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Clinical Trial Protocol 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)

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List of abbreviations

ACE/ARB	Angiotensin-Converting Enzyme inhibitor / Angiotensin-Receptor Blocker
AE	Adverse Event
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ASA	Abbreviated Schedule of Assessments
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical classification
BDI	Beck Depression Inventory
CFR	US Code of Federal Regulations
CGRP	Calcitonin Gene-related Peptide
CPO	Country Pharma Organization
CQA	Compliance Quality Assurance
CRA	Clinical Research Associate
CRF	Case Report/Record Form
CRO	Contract Research Organization
CM	Chronic migraine
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dose Administration Record
DBTE	Double-Blind Treatment Epoch
ECG	Electrocardiogram
EDC	Electronic Data Capture
EM	Episodic Migraine
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
HIT	Headache Impact Test
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICHD	International Classification of Headache Disorders
ID	Identification
IEC	Independent Ethics Committee
IHS	International Headache Society
IMP	Investigational Medicinal Product

IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD/IUS	Intrauterine Device/System
LFT	Liver function test
MAR	Missing at Random
MCS	Mental Component Summary
MedDRA	Medical dictionary for regulatory activities
MMD	Monthly Migraine Days
MMRM	Mixed Model for Repeated Measurements
MNAR	Missing not at Random
NSAID	Non-steroidal antiinflammatory -drug
PCS	Physical Component Summary
PFS	Prefilled syringe
PK/PD	Pharmacokinetic/Pharmacodynamic
PRO	Patient-reported Outcome
PSD	Premature subject discontinuation
PT	Prothrombin Time
q.m.	once a month
QM	Quality Management
RAS	Randomized Analysis Set
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SF-36	Medical Outcome Short Form Health Survey
s.c.	Subcutaneous
SGOT	Serum Glutamic Oxaloacetic Transaminase (Aspartate Aminotransferase)
SGPT	Serum Glutamic Pyruvic Transaminase (Alanine Aminotransferase)
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total Bilirubin
TD	Treatment Discontinuation
[redacted]	[redacted]
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization
WoC	Withdrawal of Consent
γGT	Gamma-Glutamyltransferase

Glossary of terms

Calendar month	A calendar month is the period from a particular date in one month to the same date in the next month.
Cohort	A specific group of patients fulfilling certain criteria
Control-IMP	Drug(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study, which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study, which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), topiramate in the highest tolerated dose/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Test-IMP	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CAMG334ADE01
Title	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)
Brief title	Study of tolerability, safety and efficacy of 70 mg and 140 mg erenumab against topiramate in the highest tolerated dose in patients with ≥4migraine days/month, who must be either naïve or not suitable for or could have failed up to three prophylactic treatments
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the safety and efficacy of 70 mg and 140 mg 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 previously failed up to three prophylactic migraine treatments out of: propranolol/metoprolol, flunarizine and amitriptyline. Data from this study, in addition to data from the pivotal trial program, will provide important data for clinicians treating migraine patients. In addition, this data will also be used to support national health technology assessments (HTAs).
Primary Objective	The primary objective of this study is to demonstrate the tolerability of 70 mg and 140 mg erenumab compared to topiramate in the highest tolerated dose as assessed by the rate of patients discontinuing treatment due to AE during the double-blind epoch of the study.
Secondary Objectives	To evaluate the effect of 70 mg and140 mg erenumab compared to topiramate in the highest tolerated dose on the proportion of patients with at least a 50% reduction from baseline in monthly migraine days
Study design	This study has a 24-week 2-arm, double-blind, double-dummy randomized, parallel-group treatment design
Population	The patient population will be comprised of 700 male and female migraine patients between the ages of 18 and 65, inclusive.
Key Inclusion criteria	- Documented history of migraine (with or without aura) for ≥12 months prior to screening according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3) - ≥4 migraine days per month (based on ICHD-3 criteria) during baseline confirmed by eDiary - Patients must be either naïve or not suitable for or have failed up to three prophylactic treatments out of: o propranolol, metoprolol, o amitriptyline, o flunarizine
Key Exclusion criteria	- Older than 50 years of age at migraine onset - Unable to differentiate migraine from other headaches - History of cluster headache or hemiplegic migraine headache - Patients who have already been treated with topiramate, valproate or onabotulinumtoxin A

	- Any previous use of a prophylactic migraine medication targeting the CGRP pathway - Use of a prophylactic migraine medication within 5 half-lives, or a device or procedure within 1 month prior to the start of the baseline phase or during the baseline phase - Use of the following for any indication in the 1 month prior to the start of the baseline phase or during the baseline phase: o opioid- or butalbital-containing analgesics ≥4 days/month
Study treatment	Erenumab 70 mg and 140 mg / topiramate in the highest tolerated dose (50 mg – 100 mg)
Efficacy assessments	- Migraine days/month
Key safety assessments	- AE-related treatment discontinuations - Adverse event monitoring - Physical exams and vital signs - Monitoring of laboratory markers in blood
Other assessments	Patient-reported outcomes: HIT-6, SF-36 v2; [redacted]
Data analysis	The primary analysis will be performed comparing treatments with respect to the primary variable in a logistic regression model with the factors treatment and stratification factor (migraine days during the baseline epoch). The odds ratio and its 95% confidence interval (CI) and p-value will be given. The null hypothesis of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor "treatment" is <0.05; however, superiority of erenumab will be claimed only if the odds of treatment discontinuation are lower under erenumab compared to topiramate. The secondary variable will be analyzed by logistic regression model for treatment comparison at end of the DBTE with missing data being imputed as non-response (non-responder imputation)..
Key words	Episodic migraine, chronic migraine, treatment failure, monoclonal antibody, CGRP, Calcitonin Gene-related Peptide

