

Statistical Analysis Plan

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients with Inadequate Response to Prior Preventive Treatments

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Statistical Analysis Plan

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A Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Period on Efficacy and Safety of Fremanezumab in Adults with Migraine

A Study to Test if Fremanezumab is Effective in Preventing Migraine in Patients Who Did Not Respond to Prior Preventive Migraine Treatments

Phase 3

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STATISTICAL ANALYSIS PLAN APPROVAL

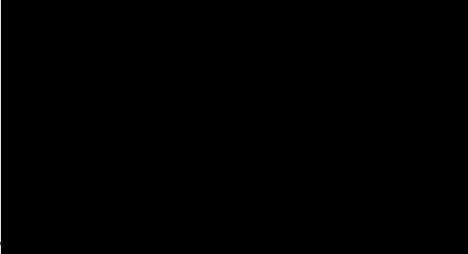
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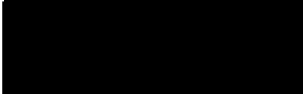
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- Interim Analysis
- Final Analysis
- Integrated Summary of Efficacy
- Integrated Summary of Safety

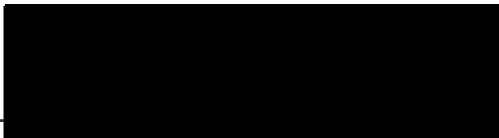
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ADA	antidrug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CGRP	calcitonin gene-related peptide
CI	confidence interval
CM	chronic migraine
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EM	episodic migraine
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D-5L	EurolQoL-5 Dimension (5-level)
FSH	follicle-stimulating hormone
GGT	gamma-glutamyl transpeptidase
HGB	hemoglobin
HIT-6	6-item Headache Impact Test
ICHD	International Classification of Headache Disorders
INR	international normalized ratio
IRT	interactive response technology
ITT	intent-to-treat
LDH	lactate dehydrogenase
LS	least square
MAA	Marketing Authorization Application

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Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MIDAS	Migraine Disability Assessment
mITT	modified intent-to-treat
MMRM	mixed-effects model repeated measures
MSQOL	Migraine Specific Quality of Life
NSAID	non-steroidal anti-inflammatory drug
PGIC	Patient Global Impression of Change
PHQ-2	2-item Patient Health Questionnaire
PHQ-9	9-item Patient Health Questionnaire
PP	per-protocol
PT	preferred term
QT _c	QT interval corrected
R&D	Research and Development
SAP	statistical analysis plan
sc	subcutaneous
SD	standard deviation
SE	standard error
SI	standard international
SOC	system organ class
SOP	standard operating procedure
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products Research and Development (R&D), Inc. study TV48125-CNS-30068, (A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients with Inadequate Response to Prior Preventive Treatments), and was written in accordance with standard operating procedure (SOP) GBP_RD_702 (Statistical Analysis Plan).

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

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

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are presented in [Table 1](#):

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
<p>The primary objective of the study is to demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous (sc) injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo</p>	<p>The primary efficacy endpoint is the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab</p>
<p>The secondary objective of the study is to further evaluate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo</p>	<p>The secondary endpoints are as follows:</p> <ul style="list-style-type: none"> • proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab • proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab • mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of fremanezumab • 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 fremanezumab

Objectives	Endpoints
<p>A secondary objective of the study is to evaluate the safety and tolerability of fremanezumab administered as monthly and quarterly sc injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo</p>	<p>Secondary safety/tolerability endpoints:</p> <ul style="list-style-type: none"> ● occurrence of adverse events throughout the study ● clinical laboratory (serum chemistry, hematology, coagulation and urinalysis) test results at specified time points ● vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit. Note: In addition, oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity ● 12-lead ECG findings at specified time points ● use of concomitant medication for adverse events during the study ● number (%) of patients who did not complete the study due to adverse events ● clinically significant changes in physical examinations, including body weight ● occurrence of severe hypersensitivity/anaphylaxis reactions ● suicidal ideations and behaviors as measured by the eC-SSRS

ECG=electrocardiogram; eC-SSRS= electronic Columbia-Suicide Severity Rating Scale; Test; sc=subcutaneous.

1.2. Exploratory Efficacy Objectives and Endpoints

The exploratory objectives are as follows:

- to further evaluate the efficacy of fremanezumab in adult migraine patients with inadequate response to 2 to 4 classes of prior preventive treatments
- to evaluate immunogenicity and impact of antidrug antibody (ADA) on clinical outcome
- to explore the correlation between pharmacokinetic parameters and efficacy of fremanezumab
- to explore the relationship between genetic polymorphisms, migraine onset/severity and efficacy and safety of fremanezumab
- to explore the relationship between soluble exploratory biomarkers versus migraine response

The exploratory endpoints for the double-blind period are as follows:

- proportion of patients reaching at least 75% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of the study drug
- proportion of patients reaching at least 50% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed valproic acid for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past

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- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the 6-item Headache Impact Test (HIT-6), at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in disability score, as measured by the Migraine Disability Assessment (MIDAS) questionnaire, at 4 weeks after the administration of the 3rd dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the Migraine-Specific Quality of Life (MSQOL) questionnaire, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EuroQol-5 Dimension (EQ-5D-5L) questionnaire at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the 2 item Patient Health Questionnaire (PHQ-2) and 9-item Patient Health Questionnaire (PHQ-9), at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) of patient satisfaction, as measured by the Patient Global Impression of Change (PGIC) scale, at 4 weeks after the 3rd dose of study drug

The exploratory endpoints for the open-label period are as follows:

- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 4th dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of study drug

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- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 4th dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 4th dose of the study drug
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed valproic acid for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period

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- after the 4th dose of fremanezumab for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the HIT-6, at 4 weeks after administration of the 6th dose of study drug
 - mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after the administration of the 6th dose of study drug
 - mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at 4 weeks after administration of the 6th dose of study drug
 - mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the 6th dose of study drug
 - mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the 6th dose of study drug
 - mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the 6th dose of study drug
 - mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale, at 4 weeks after the last 6th dose of study drug

The exploratory endpoints for both the double-blind and open-label periods are as follows:

- to evaluate the immunogenicity response of fremanezumab and the impact of ADAs on clinical outcomes in patients exposed to sc fremanezumab.
- to explore the relationship between genetic polymorphisms (including those within the calcitonin gene-related peptide (CGRP) receptor-ligand complex, in migraine-associated susceptibility genes, and in as-yet undiscovered loci) versus migraine onset/severity, adverse events to medication and fremanezumab efficacy
- to explore the relationship between exploratory biofluid biomarkers versus fremanezumab concentrations, adverse events and fremanezumab efficacy

2. STUDY DESIGN

2.1. General Design

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study with an open-label period to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc fremanezumab compared with placebo in patients with chronic migraine (CM) and episodic migraine (EM) with inadequate response to prior preventive treatments.

The study will consist of a screening visit, a run-in period (28 days), a 12-week double-blind, placebo-controlled treatment period, a 12-week open-label period, and a follow-up visit 6.0 months after the last dose of fremanezumab for ADA blood sample collection.

At the end of the open-label treatment period (4 weeks after the last dose) an end of treatment study visit (visit 8) will be scheduled and patients should return to the care of their treating physicians. Patients should be treated with standard of care after withdrawal from or termination of the 24-week treatment period/study, as appropriate.

Double-blind period

At the baseline visit (visit 2), patients will be randomly assigned to a treatment group with fremanezumab (2 different dose regimens) or placebo in a 1:1:1 ratio as follows:

- For patients with CM:
 - sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
 - sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of matching placebo for 2 months or
 - 3 monthly doses of matching placebo
- For patients with EM:
 - sc administration of fremanezumab at 225 mg plus 2 matching placebo injections as first dose followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
 - sc administration of fremanezumab at 675 mg as first dose followed by monthly sc administration of matching placebo for 2 months or
 - 3 monthly doses of matching placebo

Randomization and treatment assignment for the double-blind period will be performed using electronic interactive response technology (IRT). The study will be stratified based on CM or EM, gender, country, and a special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in Appendix H of the study protocol.

The proportion of CM and EM patients in the study should be approximately 50:50 in each subgroup.

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CM is defined as:

Patient fulfills the following criteria for CM in prospectively collected baseline information during the 28-day run-in period:

- Headache occurring on ≥ 15 days
- On ≥ 8 days, fulfilling any of the following:
 - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix U of the study protocol)
 - ICHD-3 criteria B and C for 1.2 Migraine with aura (Appendix U of the study protocol)
 - Probable migraine (a migraine subtype where only 1 migraine criterion is missing)
 - The patient used a triptan or ergot derivative to treat established headache.

EM is defined as:

The patient fulfills the following criteria for EM in prospectively collected baseline information during the 28-day run-in period:

- Headache occurring ≥ 6 days but < 15
- On ≥ 4 days, fulfilling any of the following:
 - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura
 - ICHD-3 criteria B and C for 1.2 Migraine with aura
 - Probable migraine (a migraine subtype where only 1 migraine criterion is missing)
 - The patient used a triptan or ergot derivative to treat an established headache

Blinded treatment will be administered sc once a month (approximately every 28 days) for a total of 3 doses (visits 2,3, and 4)

Open-label period

After visit 4, all patients completing the double-blind period will enter the open-label period. All patients (CM and EM) will receive sc 225 mg of fremanezumab monthly for 3 months (visits 5, 6, and 7).

The open-label period will not be randomized as all patients will receive the same monthly dose (225 mg fremanezumab).

Open-label treatment will administered for a total of 3 doses (visits 5, 6, and 7). Final study assessments will be performed at visit 8 (end-of-treatment [EOT] visit), approximately 4 weeks after administration of last dose of fremanezumab.

Follow up period

A follow-up visit will be scheduled 6.0 months (> 5 half-lives) after the last study drug administration for ADA blood sampling. Patients who discontinue early will have the follow-up visit 6.0 months after the last dose.

The total duration of patient participation in the study is planned to be 50 weeks including a run-in period lasting 28 days, a double-blind treatment period lasting 12 weeks, an open-label period lasting 12 weeks, and 1 follow-up visit at week 46.

Patients are expected to complete the entire duration of the study, including the open-label period and the follow-up visit.

The end of study is defined as the last visit of the last patient (follow-up visit, visit 9). However, an interim database lock will occur following the end of the double-blind treatment period of the last patient for analysis of that portion of the study data. A second interim lock will occur following the end of the open-label period.

Study procedures and assessments with their timing are summarized in Table 2 of the study protocol.

2.2. Randomization and Blinding

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

In this randomized study, the double-blind period will be stratified based on CM or EM, gender, country, and a special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in Appendix H of the study protocol.

Each patient will undergo randomization in a 1:1:1 ratio within the stratum to which he or she belongs to receive 1 of the 2 fremanezumab dose regimens or placebo, as assigned by the IRT. The IRT will manage initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At the time of each study visit, the IRT will be queried, and site personnel will retrieve and administer a 1.5-mL volume from each syringe contained in the appropriately numbered kit(s).

2.3. Data Monitoring Committee

There will be no Data Monitoring Committee in this study.

2.4. Sample Size and Power Considerations

In the Phase 2b study for CM (study LBR-101-021), the treatment difference between 675/225/225 mg and placebo in change from baseline in monthly average migraine days was 2.1 days (standard deviation [SD]=5.2 days). In the phase 2b study for EM (study LBR-101-022), the treatment difference between 225 mg monthly dose and placebo in change from baseline in monthly average migraine days was 2.7 days (SD=4.1 days). In the Phase 3 study for CM (study TV48125-CNS-30049), the treatment differences to placebo in change from baseline in monthly average migraine days were 1.7 days and 1.8 days for the quarterly dose and the monthly dose, respectively (SD=5.4 days). In the Phase 3 study for EM (study TV48125-CNS-30050), the treatment differences to placebo in change from baseline in monthly average migraine days were 1.3 days and 1.5 days for the quarterly dose and the monthly dose, respectively (SD=3.4 days). Combining the information above, a treatment difference of 1.8 days is used. Considering the patient population is different from the previous studies, a SD of 6 days is used to account for the complexity and uncertainty of this study.

A sample size of 705 (235 patients per treatment group) evaluable patients completing the study is needed for 90% power to show a 1.8 difference in migraine days (assuming a common SD of 6 days) at an alpha level of 0.05. Assuming a 12% discontinuation rate, 268 patients per treatment group will be randomized in the study.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

An interim analysis is planned when the last patient has completed the double-blind period. A second interim analysis is planned when the last patient has completed the open-label period. Final database lock will occur following the end of the follow-up period.

The inferential analysis of efficacy variables for comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo will be done at the time of the first interim lock. The appropriate method for type 1 error control will be applied to the first interim analysis.

Efficacy analysis for the open-label portion of this study is considered exploratory and mainly descriptive. This analysis will be done at the time of the second interim database lock.

2.5.2. Final Analyses and Reporting

All analyses identified in this SAP will be performed after the first interim database lock for the double-blind period and after the second interim database lock for the open-label period of this study as defined in the study protocol.

This SAP and any corresponding amendments will be approved before the first interim database lock, in accordance to SOP GBP_RD_702 (Statistical Analysis Plan).

The randomization codes will not be unblinded until this SAP has been approved and issued.

3. ANALYSIS SETS

3.1. Intent-to-Treat Analysis Set

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

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

3.2. Modified Intent-to-Treat Analysis Sets

The double-blind modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of study drug and have at least 10 days of post baseline efficacy assessment on the primary endpoint. The open-label mITT analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of study drug during the open-label treatment period and have at least 10 days of post baseline diary entries during the open-label treatment period.

3.3. Safety Analysis Sets

The double-blind safety analysis set will include all randomized patients who receive at least 1 dose of study drug during the double-blind treatment period. The open-label safety analysis set will include all patients who receive at least 1 dose of study drug during the open-label treatment period.

In the safety analysis sets, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

3.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the double-blind mITT analysis set including only patients who complete the double-blind treatment period without important protocol deviations which may impact the efficacy assessments or any deviations/omissions of the study drug administration. Patients with less than 75% diary compliance during the double-blind treatment period will be excluded from the PP analysis set. Patients who received study drug different from the study drug they were randomized to will be excluded from the PP analysis set. A blinded data review meeting will be conducted prior to the interim database lock in order to determine the exclusion of the patients from the PP analysis set.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

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

4.2. Specification of Baseline Values

Patients will complete electronic headache diary entries daily for 28-day run-in period and enter headache information (ie, occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use) about the previous day into the electronic headache diary device.

