Statistical Analysis Plan

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Followed by an Open-Label Extension to Evaluate the Efficacy and Safety of Fremanezumab for Preventive Treatment of Migraine in Patients with Major Depressive Disorder

Study Number TV48125-MH-40142

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SAP Approval Date: 15 September 2022

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A Randomized, Double-Blind, Placebo-Controlled Study on Efficacy and Safety of Fremanezumab for Preventing Migraine in Patients with MDD

A Study to Assess if Fremanezumab is Effective in Preventing Migraine in Patients with Major Depressive Disorder

Phase 4

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: TV48125-MH-40142

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Statistical Analysis Plan for:

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

Amendment: Final

Author: [redacted]

Approver: [redacted] **Date**

Approver: [redacted] **Date**

Executed signature pages are maintained separately within the Trial Master File

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BMI	body mass index
CGI-S	Clinical Global Impression-Severity
CI	confidence interval
CM	chronic migraine
COVID-19	Coronavirus disease 2019
CRF	case report form
DSM-V	Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
EM	episodic migraine
EOT	end of treatment
FSH	follicle-stimulating hormone
HAM-A	Hamilton Anxiety Scale
HAM-D 17	Hamilton Depression Rating Scale-17 items
HIT-6	6-item Headache Impact Test
ICHD-3	International Classification of Headache Disorders, 3rd revision
IMP	investigational medicinal product
IRT	interactive response technology
ITT	intent-to-treat
LS	least square
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent-to-treat
MMRM	mixed-effects model repeated measures
MSQoL	Migraine-Specific Quality of Life
NSAID	non-steroidal anti-inflammatory drug
PANSS	Positive and Negative Syndrome Scale

Abbreviation	Term
PHQ-9	Patient Health Questionnaire-9
PP	per-protocol
PT	preferred term
R&D	Research and Development
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	standard international
SOC	system organ class
SOP	Standard Operating Procedure
sc	subcutaneous
WHO	World Health Organization
WPAI:GH	Work Productivity and Activity Impairment Questionnaire General Health

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-MH-40142 (A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Followed by an Open-Label Extension to Evaluate the Efficacy and Safety of Fremanezumab for Preventive Treatment of Migraine in Patients with Major Depressive Disorder), and was written in accordance with Standard Operating Procedure (SOP) GSD_SOP_702 (SAP).

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.

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are in Table 1:

Table 1: Primary and Secondary Study Objectives and Endpoints

Objectives	Endpoints
Primary objective: To evaluate the efficacy of monthly 225 mg subcutaneous (sc) fremanezumab in adult patients with migraine and major depressive disorder (MDD)	Mean change in the monthly average number of migraine days from the 28-day baseline period during the 12-week period after the first dose of study drug
Key secondary objective: To evaluate the efficacy of monthly 225 mg sc of fremanezumab in adult patients with migraine and MDD on the reduction of MDD symptoms	Mean change in depression symptoms from randomization (day 1) to week 8 after the first dose of study drug as measured by: • Hamilton Depression Rating Scale-17 items (HAM-D 17)
Secondary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD in terms of responder rates in monthly migraine days	Number of patients with 50% or more reduction from the 28-day baseline period in the monthly average number of migraine days during 12 weeks after the first dose of study drug
Secondary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD in terms of improving quality of life	Mean change in quality of life from randomization visit (day 1) to week 12 after the first dose of study drug as measured by: • Migraine-Specific Quality of Life (MSQoL) questionnaire, role function-restrictive and role function-preventive domains

Objectives	Endpoints
Secondary objective: To evaluate the efficacy of monthly 225 mg sc fremanezumab in adult patients with migraine and MDD in terms of improving disability	Mean change from randomization visit (day 1) in disability score for overall impact as measured by Clinical Global Impression-Severity (CGI-S) and 6-item Headache Impact Test (HIT-6) to the following time points after administration of the first dose of study drug: • weeks 4 and 8 (CGI-S) • week 12 (CGI-S and HIT-6)
Safety and tolerability objective (Secondary objective): To evaluate the safety and tolerability of monthly 225 mg sc and quarterly 675 mg sc fremanezumab in adult patients with migraine and MDD	• occurrence of adverse events throughout the study • changes from randomization visit (day 1) in vital signs (pulse, systolic and diastolic blood pressure, body temperature, and respiratory rate) measurements • abnormal physical examination findings including body weight • use of concomitant medication for adverse events during the study • number (%) of patients who did not complete the study due to adverse events • occurrence of severe hypersensitivity/anaphylaxis reactions • suicidal ideation and behavior as suggested by eC-SSRS

CGI-S = Clinical Global Impression-Severity; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; HAM-D 17 = Hamilton Depression Rating Scale-17 items; HIT-6 = 6-item Headache Impact Test; MDD = major depressive disorder; MSQoL = Migraine-Specific Quality of Life; sc = subcutaneous.

1.2. Exploratory Objectives and Endpoints

[redacted]

[redacted]

1.3. Estimand for Primary Endpoint

The primary estimand for this study is defined by the following attributes:

1. **Target population:**

   The study population will be composed of male and female patients, aged 18 to 70 years, inclusive, with a diagnosis of migraine (as defined by the International Classification of Headache Disorders, 3rd revision [ICHD-3] criteria) and MDD (diagnosed according to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria) at least 12 months prior to the screening visit. Patients who are randomized and receive at least 1 dose of IMP and have at least 10 days of postrandomization efficacy assessment on the primary endpoint will be the population of interest.

2. **Outcome measures:**

   Change in the monthly average number of migraine days from the 28-day baseline period during the 12-week period after the first dose of study drug.

3. **Treatment description:**

Fremanezumab at monthly doses of 225 mg sc, and placebo alternatively, in the 12-week double-blind treatment period

4. **Intercurrent events strategy:**
    a. Early discontinuation due to lack of efficacy: hypothetical strategy
    b. Early discontinuation due to adverse event: hypothetical strategy
    c. Initiation of prohibited therapy: hypothetical strategy
    d. Impact of COVID-19: hypothetical strategy
5. **Population-level summary for the variables:**

    Difference in mean change in the monthly average number of migraine days from the 28-day baseline period during the 12-week between fremanezumab and placebo.