Amendment 1

The original protocol is being amended to implement a further safety procedure in line with the topiramate SmPC and to adjust the safety follow-up period considering the EU approval of erenumab. Furthermore, changes have been introduced to correct and clarify certain criteria and procedures in the protocol.

Changes to the protocol

- A one week taper off phase for Topiramate has been implemented to provide further safety for patients and align with the Topiramate SmPC. Patients taking a daily dose of 75 mg or 100 mg topiramate during the DBTE have to 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 and double-blinding is maintained during taper off phase. (Chapters: 3.1; 5; 5.5.4; 5.6.1; 5.6.2)
- The Safety follow-up epoch has been adjusted from 12 to 4 weeks. During safety follow-up patients are only allowed to use rescue treatments including acute migraine medication and non-pharmacological treatments. As both IMPs, erenumab and topiramate, are approved for migraine prophylaxis and require no safety follow up according to the SmPCs, we adjusted the safety follow-up epoch from 12 to 4 weeks in order to provide patients faster access to pharmacological migraine prophylaxes following the clinical trial. (Chapters: 3.1; 5.6.1; 5.6.2; Figure 3-1; Tables 6-1 an 6-2)
- **5.6.2** has been updated to clarify visit schedule, tapering off and safety follow-up after early discontinuation of study medication
- Footnotes of the assesment schedules (Table 6-1 and 6-2) have been updated and corrected to clarify safety follow-up procedures as described in chapter 5.6.2
- Visit intervals during visit 102 to 107 were reduced from 7 +/- 2 days to 7 +/- 1 day as topiramate blisters do only contain one extra pill (+ 1 day) during this epoch (chapter 6). Additionally, it was clarified that visit intervals refer to visit 101.
- Patient initials were removed from the ECG tracing labeling list (chapter 6.5.5).
- Information about patient stratification have been added to chapter 5.3.
- Medical history and adverse events terms have been updated to clarify database management (chapter 8.3).
- Minor changes to correct formatting errors within the document were also made.

A copy of this amended protocol will be sent to the Institutional Review Board(IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amendment require IRB/IEC and Health Authorities approval prior to implementation.

Amendment 2

[redacted]

Changes to the protocol

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- In line with the Erenumab SmPC, the investigational product should be stored at room temperature for 30 minutes prior to the administration in order to reduce irritation at the injection site (Chapter 5.5.4).
- [redacted]

1 Introduction

1.1 Background

Migraine is one of the most common neurological disorders with a high global prevalence, significant socio-economic burden and substantial impairment and disability of affected patients. It is mainly characterized by recurrent headache lasting 4 to 72 hours, which is usually accompanied by other neurological disturbances, nausea, vomiting or other nonspecific symptoms. The patient burden and disability as well as the societal impact increase with higher attack frequency. The spectrum of migraine disorders is typically differentiated according to the frequency of migraine days per month. “Episodic migraine” (EM) is characterized by the presence of 4 to 14 migraine days per months, while “Chronic migraine” (CM) is defined as 15 or more headache days per months including at least 8 typical migraine days.

Migraineurs are currently being treated for migraine prophylaxis by a variety of drug classes. Common prophylactic drugs or drug classes include beta blockers, topiramate, valproate, antidepressants (mainly amitriptyline), flunarizine, and certain angiotensin-converting-enzyme inhibitor / angiotensin II receptor blockers (ACE/ARBs) such as lisinopril and candesartan. Botulinum toxin (Botox®) is approved in most EU countries for use in CM but not for EM. Evidence for the use of these therapies in migraine is limited and many are used off-label. Amongst current prophylactic therapies for patient suffering from episodic migraine, topiramate has the broadest evidence regarding efficacy and safety. Its efficacy has been verified by several studies and it is considered efficacious in migraine treatment (Silberstein 2017). German migraine guidelines list topiramate amongst the prophylactic drugs of first choice (DGN 2018). However, the standard of care varies significantly across different regions. A general consensus on treatment recommendations does not exist and treatment decisions are often made on a case-by-case basis.

Overall, current migraine prophylactic drugs show variable efficacy and are associated with poor tolerability, often leading to discontinuation (Blumenfeld 2013). For example in a recent claims database analysis in chronic migraine, one year persistence to oral prophylactic drugs, irrespective of class, was as low as 13-16% (Hepp 2016), indicating a high unmet medical need for new therapies. Based on emerging evidence, Calcitonin Gene-related Peptide (CGRP) is a neuropeptide that prominently contributes to migraine pathophysiology. The potential mechanisms of action of CGRP receptor antagonists involve components of the trigeminal-vascular system and include normalization of CGRP-induced vasodilation, reduction of CGRP-induced neurogenic inflammation, and inhibition of pain transmission at the trigeminal ganglion and trigeminal nucleus (Wang 1995, Zimmermann 1996, Durham 2006). CGRP is an attractive target for the development of a migraine-specific prophylactic therapy with the aim of minimizing migraine days and improving patient quality of life in this common and often disabling disorder. Erenumab is a fully human monoclonal antibody targeting the CGRP receptor, which has already obtained marketing authorization in the EU.

