NOVARTIS

Clinical Development

AMG 334 (erenumab)

CAMG334ADE01 / NCT03828539

Randomized, double-blind, multicenter Head-to-head study of Erenumab against topiRamate - Migraine study to assess tolerability and efficacy in a patiEnt–centered Setting (HER-MES)

Statistical Analysis Plan (SAP)

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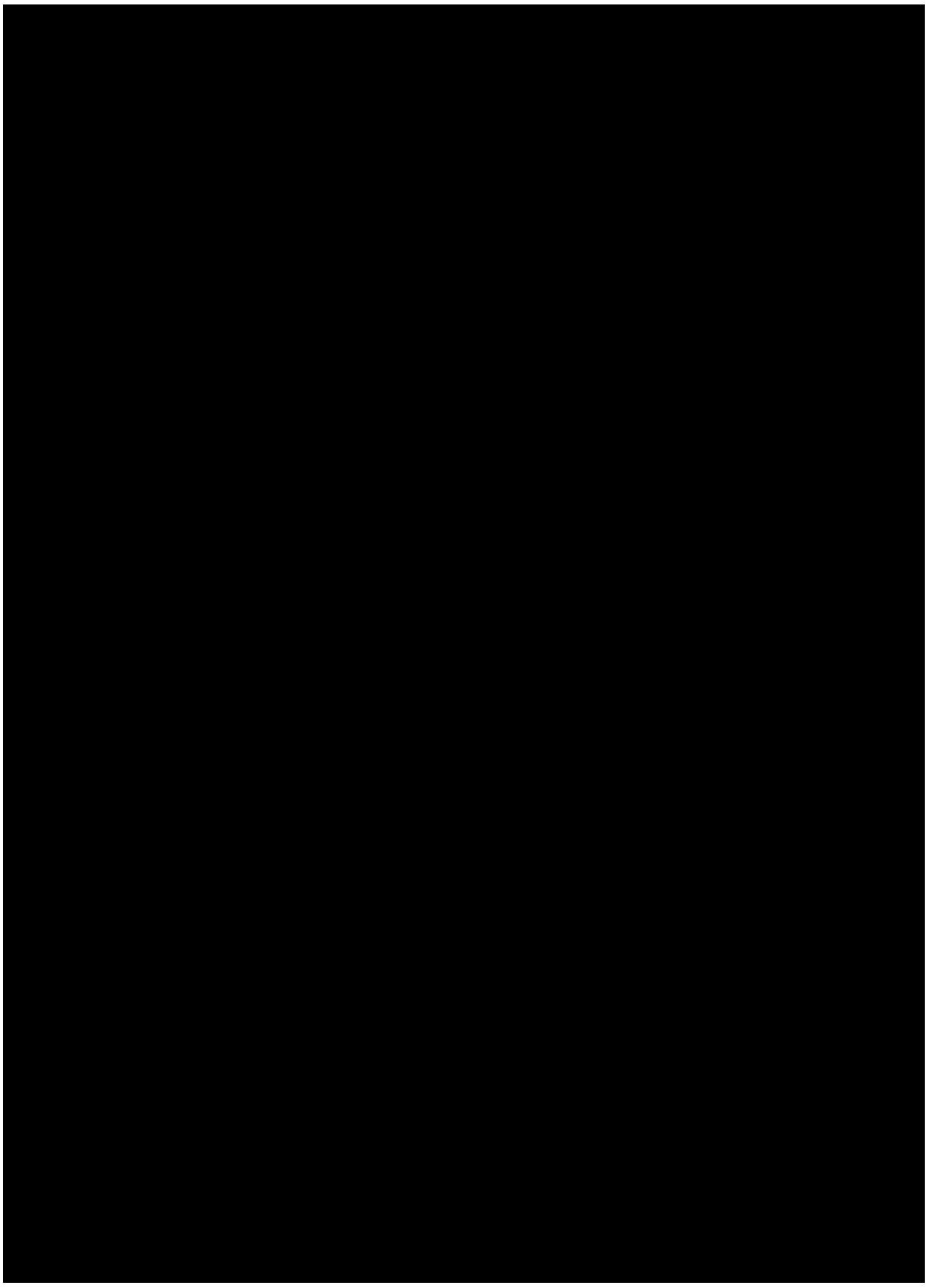

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
01-Oct-2020	Prior to DB Lock	Implementation of decisions from blind data review meeting and additional corrections before database lock	Clarified that only patients who took active study medication will be included in full analysis set and safety analysis set	Section 2.2 Analysis Sets
			Note on handling of patient reported outcomes data added	Section 2.11 Patient-reported outcomes
			Section on allocation of migraine-specific medication to events spanning midnight added	Section 5.7.3 Allocation of migraine-specific medication to events spanning midnight
			Clarified that HIT-6 scoring will be performed by the license owner "Optum"	Section 5.8.2 HIT-6 scoring
			Section for approval signatures added	Section 7 Approval signatures

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List of abbreviations

AE	Adverse event
ASA	Abbreviated schedule of assessments
ATC	Anatomic Therapeutic Chemical classification
CRO	Contact Research Organisation
DBTE	Double-Blind Treatment Epoch
ECG	Electroencephalography
eCRF	electronic Case Report Form
EoS	End of the Study
FAS	Full Analysis Set
HRQoL	Health Related Quality of Life
IMP	investigational medicinal product
IRT	Interactive Response Technology
LPLV	last patient last visit
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMD	Monthly Migraine Days
ODS	Output Delivery System
PCS	Mental Component Summary
PRO	Patient Reported Outcome
PT	Preferred Term
RAS	Randomized Analysis Set
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analysis according to Section 9 of the study protocol v02 for AMG 334 Study CAMG334ADE01 dated June 6, 2019. The scope of this plan includes the primary, secondary, and exploratory analyses, which will be executed by the CRO ([redacted]).

1.1 Study design

This study uses a single-cohort, 2-treatment arm, parallel-group randomized, double-blind, double-dummy design in adult patients with episodic migraine and chronic migraine, who must be either naïve or not suitable for or could have failed up to three prophylactic treatments out of: propranolol/ metoprolol, amitriptyline, flunarizine.

The following epochs are included in the study design:

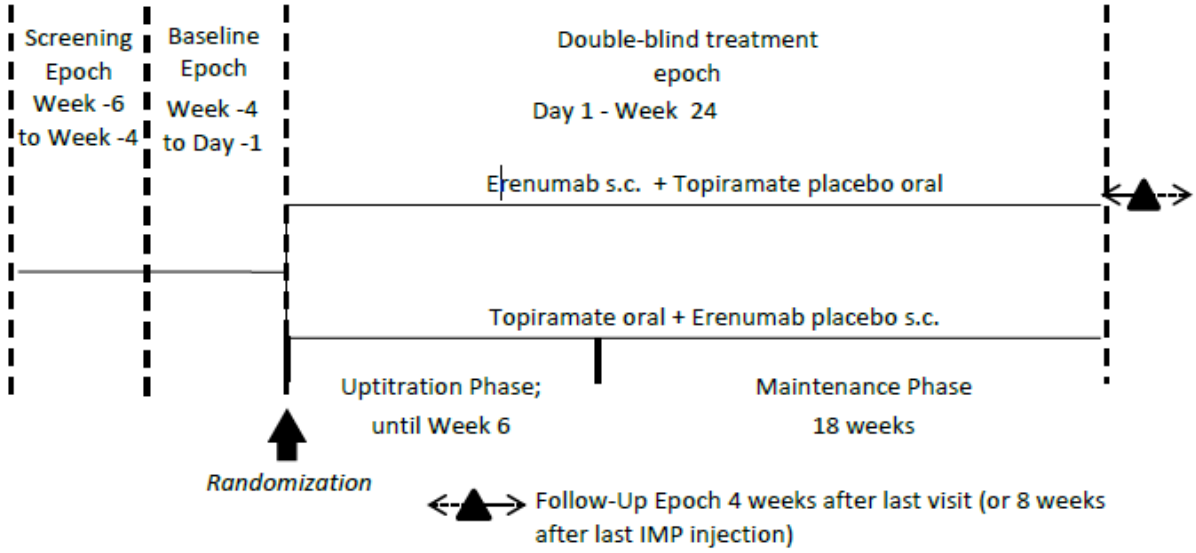
- **Screening Epoch of 2 weeks**: Required for all patients to assess initial eligibility.
- **Baseline Epoch of 4 weeks**: All patients fulfilling eligibility criteria successfully completing the Screening Epoch are invited to participate. Eligibility for randomization will be assessed based on migraine frequency and diary compliance during this epoch (migraine frequency of ≥ 4 and ≥80% eDiary compliance).
- **Double-blind, double-dummy Treatment Epoch (DBTE) of 24 weeks:** All patients completing the Baseline Epoch and fulfilling baseline eligibility criteria are invited to participate. Eligible patients will be randomized to one of two treatment arms. Double-blind treatment epoch will start with a titration phase for topiramate of a maximum of 6 weeks to determine the maximal tolerated dose and must aim to reach the recommended treatment dose of 100 mg according to the German SmPC. After the titration phase, maintenance phase will start (18 weeks). Topiramate dose has to be maintained until the end of the DBTE. Erenumab dose at beginning of the DBTE is determined patient-individually by the investigator based on the guidance provided in the SmPC and can be either 70 mg or 140 mg. Dose escalation from 70 mg to 140 mg in case of insufficient response could be considered at any time during the DBTE.