If the run-in period is greater or less than 28 days, the baseline values for calculating the change from baseline of the monthly values of the efficacy variables will be normalized to 28 days. The baseline value for calculating change from baseline of the weekly values will be normalized to 7 days.

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

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

Other efficacy baseline values that will be measured on day 0 before the 1st study drug administration include

- disability score, as measured by the HIT-6
- disability score, as measured by the MIDAS
- quality of life, as measured by the MSQOL questionnaire
- health status, as measured by the EQ-5D-5L questionnaire
- patient depression status, as measured by the PHQ-2 and the PHQ-9

- patient work productivity and activity impairment, as measured by the WPAI questionnaire

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

4.3. Handling Withdrawals and Missing Data

If a patient has ≥ 10 days of electronic headache diary data after 1st dose of the study drug, his/her monthly average number of days/hours of efficacy variables *during the 12-week period* or monthly number of days/hours of efficacy variables *during the 4-week period* will be prorated to 28 days.

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

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

- If a patient has ≥ 10 days of electronic headache 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 electronic headache diary data for a month, the monthly number of days/hours of efficacy variables will be considered as missing.

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

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

For the HIT-6 ([Appendix C](#)), if 1 or more items are missing then the total score is missing. The missing questionnaire items handling for the MSQOL questionnaire ([Appendix E](#)) is discussed in [Appendix F](#).

4.4. Study Days and Visits

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

The 4-week (28-day) visit windows for the electronic headache diary based efficacy endpoints will be determined based on the actual dosing day. The run-in phase is defined as day -28 to -1

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before the 1st injection on day 1. Treatment phase including month 1, 2, 3, 4, 5, and 6 is from the beginning of the 1st injection of study drug to visit 8/day 168 or the end of treatment visit. The 6-month visit windows are separated by each dosing date/time. Month 1 is from the date/time of the 1st dose of study drug administration on day 1 to the date/time just before the 2nd dose. Month 2 is from the date/time of the 2nd dose to the date/time just before the 3rd dose. Month 3 is from the date/time of the 3rd dose to the date/time just before the 4th dose. Month 4 is from the date/time of the 4th dose to the date/time just before the 5th dose. Month 5 is from the date/time of the 5th dose to the date/time just before the 6th dose. Month 6 is from the date/time of the 6th dose to the end of treatment on day 168 approximately.

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

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

For all other by-visit summaries, if there are multiple assessments at a postbaseline visit then the last non-missing assessment at that visit will be used for the summary. This includes assessments at the scheduled and unscheduled visits.

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 last assessment summaries.

4.5. Region of Pooled Countries

The countries will be pooled to 2 regions as presented in [Table 2](#) for the analysis.

Table 2: The Region of Pooled Countries

Region	Country
United States	United States
Europe	Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, United Kingdom

5. STUDY POPULATION

5.1. General

The ITT analysis set will be used for all study population summaries unless otherwise specified. Summaries will be presented by migraine classification (ie, CM, EM, and all), treatment group, all fremanezumab, and for all patients (ie, total).

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

5.2. Patient Disposition

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

Patients in the ITT analysis set, patients in the ITT analysis set but not treated, patients in the double-blind safety analysis set, double-blind mITT analysis set, and per-protocol analysis set, patients who complete the double-blind treatment period, patients who withdraw from the double-blind treatment period, patients in the open-label safety analysis set and open-label mITT analysis set, patients who complete treatment, patients who withdraw from treatment, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Patients who withdraw from treatment and patients who withdraw from the study will also be summarized using descriptive statistics by reason for withdrawal. The denominator for calculating the percentages will be the number of patients in the ITT analysis set.

5.3. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics (age, weight, height, body mass index [BMI], time since initial migraine diagnosis [years], migraine classification [ie, CM or EM] as randomized and as per CRF, country, region, classes of migraine preventive medications that the patients have failed in the past 10 years, special group of treatment failure [ie, patients who must have had inadequate response to valproic acid and must have had inadequate response to 2 to 3 other classes of migraine preventive medications] as randomized and as per CRF, patients who over used acute medication, patients who failed 2, 3, and 4 classes of preventive medications including or not including valproic acid, and any triptans/ergots during baseline) will be summarized.

The baseline electronic headache diary efficacy variables and the other efficacy baseline values listed in Section 4.2 will be summarized.

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

5.4. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics 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 Therapy and Medication

Any prior therapy, medication, or procedure a patient has had within 6 months before study drug administration will be recorded on the CRF. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

The incidence of prior therapies and medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior therapies and medications will include all medications taken and therapies administered prior to the 1st study drug administration.

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

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

Past preventive headache/migraine medication use will be listed.

5.6. Childbearing Potential and Methods of Contraception

For female patients, information related to childbearing potential and menopause will be collected at screening. Data will be listed.

5.7. Study Protocol Deviations

Data from patients with any important protocol deviations during the study will be summarized overall and for each category using descriptive statistics.

6. EFFICACY ANALYSIS

6.1. General

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

In addition, the following questionnaires will be used for the assessments of migraine impairment, quality of life, and satisfaction of treatment etc. during the study.

- migraine-related disability using the HIT-6 (see [Appendix C](#))
- migraine-related disability using the MIDAS (see [Appendix D](#))
- migraine-specific quality of life, as measured by the MSQOL questionnaire (see [Appendix E](#))
- health status, as measured by the EQ-5D-5L questionnaire (see [Appendix G](#))
- patient depression status, as measured by the PHQ-2 and the PHQ-9 (see [Appendix H](#))
- patient work productivity and activity impairment, as measured by the WPAI questionnaire (see [Appendix I](#))
- assessment of patient satisfaction, as measured by the PGIC scale (see [Appendix J](#))

For the purpose of this study, a migraine day is endorsed when at least one of the following occurs:

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

A headache day of at least moderate severity is endorsed when at least 1 of the following situations occurs:

- a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of headache of at least moderate severity
- a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine- specific acute medications (triptans and ergot compounds)

The derivation logic is presented in [Appendix B](#).

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

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

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

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

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

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

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

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

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

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

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

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

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

The mITT analysis sets will be used for all efficacy analyses. Summaries will be presented by treatment group as randomized, unless otherwise noted. For the double-blind treatment period, summaries will be presented for the following treatment groups: placebo, fremanezumab quarterly, and fremanezumab monthly. For the open-label treatment period, summaries will be

presented by migraine classification (ie, CM, EM, and all), double-blind treatment group (ie, placebo, fremanezumab 675 mg/placebo/placebo, fremanezumab 675/225/225 mg, fremanezumab 225/225/225 mg, all fremanezumab), and overall (ie, total). Descriptive statistics for all efficacy data will be presented by month (or week) and over 12-week period for the double-blind period and the open-label period.

The primary and secondary endpoints analysis listed in Section 6.2.1 and Section 6.3 will be repeated for the per-protocol analysis set.

6.2. Primary Efficacy Endpoint and Analysis

6.2.1. Definition

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

6.2.2. Primary Efficacy Analysis

The hypothesis testing for the primary analysis is:

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

where δ_1 and δ_2 are the estimates of mean change from baseline in the monthly average number of migraine days for the fremanezumab treatment group and the placebo group respectively. The estimated difference of fremanezumab monthly dose versus the placebo and fremanezumab quarterly dose versus the placebo will be tested following the pre-specified fixed sequence as described in Section 7.

The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) method. The model will include treatment, gender, region, special group of treatment failure (Yes or No), migraine classification (ie, CM or EM), and treatment-by-migraine classification interaction as fixed effects, and baseline number of migraine days and years since onset of migraines as covariates. The stratification factors (as randomized) will be used in the model. The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using the estimate statement. Ninety-five percent confidence intervals (CIs) will be constructed for the least square (LS) means differences between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo.

Note: Special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in Appendix H of the protocol.

Type I error will be controlled for treatment comparisons by using Hochberg's method (see Section 7).

The following sample SAS code pertains to the primary analysis.

```
ODS OUTPUT DIFFS=XXX LSMEANS=XXX TESTS3=XXX;
```

```

PROC MIXED DATA=XXX;
    CLASS TREAT GENDER REGION TRTFAIL MIGCLASS;
    MODEL CHG=BASE YOD TREAT GENDER REGION TRTFAIL MIGCLASS
    TREAT*MIGCLASS/S;
    LSMEANS TREAT/PDIFF CL ALPHA=0.05;
RUN;

```

6.2.3. Sensitivity Analysis

6.2.3.1. MMRM Analysis

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

Each patient's monthly number of migraine days during the 4-week period will be calculated by formula (2) in Section 6.1. If a patient is early terminated or has intermittent missing days and has fewer than 10 days of electronic headache diary entries for a month, that month's value will be considered as missing as described in Section 4.3.

The MMRM model will include treatment, gender, region, special group of treatment failure (Yes or No), migraine classification (ie, CM or EM), month, treatment-by-migraine classification interaction, treatment-by-month interaction, and treatment-by-migraine classification-by-month interaction as fixed effects, baseline value and years since onset of migraines as covariates, and patient in the repeated statement as a random effect. The stratification factors (as randomized) will be used in the model. The unconstructed covariance structure will be used for the repeated observations within a patient. The treatment comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo for monthly average migraine days will be conducted under this model using the estimate statement. Ninety-five percent CIs will be constructed for the LS means differences between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo. Note: Special treatment failure group defined as patients who must have had inadequate response to valproic acid. In addition, patients in the special treatment failure group must have had inadequate response to 2 to 3 other classes of migraine preventive medications as defined in Appendix H of the protocol.

The following SAS code pertains to the MMRM analysis:

```

ODS OUTPUT DIFFS=XXX LSMEANS=XXX TESTS3=XXX;
PROC MIXED DATA=XXX METHOD=REML;
    CLASS USUBJID TREAT GENDER REGION TRTFAIL MIGCLASS
    MONTH;
    MODEL CHG=BASE YOD TREAT GENDER REGION TRTFAIL MIGCLASS
    MONTH TREAT*MIGCLASS TREAT*MONTH
    TREAT*MIGCLASS*MONTH/S;

```

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```
REPEATED MONTH / SUBJECT=USUBJID TYPE=UN R;
LSMEANS TREAT TREAT*MONTH/PDIFF CL ALPHA=0.05;
RUN;
```

This sensitivity analysis will be performed on the mITT analysis set.

6.2.3.2. Analysis with Multiple Imputation Method

Sensitivity analysis will be performed by imputing missing migraine days of months 1-3 using multiple imputation method. The data will be processed by the following steps.

- If a patient has partial electronic headache diary data (ie, <28 days) for a month, that month’s value will be considered missing before the MI procedure.
- For the patients in the fremanezumab treatment group who are early terminated with reasons of adverse event or lack of efficacy, they will be assigned to placebo group so their missing values will be imputed using data from the placebo treated patients
- Run SAS PROC MI procedure to create 100 complete datasets.

The following SAS code pertains to the MI analysis:

```
PROC MI DATA=XXX SEED=SEED OUT=MI_OUT NIMPUTE=100
MAXIMUM=. . . . . 28 28 28 MINIMUM=. . . . . 0 0 0;
CLASS TREAT GENDER REGION TRTFAIL MIGCLASS;
FCS REG (AVALMI1=TREAT GENDER REGION TRTFAIL MIGCLASS
BASE YOD/DETAILS) NBITER=100;
FCS REG (AVALMI2=TREAT GENDER REGION TRTFAIL MIGCLASS
BASE YOD AVALMI1/DETAILS) NBITER=100;
FCS REG (AVALMI3=TREAT GENDER REGION TRTFAIL MIGCLASS
BASE YOD AVALMI1 AVALMI2/DETAILS) NBITER=100;
VAR TREAT GENDER REGION TRTFAIL MIGCLASS YOD BASE
AVALMI1 AVALMI2 AVALMI3;
RUN;
```

- Within each imputed data set, for a patient who has partial, say X ($X < 28$) days , electronic headache diary data in a month, the monthly value will be replaced by
- $\sum(\text{observed days}) + (28 - X) * \text{imputed value} / 28$
- The monthly average number of migraine days *during the 12-week double-blind period* after the 1st dose of study drug will be the average of month 1, month 2 and month 3 values.

Each dataset will be analyzed using the same ANCOVA model as described in Section 6.2.2. The LS means and standard errors from each analysis will be output to a SAS data set. SAS MIANALYZE procedure will be used to generate the final LS means (\pm SE) for the treatment groups and the treatment differences (fremanezumab - placebo) as well as p-values associated with treatment differences. Ninety-five percent CIs for the LS means differences between each

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fremanezumab treatment group (monthly dose and quarterly dose) and placebo will be constructed.