To date studies have been or are currently being conducted in North America, Europe, and Asia. Results from the erenumab phase 2 study (study 20120178) in patients with episodic migraine demonstrated that the 70 mg dose resulted in statistically significant and clinically meaningful reductions in monthly migraine days at Week 12 compared with placebo. The 70 mg dose produced statistically significant improvements in multiple secondary and exploratory outcome

measures, including the 50% responder rate, monthly headache days, and monthly migraine-specific medication treatment days.

Final results from the erenumab phase 2 study (study 20120295) in patients with chronic migraine showed a positive outcome. Patients randomized to the 70 mg and 140 mg dose groups experienced a mean 6.6-day reduction from baseline in monthly migraine days during Weeks 9 –12 in both groups. The results were statistically significant compared with 4.2 days observed in the placebo group The 50% responder rate was increased to 39.9% and 41.2% with 70 mg and 140 mg erenumab, respectively, compared to 23.5% with placebo (Tepper 2017). For patients having already failed one or more prophylactic pharmacotherapy treatment with erenumab resulted in an even higher proportion of at least 50% responders in MMD reduction (40.8% for 140 mg, 34.7% for 70 mg versus 17.3% for placebo). Another analysis of data from the STRIVE study (study 2012096 see below) which assessed EM at doses of 70 mg and 140 mg [10] showed that patients that failed at least 2 prior prophylactic also even had a greater benefit versus placebo and even more from the 140 mg dose.For the > 50% MMD reduction endpoint, the results showed that the OR was 2.9-fold greater than placebo at 70 mg compared to placebo, while 140 mg demonstrated a 4.5-fold greater effect than placebo (Goadsby 2017b). In addition, there are no dose-dependent differences in the safety profile from the available data in the STRIVE study. For doses of 70 mg and 140 mg, the rate of adverse events is similar to what was seen with placebo (Goadsby 2017a).

The results from three recently completed phase 3 studies against placebo (studies 20120296 STRIVE 70 and 140 mg, 20120297 ARISE, 70 mg, and CAMG334A2301 LIBERTY, 140 mg) in patients with episodic migraine also showed positive outcomes for erenumab.

In ARISE (study 20120297), patients randomized to the 70 mg dose group experienced a 2.9-day reduction from baseline in monthly migraine days compared with 1.8 days observed in the placebo group with the difference being statistically significant (Dodick 2018). In STRIVE (study 20120296), patients randomized to the 70 mg and 140 mg dose groups experienced mean 3.2 and 3.7-day reductions from baseline, respectively, compared with 1.8 days observed in the placebo group over weeks 13-24 (statistically significant versus placebo). Another analysis of data from this study shows that patients with a previous treatment failure on at least 2 prophylactics benefit particularly from the higher dosage (Goadsby 2017a). For the ≥ 50% MMD reduction endpoint, the results showed that OR was 2.9-fold greater than placebo at 70 mg compared to placebo, while 140 mg demonstrated a 4.5-fold greater effect than placebo (Goadsby 2017b). LIBERTY, study CAMG334A2301, confirmed the efficacy and safety of 140 mg erenumab in a difficult to treat population with 2-4 prior preventive migraine treatment failures. The proportion of patients achieving ≥50% reduction in MMD was significantly increased in erenumabtreated patients compared to placebo (30.3% vs 13.7%) meeting the primary endpoint. Additionally, all secondary endpoints were met and significant effects of erenumab over placebo were observed as early as week 4 (Reuter 2018).

The safety and tolerability profile of erenumab was similar to placebo in both treatment groups for all studies. Most commonly reported AEs (≥3% in any group) included nasopharyngitis, fatigue, headache, back pain and influenza. There were no clinically significant changes in laboratory values, vital signs and electrocardiograms. The overall safety and tolerability profile is similar to placebo for both doses across the phase 2 and 3 study

program, so that to date no clinical significant dose related tolerability concerns arose (Goadsby 2017a, Dodick 2018, Reuter 2018)

In the absence of a clear dose-dependent safety signal, a comparable overall efficacy trend between 70 mg and 140 mg erenumab with a proven efficacy of 140 mg erenumab in patients with 2-4 prior preventive migraine treatment failures, both dose groups (70 mg and 140 mg) are considered to offer an optimal benefit-risk ratio for the chosen patient population with certain patients obtaining an additional benefit from the 140 mg dose. CGRP targeting in migraine represents a new and specific approach in migraine therapy. Until now, no active comparator studies were conducted in the pivotal CGRP program. In view of the adherence issues with current standard of care (SoC) therapies prompted by poor tolerability and/or lack of efficacy (Hepp 2014), an important question is whether this new approach can provide additional benefit that leads to improved persistence and sustained efficacy for migraine patients over SoC therapies. This study was designed to elucidate the possible benefits of a targeted migraine therapy in comparison to current SoC prophylactic treatment.