2. STUDY DESIGN

2.1. General Design

This is an approximately 28-week, multicenter, randomized, double-blind, placebo investigational medicinal product (IMP)-controlled, parallel-group study to evaluate the efficacy and safety of fremanezumab self-administered at monthly doses of 225 mg sc and a quarterly dose of 675 mg sc (ie, one dose using 3 prefilled syringes with 225 mg each) in adult patients with migraine and MDD. The study will consist of a 28-day (ie, 4-week) baseline period, a 12-week double-blind treatment phase followed by a 12-week open-label extension phase, and an end-of-treatment visit (approximately 12 weeks after the final dose of study drug).

The total duration of patient participation in the study is planned to be approximately 28 weeks. Patients are expected to complete the entire duration of the study.

Patients who fulfill the criteria for migraine will be further delineated as patients with chronic migraine (CM) or episodic migraine (EM), for stratification and other analyses.

CM is defined as:

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

- headache occurring on ≥15 days
- on ≥8 days, fulfilling any 1 of the following:
  - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix I of the study protocol)
  - ICHD-3 criteria B and C for 1.2 Migraine with aura (Appendix I of the study protocol)
  - probable migraine (a migraine subtype where only 1 migraine criterion is missing)
  - triptan or ergot derivative used 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 baseline period:

- headache occurring ≥4 days but <15
- on ≥4 days, fulfilling any 1 of the following:
  - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (Appendix I of the study protocol)
  - ICHD-3 criteria B and C for 1.2 Migraine with aura (Appendix I of the study protocol)

- probable migraine (a migraine subtype where only 1 migraine criterion is missing)
- triptan or ergot derivative used to treat an established headache

At the randomization visit (day 1), patients will be randomly assigned to 1 of 2 treatment groups of 225 mg sc fremanezumab or placebo in a 1:1 ratio. Patients will receive their assigned study treatment on visit 2 (day 1), visit 3 (day 29), and visit 4 (day 57) and then continue into the open-label extension phase in which all patients will receive a quarterly dose of 675 mg sc fremanezumab on visit 5 (day 85). Investigators can contact patients in between study visits per their clinical judgment.

Patients who complete all scheduled visits will have procedures and assessments performed at visit 6 (end of treatment [EOT]). Patients who withdraw from the study before completing the 24-week treatment phase will have visit 6 (EOT) procedures and assessments performed at their final visit. The end of study is defined as the last visit (end-of-treatment/early withdrawal visit [visit 6]) of the last patient.

Study procedures and assessments with their timing are summarized in Table 4 of the study protocol.

2.2. Randomization and Blinding

After the 28-day baseline period, the first 12 weeks of this study will be double-blind. Patients and investigators will remain blinded to IMP assignment during this part of the study. This will be followed by a 12-week open-label extension phase.

Patients will receive 225 mg sc fremanezumab (visit 2, visit 3, and visit 4) or matching placebo (visit 2) in monthly doses.

For the first phase of this study, the sponsor, investigators, study staff, and patients will be blinded to treatment assignment. A computer-generated master randomization list will be provided to drug packaging facilities. The 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 either active drug or placebo.

Patients will be stratified based on sex, country, migraine classification (ie, CM or EM), and PHQ-9 score category (10 to 14, 15 to 19, and ≥20) to ensure balance for the covariates.

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list using electronic interactive response technology (IRT). This system is used to ensure a balance across treatment groups. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

At randomization visit (day 1), each patient will be randomized in a 1:1 ratio within the stratum to which he or she belongs to receive monthly 225 mg sc fremanezumab or placebo, as assigned by the IRT. In the open-label extension phase starting at week 12, however, all patients will receive active treatment with a quarterly dose of 675 mg sc fremanezumab.

2.3. Data Monitoring Committee

There will be no Data and Safety Monitoring Board in this study.

2.4. Sample Size and Power Considerations

A sample size of 288 (144 per treatment group) evaluable patients completing the study will provide 90% power to detect a treatment difference of 2 days with a common standard deviation of 5.2 days in changes from the 28-day baseline period in monthly average migraine days between active and placebo groups at a 2-sided alpha level of 0.05. This sample size will provide approximately 80% power to detect a treatment difference of 2 points with a common standard deviation of 6 points in the change from randomization visit (day 1) in HAM-D 17 total score at a 2-sided alpha level of 0.05. Assuming a 15% drop-out rate, approximately 340 patients (approximately 170 patients per treatment group) will be randomized.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

No interim analysis is planned for this study.

2.5.2. Final Analyses and Reporting

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

3. ANALYSIS SETS

3.1.1. 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.

3.1.2. 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 IMP and have at least 10 days of postrandomization 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 IMP during the open-label treatment period and have at least 10 days of diary entries during the open-label period.

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

3.1.3. Safety Analysis Sets

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

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

Patients who begin prohibited therapies during the study will be included in the safety analysis sets but not the per-protocol (PP) analysis set (Section 3.1.4).

3.1.4. Per-Protocol Analysis Set

The PP analysis set is a subset of the mITT analysis set including only patients without important protocol deviations during the double-blind treatment period, including any deviation of the inclusion/exclusion criteria or any deviations or omissions of the IMP administration. Patients with less than 75% diary compliance during the double-blind treatment period will be excluded from the PP analysis set. A blinded data review meeting will be conducted prior to the database lock in order to determine the exclusion of the patients from the PP analysis set. After database lock and unblindng, patients who received study drug different from the study drug they were randomized to will also be excluded from the PP analysis set.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

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

4.2. Specification of Baseline Values

For migraine days, the baseline value is the total number of migraine days during the 28-day baseline period. If the baseline period is greater or less than 28 days, the baseline value for will be normalized to 28 days. In addition, if the baseline period is 28 days but there are days with missing diary, the baseline value will be normalized to 28 days.