```
ODS OUTPUT DIFFS=MIXED_OUT;  
PROC MIXED DATA=UPDATED_MI_OUT METHOD=REML;  
BY _IMPUTATION_;  
CLASS TREAT GENDER REGION TRTFAIL MIGCLASS;  
MODEL CHG=BASE YOD TREAT GENDER REGION TRTFAIL MIGCLASS  
TREAT*MIGCLASS;  
LSMEANS TREAT/DIFF;  
RUN;
```

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

```
ODS OUTPUT PARAMETERESTIMATES=PARMEST;  
PROC MIANALYZE DATA=MIXED_OUT ALPHA=0-.05 THETA0=0;  
BY TRTN;  
MODELEFFECTS ESTIMATE;  
STDERR=STDERR;  
RUN;
```

This sensitivity analysis will be performed on the ITT analysis set.

6.2.3.3. ANCOVA Analysis

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

6.2.4. Sub-Group Analyses

The ANCOVA analysis defined in Section 6.2.2 and MMRM analysis defined in Section 6.2.3.1 will also be applied for the following subgroups for the primary endpoint.

- age group (18-45 years, >45 years)
- sex (male, female)
- region (USA, Europe)
- country (Countries with less than 20 patients will be excluded from the subgroup analysis)
- migraine classification (CM, EM)

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- 4 classes of preventive medications for migraine in the past not including valproic acid failures (yes, no)
- number of classes of preventive medications for migraine in the past failures (2, 3, 4)
- overuse of acute medication (yes, no)
- frequency of headache days at baseline for EM patients (4-9, 10-14)

An exploratory analysis for the primary endpoint will also be performed by adding the treatment-by-region interaction to the primary analysis model to test whether treatment effects are homogenous across regions.

6.3. Secondary Efficacy Endpoints and Analysis

The secondary endpoints to further demonstrate efficacy are as follows:

- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab
- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of fremanezumab
- 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 fremanezumab

6.3.1. Electronic Headache Diary Data

6.3.1.1. Definition

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

The percent reduction in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab will be calculated by formula (4) where the postbaseline value will be the number of migraine days prorated to 28 days for month 1. If the patient has 50% reduction or more in month 1, he/she will be considered a responder during the 4-week period after the 1st dose of fremanezumab.

The change from baseline in the monthly average number of headache days of at least moderate severity and the change from baseline in the monthly average number of days of use of any acute headaches medications during the 12-week period after the 1st dose of fremanezumab will be derived similar to the primary efficacy variable using the electronic diary data collected through the corresponding headache diary questions. The baseline values and the postbaseline values will be derived using formula (3) and (1) in Section 6.2.1, and the change is calculated as *postbaseline value – baseline value*.

The change from baseline in the monthly average number of migraine days and the change from baseline in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of fremanezumab will be calculated using formula (2) and (1) in Section 6.2.1, and the change is calculated as *postbaseline value – baseline value*.

6.3.1.2. Analysis

The change from baseline secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint. For the proportion of responders, a logistic regression model will be used with the following effects: treatment, gender, region, special group of treatment failure (Yes or No), and migraine classification (ie, CM or EM). The stratification factors (as randomized) will be used in the model. The odds ratios, 95% CIs for odds ratios, and p-values will be presented for each fremanezumab treatment group (monthly dose and quarterly dose).

6.4. Other Efficacy Endpoints Analysis

The exploratory endpoints for the double-blind period are as follows:

- proportion of patients reaching at least 75% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 1st dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 1st dose of the study drug
- proportion of patients reaching at least 50% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- proportion of patients reaching at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 1st dose of study drug

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- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 1st dose of study drug
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for patients who failed valproic acid for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 1st dose of study drug for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past
- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the HIT-6, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after the administration of the 3rd dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the 3rd dose of study drug
- mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale, at 4 weeks after the 3rd dose of study drug

The exploratory endpoints for the open-label period are as follows:

- mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 4th dose of fremanezumab
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 4th dose of fremanezumab
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of study drug
- proportion of patients reaching total (100%) response (no headache) during the 12-week period after the 4th dose of study drug
- proportion of patients reaching total (100%) response (no headache) for at least one month during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of headache hours of at least moderate severity during the 12-week period after the 4th dose of the study drug
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug
- proportion of patients reaching at least 75% reduction from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 4th dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with nausea or vomiting during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days with photophobia and phonophobia during the 12-week period after the 4th dose of study drug