  Dose reduction of topiramate and erenumab is not allowed during DBTE (Visit 101-199). After visit 199 or if the patient discontinues study drug, a one week double-blind taper off phase will follow to ensure proper down titration for topiramate.

  At the end of the DBTE (24 weeks) the final assessment to address the objectives will occur.
- **Follow-Up Epoch (4 weeks)** –A Follow-Up Visit 4 weeks after last study visit (or 8 weeks after last IMP injection for discontinued patients) will be required as part of routine safety monitoring. The primary analysis will be triggered when all patients have completed their respective last visit of the double-blind treatment epoch.

End of trial will occur when the last patient completes last visit (LPLV).

Figure 1-1 Study Design



Patients will be stratified into groups according to their number of migraine days during the baseline epoch (4 - 7 vs. 8 - 14 vs. ≥ 15 monthly migraine days).

The study will recruit approximately 375 patients per arm (750 total) including up to a maximum of 35 patients with ≥ 15 monthly migraine days per arm (approx. 10 % of patients per arm). Assumptions were based on clinical studies with topiramate and erenumab.

No interim analysis is planned.

1.2 Study objectives and endpoints

The purpose of this study is to determine the safety and efficacy of erenumab compared to topiramate in the highest tolerated dose in patients suffering from ≥4 migraine days/month, who are naïve or not suitable for or have failed up to three prophylactic migraine treatments out of: propranolol/metoprolol, flunarizine and amitriptyline.

Objective	Endpoint
Primary	
To demonstrate the tolerability of erenumab compared to topiramate assessed by the rate of patients discontinuing treatment due to AE during the double-blind epoch of the study.	Discontinuation of treatment due to AE during the double-blind epoch of the study.
Secondary	
To evaluate the effect of erenumab compared to topiramate on the proportion of patients with at least 50% reduction from baseline in monthly migraine days.	Achieving at least a 50% reduction from baseline in MMD over the last 3 months (months 4, 5, and 6) of the double-blind epoch.
Exploratory:	

[redacted]	
To evaluate the effect of erenumab compared to topiramate on functional impairment, as measured by the Headache Impact Test (HIT-6)	HIT-6 at week 24
To evaluate the effect of erenumab compared to topiramate on generic health-related quality of life, as measured by the Short Form-36 (SF-36 v2)	SF-36 quality of life at week 24
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The primary analysis will be conducted on all patient data after database lock (after LPLV). Analyses will be performed by [redacted].

SAS Version 9.2 or higher will be used for all analyses. Tables and lists will be produced by the SAS Output delivery system (ODS) as rtf document which is transferred into docx-Format to reduce size.

General descriptive statistical rules:

Parameters which are at least interval scaled will be tabulated by the following sample statistics: Number of non-missing data, mean, standard deviation, minimum, median, and maximum.

Parameters which are nominally or ordinally scaled will be tabulated by absolute and relative frequencies. In general, missing values are not considered for calculation of percentages (i.e., adjusted percentages are calculated) if not otherwise specified.

General information on treatment arm handling, decimal places and other output-related information will be specified in tables, figures and listing (TFLs) shells accompanying this analysis plan.

2.1.1 General definitions

Study treatment
Novartis will supply the investigational medicinal products (IMP) listed below in a double-dummy setting:

Verum for Test-IMP:

- 1x Erenumab 70mg/1mL (70 mg), in pre-filled syringe, administered every 4 weeks;
- 2x Erenumab 70mg/1mL (140 mg), in pre-filled syringes, administered every 4 weeks;

  Dose for erenumab is 70 mg or 140 mg throughout the trial. If the response is insufficient, dose may be uptitrated from 70 mg to 140 mg. Down titration from 140 mg to 70 mg is not allowed.

Verum for Control-IMP:

- Topiramate 25 mg and 50 mg in blisters applied according to following scheme:

  Titration phase (6 weeks)
  The recommended dose for Topiramate is 100 mg/day in accordance with the SmPC. The titration phase must aim to reach the recommended dose as follows:

  First week: Topiramate 25 mg (1x 25 mg/day) in the evening

  After first week on 25 mg, dose has to be increased weekly by up titration in 25 mg increments to the highest tolerated dose. Individual patients may maintain dose for longer than one week, if deemed necessary but all efforts should be made to achieve the recommended 100 mg dose and only if that is not deemed feasible should the patient enter the maintenance phase at a lower dose. The patient will then enter the maintenance phase with the highest tolerated dose reached within the 6 week titration phase, whereas minimal dose is 50 mg topiramate (2x 25 mg/day), intermediate dose is 75 mg (1x 25 mg and 1x 50 mg/day) and maximal and recommended dose is 100 mg (2x 50 mg/day). Starting with the 50 mg dose, patients will have to take one tablet in the morning and one in the evening. Downtitration is not allowed.

  Maintenance phase (18 weeks)
  Patients stay on highest tolerated dose determined during titration phase
  Tapering off (1 week)

Patients taking a daily dose of 75 mg or 100 mg topiramate during the DBTE should taper off topiramate after visit 199 or when discontinuing study drug. Tapering off is performed with a daily dose of topiramate reduced by 50 mg for one week.

Placebo for Test-IMP:

- 1x Erenumab matching placebo, in pre-filled syringe, administered every 4 weeks;
- 2x Erenumab matching placebo, in pre-filled syringes, administered every 4 weeks;

Placebo for Control-IMP:

- Matching topiramate tablets for 25 mg and 50 mg in blisters

Erenumab

When not specifically specified, "erenumab" refers to the individual erenumab dose of 70 mg or 140 mg.

Topiramate

When not specifically specified, "topiramate" refers to the highest tolerated dose of topiramate.

Tablets Dose Level per visit in the titration phase

Titration phase (i.e. day 1 to week 6) tablets dose level per visit is defined as follows:

- At day 1: Dose level is equal to first dose in the study.
- At week 1 to 6: Dose level is defined as the mode of the documented doses in the interval [target date of the visit, target date of visit + 7 days].

Doses documented after date of discontinuation of double-blind treatment (i.e. tapering-off doses) are not considered for calculation of dose level in the titration phase.

Migraine-specific medication

Medication belonging to the triptan or ergotamine family.

Compliance with the eDiary (daily and retro)

The protocol requirement is 80% compliance with the eDiary (daily or retro) during baseline period. See Appendix A: Calculation rules for eDiary day calculation. Compliance with the eDiary at each month is calculated as

a number of eDiary entered in baseline period or between IMP syringe doses/ number of actual days in Baseline period or interval between IMP syringe doses*100%

Stratification factor (for randomization)

Monthly Migraine Days (MMD) category (4 - 7, 8 - 14, ≥ 15 MMD) at baseline as used for randomization of patients.

2.1.1.1 Study dates

eDiary Device Assignment Date

The date on which an eDiary device is assigned to a subject for the first time after completion of initial screening, i.e. the date of baseline visit.