For all other assessments, the baseline value is the last observed data prior to the first 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 migraine days ***during the 12-week period*** or monthly number of migraine days ***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 migraine days ***during the 4-week period*** after each dose of study drug will be calculated for months 1, 2, 3, and 6. If a patient has missing diary days when calculating the monthly number of migraine days, 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 migraine days 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 migraine days will be considered as missing.

For the HAM-D, HAM-A and HIT-6, if 1 or more items are missing then the total score is missing. The missing questionnaire items handling for the MSQOL questionnaire is discussed in Appendix E .

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 before the 1st injection on day 1. Treatment phase including month 1, 2, 3, and 6 is from the beginning of the 1st injection of study drug to visit 6/day 169 or the EOT visit. The monthly 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 6 is from 57 days after the date/time of the 4th dose to the EOT on day 169 approximately.

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

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

For patients who withdraw from the study, their efficacy and 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 3 regions as presented in Table 2 for the analysis.

Table 2: The Region of Pooled Countries

Region	Country
United States	United States
Europe	Czech Republic, Finland, France, Germany, Greece, Italy, Poland, Spain, United Kingdom
Rest of World	Israel, Russia, Ukraine

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 treatment group and for all patients (ie, total).

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 total group using patient counts.

Patients in the ITT analysis set, ITT analysis set but not treated, double-blind safety analysis set, double-blind mITT analysis set, double-blind mITT analysis set but not PP analysis set (with reason not in the PP set), and PP analysis set, patients who complete and withdraw from the double-blind treatment period, patients in the open-label safety analysis set and open-label mITT analysis set, and patients who complete and withdraw from the study will be summarized using descriptive statistics. Patients who withdraw from double-blind 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

The continuous variables of patient age, weight, height, and body mass index (BMI), and time since initial migraine diagnosis (years) will be summarized using descriptive statistics. The categorical variables of patient sex, race, ethnicity, migraine classification, country, region, PHQ-9 score category, patient sex as randomized, migraine classification as randomized, and PHQ-9 score category as randomized will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

This summary will also be done for the open-label safety analysis set.

The baseline total number of migraine days, HAM-D 17 total score, MSQOL domain scores, CGI-S rating, HIT-6 disability score, PHQ-9 total score, HAM-A total score, and WPAI domain scores will be summarized using descriptive statistics.

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 category, and only once in each PT category.

5.5. Prior Therapy and Medication

Any prior or concomitant medication, treatment, psychotherapy, or procedure a patient has had for migraine and/or depression within the past 10 years or for any indication within the past 5

months before IMP administration and up to the end of study, including follow-up, will be recorded on the eCRF. 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 PT. Patients are counted only once in each therapeutic class category, and only once in each PT category. Prior therapies and medications will include all medications taken and therapies administered before the first day of study drug administration administration.

The subset of prior therapies and medications for migraine /headache will be summarized for the following categories:

- preventive medication from protocol appendix for migraine/headache
- opioids for migraine/headache
- NSAIDS for migraine/headache
- triptans for migraine/headache
- ergots for migraine/headache
- butalbital for migraine/headache
- medication from protocol appendix for other reason than depression
- benzodiazepines for other reason than anxiety/insomnia
- other

5.6. Electrocardiography

ECG findings (normal, abnormal not clinically significant, and abnormal clinically significant) at baseline will be summarized using descriptive statistics.

5.7. Physical Examinations

Patients with a physical examination, patients with at least 1 abnormal finding, and abnormal findings for each category at baseline will be summarized using descriptive statistics.

5.8. 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.

5.9. Study Protocol Violations

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

Migraine days will be defined as follows. If the headache fulfills the criteria for migraine on any given day, the consecutive days are part of the same migraine attack and are therefore considered to be migraine days as well (even if they do not fulfill the criteria for migraine). These days only reflect normal fluctuations in migraine severity that lead to or represent the resolution of a full-blown migraine attack. Accordingly, for the purpose of this study, a migraine day is endorsed when at least one of the following situations occurs:

- a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting the criteria for migraine with or without aura
- a calendar day (00:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting the criteria for probable migraine, a migraine subtype where only 1 migraine criterion is missing
- a calendar day (00:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds)
- a calendar day (00:00 to 23:59) that is immediately consecutive (happening 1 day before or 1 day after) of any day fulfilling any of the 3 criteria above, where individuals report headache of any duration

The ***monthly average number of days or hours*** of efficacy variables (migraine days) ***during the 12-week period*** after the 1st dose of study drug will be derived and normalized to **28** days equivalent using the following formula.

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

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

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

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

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

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

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

where the baseline value is calculated by formula (3) and the postbaseline value in the equation is calculated by formula (1) for the variables ***during the 12-week period*** or by formula (2) for the variables ***during the 4-week period*** after each dose for months 1, 2 3, and 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 by treatment group. For the open-label treatment period, summaries will be presented by double-blind treatment group and all patients (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 at month 6 (or week 24) for the open-label treatment period. For migraine days and PHQ-9 total score, months 1, 2, and 3 (or weeks 4, 8, and 12) will also be included in the open-label treatment period summaries.

The primary and secondary endpoints analysis listed in section 6.2.1 and section 6.3 will be repeated for the PP analysis set.

6.2. Primary Efficacy Endpoint and Analysis

6.2.1. Definition

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

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 mean change from baseline in the monthly average number of migraine days for the fremanezumab treatment group and the placebo treatment group respectively.

The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) model with sex, region (United States, European, or rest of world), migraine classification (ie, CM or EM), baseline PHQ-9 score category (10 to 14, 15 to 19, and ≥20), and treatment as factors and baseline number of migraine days as a covariate. The stratification factors (as randomized) will be used in the model. The least square (LS) mean treatment difference (fremanezumab - placebo), 95% confidence interval (CI) for the LS mean treatment difference, and the associated p-value will be generated from this model.

