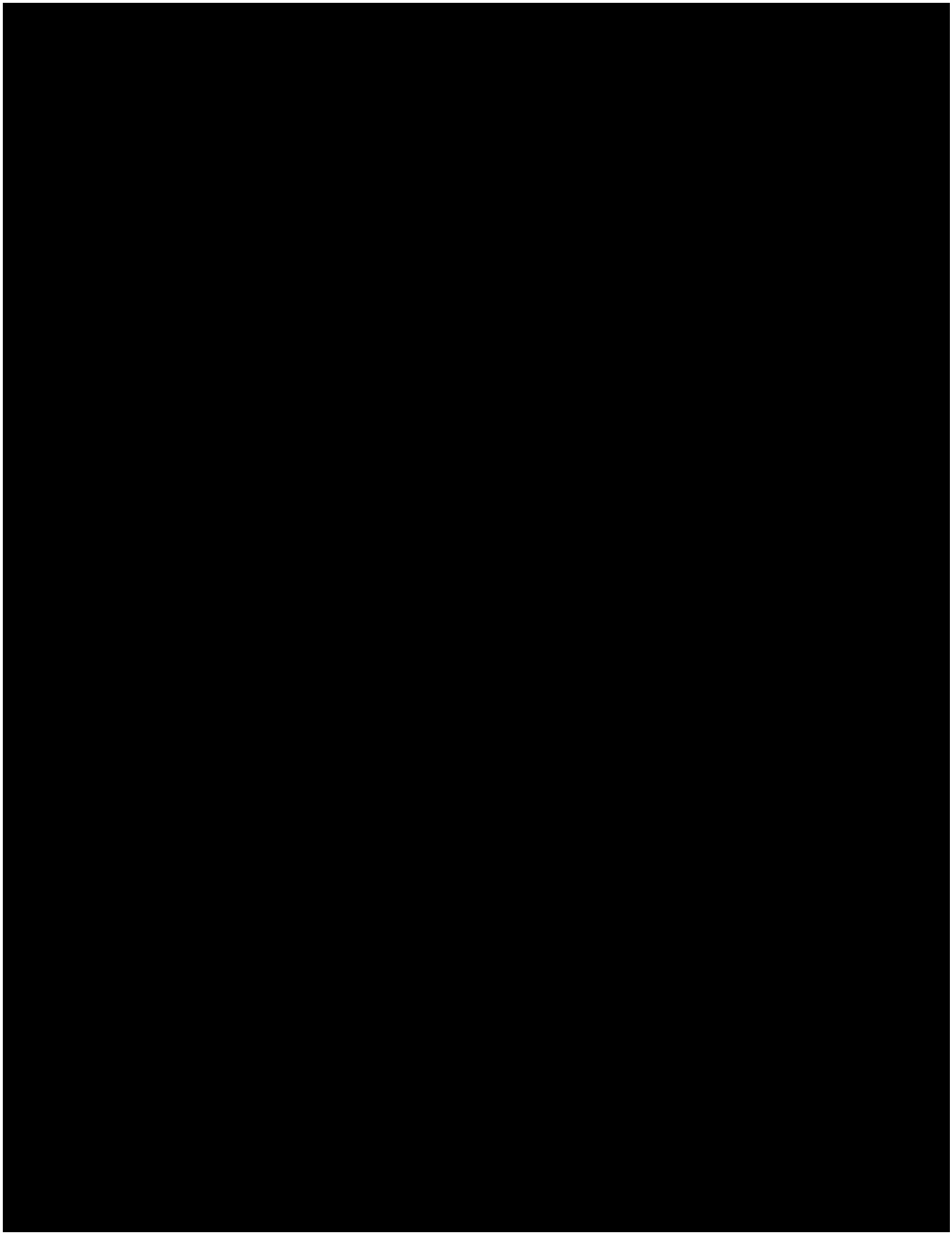




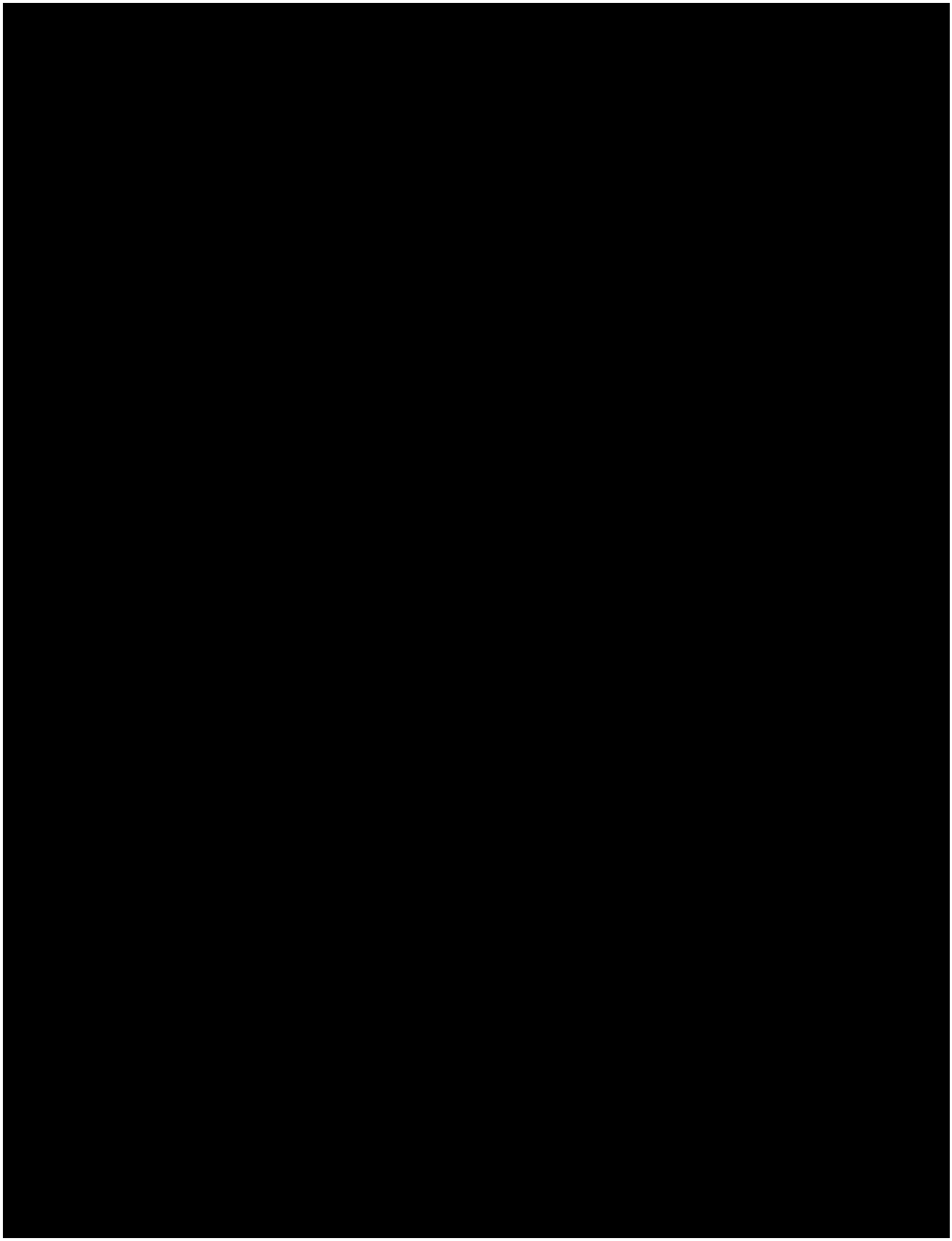