Randomization Date in DBTE

Randomization date in DBTE is the date on which a patient is assigned to one of the two treatment arms via Interactive Response Technology (IRT).

First IMP Dose Date

The first IMP dose date is the date on which a subject is administered the first dose of IMP (i.e. verum test- or control-IMP) following randomization, which may be the same day or after the randomization date. For subjects who are randomized but not dosed with double-blind IMP after randomization, first IMP Dose Date is considered missing.

Last IMP Syringe Dose Date

The last IMP syringe dose date for each subject is defined as the latest date of a syringe administration.

Last IMP Tablet Dose Date out of tapering off phase

The last IMP tablet dose date out of tapering off phase for each subject is defined as the date of the last tablet administration prior to the start date of tapering off phase.

Last IMP Tablet Dose Date (tapering off phase included)

The last IMP tablet dose date for each subject is defined as the date of the latest administration of a tablet.

Study Day

Study Day 1 is defined as the first IMP dose date. For patients who are randomized but not dosed after randomization, Study Day 1 is defined as the date of randomization.

Study Day is defined as the number of days from Study Day 1.

Before Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1)

On or after Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1) + 1

Therefore the day prior to Study Day 1 is -1.

Baseline

The baseline period for efficacy endpoints collected by the eDiary (e.g. monthly migraine days) is defined as the period between the eDiary device assignment date and the day prior to study day 1 (study day one is not included).

A baseline for PROs (for SF-36v2, HIT-6, BDI-II) and safety endpoints (including C-SSRS) refers to the last evaluable measurement prior to or on the study day 1.

Note: Assessments on the day of randomization are assumed to have been taken as per protocol, i.e. if the assessment should be performed before dosing, the assessment will be treated as pre-dose as per protocol. Practically, i.e. that the time part of the date/time entry will be ignored.

Exception: In case there is a protocol deviation or a comment that specifically indicates that the assessment has been taken post-dose, the assessment will not be treated as pre-dose.

Patient-level End of Study (EoS) Date

The end of study (EoS) date for each subject is defined as the last date on which the subject participated in the study. The date will be recorded on the Study Completion eCRF page.

2.1.1.2 Visit and analysis window

Since the actual visit for a subject may not exactly coincide with their targeted visit date, the actual visit date is mapped to a study visit.

The nearest study day window will be utilized to define study visit for lab, vital signs, ECG, C-SSRS and some PROs collected during office visits (HIT-6, SF-36v2, [redacted]) before dose is administered.

Table 2.1.1.2-1. Study Visit Windows in the DBTE

Study visit	Target day	Study Day
Week 0	1	1
Week 1	8	2 - 11
Week 2	15	12 - 18
Week 3	22	19 - 25
Week 4	29	26 - 32
Week 5	36	33 - 39
Week 6	43	40 - 49
Week 8	57	50 - 70
Week 12	85	71 - 98
Week 16	113	99 - 126
Week 20	141	127 - 154
Week 24	169	155 - 182

2.1.1.3 Demographics and other baseline characteristics

Beck Depression Inventory II (BDI-II)

The BDI-II is a 21-item questionnaire that assesses severity of depression with the recall period of two weeks, including the day of completion. Each item is scored from 0 to 3. The total score varies between 0 and 63 and can be categorized into 4 severity grades:

- minimal depression (0-13)
- mild depression (14-19)

- moderate depression (20-28)
- severe depression (29-63)

The BDI-II is completed once during the study at screening visit via eDiary. Moderate and severe depression belong to the study exclusion criteria.
Please refer to BDI-II scoring for scoring details.

2.1.1.4 Efficacy endpoints

eDiary

Patients record the efficacy information using the provided eDiary platform. If a patient did not made a contribution to the eDiary at a particular day, it is possible to provide information retrospectively (**retro diary**). In this case, by the next eDiary usage a patient will be first asked to provide information on up to 48 hours prior to the time of completion of this diary and then about the actual state.

eDiary Day

A calendar day to which the information from the eDiary refers. Please refer to Appendix A: Calculation rules for calculation details.

Headache Day

A headache day is any calendar day on which the subject experiences a qualified migraine or non-migraine headache (initial onset, continuation or recurrence of the headache). Please see exceptions in Appendix B: MMD derivation, exceptions. A qualified headache is defined as**:**

- a qualified migraine headache or
- a qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or
- a headache of any duration for which acute headache treatment is administered. Unknown medications (with no available information on the type of treatment) will not be counted as acute headache treatment.

Information Day

A day which is either a headache day or an eDiary day.

Migraine day

A migraine day is defined as any calendar day in which the patient experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). Please see exceptions in Appendix B: MMD derivation, exceptions. A qualified migraine headache is defined as a migraine with or without aura, **lasting for ≥30 minutes**, and meeting **at least one** of the following criteria:

- ≥2 of the following pain features:
    - Unilateral
    - Throbbing
    - Moderate to severe

- Exacerbated with exercise/physical activity

- ≥1 of the following associated symptoms:
  - Nausea and/or vomiting
  - Photophobia and phonophobia

If the patient took a migraine-specific medication (i.e., triptane or ergotamine) during aura, or to treat a headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms. In case of a retro diary spanning the last two days, documentation regarding aura will be considered to apply for both days.

Monthly Migraine Days (MMD)

Monthly migraine days at baseline are the number of migraine days in the baseline period that are normalized in a 28-day interval. Monthly migraine days after baseline are the number of migraine days between each monthly IMP dose that are normalized in a 28-day interval. Days without eDiary data in each normalized monthly interval will be prorated. Calculation details are described in eDiary data.

Monthly Intervals for Monthly Migraine Days

Monthly migraine days will be calculated based on the patient's IMP dosing schedule defined below using eDiary data collected from beginning of the baseline epoch up to the end of the DBTE.

Table 2.1.1.4-1. Monthly Intervals for MMD

Study Epoch	**Assessment Time point**	**Interval Based on Syringe Dose Dates**	
		Start date	**End date**
Baseline Epoch	Baseline	From eDiary device assignment date (i.e. baseline visit)	Day prior to study day 1
Double-Blind Treatment Epoch	Week 4 (**Month 1**)	• Study Day 1	• Week 4 syringe dose date -1 • Study day 28 if Week 4 syringe dose is not received (either missed or IMP discontinued prior to Week 4)
	Week 8 (**Month 2**)	• Week 4 syringe dose date • Study day 29 if Week 4 syringe dose is not received or IMP	• Week 8 syringe dose date -1 • Study day 56 if Week 8 syringe dose is not received (either missed or

		discontinued prior to Week 4	IMP discontinued prior to Week 8)
	Week 12 (**Month 3**)	• Week 8 syringe dose date • Study day 57 if Week 8 syringe dose is not received or IMP discontinued prior to Week 8	• Week 12 syringe dose date -1 • Study day 84 if Week 4 syringe dose is not received (either missed or IMP discontinued prior to Week 12)
	Week 16 (**Month 4**)	• Week 12 syringe dose date • Study day 85 if Week 12 syringe dose is not received (either missed or IMP discontinued prior to Week 12)	• Week 16 syringe dose date -1 • Study day 112 if Week 16 syringe dose is not received (either missed or IMP discontinued prior to Week 16)
	Week 20 (**Month 5**)	• Week 16 syringe dose date • Study day 113 if Week 16 syringe dose is not received (either missed or IMP discontinued prior to Week 16)	• Week 20 syringe dose date -1 • Study day 140 if Week 20 syringe dose is not received (either missed or IMP discontinued prior to Week 20)
	Week 24 (**Month 6**)	• Week 20 syringe dose date • Study day 141 if Week 20 syringe dose is not received (either missed or IMP discontinued prior to Week 20)	• Week 20 syringe dose date + 27 if Week 20 syringe dose is received • Study day 168 if Week 20 syringe dose is not received (either missed or IMP discontinued prior to Week 20)

Monthly migraine days over the last three months (months 4, 5, and 6) of the double-blind epoch

Monthly migraine days over the last three months are calculated as the mean MMD over months 4, 5, and 6. In case of missing data at some time point, mean value will be calculated based on available data.