1.2 Purpose

The purpose of this study is to determine the safety and efficacy of erenumabcompared 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. Data from this study will provide important data for clinicians treating migraine patients as particularly in comparison to current treatment options. In addition, this data will also be used to support national health technology assessments (HTAs) and reimbursement negotiations.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Objective	Endpoint
Primary To demonstrate the tolerability of 70 mg and 140 mg erenumab compared to topiramate in the highest tolerated dose 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.

Objective	Endpoint
Secondary: To evaluate the effect of erenumab compared to topiramate in the highest tolerated dose 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 70 mg and 140 mg erenumab compared to topiramate in the highest tolerated dose on functional impairment, as measured by the Headache Impact Test (HIT-6)	HIT-6 at week 24
To evaluate the effect of 70 mg and 140 mg erenumab compared to topiramate in the highest tolerated dose on generic health-related quality of life, as measured by the Short Form-36 (SF-36 v. 2)	SF-36 quality of life at week 24
[redacted]	

3 Investigational plan

3.1 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. Patients will be stratified to into groups according to their number of migraine days during the baseline epoch.

The following epochs are included in the study design:

- **Screening Epoch (0 – 2 weeks) –** Required for all patients to assess initial eligibility.
- **Baseline Epoch (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.
- **Double-blind, double-dummy Treatment Epoch (DBTE, 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 (see 5.5.4).

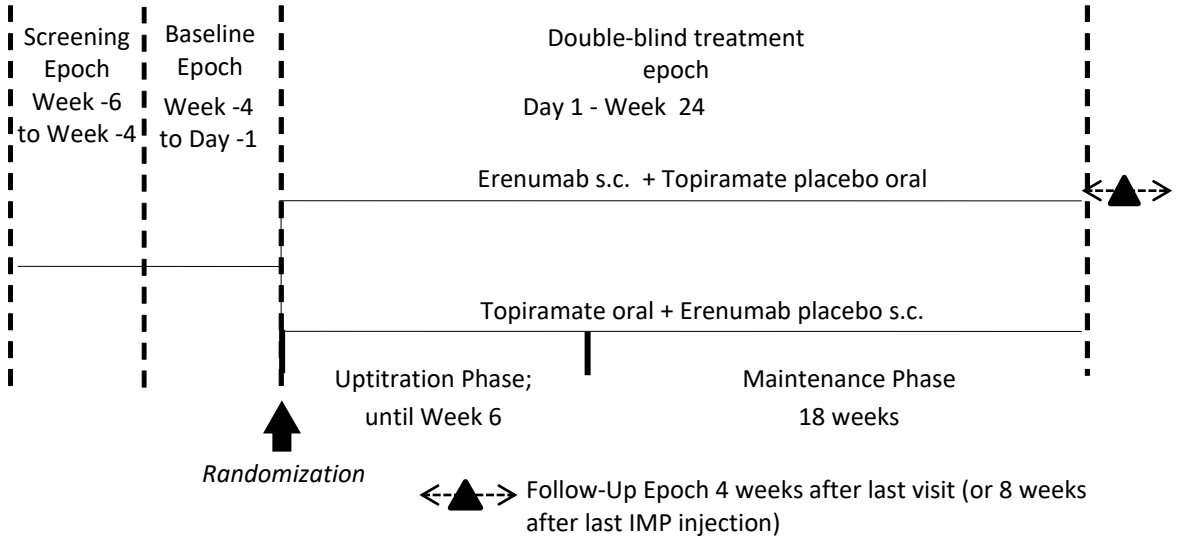
  Dose reduction of topiramate and erenumab is not allowed during DBTE (Visit 101-199). After visit 199 or if the patient discontinues study drug, a one week double-blind taper off phase will follow to ensure proper down titration for topiramate.

  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 3-1 Study design



3.2 Rationale for study design

The study design was developed in accordance with the International Headache Society (IHS) guidelines for Controlled Trials of Drugs in Migraine (Tfelt-Hansen 2012), including input from leading clinical migraine experts. A parallel-group, double-blind design is a standard way of assessing efficacy and safety of new agents. Topiramate will be used as comparator in this trial, it will be applied according to current SmPC, starting with an uptitration phase to 100 mg/day. erenumab, a novel antibody therapy for the prophylaxis of migraine in patients with ≥4 migraine days/month recently approved by the European Commission, is administered according to current product information. Current migraine prophylactic treatments have been initially developed for other indications. They are variably effective regarding migraine treatment, however, patients often suffer from severe side effects. Hence, the discontinuation rates for approved migraine treatments are high. As lack of tolerability is described as the biggest problem of current prophylactic migraine treatments leading to an inability to sustain efficacy for a chronic disorder, superiority regarding tolerability displayed by treatment discontinuation rate due to AE has been chosen as primary endpoint.

The specifics of population and treatment requirements were designed based on feedback from clinical experts and consultations with national HTA body (G-BA).