The statistical test will be two-sided at the alpha=0.05 level of significance. The SAS code for this test is as follows:

```
PROC MIXED;
  CLASS TREAT SEX REGION MIGCLASS PHQCAT;
  MODEL CHG= TREAT SEX REGION MIGCLASS PHQCAT  BASE;
  LSMEANS TREAT / DIFF CL;
 RUN;
```

The normality assumption for the ANCOVA model will be checked to ensure validity of the primary analysis. If the model assumptions are not met (p-value <0.01), a nonparametric method such as Wilcoxon Rank Sum test will be conducted as a sensitivity analysis.

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, sex, region, migraine classification, baseline PHQ-9 score category, month, treatment-by-month interaction as fixed effects, baseline value as a covariate, 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 LS mean treatment difference (fremanezumab - placebo), 95% CI for the LS mean treatment difference, and the associated p-value for fremanezumab versus placebo will be generated from this model for each month and overall 3 months.

The SAS code for this test is as follows:

```
PROC MIXED;
   CLASS USUBJID TREAT SEX REGION MIGCLASS PHQCAT MONTH;
   MODEL CHG= TREAT SEX REGION MIGCLASS PHQCAT  BASE MONTH TREAT*MONTH;
   REPEATED MONTH / SUBJECT=USUBJID TYPE=UN;
   LSMEANS TREAT TREAT*MONTH / DIFF CL;
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 MI 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 (AE) 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 SEX REGION MIGCLASS PHQCAT;
  FCS REG (AVALMI1=TREAT SEX REGION MIGCLASS PHQCAT BASE/DETAILS)
  NBITER=100;
  FCS REG (AVALMI2=TREAT SEX REGION MIGCLASS PHQCAT BASE
  AVALMI1/DETAILS) NBITER=100;
  FCS REG (AVALMI3= TREAT SEX REGION MIGCLASS PHQCAT BASE AVALMI1
  AVALMI2/DETAILS) NBITER=100;
  VAR TREAT SEX REGION MIGCLASS PHQCAT 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
- $\sum(observed\ value) + (28 - X) * imputed\ value/28$
- 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 SEs from each analysis will be output to a SAS data set. The SAS code for this analysis is as follows:

```
ODS OUTPUT DIFFS=MIXED_OUT;

PROC MIXED DATA=UPDATED_MI_OUT METHOD=REML;
  BY _IMPUTATION_;
  CLASS TREAT SEX REGION MIGCLASS PHQCAT;
  MODEL CHG=TREAT SEX REGION MIGCLASS PHQCAT BASE;
  LSMEANS TREAT / DIFF CL;
RUN;
```

The output dataset from the above SAS code will contain the estimate of the LS mean treatment difference and the SE of the estimate from each of the 100 datasets. SAS procedure, PROC MIANALYZE, will be used to generate an overall LS mean treatment difference, 95% CI for the LS mean treatment difference, and associated p-value. The SAS code is as follows:

```
ODS OUTPUT PARAMETERESTIMATES=PARMEST;

PROC MIANALYZE DATA=MIXED_OUT ALPHA=0-.05 THETA0=0;
  BY TREAT;
  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.

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

6.3. Secondary Efficacy Endpoints and Analysis

The key secondary efficacy endpoint is the mean change in depression symptoms from randomization visit (day 1) to week 8 after the first dose of study drug as measured by HAM-D 17.

Other secondary endpoints include the following:

- Number of patients with 50% or more reduction from the 28-day baseline period until 12 weeks after the first dose of study drug, in the monthly average number of migraine days
- Mean change in quality of life from randomization visit (day 1) to week 12 after the first dose of study drug as measured by the MSQoL questionnaire, role function-restrictive, role function-preventive, and emotional function domains
- Mean change from randomization visit (day 1) in disability score for overall impact, as measured by CGI-S and HIT-6, to the following time points after administration of the first dose of study drug:
  - weeks 4 and 8 (CGI-S)
  - week 12 (CGI-S and HIT-6)

6.3.1. Hamilton Depression Rating Scale-17

6.3.1.1. Definition

The HAM-D 17 (Appendix C) is a list of 17 items used to determine a patient's level of depression. A total score of 0-7 is generally accepted to be within the normal range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) is usually required for entry into a clinical trial.

6.3.1.2. Analysis

The HAM-D 17 total score change from baseline to week 8 will be analyzed using the same MMRM method as described in section 6.2.3.1. The analysis will also be done at weeks 4 and 12.

6.3.2. Migraine Days

6.3.2.1. Definition

The 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of study drug will be calculated by formula 4 in section 6.1. If a patient is early discontinued from the study, they will be counted as not having a ≥50% reduction.

6.3.2.2. Analysis

For the proportion of patients with ≥50% reduction, a logistic regression model will be used with the following effects: treatment, sex, region, migraine classification, and baseline PHQ-9 score category. The stratification factors (as randomized) will be used in the model. The odds ratios (fremanezumab vs. placebo), 95% CI for the odds ratio, and associated p-value will be generated from this model.

6.3.3. Migraine-Specific Quality of Life

6.3.3.1. Definition

The MSQoL version 2.1 (Appendix D) is a 14-item questionnaire that assesses the impact of migraine and migraine treatment on a patient's quality of life during the previous 4 weeks, which has been shown to be a reliable and valid tool for use in CM and EM. The MSQoL measures the degree to which performance of normal activities is limited by migraine (Role Function-Restrictive domain comprising 7 items), the degree to which performance of normal activities is prevented by migraine (Role Function-Preventive domain comprising 4 items), and the emotional effects of migraine (Emotional Function domain comprising 3 items). Scores range from 0 to 100, with higher scores indicating better health-related quality of life. Appendix E provides the scoring instructions on how to rescale the raw score to the scales that will be used for the analysis.

6.3.3.2. Analysis

The MSQOL domains (Role Function-Restrictive, Role Function-Preventive, and Emotional Function) scores change from baseline to week 12 will be analyzed using the same MMRM method as described in section 6.2.3.1. The analysis will also be done at weeks 4 and 8.

6.3.4. Clinical Global Impression-Severity Scale

6.3.4.1. Definition

The CGI-S (Appendix F) is a short questionnaire filled out by the investigator that rates a patient's mental health from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

6.3.4.2. Analysis

The CGI-S rating change from baseline to weeks 4, 8, and 12 will be analyzed using the same MMRM method as described in section 6.2.3.1.