Achievement of at least a 50% reduction from baseline in monthly migraine days over the last three months (months 4, 5, and 6) of the double-blind epoch

A patient achieves at least 50% reduction from baseline over the last three months, if

$$\frac{(Baseline\ MMD - \ average\ MMD\ over\ the\ last\ three\ month\ of\ DBTE) * 100}{Baseline\ MMD} \geq 50$$

Achievement of at least a 50% reduction from baseline in monthly migraine days during the first month of the double-blind epoch

A patient achieves at least 50% reduction from baseline in the first month of DBTE, if

$$\frac{(Baseline\ MMD - \ MMD\ in\ the\ first\ month\ of\ DBTE) * 100}{Baseline\ MMD} \geq 50$$

Headache Impact Test (HIT-6)

The Headache Impact Test (HIT-6) is a short-form self-administered questionnaire based on the Internet-HIT question pool. The HIT-6 was developed as a global measure of adverse headache impact to assess headache severity in the previous month and change in a patient's clinical status over a short period of time. Six questions cover:

- severe pain,
- limitation of daily activity (household, work, school and social),
- wanting to lie down when headache is experienced,
- feeling too tired to work or do daily activities because of headache,
- feeling fed up or irritated because of headache, and
- headache limiting ability to concentrate or work on daily activities.

The points are summed over six questionnaire items using special algorithm to produce a total HIT-6 score that ranges from 36 to 78. HIT-6 scores can be categorized into 4 grades, representing

- little or no impact (49 or less)
- some impact (50-55)
- substantial impact (56-59)
- severe impact (60-78)

due to headache. No recall period is specified for the first 3 items. The recall period is the past 4 weeks for the last 3 items.
Subjects complete the HIT-6 using the eDiary during their scheduled clinic visit. Please refer to HIT-6 scoring for scoring details.

Short Form Health Survey Version 2, 4-week recall period (SF-36v2)

The SF-36 is a widely used measure of health-related quality of life (HRQoL) among healthy subjects and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually:

- Physical Functioning
- Role-Physical
- Bodily Pain
- General Health
- Vitality
- Social Functioning
- Role-Emotional

- Mental Health

Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed.
Subscale- and component summary scores are scaled to vary between 0 and 100 with 0 indicating worst possible health state and 100 best possible health state.
Calculation of SF-36 scores utilizes general population norm values. Scores are constructed to have an average value of 50 and a standard deviation of 10. Therefore, patients with the SF-36 scores below 50 have a health state below the average health state level of the general population. Patient's SF-36 score values below 40 may indicate impaired health state. Please refer to SF-36v2 scoring for scoring details.

[redacted]

2.1.1.5 Safety Endpoints

Analyses on Adverse Events will be performed for the entire study without differentiating between the DBTE and Follow-up epoch. Independently, whether a patient is an ASA-patient or not, AEs will be analysed in the following analysis window:

[Study Day 1; EoS Date]

Remaining safety analyses will be performed for the DBTE and Follow-up Epoch separately. Laboratory, vital signs, ECG and C-SSRS are assessed during study visits and, therefore, will be assigned to the DBTE based on (Table 2.1.1.2-1).

Concomitant medications will be assigned to the DBTE based on the following analysis window:

[Study Day 1; Week 24 visit date if the visit was performed / MIN(EoS, study day 169) if the visit was not performed]

Discontinuation of treatment due to AE during the DBTE

Discontinuation of treatment due to AE during the DBTE is determined by the flag on the Treatment Completion eCRF page. "Death" as a reason for treatment discontinuation will be also included in AEs leading to treatment discontinuation.

Treatment-Emergent Adverse Event (TEAE)

Treatment emergent adverse events are defined as AEs occurred on or after the first dose of study treatment. AEs registered prior and after the first dose of study treatment are considered

as treatment emergent if they have increased severity based on preferred term any time after the first dose of study treatment.
In case of missing data on a day of AE start date, the AE is considered as treatment emergent if

date of first dose of study treatment $\leqslant$ *latest possible start date*

Please, see AE and Concomitant medication date imputation for "latest possible start date" definition.

Serious Adverse Event (SAE)
SAEs are determined by the flag on the Adverse Events eCRF page.

Treatment-Related Adverse Event
Treatment-emergent adverse event is defined as treatment-related, if investigator considered it as having a reasonable possibility to be related to study treatment, which is reflected in the eCRF with a corresponding flag.

Adverse Event leading to dose adjustment
Adverse event is defined as leading to dose adjustment if at least one of the following actions was taken with the study treatment due to AE:

- dose increased
- dose reduced
- drug interrupted
- drug withdrawn

Adverse Event leading to pausing in uptitration
Adverse event leading to pausing in uptitration are determined by the flag on the Adverse Events eCRF page.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior based on following categories:

Suicidal Ideation

- Cat. 1 - Wish to be dead
- Cat. 2 - Non-specific active suicidal thoughts
- Cat. 3 - Active suicidal ideation with any methods (not plan) without intent or act
- Cat. 4 - Active suicidal ideation with some intent to act, without specific plan
- Cat. 5 - Active suicidal ideation with specific plan and intent

Suicidal behavior

- Cat. 6 - Actual attempt (non-fatal)
- Cat. 7 - Interrupted attempt
- Cat. 8 – Aborted or self-interrupted attempt
- Cat. 9 - Preparatory acts or behavior
- Cat. 10 - Suicide

The C-SSRS is administered at each visit, including unscheduled visits. Two versions depending on the type of visits will be used in this study: Screening and Since Last Visit. Please refer to C-SSRS scoring for scoring details.

Duration of exposure to Test-IMP

For all calculations of exposure, dose date refers to receiving dose > 0.
The duration of exposure to test-IMP is computed as

min (last IMP syringe dose date + 27, EoS date) – first IMP syringe dose date + 1.

Duration of exposure to control-IMP (tapering off phase included)

For all calculations of exposure, dose date refers to receiving dose > 0.
The duration of exposure to control-IMP is computed as

last IMP tablet dose date - first IMP tablet dose date + 1.

Duration of exposure to control-IMP out of tapering off phase

For all calculations of exposure, dose date refers to receiving dose > 0.
The duration of exposure to topiramate out of tapering off phase is computed as

last IMP tablet dose date out of tapering off phase – first IMP tablet dose date + 1

Subject Incidence

The subject incidence for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects who entered that period. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

2.2 Analysis sets

The Randomized Set (RS) will consist of all participants who received a randomization number, regardless of receiving study medication.

The Full analysis set (FAS) will consist of all participants who received at least one dose of active study medication. In FAS, subjects will be analyzed according to randomized treatment, regardless of the actual treatment received.

The Safety analysis set (SAF) will consist of all randomized subjects who received at least one dose of active study medication and will be analyzed based on actual treatment received.

2.2.1 Subgroup of interest

Subgroup analyses are planned only for the primary endpoint (see Subgroup analyses).

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Screening and baseline epoch patient disposition will be based on all screened patients data.

A patient disposition summary for the screening and baseline epoch will include number and percentage of patients, concerning

- Screening

  A patient is defined as screened if signed informed consent is available

- Screening failure

  A patient is defined as screening failure if he was screened but not randomized

- Randomization
  Subjects are considered randomized if they have been assigned a randomization number.
- Non-randomization
  - Reason for non-randomization

The total number of patients screened and the number of patients with screening failure will be summarized, including the reason for screening failure.
The reason for non-inclusion into the study will be listed for screened/baseline patients who discontinued from study prior to randomization.

Patient disposition for the DBTE and follow-up epoch will be presented based on the randomized set (RS).

A corresponding summary will include number and percentage of patients (treatment group specific and overall), concerning

- Completion of double-blind treatment

  A patient is defined as completer for the double-blind treatment if double-blind treatment completion status on the eCRF page is ticked as not prematurely discontinued

- Discontinuation of double-blind treatment
  - Reason for discontinuation of double-blind treatment

- Study completion

  A patient is defined as completer for the study if study completion status on the eCRF page is ticked as not prematurely discontinued

- Discontinuation of the study
  - Primary reason for discontinuation of the study

Protocol deviations (PDs) will be summarized separately for PDs not related to COVID-19 and for PDs related to COVID-19. For PDs not related to COVID-19, the number of patients with at least one PD will be presented (based on RS) and the results of the PDs will be grouped using

the broad categories (Inclusion/Exclusion Criteria (Study eligibility), Withdrawal criteria met, but subject not discontinued, Treatment Deviation, Prohibited Concomitant Medication, Other). For PDs related to COVID-19, the number of patients with at least one PD will be presented (based on RS) and the results of the PDs will be grouped by category of COVID-19 PD and type of relationship to COVID-19.