3.3 Rationale for dose/regimen, route of administration and duration of treatment

Phase 2 results for erenumab in EM patients are currently available for the doses of 7 mg and 21 mg (both of which have proven to be ineffective compared to placebo) and 70 mg, which has been shown to be effective. PK-exposure response modelling suggests that with higher doses, a potential additional benefit in terms of efficacy might be observed. The safety profile of erenumab has been investigated up to 280 mg in healthy volunteers in Phase 1 without a

difference in safety profile. For these reasons, an additional dose of 140 mg was introduced into the CM Phase 2b trial as well as one of the Phase 3a trials for EM.

Results from the EM Phase 3 trials and the CM Phase 2b trial showed a significant effect compared to placebo across the primary endpoint and the vast majority of secondary and exploratory endpoints. The safety and tolerability profile of erenumab was similar to placebo in both treatment groups. In addition, the 140 mg dose in EM study 20120296 and in the CM 20120295 study showed consistently stronger improvement compared to the 70 mg dose across patients with one or more prior prophylactic migraine treatment failures, suggesting an additional efficacy in this subpopulation of patients with episodic and chronic migraine with the higher dose. Additionally, data from the Phase 3b study CAMG334A2301 confirmed the efficacy and safety of 140 mg erenumab in a difficult to treat EM population with 2-4 prior prophylactic migraine treatment failures compared to placebo (Reuter 2018).

To ensure treatment according to current product information, both doses (70 mg and 140 mg) were selected for this study. 70 mg or 140 mg can selected as starting dose at the choice of the investigator and also, dose escalation from 70 mg to 140 mg is allowed during the study, at the discretion of the investigator.

This study features a double-blind, double-dummy approach. Patients will receive either erenumab 70 mg or 140 mg q.m. subcutaneously + topiramate placebo orally or topiramate orally + erenumab placebo subcutaneously for 24 weeks in the double-blind treatment epoch. The maximally tolerated topiramate dose will be determined throughout the 6 week uptitration phase. Within this phase the dose is increased weekly by 25 mg increments and must aim to reach 100 mg/day as recommended by the German SmPC. Patients may maintain a dose for longer than one week if deemed necessary but must reach at least 50 mg/day within the uptitration phase in order to enter the maintenance phase. Thus, the recommended dose to enter the maintenance phase is 100 mg/day but may also be 75 mg/day or 50 mg/day for individual patients in accordance with the product information. Topiramate dose has to be maintained during the 18 week maintenance phase and down titration is not allowed till end of DBTE. As 200 mg is not likely to improve response but in contrast can add to tolerability issues (Silberstein 2017), this dose will not be included in this trial. For 50 mg, 75 mg and 100 mg dose, patients will have to take two tablets a day, one in the morning, one in the evening. The erenumab dose will be determined for each patient individually by the investigator in accordance with the product information.

3.4 Rationale for choice of comparator

The choice of a specific therapy for a migraine headache prophylaxis often takes into account individual circumstances, comorbidities and patient preferences. Patients are currently being treated by a variety of drug classes that were originally developed for other indications, but were repurposed for migraine prophylaxis. In Germany approved prophylactic drugs for episodic migraine are propranolol, metoprolol, topiramate, amitriptyline and flunarizine.

Amongst current prophylactic therapies for patient suffering from episodic migraine, topiramate has the broadest evidence regarding efficacy and safety. Its efficacy has been verified in several RCTs and it is considered an efficacious drug in migraine treatment (Silberstein 2017). Also,

German migraine treatment guidelines list topiramate amongst the prophylactic drugs of first choice (DGN 2018). Therefore, topiramate is a reasonable comparator choice, which is considered to provide patients with an adequate prophylactic treatment for their migraine. Topiramate dose will be determined, in accordance to current topiramate SmPC, during a 6 week titration phase. During the following 18 week maintenance phase, patients may stay on the dose they were maximally titrated to of either 50 mg, 75 mg or 100 mg topiramate.

All patients continue to receive best supportive care in form of acute medications and other non-pharmacological interventions as appropriate.

3.5 Purpose and timing of interim analyses/design adaptations

The primary analysis will occur when the last patient completes the double-Blind Epoch (V199/V199-ASA), prior to the Follow-Up Epoch. A study report will be prepared and finalized for the double-Blind Epoch, and a second study report will be prepared incorporating data from the Follow-Up Epochs after all patients have completed their respective last visit (LPLV; V201/V201-ASA).

3.6 Risks and benefits

Erenumab is being developed for migraine prophylaxis in a large clinical development program including more than 3.000 patients and has shown efficacy across the migraine spectrum. Key risks and benefits are briefly summarized below. For further information, please refer to the most recent Investigator Brochure.
There were no significant findings in the toxicology studies with erenumab that would predict a risk to human patients. There were no significant effects on electrocardiogram (ECG) parameters, blood pressure or respiration rate in the single dose cardiovascular study in cynomolgus monkeys.

Safety results from studies (studies 20120178, 20120295, 20120296 and 20120297, and CAMG334A2301) indicate that the frequency of treatment-emergent adverse events (AEs) and discontinuations due to AE were similar between erenumab and placebo. Overall, there was no apparent dose-dependency in the incidence of AEs. Most treatment-emergent adverse events were grade 1 or 2 based on the Common Terminology Criteria for Adverse Events (CTCAE). Most commonly reported AEs (≥3% in any group) included nasopharyngitis, fatigue, headache, back pain and influenza. There were no clinically significant changes in laboratory values, vital signs and electrocardiograms.