- mean change from baseline (28-day run-in period) in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the 4th dose of study drug

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- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed topiramate for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed onabotulinumtoxinA for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed valproic acid for migraine in the past
- mean change from baseline (28-day run-in period) in the number of migraine days during the 12-week period after the 4th dose of study drug for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- proportion of patients reaching at least 50% reduction from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past
- mean change from baseline (day 0) in disability score, as measured by the HIT-6, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after the administration of the 6th dose of study drug
- mean change from baseline (day 0) in quality of life, as measured by the MSQOL questionnaire, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in the health status, as measured by the EQ-5D-5L questionnaire at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in patient depression status, as measured by the PHQ-2 and PHQ-9, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) in patient work productivity and activity impairment, as measured by the WPAI questionnaire, at 4 weeks after administration of the 6th dose of study drug
- mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale, at 4 weeks after the last 6th dose of study drug

The exploratory endpoints for both the double-blind and open-label periods are as follows:

- to evaluate the immunogenicity response of fremanezumab and the impact of ADAs on clinical outcomes in patients exposed to sc fremanezumab.
- to explore the relationship between genetic polymorphisms (including those within the CGRP receptor-ligand complex, in migraine-associated susceptibility genes, and in as-yet undiscovered loci) versus migraine onset/severity, adverse events to medication and fremanezumab efficacy

- to explore the relationship between exploratory biofluid biomarkers versus fremanezumab concentrations, adverse events and fremanezumab efficacy

6.4.1. Electronic Headache Diary Data

6.4.1.1. Definition

The percent reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab will be calculated by formula (4) in Section 6.1. The patient is considered as a responder reaching 50%, 75% or 100% reduction if his/her percent reduction is 50% or more, 75% or more, or 100% respectively. If a patient is early discontinued from the study, he/she will be counted as a non-responder. 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 migraine days during the 12-week period after the 4th dose of fremanezumab. Similar definition will be applied to calculate the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past and to calculate the proportion of patients reaching at least 50% in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab for the subset of patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past.

The percent reduction in the monthly average number of migraine days for at least 1 month during the 12-week period after the 1st dose of fremanezumab will be calculated by formula (4) where the postbaseline value will be the number of migraine days prorated to 28 days for months 1, 2, and 3. If the patient has 100% reduction or more for at least 1 month, he/she will be considered a responder for that month during the 12-week period after the 1st dose of fremanezumab. Similar definition will be applied to calculate the percent reduction in the monthly average number of migraine days for at least 1 month during the 12-week period after the 4th dose of fremanezumab.

The percent reduction on the monthly average number of migraine days during the 4-week period after each dose for months 1, 2, and 3 will be calculated by formula (4) in Section 6.1 where the postbaseline value will be the number of migraine days prorated to 28 days for month 1, month 2, and month 3, respectively. If the patient has 50% reduction or more in month 1, he/she will be considered a responder during the 4-week period after the 1st dose of study drug. In addition, if the patient also has 50% reduction or more in month 2 and month 3, he/she is a responder for months 2 and 3, and the level of effect is sustained throughout the 12-week period after the 1st dose of study drug for this patient. Similar definition will be applied to calculate the proportion of patients reaching at least 75% reduction in the number of migraine days during the 4-week period after the 1st dose of study drug for whom this level of effect is sustained throughout the 12-week period after the 1st dose of study drug. Similar definition will be applied to calculate the proportion of patients reaching 50% and 75% reduction in the number of migraine days during the 4-week period after the 4th dose of fremanezumab.

The change from baseline in the monthly average number of days or hours of exploratory efficacy variables for the double-blind period (e.g., headache hours of at least moderate severity, days with nausea or vomiting, days with photophobia and phonophobia, days of use of migraine-

specific acute headache medications [triptans and ergot compounds], migraine days for patients who failed topiramate for migraine in the past, migraine days for patients who failed onabotulinumtoxinA for migraine in the past, migraine days for patients who failed valproic acid for migraine in the past, and migraine days for the subset of patients who failed 2 to 3 classes of preventive medications and valproic acid for migraine in the past) during the 12-week period after the 1st dose of fremanezumab and the change from baseline in the monthly average number of days or hours of exploratory efficacy variables for the open-label period (e.g., headache days of at least moderate severity, days of use of any acute headache medications, headache hours of at least moderate severity, days with nausea or vomiting, days with photophobia and phonophobia, days of use of migraine-specific acute headache medications [triptans and ergot compounds], migraine days for patients who failed topiramate for migraine in the past, migraine days for patients who failed onabotulinumtoxinA for migraine in the past, migraine days for patients who failed valproic acid for migraine in the past, and migraine days for patients who failed 2 to 3 classes of preventive medications in addition to valproic acid for migraine in the past) during the 12-week period after the 4th dose of fremanezumab will be derived similar to the primary efficacy variable using the electronic diary data collected through the corresponding headache diary questions ([Appendix A](#)). The baseline values and the postbaseline values will be derived using formula (3) and (1) in Section 6.2.1, and the change is calculated as *postbaseline value – baseline value*. Similar definition will be applied for the change from baseline in the monthly average number of migraine days during the 12-week period after the 4th dose of fremanezumab.