6.3.5. 6-Item Headache Impact Test

6.3.5.1. Definition

Migraine related disability will be assessed using the HIT-6 (Appendix G). 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.

6.3.5.2. Analysis

The HIT-6 disability score change from baseline to week 12 will be analyzed using the same MMRM method as described in section 6.2.3.1. The analysis will also be done at weeks 4 and 8.

6.4. Other Efficacy Endpoints Analysis

The exploratory efficacy endpoints are listed in section 1.2.

6.4.1. Patient Health Questionnaire-9

6.4.1.1. 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 MDD. Each of the items is scored on a scale of 0 (“not at all”), 1 (“several days”), 2 (“more than half the days”), and 3 (“nearly every day”) based on the frequency of symptoms during the past 2 weeks. The PHQ-9 is a validated measure for detecting and monitoring depression, anxiety, and somatization.

6.4.1.2. Analysis

The PHQ-9 total score change from baseline to weeks 4, 8, and 12 will be analyzed using the same MMRM method as described in section 6.2.3.1, except that the baseline value will not be included in the model.

6.4.2. Hamilton Anxiety Scale

6.4.2.1. Definition

The HAM-A Scale (Appendix I) is a 14-item scale that measuring the severity of a patient’s anxiety. Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe.

6.4.2.2. Analysis

The HAM-A total score change from baseline to weeks 4, 8, and 12 will be analyzed using the same MMRM method as described in section 6.2.3.1.

6.4.3. Work Productivity and Activity Impairment Questionnaire General Health V2.0

6.4.3.1. Definition

The generic version of the WPAI questionnaire (Appendix J) measures the overall effect of health on productivity at work and daily activities. The specific health problems version of the WPAI questionnaire allows investigators to attribute productivity and activity impairment issues to specific health conditions. After the employment status of a respondent is identified, 3 open

ended questions are asked concerning (1) hours absent from work due to health problems (or specific condition), (2) hours absent from work due to other reasons, and (3) hours actually worked. Two additional questions are included that ask about the impact of health on productivity, 1 concerning productivity at work and the other concerning daily activities outside of work. The response format of each item of the WPAI questionnaire consists of an 11-point scale ranging from 0 (no impairment) to 10 (complete impairment).

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: $\frac{Q6}{10}$

6.4.3.2. 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

change from baseline to week 12 will be analyzed using the same MMRM method as described in section 6.2.3.1. The analysis will also be done at weeks 4 and 8.

6.4.4. Other Analysis

Correlation between the change from baseline in the PHQ-9 total score and the change from baseline in the monthly average number of migraine days will be presented with all visits combined through the 24-week period after the first dose of study drug. All visits will be combined and both treatments will be combined in the analysis. The open-label mITT analysis set will be used for the analysis. A scatter plot will also be presented.

To assess whether improvements in headaches precede changes in depression, a graph of mean change from baseline in monthly number of migraine days versus mean change from baseline in PHQ-9 total score during the 6-month treatment period will be presented by month and double-blind treatment group. The open-label mITT analysis set will be used for the graph.

7. MULTIPLE COMPARISONS AND MULTIPLICITY

A fixed-sequence (hierarchical) testing procedure will be implemented to control the type 1 error rate at 0.05. The primary endpoint will be tested first at a type I error rate of 5%. If the analysis is statistically significant (p-value <0.05), then the key secondary hypothesis will be tested. If not statistically significant, confirmatory hypothesis testing will not be carried out on the remaining hypotheses. This process will repeat accordingly to the order of the secondary endpoints as specified in section 6.3. [redacted]

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 treatment group, unless otherwise stated. For the open-label treatment period, summaries will be presented by double-blind treatment group and all patients (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 the week 12 or double-blind early withdrawal visit day (week 12 or double-blind early withdrawal visit day – first day of study drug + 1). For patients who are lost to follow-up during the double-blind treatment period, the EOT visit date is defined as the last study drug administration + 27.

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 week 24 or open-label early withdrawal visit day (week 24 or open-label early withdrawal visit day – first day of study drug in the open-label treatment period + 1). For patients who are lost to follow-up during the open-label treatment period, 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 treatment period will be summarized using descriptive statistics. Duration of treatment (days) during the double-blind and open-label periods will also be summarized using descriptive statistics.

8.3. Adverse Events

All AEs will be coded using MedDRA.

The following are considered protocol-defined AEs of special interest: events of anaphylaxis and severe hypersensitivity reactions and ophthalmic events of at least moderate severity.

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

The incidence of AEs will be summarized using descriptive statistics by SOC and PT (all treatment-emergent AEs overall will also be presented by just PT category). Patients are counted only once in each SOC category, and only once in each PT category. For the summaries by severity, patients are counted at the greatest severity. AEs with the missing flag indicating serious will be excluded from the summary of serious AEs but included in the summary of non-serious AEs.

Listings for deaths, AEs, serious AEs, AEs causing withdrawal from treatment, injection site-related AEs, and protocol defined AEs of special interest 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, weeks 4, 8, 12, and 24, and last on study assessment (double-blind and open-label). 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.

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
Uric acid	Men	≥625 µmol/L
	Women	≥506 µmol/L
Bilirubin (total)		≥34.2 µmol/L
Hematology		
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L
Hemoglobin	Men	≤115 g/L

Test	Criterion value
Women	≤95 g/L
WBC counts	≤3 x 10^9/L ≥20 x 10^9/L
Eosinophils	≥10%
ANC	≤1 x 10^9/L
Platelet counts	≤75 x 10^9/L ≥700 x 10^9/L
Urinalysis	
HGB	≥2 unit increase from baseline
Glucose	≥2 unit increase from baseline
Ketones	≥2 unit increase from baseline
Total protein	≥2 unit increase from baseline
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. Urine pregnancy tests will be performed for all women of childbearing potential at the randomization visit, weeks 1, 2, and 3, and the EOT/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

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 weeks 4, 8, 12, and 24, and last on study assessment (double-blind and open-label) 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, weeks 4, 8, 12, and 24, and last on study assessment (double-blind and open-label). 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

Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered an adverse event.