As of 31 January 2018 an estimated 4298 subjects (3576.67 subject-years) have been exposed to erenumab in clinical trials conducted by Amgen and Novartis since the beginning of the development program. The integrated safety data set comprised 2537 subjects with migraine, representing 2310.3 SY of exposure.

A theoretical cardiovascular safety risk with CGRP receptor blockade is lack of compensatory vasodilation, particularly in the context of the coronary circulation during ischemic-related conditions. Overall, to date, there is no evidence from nonclinical and clinical data of risk of cardiovascular effects. However, based on the theoretical basis of the mechanism of action of erenumab, cardiovascular effects continue to be monitored in clinical trials.

Plasma levels of CGRP increase with advancement of pregnancy up to the time of delivery, followed by a sharp decline at term and postpartum in rats and humans. Endogenous CGRP may play an important role in maintaining normal fetoplacental development, fetal survival, and vascular adaptation during pregnancy. Women who are breastfeeding, pregnant, or planning to become pregnant are excluded from study participation, as well as patients who are unwilling to comply with the protocol-specified contraception requirements. All women of child-bearing potential will be screened for pregnancy at each study visit.

Adverse reactions for erenumab are generally mild in nature and include injection site reactions, constipation, muscle spasm and pruritus (common frequency, ≥1/100 to <1/10). Injection Site Reactions includes multiple preferred terms, such as injection site pain and injection site erythema. Pruritus includes preferred terms of generalized pruritus, pruritus, and pruritic rash. The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and use of rescue medications.

Current migraine prophylaxis treatments are often accompanied by lack of efficacy or tolerability issues (Blumenfeld 2013). Commonly reported adverse events of topiramate are parasthesia, fatigue, memory/cognitive disturbances and mood problems (Topiramate TEVA 25 mg SmPC 2015, Topiramate TEVA 50 mg SmPC 2015). Other approved prophylactic medications such as propranolol or amitriptyline also face tolerability concerns (Hepp 2014). Currently there is a high unmet need for a therapy that is well-tolerated, has sustained response rates and excellent compliance.

4 Population

The study population will consist of male and female patients, ages 18 – 65, with a documented history of episodic migraine (4 – 14 baseline migraine days) or chronic migraine (≥15 baseline headache days), who are naïve to or not suitable for or have failed up to three previous prophylactic treatments out of: metoprolol/propranolol, amitriptyline, flunarizine due to lack of efficacy or tolerability. See inclusion criteria 6 for detailed definitions.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria. For inclusion purposes, one month equals one full calendar month.

<u>During the Screening Epoch:</u>

1. Patient is capable of understanding the nature, significance and implications of the clinical trial .Written informed consent must be obtained before any assessment is performed
2. Adults ≥18 to ≤65 years of age upon entry into screening
3. Documented history of migraine (with or without aura) for ≥12 months prior to screening according to the International Classification of Headache Disorders-3rd Edition (ICHD-3)

4. ≥4 migraine days per month (in at least two separate attacks) (based on ICHD-3 criteria) on average across the last 3 fully completed calendar months prior to screening based on retrospective reporting
5.
6. Patients must be either naïve *or* not suitable for *or* could have failed up to three prophylactic treatments out of:
    - propranolol/metoprolol, amitriptyline, flunarizine
7. Patients on non-pharmacologic treatments (e.g., biofeedback, psychotherapy or other locally accepted and endorsed interventions for migraine) must have been stable on this treatment for at least 3 months prior to baseline

* The following definitions are applicable for inclusion criteria 6:

- Efficacy failure is defined as "no meaningful reduction in headache frequency after administration of the respective medication for an adequate period of time (at least 2 – 3 months are recommended by the European Headache Federation treatment guidelines) at generally accepted therapeutic dose(s) based on the investigator's assessment within the last 5 years prior to screening."
- Tolerability failure is defined as "documented discontinuation due to adverse events of the respective medication at any previous time."
- "Not suitable" for the purpose of this study is defined as "patient is not considered to be suitable for the treatment for medical reasons such as contraindications or precautions included in local labels, national guidelines or other locally binding documents" as confirmed by the treating physician.

<u>During the Baseline Epoch:</u>

8. Migraine frequency of ≥4 days during the Baseline Epoch, confirmed by the eDiary
9. ≥80% eDiary compliance during the Baseline Epoch

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients. Calendar months are used for exclusion purposes.