6.4.1.2. Analysis

The change from baseline exploratory efficacy endpoints will be analyzed similarly as the primary efficacy endpoint. The proportion of responders will be analyzed similarly as the secondary efficacy endpoints using a logistic regression model.

In addition, the mean change from baseline in the number of migraine days during each month of the 6 month treatment period after the 1st dose of study drug will be summarized using descriptive statistics and plotted.

6.4.2. Six-Item Headache Impact Test

6.4.2.1. Definition

Migraine related disability will be assessed using the HIT-6 ([Appendix C](#)). The questionnaire measures the adverse impact of headache on social functioning, role functioning, vitality, cognitive functioning, and psychological distress. It also assesses headache severity. 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 1 or more items are missing then the total score is missing.

6.4.2.2. Analysis

The change from baseline values after the 3rd dose of study drug in the HIT-6 total scores will be analyzed using the same ANCOVA method as described in Section 6.2.2 and MMRM method as described in Section 6.2.3.1.

6.4.3. Migraine Disability Assessment

6.4.3.1. Definition

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.

6.4.3.2. Analysis

The change from baseline after the 3rd dose of study drug in the MIDAS total scores will be analyzed using the same ANCOVA method as described in Section 6.2.2 and MMRM method as described in Section 6.2.3.1.

6.4.4. Migraine-Specific Quality of Life

6.4.4.1. Definition

The 14-item MSQOL questionnaire ([Appendix E](#)) 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, and Emotional Function domain comprising 3 items assessing the emotions associated with migraines. Raw dimension scores are computed as a sum of item response and rescaled to a 0 to 100 scale such that higher scores indicate better 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.

6.4.4.2. Analysis

The transformed scores for the 3 domains (ie, Role Function-Restrictive, Role Function-Preventive, and Emotional Function) of MSQOL will be derived. The change from baseline after the 3rd dose of study drug in the MSQOL domains will be analyzed using the same ANCOVA method as described in Section 6.2.2 and MMRM method as described in Section 6.2.3.1.

6.4.5. EuroQol-5 Dimension Questionnaire

6.4.5.1. Definition

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

6.4.5.2. Analysis

The number and percentages of patients rating their scale of 1 to 5 for the 5 domains will be presented. The change from baseline values after the 3rd dose of study drug on the visual analogue scale will be analyzed using the same ANCOVA method as described in Section [6.2.2](#).

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

6.4.6.1. Definition

The PHQ ([Appendix H](#)) 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 scores on a scale of 0 (“not at all”), 1 (“several days”), 2 (“more than half the days”), and 3 (“nearly every day”) based on the frequency of symptoms during the past 2 weeks ([Sptizer et al 1999](#)). The PHQ-2 was developed from the PHQ-9 to rapidly screen for depression and consisted of the first 2 questions of the PHQ-9. The PHQ-2 and the PHQ-9 are validated measures for detecting and monitoring depression, anxiety, and somatization ([Kroenke et al 2010](#)).

If the PHQ-2 is positive (ie, a score of ≥ 3), patients will complete questions 3 through 9 (unique questions) of the PHQ-9.

6.4.6.2. Analysis

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

6.4.7. Work Productivity and Activity Impairment Questionnaire

6.4.7.1. Definition

The generic version of the WPAI questionnaire ([Appendix I](#)) 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

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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: $\frac{Q6}{10}$

6.4.7.2. Analysis

For the patients who are currently employed, their scores of

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

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

6.4.8. Patient’s Global Impression of Change

6.4.8.1. Definition

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

6.4.8.2. Analysis

The percentage of patients' dichotomous scale of “ Yes” or “No” rated by PGIC assessments will be analyzed using a logistic regression model as described in Section [6.3.1.2](#).

7. MULTIPLE COMPARISONS AND MULTIPLICITY

The Hochberg's method along with hierarchical testing procedure for multiple comparisons between treatment groups (2 comparisons: fremanezumab monthly dose compared with placebo and fremanezumab quarterly dose compared with placebo) for the primary and secondary endpoint analyses will be used to maintain the experiment-wise type I error of 5%. In the primary analysis, according to the Hochberg's method, if the null hypothesis is rejected for both the fremanezumab monthly and quarterly treatment groups at an alpha level of 5%, then no adjustment to the alpha level will be performed and both comparisons will be declared as statistically significant. The secondary variables will then be tested in the order as specified in Section 6.3 for both the fremanezumab monthly and quarterly treatment groups using the same procedure as the primary analysis. If the null hypothesis is not rejected for 1 of the doses at an alpha level of 5%, then the other dose will be tested using an alpha level of $5\%/2=2.5\%$, and the sequential testing will stop.