The number of patients within each of the analysis sets (RS, FAS, SAF) used in the study will be given.

2.3.2 Demographic variables and other baseline characteristics

Demographic variables and other baseline characteristics including previous migraine treatments will be summarized for each randomized treatment group and for all participants (total) using FAS.

For continuous variables mean, median, standard deviation, minimum, and maximum will be reported, whereas for categorical variables the number and percentage of participants in each category.

Patient demographic data includes age (years), sex, race, weight (kg), height (cm), BMI (kg/m2), and source of patient referral.

Baseline disease characteristics contain following information assessed at baseline (see Section 2.1.1.1 for baseline definition):

- Monthly migraine days
- Monthly headache days
- Acute headache medication (none vs. migraine-specific vs. non migraine-specific)
- Prior treatment failure status (naïve vs. prior treatment failure, related to the prophylactic migraine treatments propranolol/metoprolol, amitriptyline, flunarizine)
- Beck Depression Inventory - II (BDI-II, minimal depression (0-13) vs. mild depression (14-19))

2.3.3 Medical history

Relevant medical history/current medical conditions present before signing the Informed consent will be recorded on the ‘Medical History’ eCRF page.

General medical history data includes medical history term, which will be summarized by system organ class and preferred term in the MedDRA dictionary.

Medical history possibly contributing to liver dysfunction data includes medical history term, which will be summarized by system organ class and preferred term in the MedDRA dictionary.

Headache and migraine frequency history data includes frequency of migraines over the past 3 months before screening (average days per month subject had migraines), frequency of headache (migraine and non-migraine) over the past 3 months before screening (average days per month subject had headache) and patient’s age at migraine onset.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The analysis of study treatment data will be based on the SAF.

For Control-IMP (topiramate or placebo):

- dose level distribution (number and percent of patients with particular dose) per visit in the titration phase summarized by treatment group
- duration of exposure out of tapering off phase summarized descriptively by treatment group
- duration of exposure including tapering off summarized descriptively by treatment group

For Test-IMP (AMG 334 or placebo):

- Number and percentage of patients receiving 1/2/3/4/5/6 doses of Test-IMP summarized by treatment group
- Duration of exposure summarized descriptively by treatment group
- Number and percentage of patients with starting dose of 70 mg or 140 mg.
- Reason for starting dose of 140 mg
- Number and percentage of patients with dose change from 70 mg to 140 mg and the corresponding reason

2.4.2 Prior, concomitant and post therapies

Number and percentage of patients with **prior prophylactic migraine treatment failure** will be presented based on RAS. A summary will be done for each failed treatment category with the primary reason for treatment discontinuation specified.

The number and percentage of patients receiving acute medications (during baseline and double-blind treatment epoch) will be reported. The number and percentage of patients receiving concomitant medications and significant non-drug therapy (during the double-blind treatment period) will be summarized by ATC level 1 and preferred name (coded by WHO Anatomic Therapeutic Chemical classification [ATC]) and by treatment group.

The use of concomitant medications and significant non-drug therapy during the follow-up period will be summarized in the same way, in a separate table.

2.5 Analysis of the primary objective

The primary objective of the study is to demonstrate the tolerability of erenumab compared to topiramate assessed by the rate of patients discontinuing treatment due to AE during the double-blind epoch of the study.

2.5.1 Primary endpoint

The primary endpoint of the study is discontinuation of treatment due to AE during the double-blind epoch of the study.

Analysis on primary endpoint should be done based on Full Analysis Set (FAS).

2.5.2 Statistical hypothesis, model, and method of analysis

Null hypothesis: odds of AE-related treatment discontinuations are equal in both treatment groups

Alternative hypothesis: odds are not equal when comparing erenumab to topiramate

Statistical hypothesis:

$$H_0: \ (p_1 / (1- p_1)) / (p_0 / (1- p_0)) = 1,$$

where
p_j –probability of AE-related treatment discontinuations for the treatment group j
j = 0 corresponds to topiramate group
j = 1 corresponds to erenumab group

The odds ratio not significantly different from one would mean that there is no evidence for a difference in AE-related treatment discontinuations between the two treatment groups.

Statistical hypothesis will be tested in the frame of logistic regression analysis controlling for the stratification factor (4-7 vs. 8-14 vs. ≥ 15 MMD at baseline):

logit (proportion) = treatment group + stratification factor

Odds ratio, its 95% confidence interval and the corresponding p-value will be presented. Significance level will be set at 5%. By significant test results (p(odds ratio = 1) ≤ 0.05) the superiority of erenumab will be claimed only by the correct direction, i.e. if the erenumab odds are lower than topiramate odds.

Additionally to the odds ratios, estimates for the relative risk and the risk difference (with 95% confidence intervals and p-values) will be calculated for the primary endpoint. Confidence intervals and p-values for the relative risks and risk difference will be calculated based on the normal distribution.

In case of zero events in only one treatment arm add 1 patient with 0.5 events to each treatment arm for calculation of the relative risk. Odds ratio will not be estimated in this case.

In case of zero events in both treatment arms no odds ratio will be estimated, the null hypothesis will not be tested and no difference between treatment arms can be claimed. Additionally, no relative risk will be calculated.

2.5.3 Handling of missing values/censoring/discontinuations

For every patient, it can be determined whether he/she discontinued for AE-related reasons. AE-related discontinuations are counted as events. Discontinuation due to the other reasons as non-AE-related treatment discontinuations or losses to follow up should not be counted as event.

[redacted]

2.6 Analysis of the secondary objective

The secondary objective of the study is to evaluate the effect of erenumab compared to the topiramate on the proportion of patients with at least 50% reduction from baseline in monthly migraine days.

Analysis on primary endpoint should be done based on the Full Analysis Set (FAS).

2.6.1 Secondary endpoint

The secondary endpoint is an achievement of at least 50% reduction from baseline in MMD over the last 3 months (month 4, 5, and 6) of the double-blind epoch.

The secondary analysis will contrast erenumab versus topiramate in the FAS.

2.6.2 Statistical hypothesis, model, and method of analysis

Null hypothesis: odds of achievement of at least 50% reduction from baseline in MMD are equal in both treatment groups.

Alternative hypothesis**:** odds are not equal when comparing erenumab to topiramate

Statistical hypothesis: H_0:

$$(p_1 / (1- p_1)) / (p_0 / (1- p_0)) = 1,$$

where
p_j – probability of patients achieved at least 50% reduction from baseline in the treatment group j
j = 0 corresponds to topiramate group
j = 1 corresponds to erenumab group

The odds ratio not significantly different from one would mean that there is no evidence for a difference in achieving at least 50% reduction from baseline between the two treatment groups.

Statistical hypothesis will be tested in the frame of logistic regression analysis controlling for the stratification factor:

logit (probability) = treatment group + stratification factor

Odds ratio, its 95% confidence interval and the corresponding p-value will be presented. Significance level will be set at 5%. By significant test results ($p(\text{odds ratio} = 1) \leq 0.05$) the superiority of erenumab will be claimed only by the correct direction, i.e. if the erenumab odds are higher than topiramate odds.

Additional to the odds ratios, estimates for the relative risk and the risk difference (with 95% confidence intervals and p-values) will be calculated for the secondary endpoint. Confidence intervals and p-values for the relative risks and risk difference should be calculated based on the normal distribution.

In case of zero events in only one treatment arm add 1 patient with 0.5 events to each treatment arm for calculation of the relative risk. Odds ratio will not be estimated in this case.

In case of zero events in both treatment arms no odds ratio will be estimated, the null hypothesis will not be tested and no difference between treatment arms can be claimed. Additionally, no relative risk will be calculated.

2.6.3 Handling of missing values/censoring/discontinuations

All the subjects' data collected regarding 50% response in MMD will be used in the analysis regardless of whether subjects discontinue study treatment or not. Subjects with missing response information on this endpoint will be imputed as non-response (non-responder imputation).