Shifts (normal and abnormal) from baseline to overall result interpretation, weeks 4, 8, 12, and 24, and last on study assessment (double-blind and open-label) 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 will be presented at baseline, weeks 4, 8, 12, and 24, and last on study assessment (double-blind and open-label). Actual values and changes from baseline to each visit and last on study assessment will be summarized using descriptive statistics.

8.9. 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 5.7 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 PT. Patients are counted only once in each therapeutic class and only once in each PT 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.

- preventive medication from protocol appendix for migraine/headache
- opioids for migraine/headache
- NSAIDS for migraine/headache
- triptans for migraine/headache
- ergots for migraine/headache
- butalbital for migraine/headache
- medication from protocol appendix for other reason than depression
- benzodiazepines for other reason than anxiety/insomnia
- other

8.10. Electronic Columbia-Suicide Severity Rating Scale

As part of the overall safety evaluation, the eC-SSRS will be used in conjunction with a qualified clinician's (ie, the investigator or a medically qualified person designated by the investigator) clinical judgment to assess the patient's suicidal ideation (severity and intensity) and behavior. The eC-SSRS Lifetime version will be completed by the patient at visit 1, and the eC-SSRS Since Last Visit version will be completed by the patient at all other time points.

The results from the eC-SSRS will be listed.

9. TOLERABILITY VARIABLES AND ANALYSIS

Tolerability is summarized with patient disposition.

10. STATISTICAL SOFTWARE

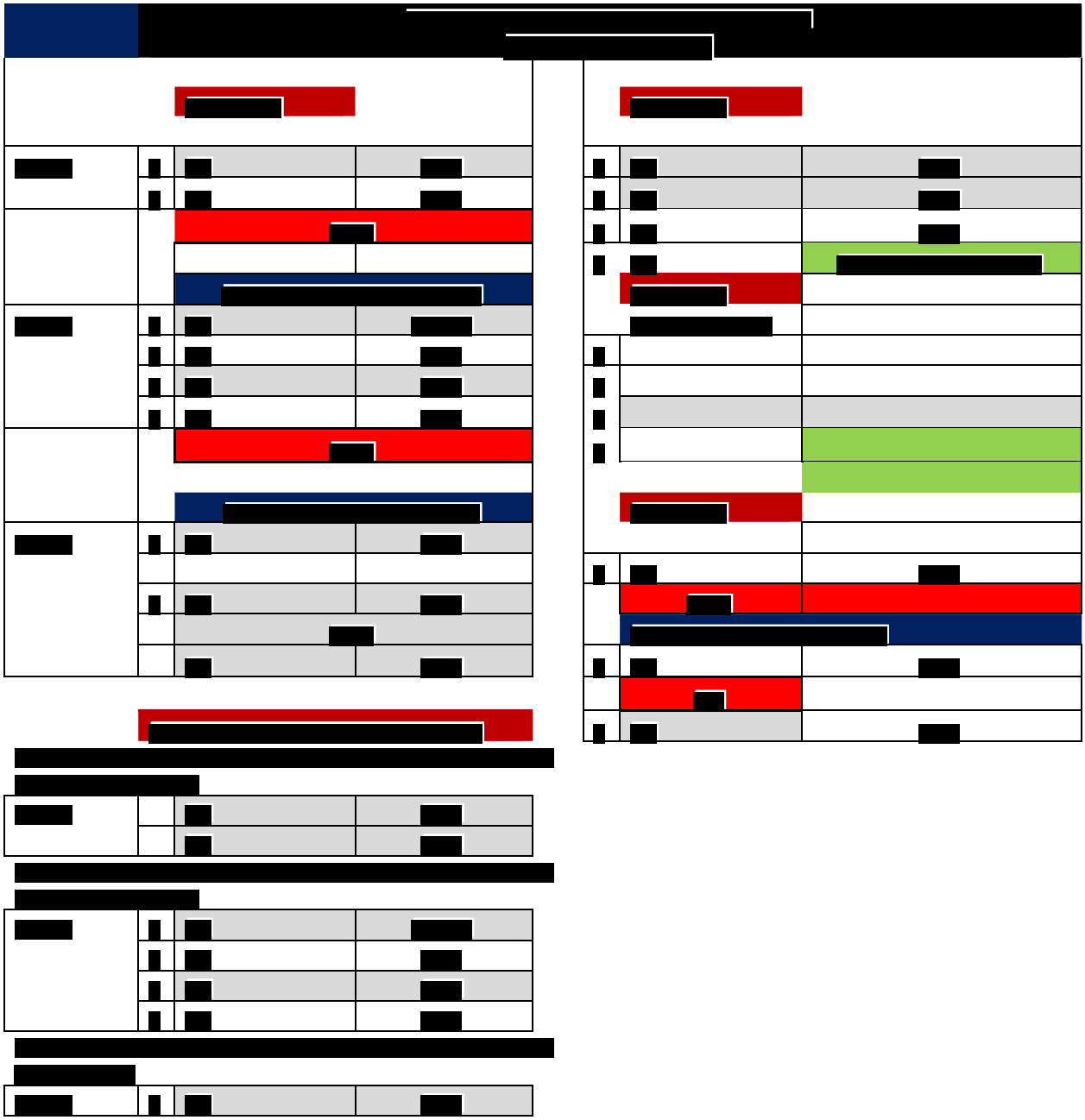
All data listings, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

11. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

There are no changes to analyses specified in the study protocol.