No multiplicity adjustments will be made for exploratory efficacy analyses.

8. SAFETY ANALYSIS

8.1. General

The safety analysis sets will be used for all safety analyses. Summaries will be presented separately for the double-blind treatment period and open-label treatment period. For the double-blind treatment period, summaries will be presented by migraine classification (ie, CM, EM, and all), treatment group and all fremanezumab, unless otherwise stated. For the open-label treatment period, summaries will be presented by migraine classification (ie, CM, EM, and all), double-blind treatment group (ie, placebo, fremanezumab 675 mg/placebo/placebo, fremanezumab 675/225/225 mg, fremanezumab 225/225/225 mg, all fremanezumab), and overall (ie, total).

8.2. Duration of Exposure to Study Drug

Duration of treatment (days treated) for the double-blind treatment period is the number of days on treatment started from the 1st study drug administration day to month 3 (visit 5) visit day (month 3 visit day – first day of study drug + 1). Duration of treatment (days treated) for the open-label treatment period is the number of days on treatment started from the 1st study drug administration day in the open-label treatment period to the EOT visit day/early withdrawal day (EOT visit day – first day of study drug in the open-label treatment period + 1). For patients who are lost to follow-up, the EOT visit date is defined as the last study drug administration + 27.

Number (%) of patients receiving 1 dose, 2 doses, and 3 doses during the double-blind and open-label treatment periods will be summarized using descriptive statistics. Duration of treatment (days) will also be summarized using descriptive statistics.

8.3. Adverse Events

All adverse events will be coded using the MedDRA.

The following are considered protocol-defined adverse events of special interest: ophthalmic adverse events of at least moderate severity, events of possible drug-induced liver injury (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥ 3 x the upper limit of the normal range [ULN], total bilirubin ≥ 2 x the ULN or international normalized ratio [INR] > 1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions.

Summaries will be presented for all treatment-emergent adverse events (overall and by severity), adverse events determined by the investigator to be treatment-related adverse events (defined as related or with missing relationship (overall and by severity), serious adverse events, protocol-defined adverse events of special interest, adverse events causing withdrawal from treatment, and non-serious adverse events. Additionally the injection site reactions recorded as adverse events will be summarized separately.

The incidence of adverse events will be summarized using descriptive statistics by system organ class, preferred term, and severity of the adverse event. Each patient will be counted only once within a system organ class or a preferred term using the adverse events with the highest severity within each category. Adverse events with the missing flag indicating serious will be excluded

from the summary of serious adverse events but included in the summary of non-serious adverse events.

Listings for deaths, adverse events, serious adverse events, adverse events causing withdrawal from treatment, injection site-related adverse events, and protocol defined adverse events of special interest will be presented. In addition, MedDRA dictionary terms for adverse event descriptions and adverse events preferred terms by patient number and treatment group will be presented.

8.4. Deaths

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

8.5. Clinical Laboratory Tests

Laboratory test results will be presented in standard international (SI) units.

Summary statistics for chemistry, hematology, urinalysis, and coagulation laboratory tests will be presented at baseline, month 1, month 3, month 4, and end of treatment visit. Laboratory values and changes from baseline to each visit and last on study assessment will be summarized using descriptive statistics. Listings of all individual patients’ laboratory tests will be presented.

Shifts (below, within, and above the normal range) from baseline to each visit and last on study assessment will be summarized using patient counts.

Summaries of potentially clinically significant abnormal values will include all postbaseline values (including scheduled, unscheduled, and early termination visits). The incidence of potentially clinically significant abnormal values will be summarized for laboratory variables using descriptive statistics with the criteria specified in [Table 3](#).

Listings of patients who have potentially clinically significant abnormal laboratory data will be presented.

Table 3: Criteria for Potentially Clinically Significant Laboratory Values

Test	Criterion value
Serum chemistry	
ALT	≥3x ULN
AST	≥3x ULN
ALP	≥3x ULN
GGT	≥3x ULN
LDH	≥3x ULN
BUN	≥10.71 mmol/L
Creatinine	≥177 µmol/L

Table 3: Criteria for Potentially Clinically Significant Laboratory Values (Continued)

Test	Criterion value	
Uric acid	Men	$\geq 625 \mu\text{mol/L}$
	Women	$\geq 506 \mu\text{mol/L}$
Bilirubin (total)		$\geq 34.2 \mu\text{mol/L}$
Hematology		
Hematocrit	Men	$< 0.37 \text{ L/L}$
	Women	$< 0.32 \text{ L/L}$
Hemoglobin	Men	$\leq 115 \text{ g/L}$
	Women	$\leq 95 \text{ g/L}$
WBC counts		$\leq 3 \times 10^9/\text{L}$ $\geq 20 \times 10^9/\text{L}$
Eosinophils		$\geq 10\%$
ANC		$\leq 1 \times 10^9/\text{L}$
Platelet counts		$\leq 75 \times 10^9/\text{L}$ $\geq 700 \times 10^9/\text{L}$
Urinalysis		
HGB		≥ 2 unit increase from baseline
Glucose		≥ 2 unit increase from baseline
Ketones		≥ 2 unit increase from baseline
Total protein		≥ 2 unit increase from baseline
Coagulation		
INR		> 1.5

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

8.5.1. Laboratory Values Meeting Hy's Law Criteria