2.6.4 Subgroup analyses

Not applicable.

2.7 Analysis of exploratory objectives

2.7.1 Exploratory endpoints

Exploratory efficacy analyses of erenumab in comparison to topiramate is based on patients' reported data assessed via eDiary, including

- [redacted]
- Patients' quality of life assessed with SF-36v2 (The Short Form (36) Health Survey)
- Headache impact on patients' functional ability assessed by HIT-6 (Headache Impact Test)
- [redacted]

Objectives of the exploratory efficacy analyses are listed in the table below.

Exploratory objective	Efficacy endpoint	Assessment time point
[redacted]		
To evaluate the effect of erenumab compared to topiramate on functional impairment	[redacted]	Week 24
	HIT-6: Proportion of patients achieving at least a 5 points reduction from baseline	Week 24
To evaluate the effect of erenumab compared to topiramate on generic health-related quality of life	[redacted]	Week 24
	SF-36 v.2: Proportion of patients achieving at least a 5 points increase from baseline in PCS- and MCS score	Week 24

[redacted]

2.7.2 Statistical hypothesis, model, and method of analysis

Analysis of exploratory efficacy endpoints will utilize the FAS. Subjects will be analyzed according to their randomized treatment group.

Methods of analysis for exploratory efficacy analyses are summarized in the table below.

Exploratory Endpoint	Model	Terms included in the model	Imputation of missing values	Additional
[redacted]				

		scheduled visit)		Treatment difference will be tested using a contrast from the model
Proportion of patients achieving at least a 5 points reduction from baseline in HIT-6 total score	Logistic regression model	- treatment group - baseline value - stratification factor	Non-response imputation	Summary statistics for observed data Relative Risk** Risk Difference**
[redacted]				
SF-36 quality of life: Proportion of patients achieving at least 5 points increase from baseline to week 24 in PCS and MCS	Logistic regression model	- treatment group - baseline value - stratification factor	Non-response imputation	Summary statistics for observed data Relative Risk** Risk Difference**
[redacted]				

* MMRM: unstructured covariance matrix will be used in the repeated statement
**Calculation of the Relative Risk and Risk Difference will be based on rules described for primary analysis, see Statistical hypothesis, model, and method of analysis

2.7.3 Handling of missing values/censoring/discontinuations

For the exploratory endpoints "Proportion of patients achieving at least a 5 points reduction from baseline in HIT-6 total score" and "Proportion of patients achieving at least 5 points increase from baseline to week 24 in PCS and MCS (SF-36v2)" missing response data will be imputed as non-response (non-responder imputation).

2.8 Safety analyses

Safety analyses will be based on safety data set (SAF).

All safety analyses will be performed for the Double-Blind Treatment Epoch and Follow-up Epoch separately and in descriptive manner.

Missing data will not be imputed for safety endpoints.

2.8.1 Adverse events (AEs)

In the frame of safety analysis the following treatment-emergent AE types will be considered:

- Any AE
- Study treatment related AE
- AE leading to study treatment discontinuation
- AE leading to dose adjustment (including study treatment discontinuation)
- AE leading to pausing in uptitration

- Serious AE (SAE)
- Study treatment related SAE
- SAE leading to study treatment discontinuation
- Death

All adverse events tables will be summarized by treatment group.

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or later will be used to code all adverse events (AE) to a system organ class (SOC) and a preferred term (PT).

Overview table of the number and percentage of patients having each type of AE.

Tables with the *summary types I* will be provided for all AEs listed above except for death. Tables with the *summary types II* will only be provided for AE type 'any AE'.

> *Summary type I*: Tables with number and percentage of patients having particular AE summarized by treatment group, SOC and PT. Summaries will be provided for each AE type separately.
>
> *Summary type II*: Tables with number and percentage of patients having particular AE summarized by treatment group, SOC, PT and severity. Summaries will be provided for each AE type separately.

The SOCs will be presented in the alphabetic order and PTs will be ordered within the SOCs by decreasing order of frequency in the erenumab treatment group.

If a patient reported more than one adverse event with the same PT, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

All AEs, deaths (see Section 2.8.2 for details), SAEs and AEs leading to permanent study drug discontinuation will be listed separately.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.8.2 Deaths

Deaths will be listed by treatment group including the start date of the study treatment, the last date on study treatment, the death date and the reason for death.

2.8.3 Laboratory data

Summary statistics of laboratory hematology- and blood chemistry results will be presented as absolute value as well as change from baseline by visit, treatment and laboratory test category. Change from baseline will be summarized for each time point and only for patients with both baseline and post-baseline assessment.

Clinically notable laboratory values will be flagged and listed by treatment group.

Table 2.8.1.1-1. Clinically notable laboratory values

Notable values			
Laboratory variable	**Gender (M/F/Both)**	**Standard Units**	**SI Units**
Liver function and related variables			
SGOT (AST)	F	> 93 U/L	> 93 U/L
SGOT (AST)	M	> 111 U/L	> 111 U/L
SGPT (ALT)	F	> 90 U/L	> 90 U/L
SGPT (ALT)	M	> 123 U/L	> 123 U/L
Total bilirubin	Both	> 3.6 mg/dL	> 63 µmol/L
Alkaline Phosphatase	F	> 832 U/L	> 832 U/L
Alkaline Phosphatase	M	> 1032 U/L	> 1032 U/L
Hematology variables			
Neutrophils	Both	< 1.5 x 10^3 /µL	< 1.5 x 10^9 /L

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

For the numeric ECG measurements

- ECG Mean Heart Rate
- PR Interval
- QRS Duration
- QT Interval
- QTcF Interval
- RR Interval

summary statistics will be presented for baseline and week 24 separately for each treatment group. Descriptive summary statistics for the change from baseline to the week 24 will be calculated for patients with available ECG data at both time points.

2.8.4.2 Vital signs

Assessed vital signs include:

- systolic/diastolic blood pressure
- pulse rate
- temperature

Patient's values on blood pressure and pulse rate will be calculated as a mean of three readings. Readings with missing values will be ignored.
Descriptive summary statistics presented by type of measurement and treatment group will contain vital signs measurements for each study visit as well as change from baseline.

2.8.4.3 Columbia Suicide Severity Rating Scale (C-SSRS)

The number and percentage of subjects reporting any suicidal ideation or any suicidal behavior will be summarized descriptively by treatment group and by visit, for DBTE and for safety follow-up period, respectively.

Shift table of C-SSRS maximum severity of suicidal ideation/behavior compared to baseline will be provided by treatment group for DBTE and for safety follow-up period, respectively.

No statistical testing will be performed on C-SSRS.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Patient reported outcomes assessed in the study are limited to those used for exploratory efficacy analyses (MMD, HIT-6, SF-36v2, [redacted]), safety analyses (C-SSRS) and patient's baseline characteristics (BDI-II).

[redacted]

2.12 Biomarkers

Not applicable.