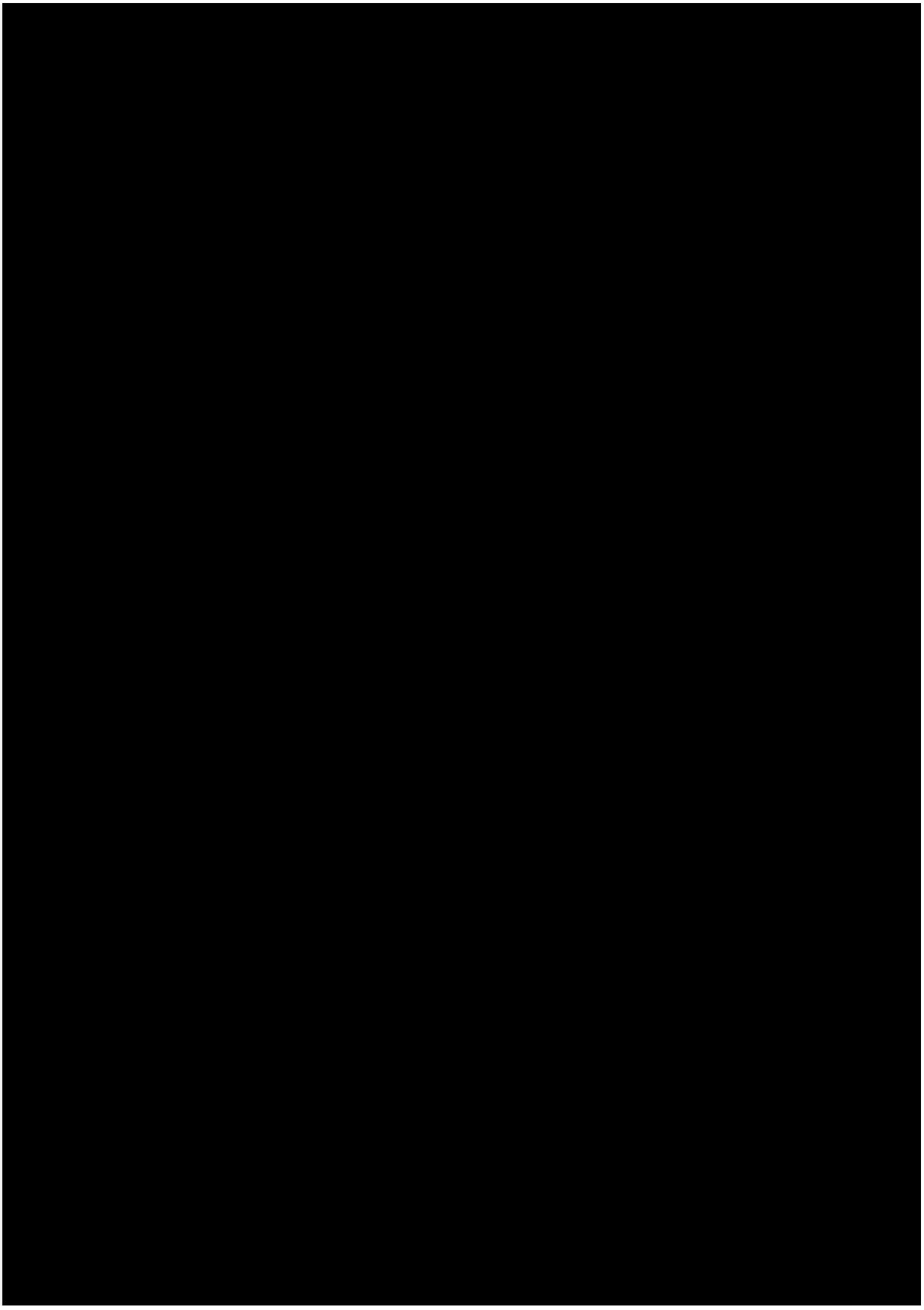
APPENDIX F. SCORING INSTRUCTIONS FOR MSQ (VERSION 2.1)