All occurrences of possible drug-induced liver injury that meet Hy's law criteria as defined in the protocol Section 7.1.5.1 will be included in adverse events reporting.

8.5.2. Other Clinical Laboratory Tests

8.5.2.1. Human Chorionic Gonadotropin Test

Serum beta-human chorionic gonadotropin (β -HCG) tests will be performed for all women of childbearing potential at screening and end of treatment/early termination visit. Urine pregnancy tests will be performed for all women of childbearing potential at baseline, months 1 through 5, and end of treatment/early termination visit. Pregnancy test results will be listed.

8.5.2.2. Follicle-Stimulating Hormone Test

Postmenopausal women will have a follicle-stimulating hormone (FSH) test at screening. Results will be listed.

8.6. Physical Examinations

Physical examinations, including height (to be measured at the screening visit only) and weight, will be performed at screening, baseline, month 3, and end of treatment/early withdrawal visit. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2 of the study protocol. Shifts from baseline to each visit and last on study assessment will be summarized using patient counts.

Descriptive statistics for weight and height will be provided.

8.7. Vital Signs

Summary statistics for vital signs (pulse, systolic and diastolic blood pressure, body temperature, and respiratory rate) will be presented at baseline, each visit, and last on study assessment. Vital signs values and changes from baseline to each visit and last on study assessment will be summarized using descriptive statistics.

Summaries of potentially clinically significant abnormal values will include all postbaseline values (including scheduled, unscheduled, and early termination visits). The incidence of potentially clinically significant abnormal values will be summarized using descriptive statistics with the criteria specified in [Table 4](#).

[Table 4](#) specifies the criteria for identifying vital signs as potentially clinically significant abnormal values. Note that in order to qualify as potentially clinically significant abnormal, a value needs to meet both criteria below: ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change relative to baseline column.

Table 4: 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

bpm=beats per minute

8.8. Electrocardiography

Twelve-lead ECGs will be performed in triplicate, with approximately 1-5 minutes between recordings. The average of the recorded measurements will be calculated for each visit.

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

Shifts (normal and abnormal) from baseline to overall result interpretation and by visit will be summarized using patient counts. For overall result interpretation the worst postbaseline finding for the patient (the abnormal finding if there are both normal and abnormal findings) will be used in the summaries. Summary statistics for ECG variables and their corrected values will be presented. Actual values and changes from baseline to month 4, end of treatment visit, and last on study assessment will be summarized using descriptive statistics.

8.9. Electronic Columbia-Suicide Severity Rating Scale

The eC-SSRS will be used to assess the patient's suicidal ideation (severity and intensity) and behavior ([Posner et al 2011](#)). The eC-SSRS 'Baseline/Screening version' will be completed by the patient at visit 1 (screening), and the eC-SSRS 'Since Last Visit version' will be completed by the patient at months 1, 2, 3, 4, and 5, and at the end of treatment visit.

The results from the eC-SSRS will be listed.

8.10. Concomitant Medications or Therapies

Concomitant therapies and medications, including medications that are taken on an as needed basis and occasional therapies, will be monitored during the study. Details of prohibited medications may be found in Section 5.6 of the study protocol. All concomitant medications will be coded using the WHO Drug.

The incidence of concomitant therapies and medications will be summarized using descriptive statistics by therapeutic class category and preferred term. Patients are counted only once in each therapeutic class and only once in each preferred term category. Concomitant therapies and medications will include all medications up to the end of study as defined in the study protocol.

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

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

Statistical Analysis Plan

- opioids for reasons other than migraine/headache
- preventive medication for other reasons

9. TOLERABILITY VARIABLES AND ANALYSIS

Local tolerability findings will be listed and summarized descriptively.

10. PHARMACOKINETIC ANALYSIS

Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point by treatment group and indication. In addition, the most appropriate population pharmacokinetic model may be developed, and covariates that may affect it will be tested for inclusion in the model. If performed, this analysis will be reported separately.

11. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The pharmacokinetic/pharmacodynamic relationship may be estimated by compartmental techniques. The pharmacokinetic parameters will be based on IMP measurements. The pharmacodynamics analysis will be the efficacy response(s).

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

12. BIOMARKER ANALYSIS

Exploratory biomarker measurements will be made using appropriately validated assays. Results, if generated, will typically be expressed as % change from baseline and reported in a separate report.

13. PHARMACOGENOMIC ANALYSIS

Pharmacogenomic analysis will be conducted to correlate clinical observations (pharmacokinetics, safety, efficacy, or other effects) with genotypes observed in the study. Pharmacogenomic analysis may be conducted at a later time and will be reported in a separate report.

14. IMMUNOGENICITY ANALYSIS

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

15. PLANNED INTERIM ANALYSIS

An interim analysis is planned when the last patient has completed the double-blind period. Final database lock will occur following the end of the open-label period.