Appendix A. E-DIARY QUESTIONNAIRE

Appendix B. LOGICS FOR ENDPOINTS DERIVATION



APPENDIX C. HAMILTON DEPRESSION RATING SCALE-17

Hamilton Depression Rating Scale (HDRS)

Reference: **Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62**
Rating Clinician-rated
Administration time 20–30 minutes
Main purpose To assess severity of, and change in, depressive symptoms
Population Adults

Commentary

The HDRS (also known as the Ham-D) is the most wide- ly used clinician-administered depression assessment scale. The original version contains 17 items (HDRS17) pertaining to symptoms of depression experienced over the past week. Although the scale was designed for completion after an unstructured clinical interview, there are now semi-structured interview guides available. The HDRS was originally developed for hospital inpatients, thus the emphasis on melancholic and physical symptoms of depression. A later 21-item version (HDRS21) included 4 items intended to subtype the depression, but which are sometimes, incorrectly, used to rate severity. A limitation of the HDRS is that atypical symptoms of depression (e.g., hypersomnia, hyperphagia) are not assessed (see SIGH-SAD, page 55).

Scoring

Method for scoring varies by version. For the HDRS17, a score of 0–7 is generally accepted to be within the normal range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) is usually required for entry into a clinical trial.

Versions

The scale has been translated into a number of languages including French, German, Italian, Thai, and Turkish. As well, there is an Interactive Voice Response version (IVR), a Seasonal Affective Disorder version (SIGH-SAD, see page 55), and a Structured Interview Version (HDS-SIV). Numerous versions with varying lengths include the HDRS17, HDRS21, HDRS29, HDRS8, HDRS6, HDRS24, and HDRS7 (see page 30).

Additional references

Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967; 6(4):278–96.
Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry 1988; 45(8):742–7.

Address for correspondence

The HDRS is in the public domain.

Hamilton Depression Rating Scale (HDRS)

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW
Instructions: for each item select the one “cue” which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

1 DEPRESSED MOOD *(sadness, hopeless, helpless, worthless)*
0 |__| Absent.
1 |__| These feeling states indicated only on questioning.
2 |__| These feeling states spontaneously reported verbally.
3 |__| Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
4 |__| Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2 FEELINGS OF GUILT
0 |__| Absent.
1 |__| Self reproach, feels he/she has let people down.
2 |__| Ideas of guilt or rumination over past errors or sinful deeds.
3 |__| Present illness is a punishment. Delusions of guilt.
4 |__| Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3 SUICIDE
0 |__| Absent.
1 |__| Feels life is not worth living.
2 |__| Wishes he/she were dead or any thoughts of possible death to self.
3 |__| Ideas or gestures of suicide.
4 |__| Attempts at suicide (any serious attempt rate 4).

4 INSOMNIA: EARLY IN THE NIGHT
0 |__| No difficulty falling asleep.
1 |__| Complains of occasional difficulty falling asleep, i.e. more than 1⁄2 hour.
2 |__| Complains of nightly difficulty falling asleep.

5 INSOMNIA: MIDDLE OF THE NIGHT
0 |__| No difficulty.
1 |__| Patient complains of being restless and disturbed during the night.
2 |__| Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

6 INSOMNIA: EARLY HOURS OF THE MORNING
0 |__| No difficulty.
1 |__| Waking in early hours of the morning but goes back to sleep.
2 |__| Unable to fall asleep again if he/she gets out of bed.

7 WORK AND ACTIVITIES
0 |__| No difficulty.
1 |__| Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
2 |__| Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
3 |__| Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
4 |__| Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8 RETARDATION (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)
0 |__| Normal speech and thought.
1 |__| Slight retardation during the interview.
2 |__| Obvious retardation during the interview.
3 |__| Interview difficult.
4 |__| Complete stupor.

9 AGITATION
0 |__| None.
1 |__| Fidgetiness.
2 |__| Playing with hands, hair, etc.
3 |__| Moving about, can't sit still.
4 |__| Hand wringing, nail biting, hair-pulling, biting of lips.

10 ANXIETY PSYCHIC
0 |__| No difficulty.
1 |__| Subjective tension and irritability.
2 |__| Worrying about minor matters.
3 |__| Apprehensive attitude apparent in face or speech.
4 |__| Fears expressed without questioning.

11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:
gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing
urinary frequency
sweating
0 |__| Absent.
1 |__| Mild.
2 |__| Moderate.
3 |__| Severe.
4 |__| Incapacitating.

12 SOMATIC SYMPTOMS GASTRO-INTESTINAL
0 |__| None.
1 |__| Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 |__| Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13 GENERAL SOMATIC SYMPTOMS
0 |__| None.
1 |__| Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
2 |__| Any clear-cut symptom rates 2.

14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)
0 |__| Absent.
1 |__| Mild.
2 |__| Severe.

15 HYPOCHONDRIASIS
0 |__| Not present.
1 |__| Self-absorption (bodily).
2 |__| Preoccupation with health.
3 |__| Frequent complaints, requests for help, etc.
4 |__| Hypochondriacal delusions.

16 LOSS OF WEIGHT ***(RATE EITHER a OR b)***

a) According to the patient:	**b) According to weekly measurements:**
0 |__| No weight loss.	0 |__| Less than 1 lb weight loss in week.
1 |__| Probable weight loss associated with present illness.	1 |__| Greater than 1 lb weight loss in week.
2 |__| Definite (according to patient) weight loss.	2 |__| Greater than 2 lb weight loss in week.
3 |__| Not assessed.	3 |__| Not assessed.

17 INSIGHT
0 |__| Acknowledges being depressed and ill.
1 |__| Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 |__| Denies being ill at all.

Total score: |__|__|

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 ❑ None of the time

2 ❑ A little bit of the time

3 ❑ Some of the time

4 ❑ A good bit of the time

5 ❑ Most of the time

6 ❑ All of the time

APPENDIX E. SCORING INSTRUCTIONS FOR MSQOL (VERSION 2.1)

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

Scoring

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

The scoring of the MSQOL is completed in 3 steps:

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

Final item value assignment

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

How to handle missing values

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

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

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

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

Raw score computation

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

Transformation of dimension scores

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

Scoring checks

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

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

Table 1 Precoded and final item values for MSQOL item responses

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

Table 2 Raw score and transformation formula for each MSQOL dimension

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

APPENDIX F. CLINICAL GLOBAL IMPRESSION-SEVERITY SCALE

Clinical Global Impression (CGI)

Reference: **Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare**

Rating Clinician-rated

Administration time Varies with familiarity with patient

Main purpose To provide a global rating of illness severity, improvement and response to treatment

Population Adults

Commentary

Amongst the most widely used of extant brief assessment tools in psychiatry, the CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. The illness severity and improvement sections of the instrument are used more frequently than the therapeutic response section in both clinical and research settings. The Early Clinical Drug Evaluation Program (ECDEU) ver- sion of the CGI (reproduced here) is the most widely used format, and asks that the clinician rate the patient relative to their past experience with other patients with the same diagnosis, with or without collateral information. Several alternative versions of the CGI have been developed, how- ever, such as the FDA Clinicians' Interview-Based Impression of Change (CIBIC), which uses only informa- tion collected during the interview, not collateral. The CGI has proved to be a robust measure of efficacy in many clinical drug trials, and is easy and quick to admin- ister, provided that the clinician knows the patient well.