1. Older than 50 years of age at migraine onset
2. Unable to differentiate migraine from other headaches
3. History of cluster headache or hemiplegic migraine headache
4. Patients who have already been treated with topiramate, valproate or onabotulinumtoxin A
5. Use of a prophylactic migraine medication within 5 half-lives, or a device or procedure within one month prior to the start of the baseline phase or during the baseline phase
6. Use of the following for any indication in the 1 month prior to the start of the baseline phase or during the baseline phase:

- Opioid- or butalbital-containing analgesics ≥4 days/month

7. Anticipated to require any excluded medication (see Section 5.5.8, Table 5-1), device or procedure (e.g., occipital nerve stimulators, transcranial magnetic stimulation,) during the study
8. Active chronic pain syndromes (e.g., fibromyalgia or chronic pelvic pain)
9. History or current evidence of major psychiatric disorder (such as schizophrenia, bipolar disorder or type B personality disorder that might interfere with the ability to properly report clinical outcomes)
10. Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records or patient self-report
11. Current evidence of depression based on a BDI-II total score of >19 at screening. Patients with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable and are taking no more than one medication per disorder. Patients must have been on a stable dose within the 3 months prior to the start of the baseline phase
12. History of seizure disorder or other significant neurological conditions other than migraine
13. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale (C-SSRS), if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years
14. Myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedures within 12 months prior to screening
15. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study
16. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
17. Hepatic disease by history or total bilirubin ≥2×ULN or ALT or AST ≥3xULN as assessed by central laboratory at initial screening
18. Pregnant or nursing (lactating) women
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 110 days after stopping of study medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient and should have received medical assessment of surgical success.
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), e.g. hormone vaginal ring or transdermal hormone contraception
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

20. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
21. History of hypersensitivity to the study drug or its excipients (including topiramate) or latex.
22. Patients not suitable for treatment with topiramate according to topiramate SmpC. Conditions listed under 4.4 Warnings and precautions in topiramate SmPC (e.g., risk of/history of nephrolithiasis, decreased renal function, risk of/history of eye disorders, risk of/history of metabolic acidosis) could be deemed as exclusion criterion at discretion of the investigator.
23. Any prior exposure to (investigational) prophylactic migraine products targeting the CGRP pathway, including previous erenumab studies.
24. Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (e.g., independent completion of electronic diary items) to the best of the patient's and investigator's knowledge
25. Patients who may be dependent on the sponsor or investigator
26. Patient has not been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities,

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

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

Verum:

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.

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 50mg 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

5.1.2 Additional treatment

No additional treatment beyond test-IMP and control-IMP and matching placebos is included in this trial.

5.2 Treatment arms

Patients will be assigned to either erenumab or topiramate at the Randomization Visit (Visit 101), in a 1:1 ratio,

5.3 Treatment assignment and randomization

At visit 101 all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the two treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first packages of study drug to be dispensed to the patient. Randomization will be stratified by monthly migraine frequency. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers stratified by monthly migraine frequency (4-7 migraine days per month during the Baseline Epoch vs 8-14 migraine days per month during the Baseline Epoch vs ≥15 migraine days per month during the Baseline Epoch). These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and Novartis personnel and their delegates will remain blinded to the identity of the treatment from the time of randomization until the conclusion of the double-blind treatment epoch and primary analysis.

Following methods will be used: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the randomization office, (2) the identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9). Randomization information will be available to the investigator when the study report has been finalized.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified by a subject number which is composed by the site number assigned by Novartis (4 digits) and a sequential number (3 digits) assigned by the investigator. Once assigned to a patient, the subject number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The first patient is assigned patient number 001, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 002, the third patient is assigned patient number 003). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the eCRF with a matching subject number from the EDC system to enter data. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography eCRF should also be completed.

Investigators may re-screen a patient if there is reasonable certainty that reasons for screening failure will be resolved prior to or during a repeat screening attempt. Should this occur, the site should re-consent the patient and assign a new subject identification number.

Some examples of re-screening reasons are listed below. If needed, questions regarding re-screening eligibility may be discussed with Novartis.

- Laboratory value(s) out of range due to sampling error or that might be within range after medically-appropriate supplementation. (Note: Before screen failing and then re-screening the subject, efforts should be made to repeat the laboratory assessment(s) during the original initial screening phase.)
- The patient has a medical condition that can be stabilized or resolved prior to the repeat screening attempt.

Only one re-screening is allowed per patient. Patients who had <4 monthly migraine days during Baseline Phase cannot be re-screened.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will comply with the legal requirements and be printed in German. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging for every study visit and at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator, supported by the Novartis monitoring team, will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

The investigational product dose is either 70 mg or 140 mg depending on the investigators decision, which has to be made for each patient individually and in accordance with the product information: the recommended dose is 70 mg, some patients may benefit from 140 mg (see Section 5.1 of AIMOVIG® SmpC).

In case of insufficient response, the dose may be escalated from 70 mg to 140 mg. Possible reasons for uptitration could be, but are not limited to:

- insufficient response as deemed by physician and/or patient
- reduction of acute medication use not satisfactory
- insufficient improvement in life quality

An adjustment of the 70 mg dose to 140 mg can be performed at any time during the DBTE. The investigational product dose of 140 mg must not be changed once a patient received the dose during DBTE.

Reference treatment doses are determined during the uptitration phase and must aim to reach the recommended daily treatment dose of 100 mg topiramate in accordance to the German SmPC. The reference treatment dose established during the up titration phase must not be changed during the 18-week maintenance phase.

There are no temporal restrictions for the investigational or the reference treatment (e.g., proximity to meals, sleep or activity).