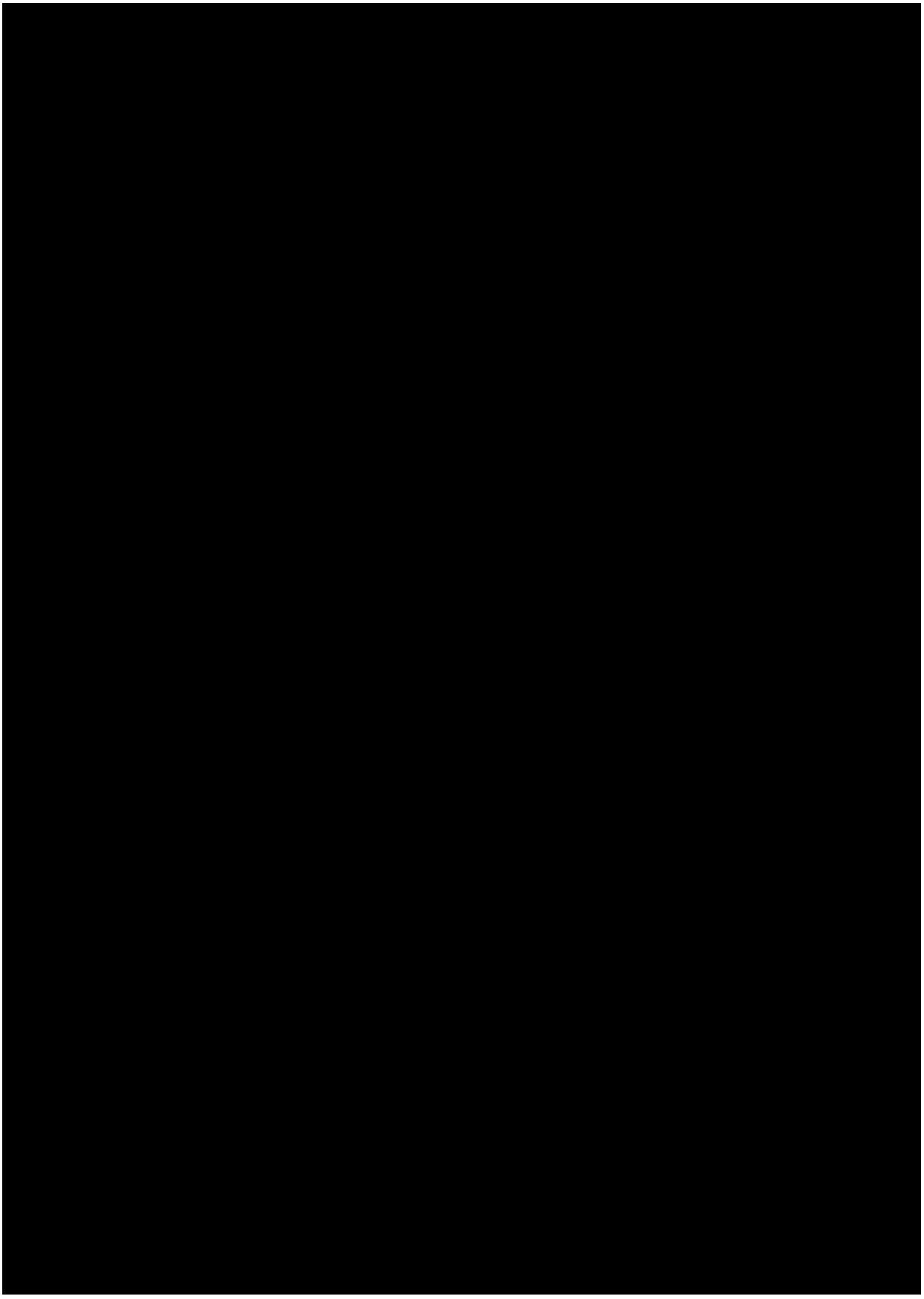
2.13 Other Exploratory analyses

See Analysis of exploratory objectives. No additional exploratory variables are specified.

2.14 Interim analysis

No interim analyses is planned.

[redacted]



[redacted]

5 Appendix

5.1 Imputation rules

No imputation will be done for missing primary and exploratory endpoints. Subjects with missing response information on the secondary endpoint (achievement of at least 50% reduction from baseline in MMD over the last 3 months (month 4, 5, and 6) of the double-blind epoch) will be imputed as non-response.

5.1.1 Study drug

5.1.2 Concomitant medication date imputation

Incomplete day
Incomplete start day will be imputed as MAX(date of study day 1, *earliest possible start date*).
Incomplete end day will be imputed as MIN(EoS, *latest possible end date*).

Earliest possible start/end date is calculated on the eCRF page and refers to the first day of the corresponding month. *Latest possible start/end date* is calculated on the eCRF page and refers to the last day of the corresponding month.

Incomplete day/month
Incomplete start day/month will be imputed as MAX(date of study day 1, 1st January of the year entered).
Incomplete end day/month will be imputed as MIN(EoS, 31th December of the year entered).

Incomplete day/month/year
Incomplete day/months/year will not be imputed.

Prior therapies date imputation

Incomplete day
Incomplete start day will be imputed as earliest possible start date.
Incomplete end day will be imputed as MIN (date of the day prior to study day 1, *latest possible end date*).

Incomplete day/month
Incomplete start day/month will be imputed as 1st January of the year entered.
Incomplete end day/month will be imputed as MIN(31th December of the year entered, date of the day prior to study day 1).

Incomplete day/month/year
Incomplete start date will be imputed as very early date
Incomplete end date will be imputed as a date of the day prior to study day 1.

5.1.2.1 Post therapies date imputation

Not applicable.

5.1.2.2 Other imputations

5.1.2.2.1 eDiary data

Missing eDiary data in the calculation of monthly measurements about patients' migraine and non-migraine headaches will be handled using the following method:

1. For **monthly intervals with ≥ 14 days of eDiary days** (including retrospective eDiary days) in each interval**:**

   Monthly migraine days will be prorated to 28-day equivalents**.** Prorated result does not need to be rounded.

2. For **monthly intervals with < 14 days of eDiary** use (including retrospective eDiary days), all monthly measurement will be set to missing.

Monthly Endpoint	**Condition**	**Proration Method (does not need to be rounded)**
Monthly migraine days	If eDiary days in entire baseline or interval post baseline >=14 (including retrospective eDiary days), then do proration; Else monthly measurement is set to missing [eDiary day is a day with all headache related questions completed retrospectively or not]	Number of observed migraine days * 28/ Number of information days in interval [information day is an eDiary day or headache day]

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.
Severity of adverse events is graded by investigator (mild, moderate, severe) and reflected in the eCRF.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