Scoring

The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGI-C scores range from 1 (very much improved) through to 7 (very much worse). Treatment response ratings should take account of both therapeutic efficacy and treatment-related adverse events and range from 0 (marked improvement and no side-effects) and 4 (unchanged or worse and side-effects outweigh the thera- peutic effects). Each component of the CGI is rated sepa- rately; the instrument does not yield a global score.

Versions

CGI for bipolar disorder (CGI-BD), FDA Clinicians' Interview-Based Impression of Change (CIBIC), Clinicians' Interview-Based Impression of Change-Plus (CIBIC+), NYU CIBIC+, Parke-Davis Pharmaceuticals Clinical Interview-Based Impression (CIBI); the CGI has been translated into most languages.

Additional references

Leon AC, Shear MK, Klerman GL, Portera L, Rosenbaum JF, Goldenberg I. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. J Clin Psychopharmacol 1993; 13(5):327–31.

Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997; 73(3):159–71.

Zaider TI, Heimberg RG, Fresco DM, Schneier FR, Liebowitz MR. Evaluation of the clinical global impression scale among individuals with social anxiety disorder. Psychol Med 2003; 33(4):611–22.

Address for correspondence

Not applicable – the CGI is in the public domain.

Clinical Global Impression (CGI)

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed 4 = Moderately ill
   1 = Normal, not at all ill 5 = Markedly ill
   2 = Borderline mentally ill 6 = Severely ill
   3 = Mildly ill 7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment. Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed 4 = No change
   1 = Very much improved 5 = Minimally worse
   2 = Much improved 6 = Much worse
   3 = Minimally improved 7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

APPENDIX G. HIT-6™ HEADACHE IMPACT TEST

HIT is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36® health assessment tool. This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

When you have headaches, how often is the pain severe?

never rarely sometimes very often always

How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

never rarely sometimes very often always

When you have a headache, how often do you wish you could lie down?

never rarely sometimes very often always

In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

never rarely sometimes very often always

In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

never rarely sometimes very often always

In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

never rarely sometimes very often always

☐	+	☐	+	☐	+	☐	+	☐
COLUMN 1		COLUMN 2		COLUMN 3		COLUMN 4		COLUMN 5
6 points each		8 points each		10 points each		11 points each		13 points each

To score, add points for answers in each column.

If your HIT-6 is 50 or higher:

You should share your results with your doctor. Headaches that stop you from enjoying the important things in life, like family, work, school or social activities could be migraine

☐

TOTAL SCORE

APPENDIX H. PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9
(PHQ-9)

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

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

=Total Score: _____

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

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

APPENDIX I. HAMILTON ANXIETY SCALE

Hamilton Depression Rating Scale (HAM-A)

Reference: **Hamilton M.The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55**

Rating Clinician-rated

Administration time 10-15 minutes

Main purpose To assess the severity of symptoms of anxiety

Population Adults, adolescents and children

Commentary

The HAM-A was one of the first rating scales developed to measure the severity of anxiety symptoms, and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Although the HAM-A remains widely used as an outcome measure in clinical trials, it has been criticized for its sometimes poor ability to discriminate between anxiolytic and antidepressant effects, and somatic anxiety versus somatic side effects. The HAM-A does not provide any standardized probe questions. Despite this, the reported levels of interrater reliability for the scale appear to be acceptable.

Scoring

Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe.

Versions

The scale has been translated into: Cantonese for China, French and Spanish. An IVR version of the scale is available from Healthcare Technology Systems.

Additional references

Maier W, Buller R, Philipp M, Heuser I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord 1988;14(1):61–8.
Borkovec T and Costello E. Efficacy of applied relaxation and cognitive behavioral therapy in the treatment of generalized anxiety disorder. J Clin Consult Psychol 1993; 61(4):611–19

Address for correspondence

The HAM-A is in the public domain.

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

1	**Anxious mood**	0	1	2	3	4
	Worries, anticipation of the worst, fearful anticipation, irritability.					
2	**Tension**	0	1	2	3	4
	Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.					
3	**Fears**	0	1	2	3	4
	Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.					
4	**Insomnia**	0	1	2	3	4
	Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.					
5	**Intellectual**	0	1	2	3	4
	Difficulty in concentration, poor memory.					
6	**Depressed mood**	0	1	2	3	4
	Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.					
7	**Somatic (muscular)**	0	1	2	3	4
	Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.					
8	**Somatic (sensory)**	0	1	2	3	4
	Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.					
9	**Cardiovascular symptoms**	0	1	2	3	4
	Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.					
10	**Respiratory symptoms**	0	1	2	3	4
	Pressure or constriction in chest, choking feelings, sighing, dyspnea.					
11	**Gastrointestinal symptoms**	0	1	2	3	4
	Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.					
12	**Genitourinary symptoms**	0	1	2	3	4
	Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.					
13	**Autonomic symptoms**	0	1	2	3	4
	Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.					
14	**Behavior at interview**	0	1	2	3	4
	Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing,					

etc.

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

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

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

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

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

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

   _____HOURS

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

   _____HOURS

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

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

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

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

Consider only how much <u>health problems</u> affected productivity <u>while you were working</u>.

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

CIRCLE A NUMBER

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

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

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

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

CIRCLE A NUMBER