The inferential analysis of efficacy variables for comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo will be done at the time of the first interim lock. The appropriate method for type 1 error control will be applied to the first interim analysis.

Efficacy analysis for the open-label portion of this study is considered exploratory and mainly descriptive. This analysis will be done at the time of the final database lock.

16. STATISTICAL SOFTWARE

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

17. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

The planned interim analyses (see Section 2.5.1) have been updated to indicate that there will be 2 interim database locks and a final database lock. This was updated as clarification.

The PP analysis set definition (see Section 3.4) has been modified to update “completing the study” to “completing the double-blind treatment period”. This change has been made as this analysis set is only used for the primary and secondary efficacy endpoints which are for the double-blind treatment period only. Additional details have also been added regarding compliance and incorrect study drug administered. A statement has also been added to clarify that a blinded data review meeting will be conducted prior to the interim database lock to determine the exclusion of the patients.

18. 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. *Pharmacoeconomics* 1993; 4(5):353-65.

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 mental disorders. Patient health questionnaire. *JAMA* 1999; 282(18):1737-44.

APPENDIX A. E-DIARY QUESTIONNAIRE

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

The following questions are referring to yesterday (00:00 - 23:59) AT THE TIME WHEN YOUR HEADCAHE REACHED THE WORST SEVERITY	
B1	Was it worse on one side of the head than on the other, and/or limited to one side of the head?
B2	Was it pounding, pulsating, or throbbing?
B3	Was it made worse by routine activities such as walking or climbing stairs?
B4	Did you have nausea, or get sick to your stomach?
B5	Did light bother you more than when you didn't have a headache (did you experience photophobia)?
B6	Did sounds bother you more than when you didn't have a headache (did you experience phonophobia)?
The following questions are referring to yesterday (00:00 - 23:59)	
B7	Did you experience something like seeing spots, stars, lines, flashing lights, zigzag lines, or "heat waves" around the time of your headache? (This is different from "light bothers you")
B8	Did you have feelings such as numbness or tingling in any part of your body or face around the time of your headache?
B9	Did you experience something like seeing spots, stars, lines, flashing lights, zigzag lines, or "heat waves" similar to those you may have seen when you have a headache? (This is different from "light bothers you")
B10	Did you have feelings such as numbness or tingling in any part of your body or face, similar to what you may have felt when you have a headache?
C0	Did you take any medications yesterday for your headache/migraine?
C1	Were any of the following Medications taken yesterday?
	Local list of Triptans, Ergots and Opioid combinations, Presented in groups of 5 per screen, with Yes / No option to answer.

For the following questions please do not consider any medications you listed in the above questions.	
D1	Did you use any other prescription medications (i.e., opioids) in an effort to get relief from your headache/migraine?
D5	Did you use any other over the counter medications in an effort to get relief from your headache/migraine?
E1	Did you have problems falling sleep last night?
E2	Which of the following situations best describe your work/school performance yesterday, when you did not have a headache?
E3	What would better describe in general, how did you feel yesterday?
E4	How much of the time yesterday did you find it difficult to concentrate on what you needed to do?
E5	On average, how much of the time yesterday were you very tired, asleep, or feeling drained?
E6	Which of the following situations best describe your ability to perform household chores yesterday, when you did not have a headache?
E7	How engaged were you with your partner's or children's activities yesterday, when you didn't have a headache?
E8	Overall, how interested were you in doing daily activities yesterday?

APPENDIX B. LOGICS FOR ENDPOINTS DERIVATION

Migraine day: 1 of the following 5 options <i>Primary endpoint</i>			
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 from option 1, **Part 3** needs ONLY one of the following:

Part 3		B5	YES
		B6	YES

If **Part 1** and **Part 3** met from option 1, **Part 2** needs ONLY one of the following:

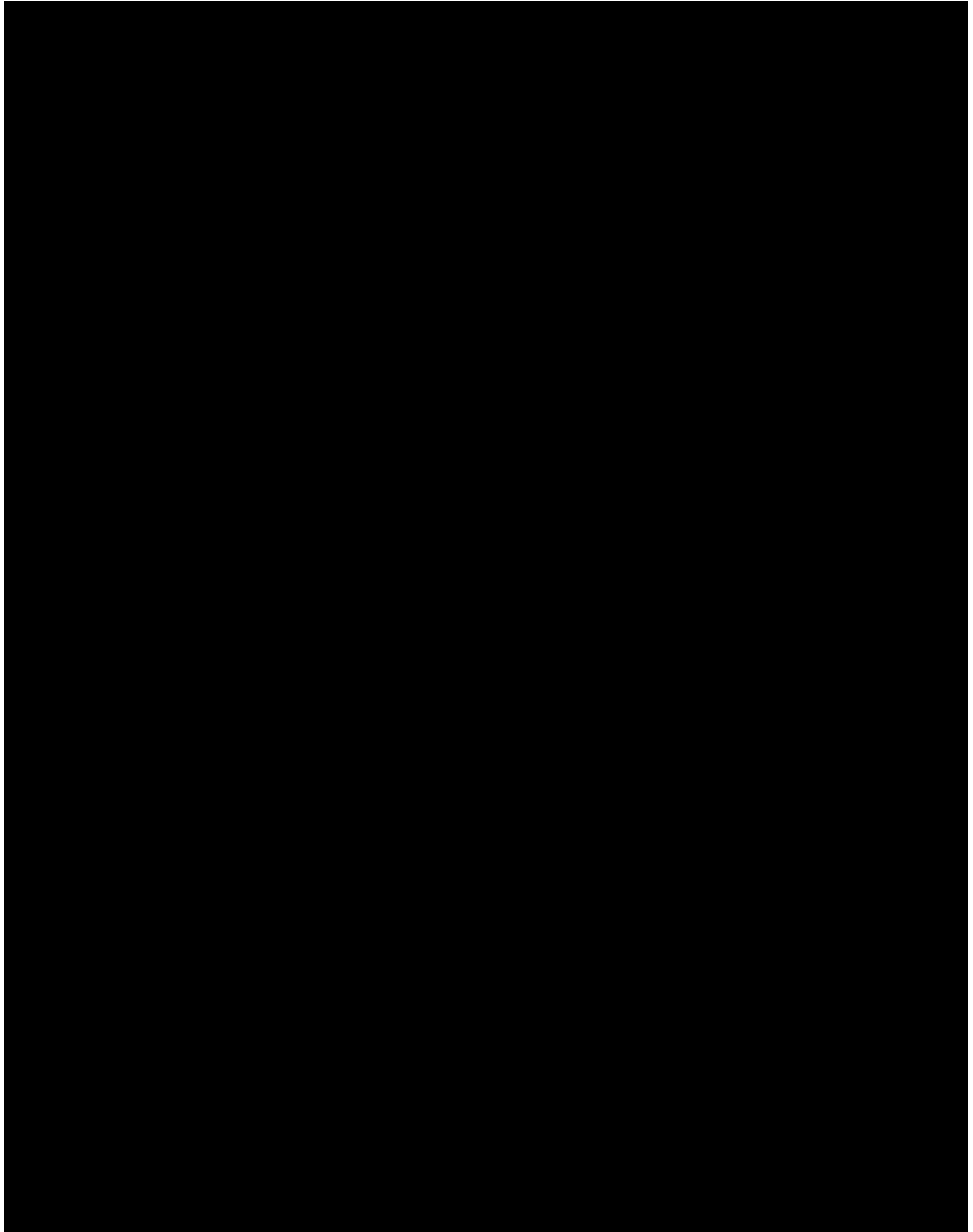
Part 2	1	A4	Mod-S
	2	B1	YES
	3	B2	YES
	4	B3	YES

If **Part 2** and **Part 3** met from option 1, **Part 1** needs ONLY the following:

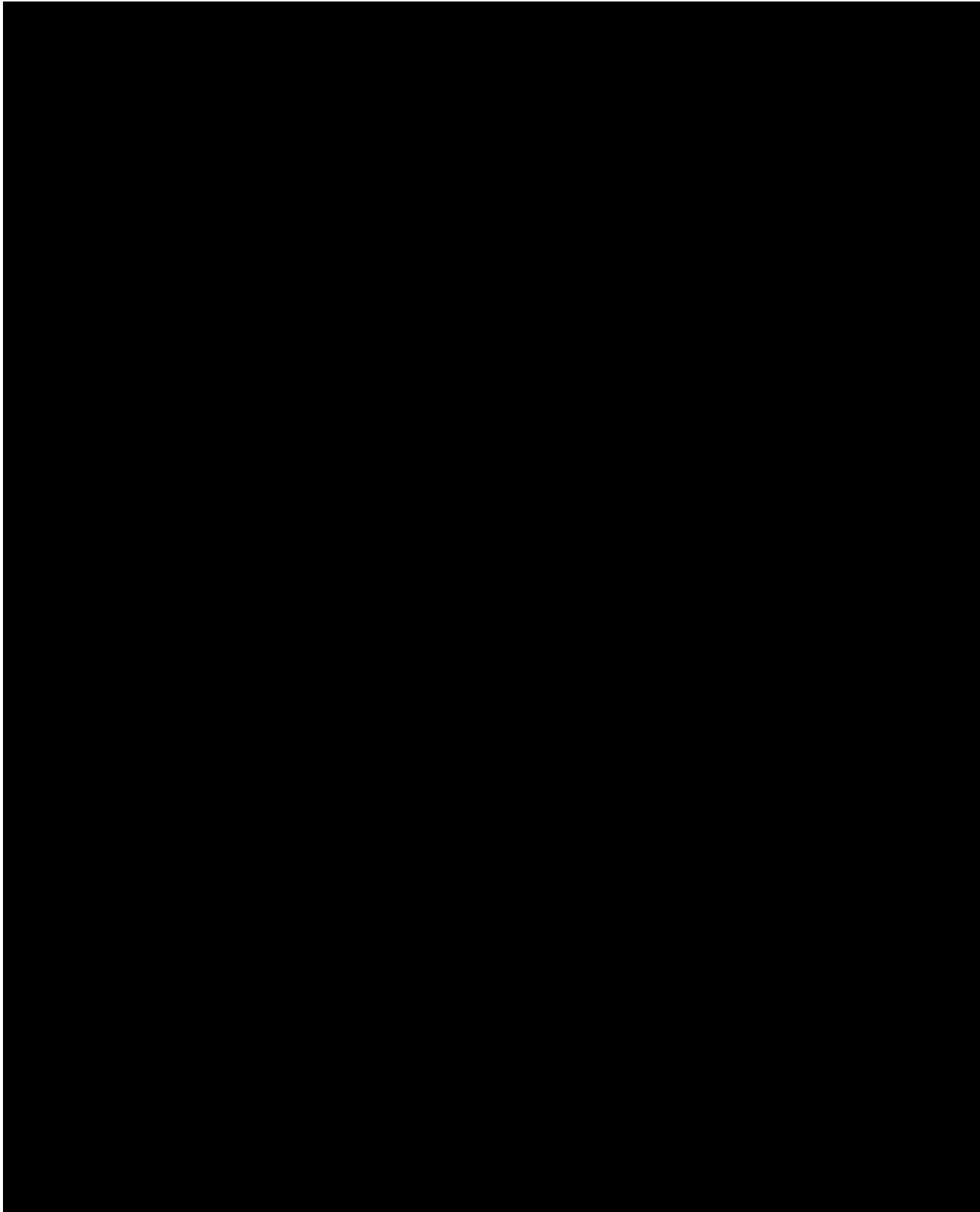
Part 1	1	A1	YES
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Headache day of at least moderate severity: 1 of the following 3 options		
OPTION 1		
1	A1	YES
2	A2	YES
3	A4	Moderate or Severe
OPTION 2		
1	A1	YES
2	C0	YES
3	C1	YES
4	C1	ERGOT OR TRIPTAN
OPTION 3		
1	A1	YES
2	C0	YES
3	D1	YES
4	D1	ERGOT OR TRIPTAN

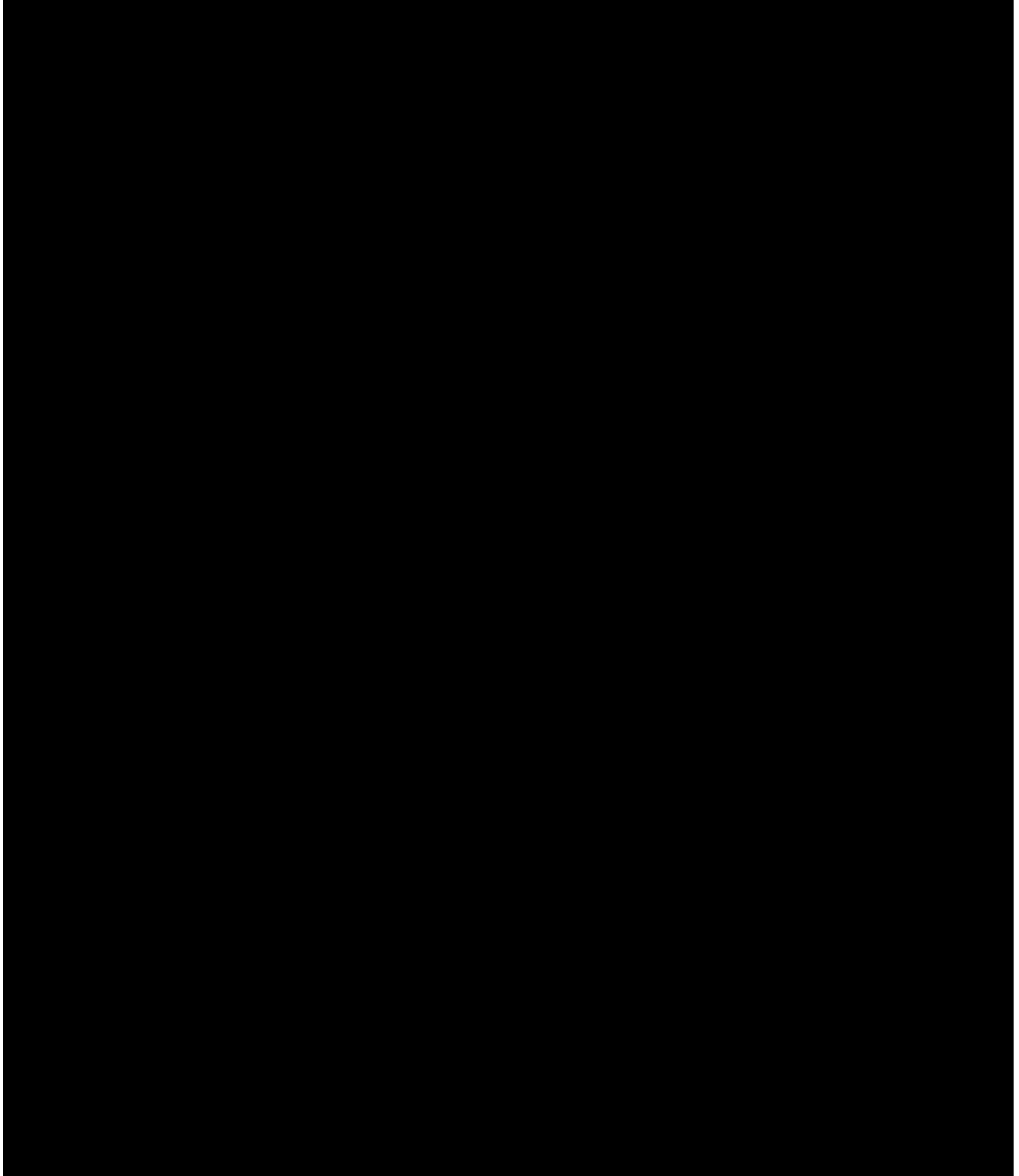
APPENDIX C. HIT-6™ HEADACHE IMPACT TEST

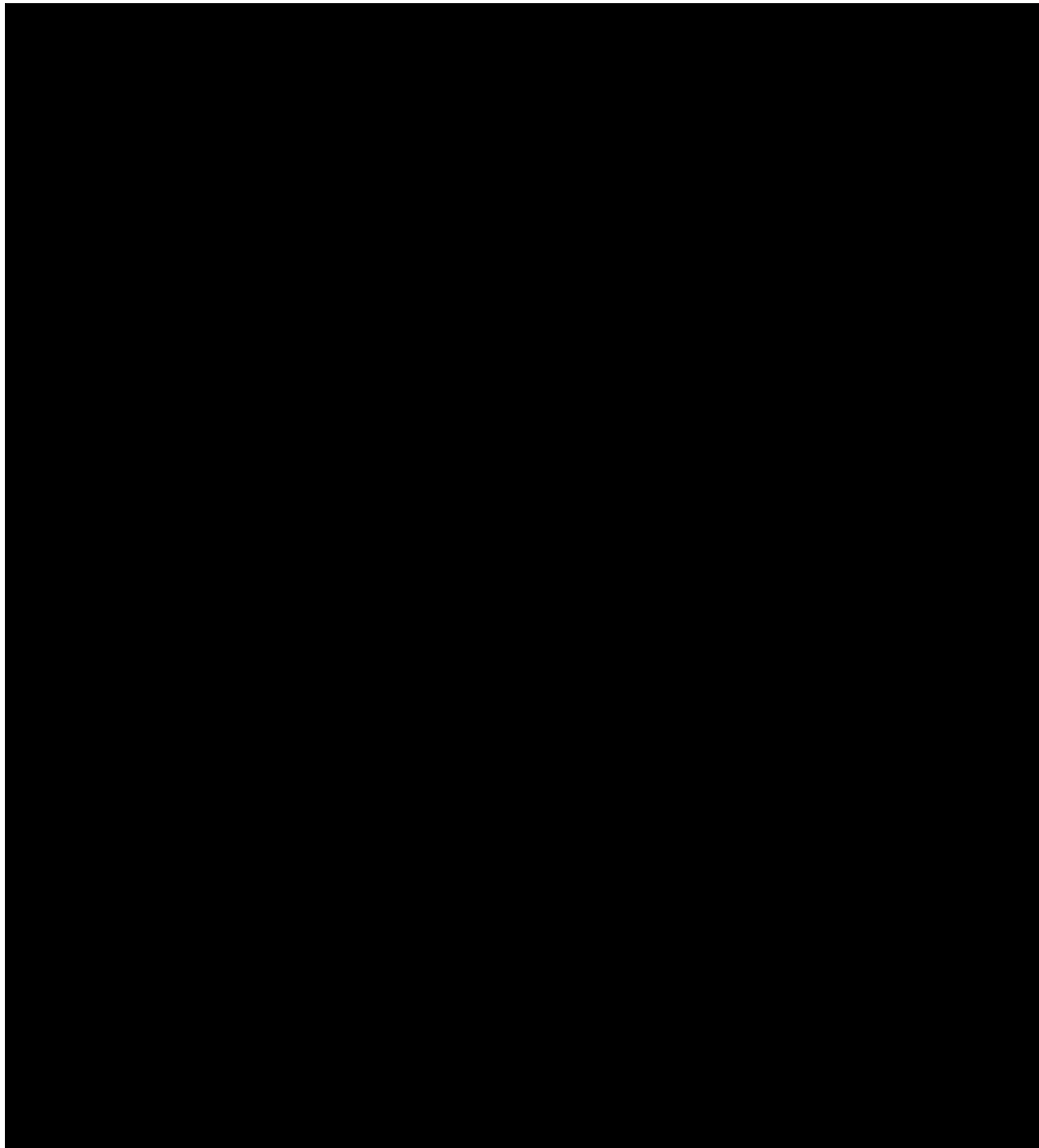


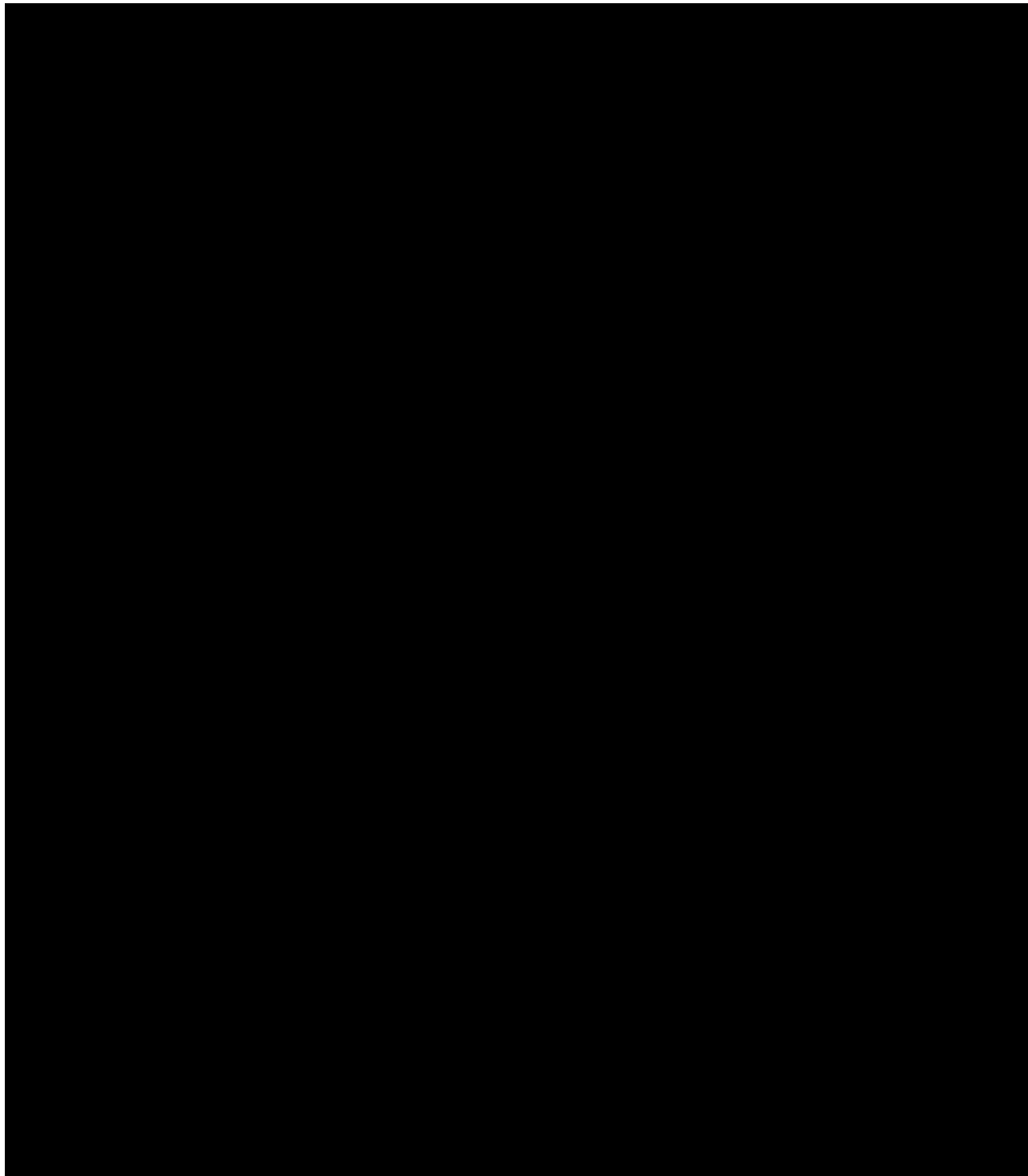
APPENDIX D. THE MIGRAINE DISABILITY ASSESSMENT

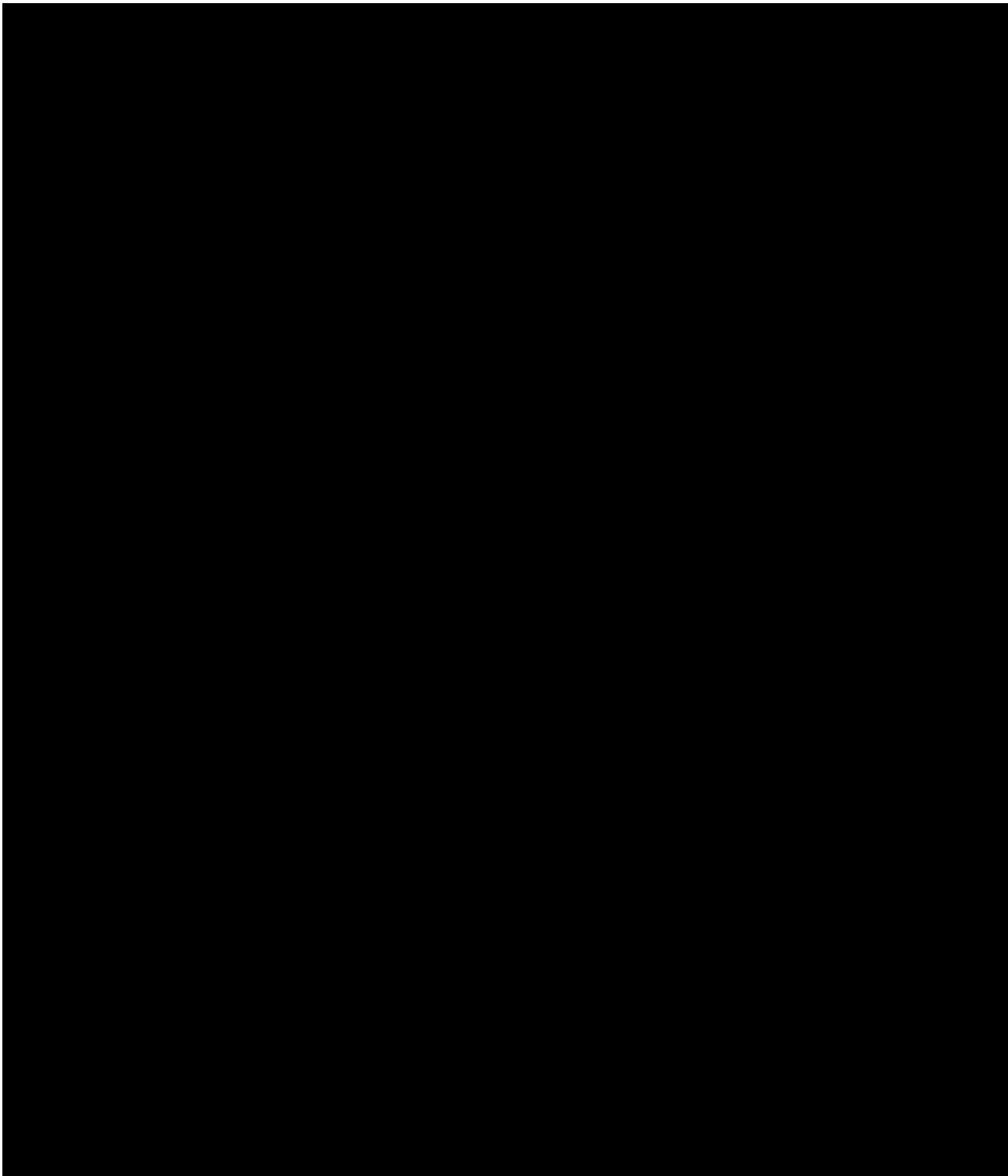


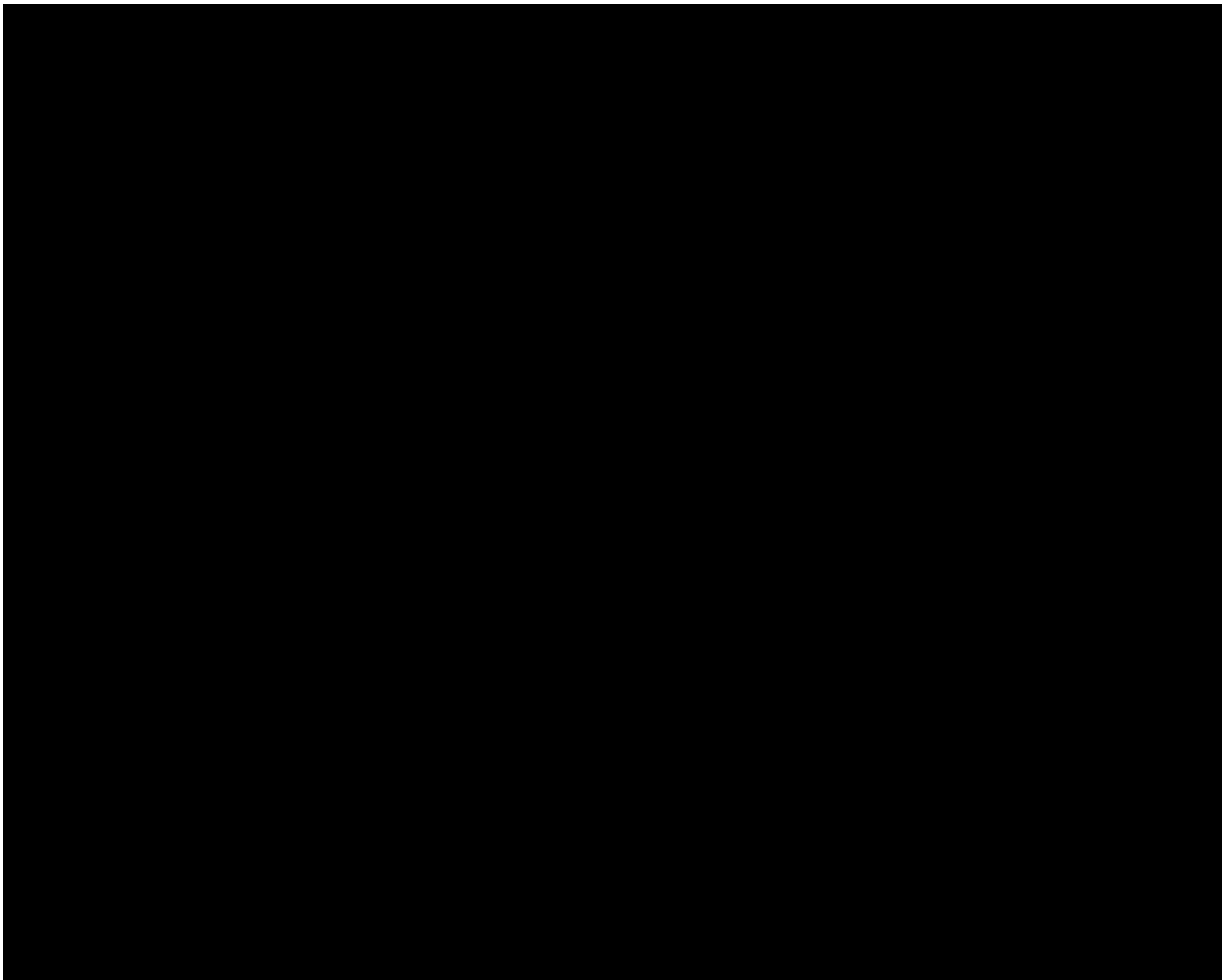
**APPENDIX E. MIGRAINE-SPECIFIC QUALITY OF LIFE
QUESTIONNAIRE (MSQ) (VERSION 2.1)**



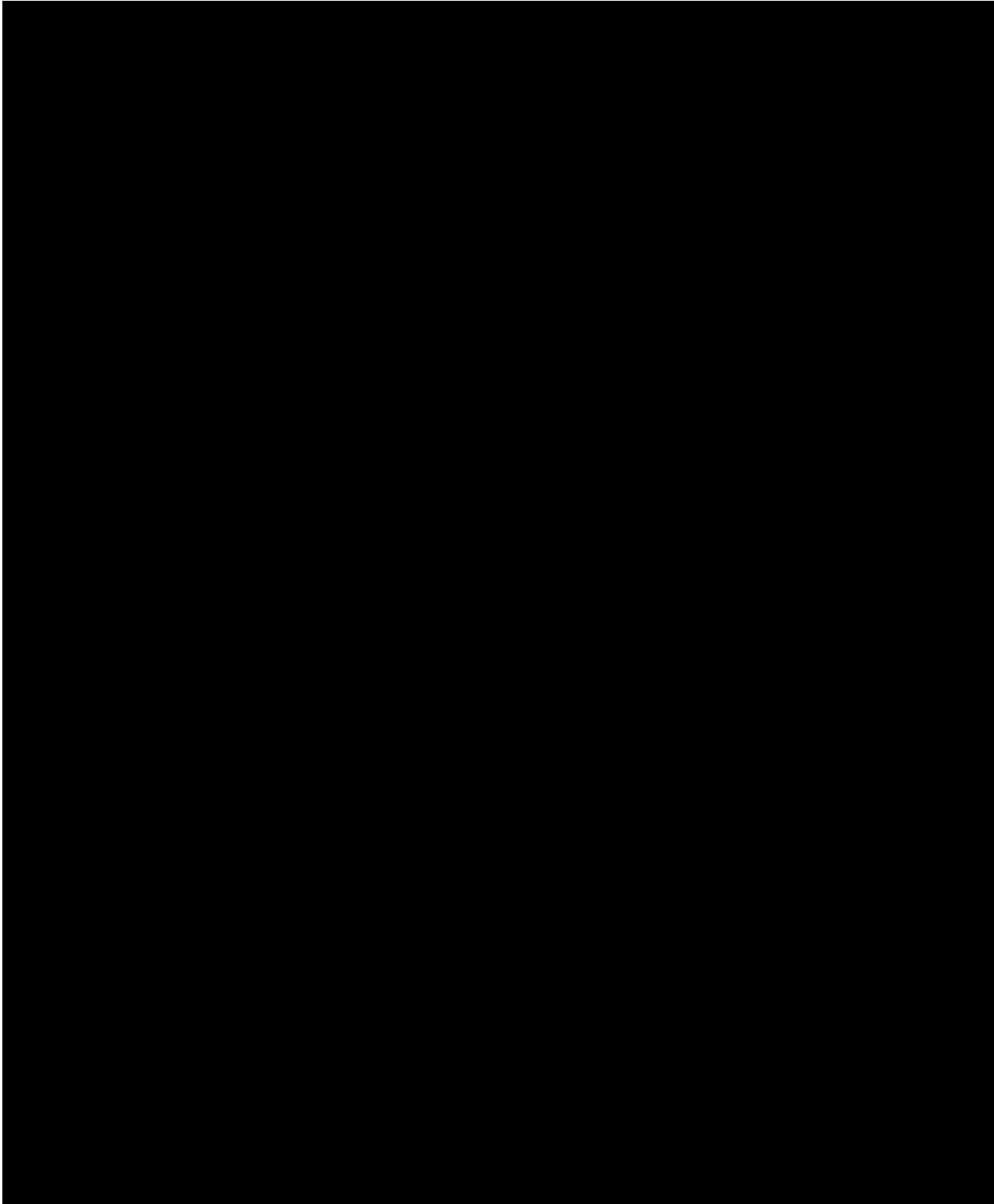


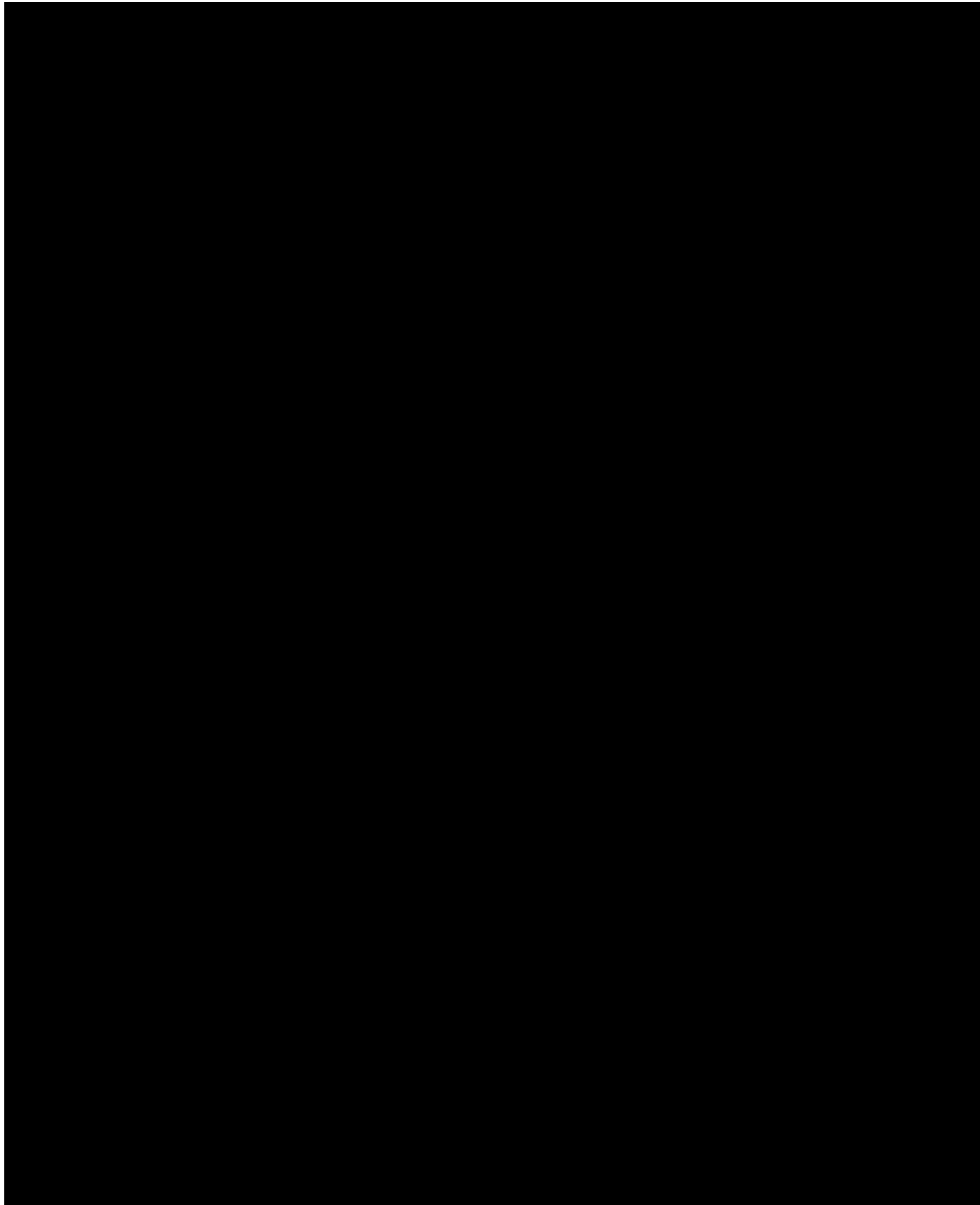




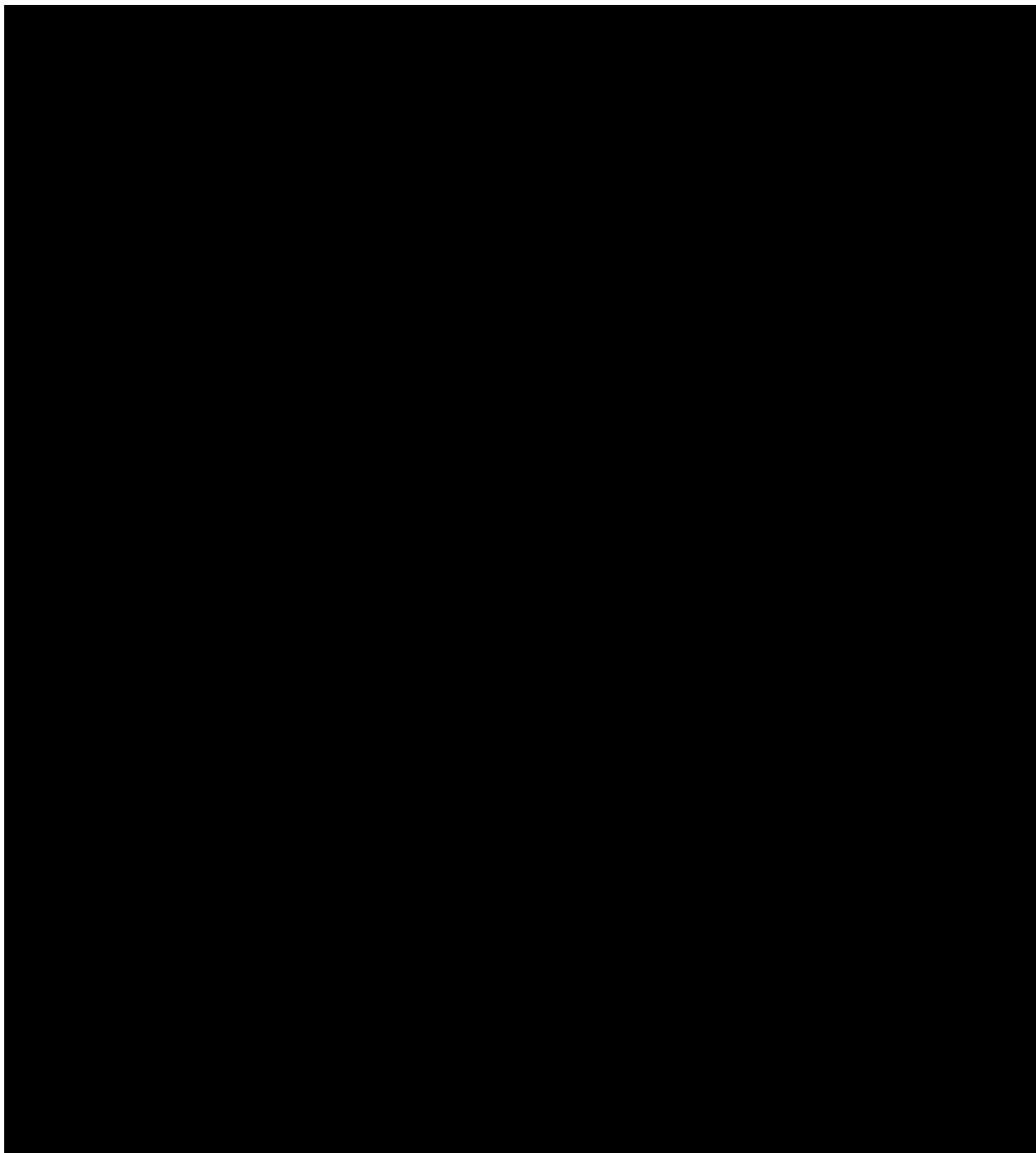


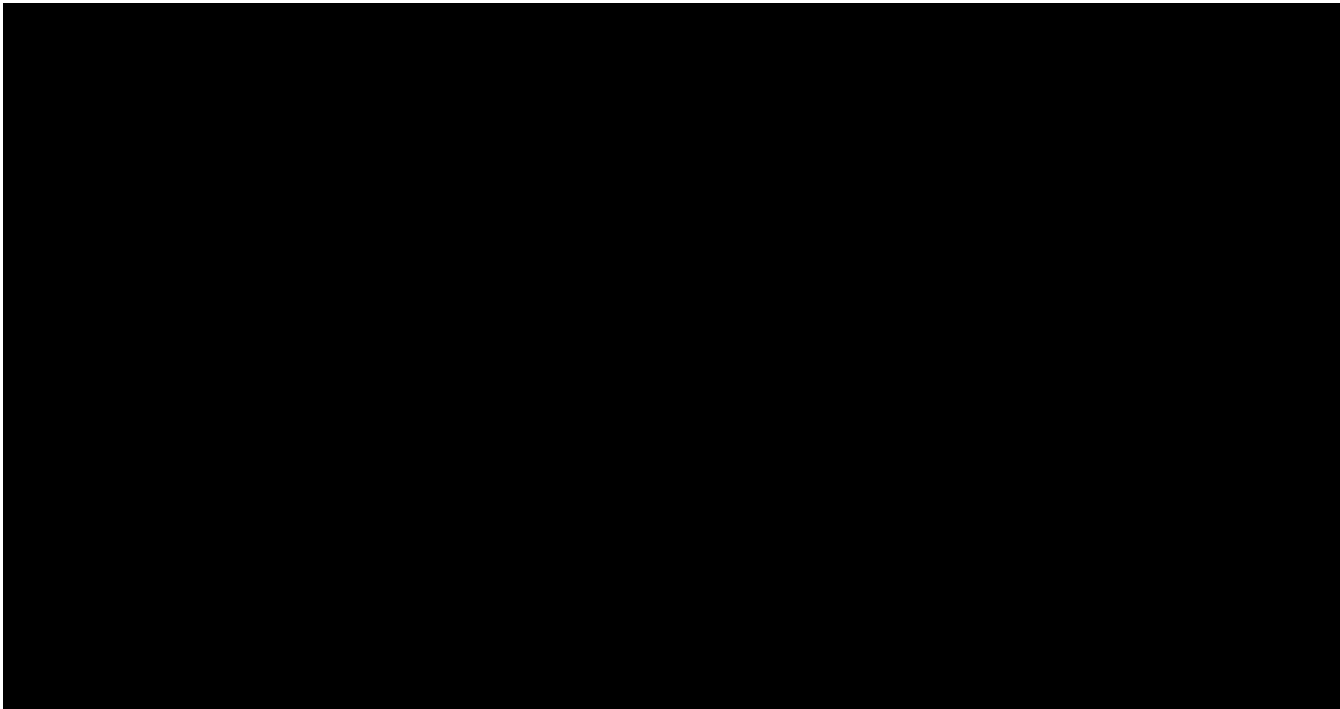
APPENDIX F. SCORING INSTRUCTIONS FOR MSQOL (VERSION 2.1)

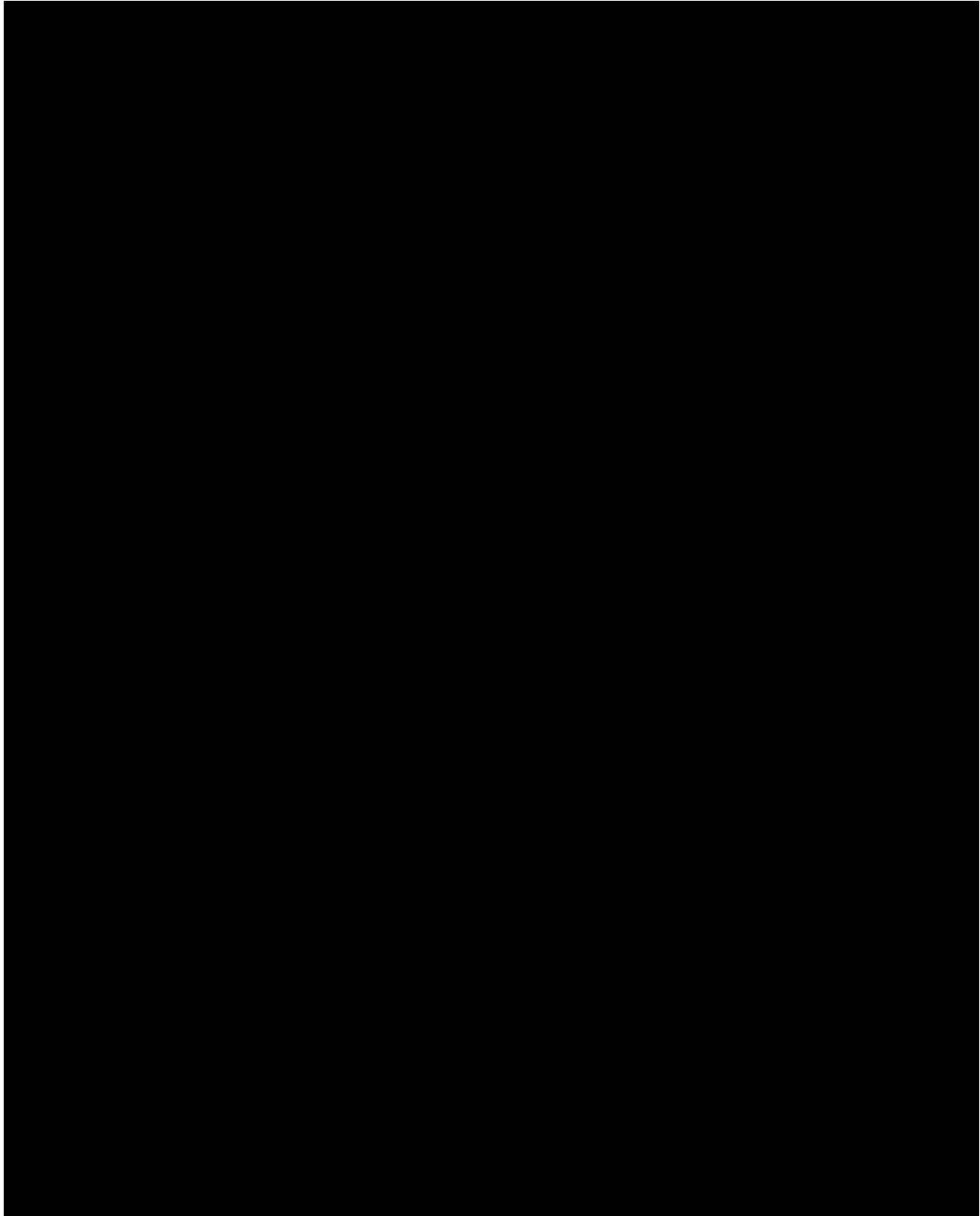




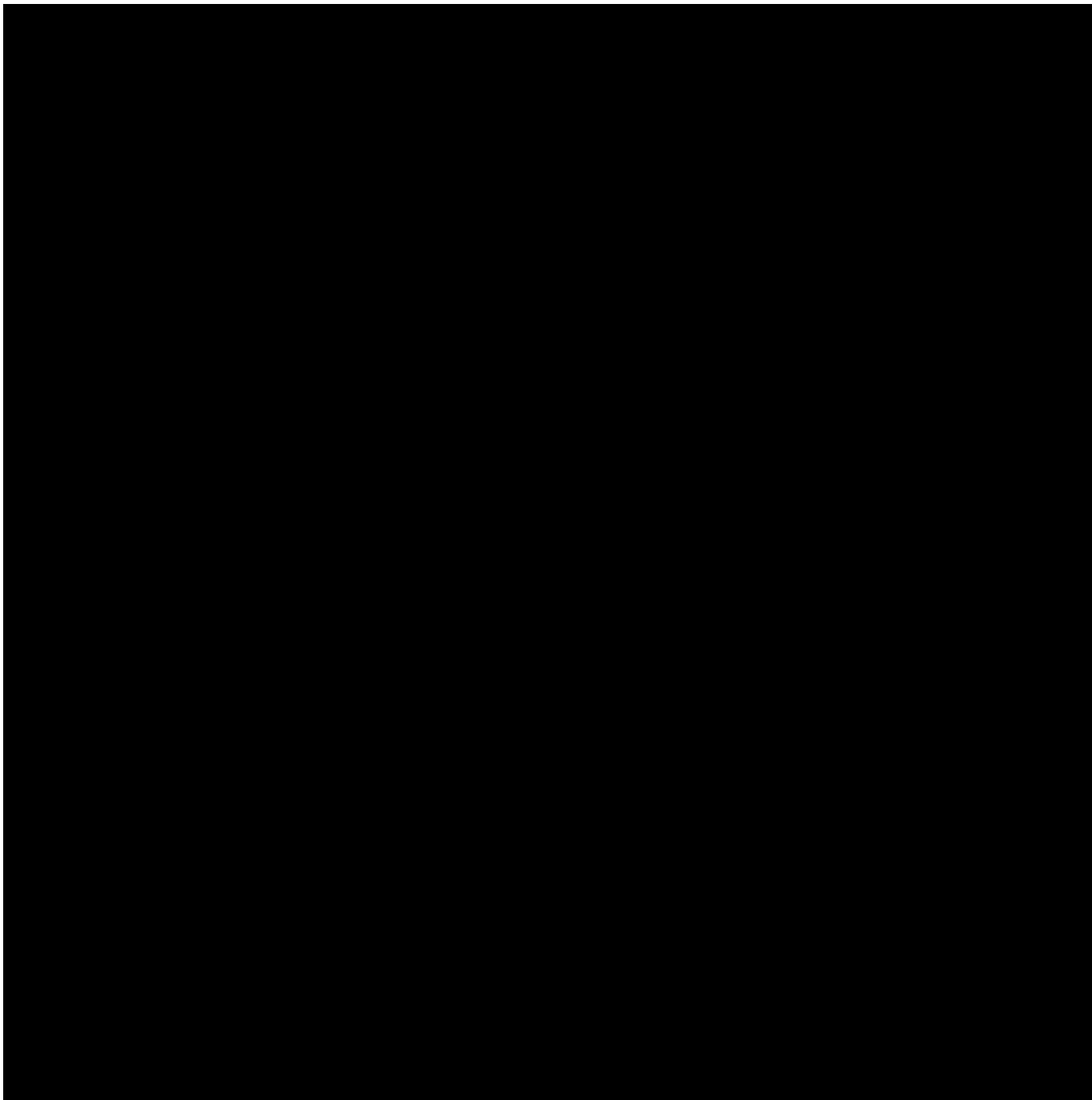
APPENDIX G. EQ-5D-5L AND EQ VAS

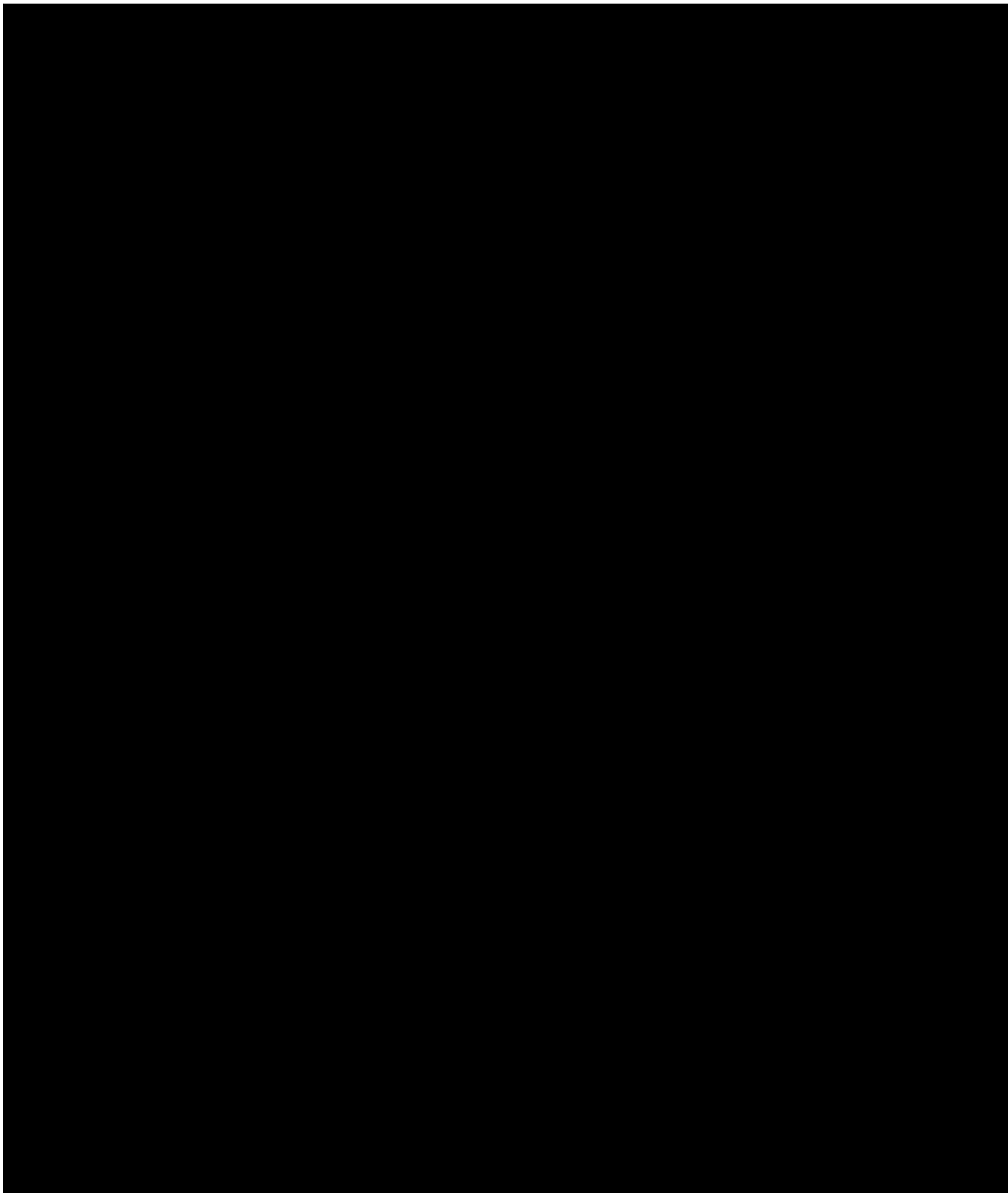




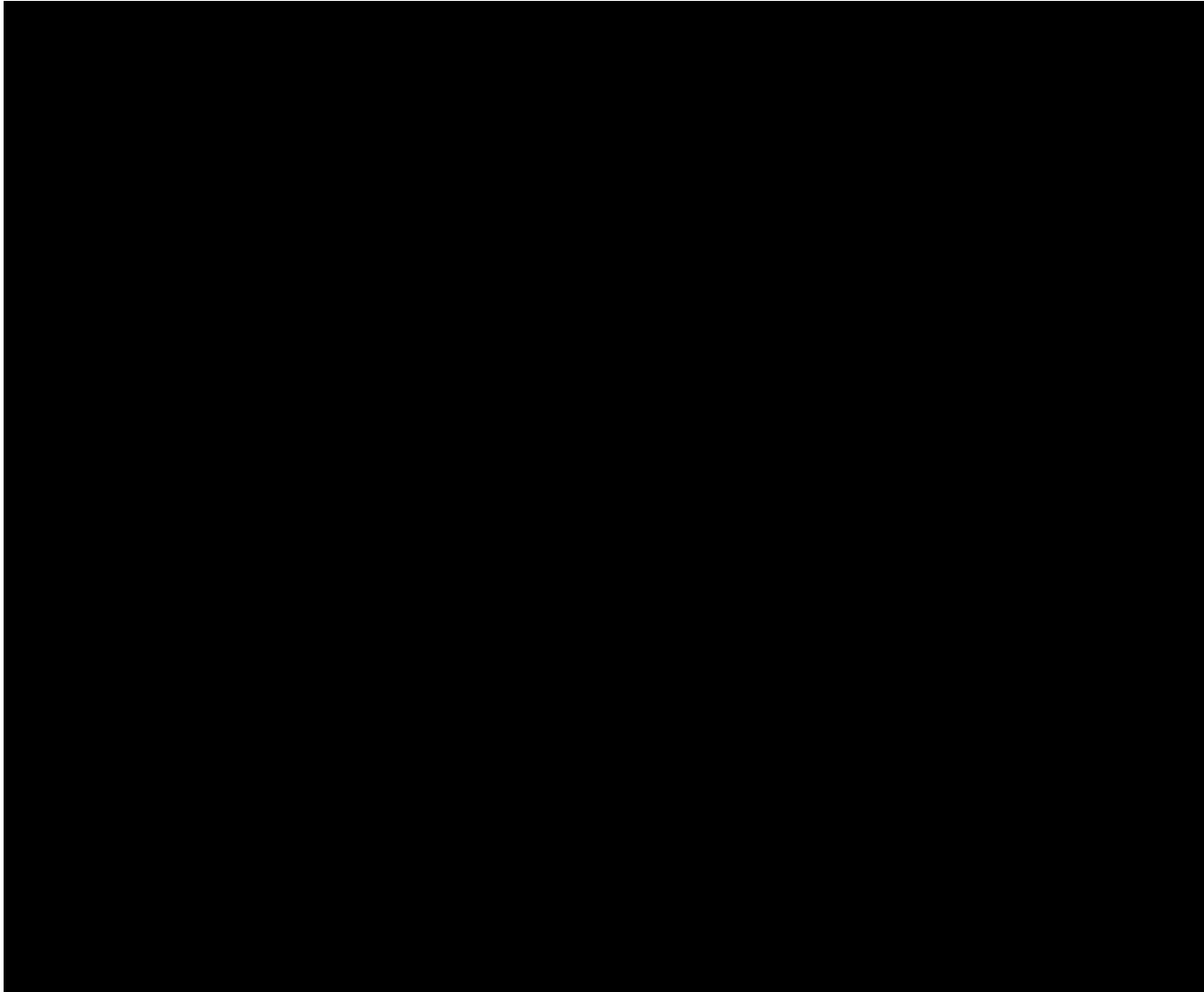


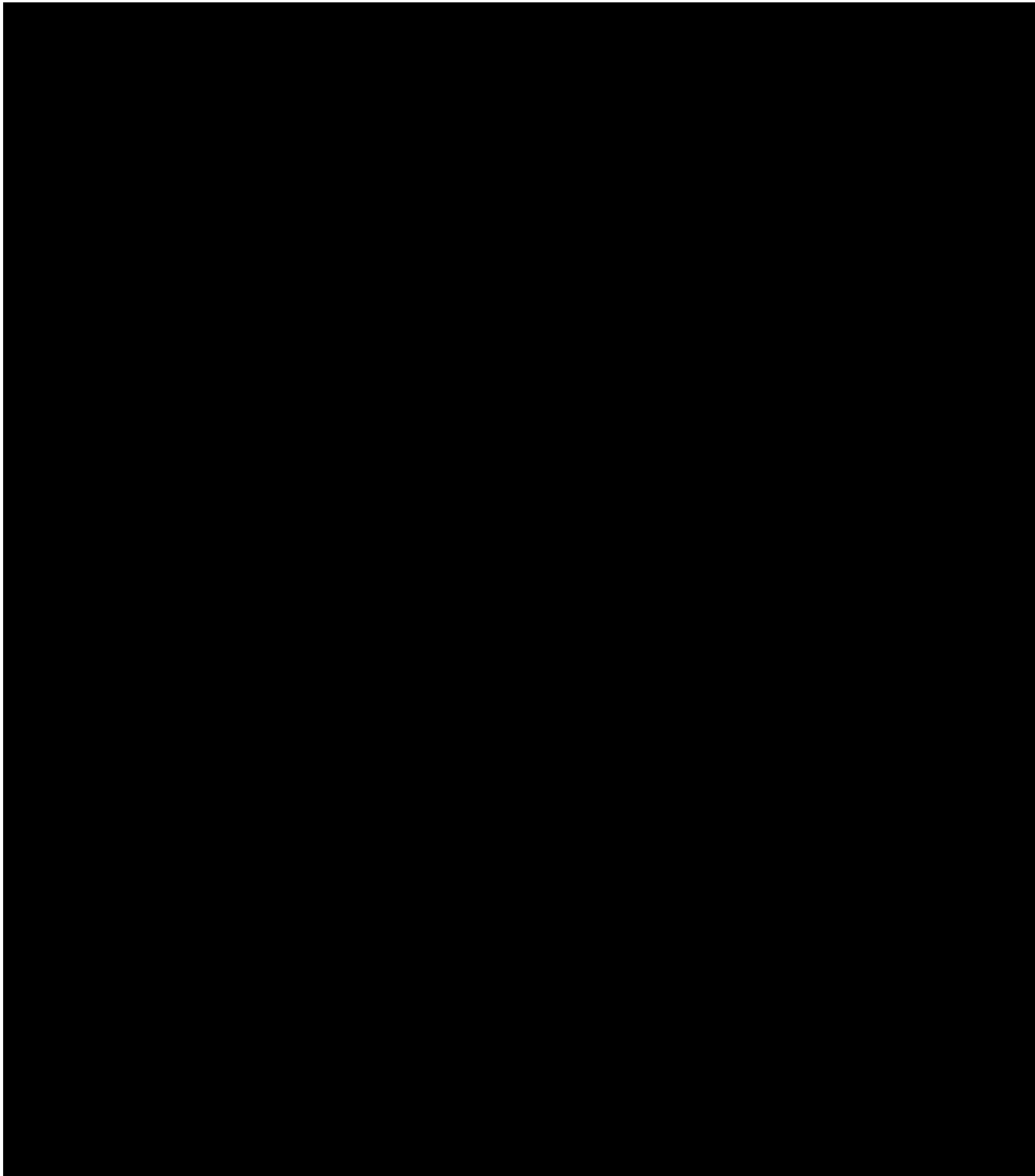
**APPENDIX H. PATIENT HEALTH QUESTIONNAIRE (PHQ-2) AND
(PHQ-9)**





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





**APPENDIX J. PATIENT’S GLOBAL IMPRESSION OF CHANGE (PGIC)
SCALE**