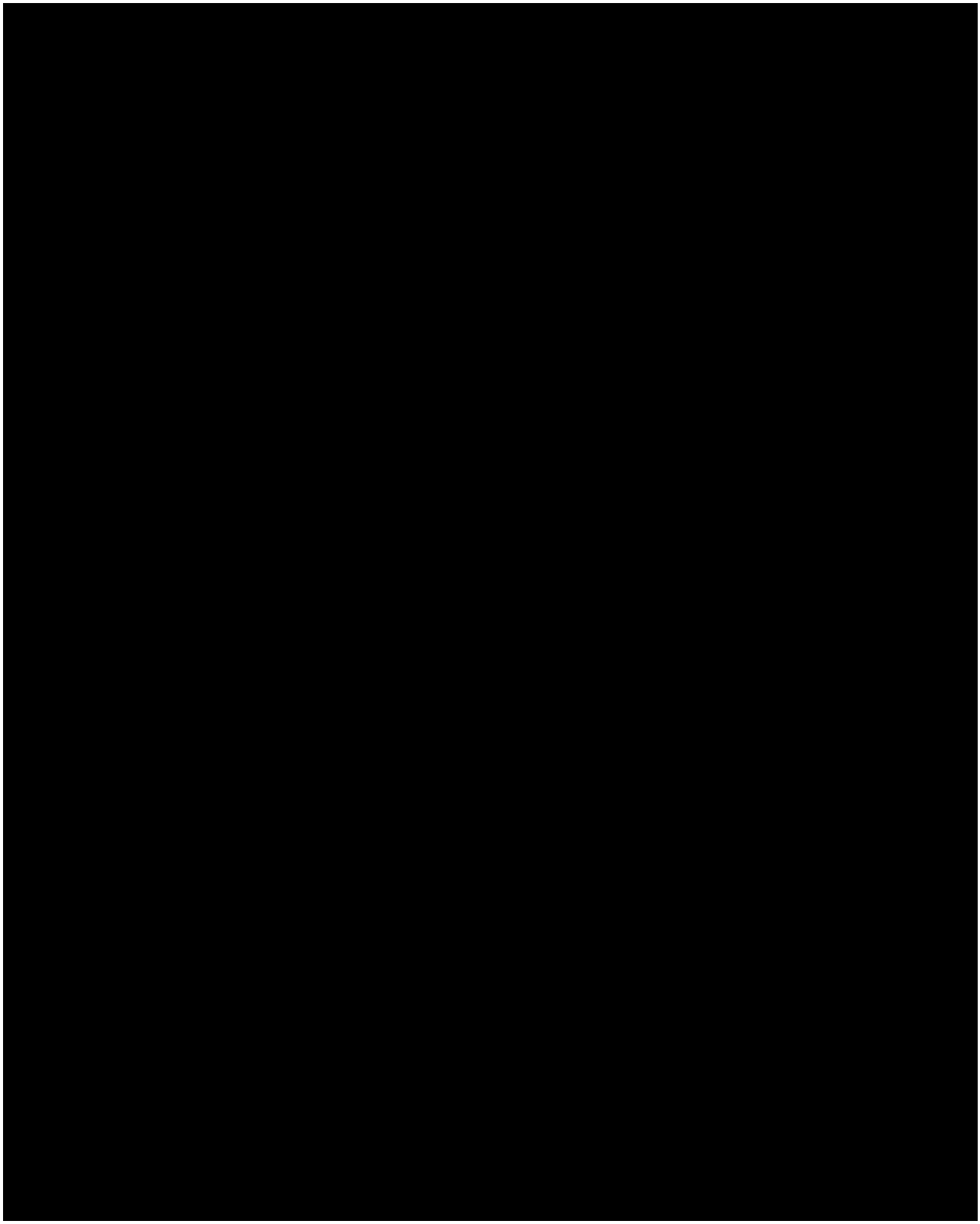


APPENDIX G. EQ-5D-5L AND EQ VAS

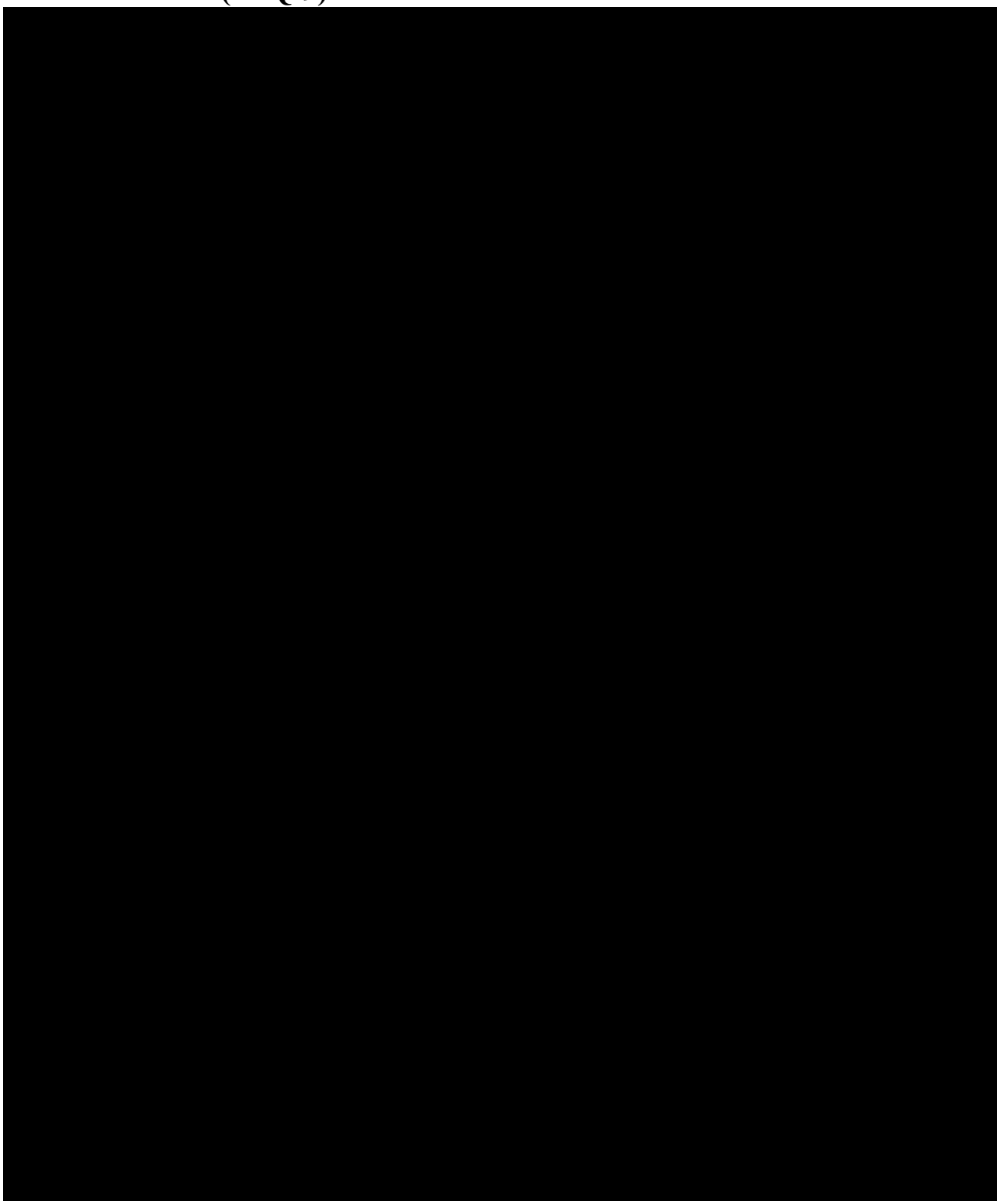




APPENDIX H. PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE



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



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