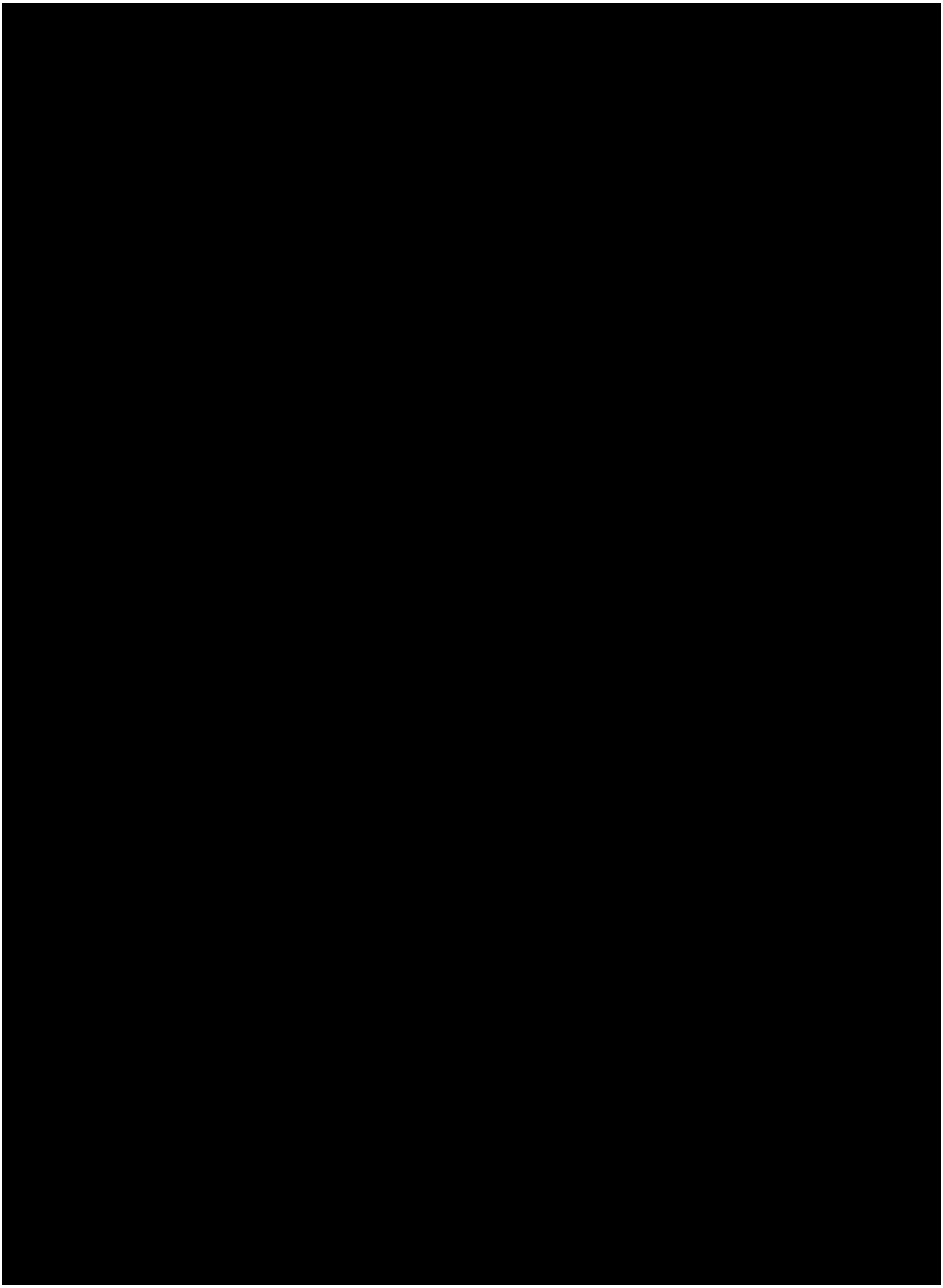
See Analysis of the primary objective

5.4.2 Key secondary analysis

See Analysis of the secondary objective

5.5 Rule of exclusion criteria of analysis sets

Exclusion criteria of analysis sets are complementary to those used for corresponding analysis set definitions (see Analysis sets).



5.8 Appendix C: Patient-reported Outcome Scoring rules/Forms/Instruments

5.8.1 BDI-II scoring

Beck Depression Inventory II (BDI-II) consists of 21 items, each with 4 or 6 response options.

Missing data

If more than 2 items have missing values, the total BDI score will be missing. If one or two items are missing, their score can be imputed with the mean of the non-missing scores before summing.

Items should be rescored according following rules:

Item number	Item label in the data set	Original value	Rescored value
1 - 15, 17, 19 - 21		0	0
		1	1

		2	2
		3	3
16	BDI_161L	0	0
18	BDI_181L	1	1
		2	1
		3	2
		4	2
		5	3
		6	3

Scoring

A single score is calculated by adding up the rescored values of 21 items. The range of values is 0 - 63.

5.8.2 HIT-6 scoring

The Headache Impact Test (HIT-6) is as a global measure of adverse headache impact, which assesses headache severity in the previous month and change in a patient's clinical status over a short period of time.

Scoring

HIT-6 score will be calculated by the HIT-6 license owner "Optum" and ranges from 36 to 78.

Score categorization

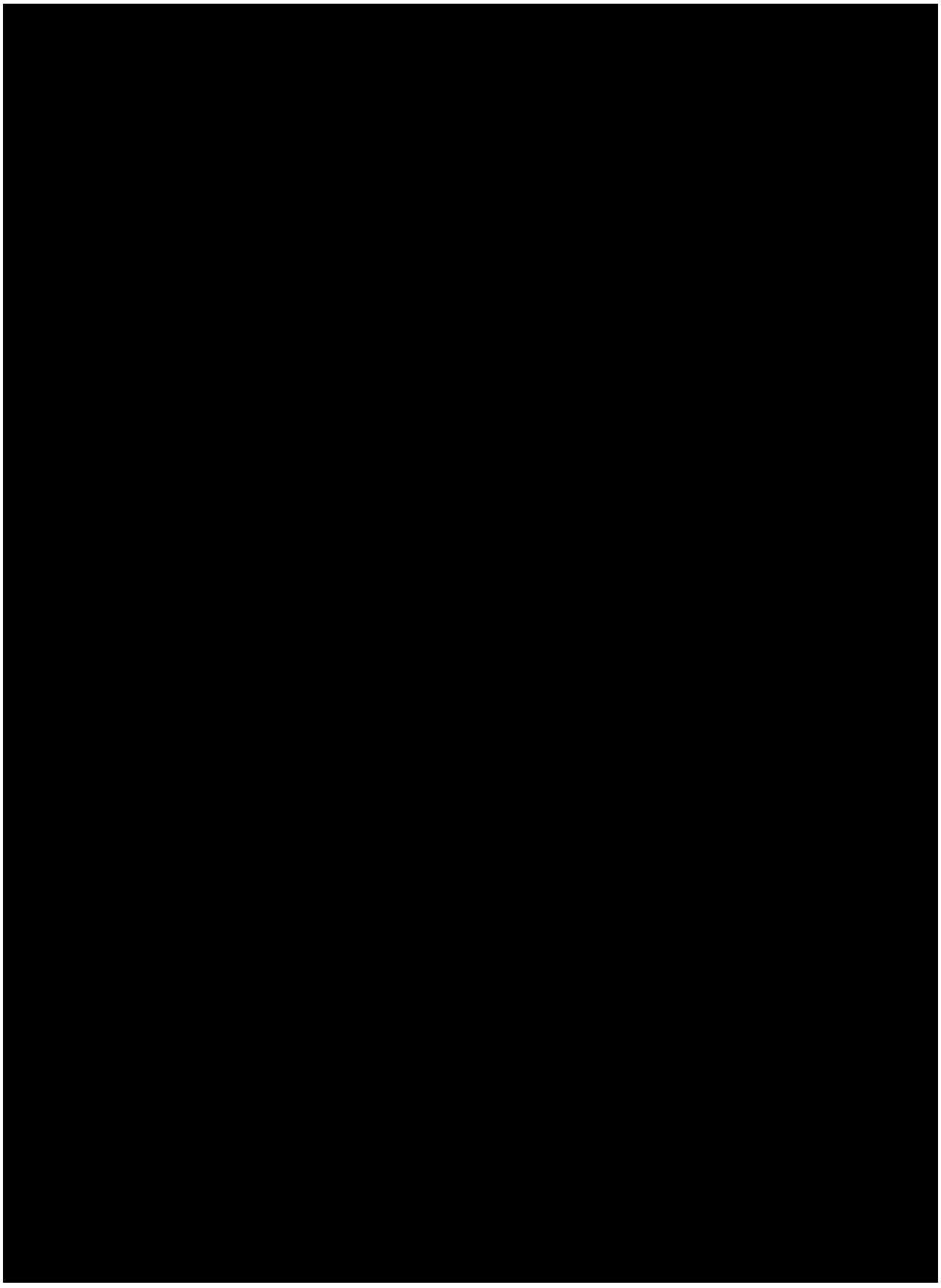
HIT-6 score can be categorized into 4 grades:

- ≤ 49: little or no impact (49 or less)
- 50 - 55: some impact
- 56 - 59: substantial impact
- 60 - 78: severe impact

5.8.3 SF-36v2 scoring

SF-36v2 scores (eight subscores and two component summary scores) will be calculated by the SF-36v2 license owner "Optum".

[redacted]



[redacted]

5.8.5 C-SSRS scoring

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior based on following categories:

Suicidal Ideation

- Cat. 1 - Wish to be dead
- Cat. 2 - Non-specific active suicidal thoughts
- Cat. 3 - Active suicidal ideation with any methods (not plan) without intent or act
- Cat. 4 - Active suicidal ideation with some intent to act, without specific plan
- Cat. 5 - Active suicidal ideation with specific plan and intent

Suicidal behavior

- Cat. 6 - Actual attempt (non-fatal)
- Cat. 7 - Interrupted attempt
- Cat. 8 – Aborted or self-interrupted attempt
- Cat. 9 - Preparatory acts or behavior
- Cat. 10 - Suicide

Any suicidal ideation is identified by answer “yes” to at least one of the 5 suicidal ideation categories (cat. 1-5) for specific visit.

Any suicidal behavior is identified by answer “yes” to at least one of the 5 suicidal behavior categories (cat. 6-10) for specific visit.

Any suicidal ideation or behavior is identified by answer “yes” to at least one of the 10 categories (cat. 1-10) for specific visit.

6 Reference

Not applicable.

7 Approval signatures

This Statistical Analysis Plan was subject to critical review and has been approved after review by:

Dr. [redacted]		
[redacted]	Signature	Date
[redacted]		
HTA [redacted]	Signature	Date
[redacted]		
CRO [redacted]	Signature	Date