Test-IMP:

70 mg and 140 mg erenumab or respective placebos will be administered by qualified study staff at each dosing visit during the 24 week double-blind treatment epoch (i.e., at Day 1 and Week 4, Week 8, Week 12, Week 16 and Week 20). Subcutaneous (s.c.) injections are to be given for each investigational product administration. For purposes of study treatment dosing, "q.m." refers to an every 4 weeks injection regimen. The study drug administration date should be in 4 week increments (+/ – 4 days) from the first dose of study drug. Any dose administrations that may occur greater than +/ – 4 days from the 4 week time point (e.g., patient unavailability) should be discussed with the Sponsor prior to dosing. The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen; the location of the injection site should be documented in the source document. In order to reduce irritation at the injection site, the investigational product should be stored at room temperature for 30 minutes prior to the administration.

Control-IMP:

Topiramate and oral placebo will be administered by the patient himself. During the first week of the titration phase topiramate 25 mg or matching placebo will be administered once daily. After the first week, topiramate titration will be done according to the SmPC in 25 mg increments each week and must aim to reach the recommended daily treatment dose of 100 mg (50/75/100 mg). Topiramate 50/75/100 mg or matching placebo will be administered twice daily during titration phase and maintenance phase. The physician may decide to allow the patient to remain on this dose for another week if there are tolerability concerns. If a patient is not deemed suitable for uptitration during the 6 weeks titration period, the patient may remain on highest tolerated dose throughout the trial. Minimal dose to enter maintenance phase has to be 50 mg, patients not tolerating 50 mg topiramate have to be taken off prophylactic study treatment, but maintain in study on supportive care. Maximal dose for topiramate is 100 mg.

Downtitration is not allowed in this trial. Patients who discontinue study treatment or complete the study with a daily dose of 75 mg or 100 mg topiramate should taper off topiramate for one week with a daily dose of topiramate reduced by 50 mg.

Titration phase (week 1 till end of week 6) (according to current topiramate product information)

Titration of topiramate has to be made in 25 mg increments each week and must aim to reach the recommended migraine treatment dose of 100 mg in accordance to the SmPC. If a patient initially cannot tolerate the next dose step, he may stay on the current dose for another week. However, at the end of the 6 week titration phase, patients must reach at least the 50 mg topiramate dose to maintain in the DBTE.

Exemplatory titration scheme:

Week 1: 25 mg topiramate (= 1x 25 mg /day in the evening)

Week 2 : If patient tolerates 25 mg topiramate--> uptitration to 50 mg topiramate (2x 25 mg/day)

Week 3: If patient tolerates 50 mg topiramate --> uptitration to 75 mg topiramate (25 mg and 50 mg, each 1x/day) (=75 mg topiramate/day)

Week 4: If patient tolerates 75 mg --> uptitration to 100 mg topiramate (2x 50 mg/day)

Week 5 and 6: further uptitration to next dose for patients who had to prolong titration during weeks 1 – 4 due to initial poor tolerability.

Starting with week 7, patient has to take a stable dose (50 mg, 75 mg or 100 mg topiramate).

Patients who are not able to tolerate 50 mg have to be discontinued from drug, but should remain in the trial for documentation purposes. During this time, patients may use treatments described under 5.5.6 for their acute migraine attacks.

Maintenance phase (start of week 7 to end of week 24):

Control-IMP doses are determined during the uptitration phase and must not be changed during the 18-week maintenance phase. Patients have to remain on their highest tolerated dose (50 mg, 75 mg or 100 mg topiramate) throughout maintenance phase. If a patient cannot tolerate dose during maintenance phase, he/she has to be discontinued from all study treatment, but should remain in the trial. This patient is allowed to continue using rescue medication as described under 5.5.6.

All kits of study treatment assigned will be recorded in the IRT. Novartis monitors will reconcile treatment assigned vs treatment administered and ensure that the information is congruent during their monitoring visits.

Tapering off

Control-IMP should be tapered off by patients who complete the study (Visit 199, end of week 24) or discontinue study treatment after receiving a daily dose of 75 mg or 100 mg Control-IMP. Tapering off is performed by reducing the daily dose of Control-IMP by 50 mg for one week before a patient stops taking the drug.

Exemplatory Tapering off scheme:

Patient on 100 mg/day topiramate --> One week 50 mg/day topiramate --> No more medication

Patient on 75 mg/day topiramate --> One week 25 mg/day topiramate --> No more medication

Patient on 50 mg/day topiramate --> No more medication (no tapering off required)

Patient on 25 mg/day topiramate --> No more medication (no tapering off required)

5.5.5 Permitted dose adjustments and interruptions of study treatment

Control-IMP dose adjustments are allowed during the 6-week up titration phase only and must be kept stable during the 18-week maintenance phase. Investigational treatment dose adjustments from 70 mg to 140 mg can be made throughout the whole trial. Titration for topiramate and for erenumab 70 mg to 140 mg can be done independently. Interruptions are allowed as specified in Section 5.5.9. Additionally, investigator-initiated interruptions will be considered on a case-by-case basis.

5.5.6 Rescue treatments

Patients can continue to use acute migraine medication and non-pharmacological interventions as rescue treatments. These may include both pharmacologic interventions (i.e., treatments for acute attacks such as triptans and NSAID) and non-pharmacologic treatments (e.g., biofeedback, psychotherapy or other locally accepted and endorsed interventions for migraine). Non-pharmacological treatment options may only be used as rescue therapy, if patient has been stable on the specific non-pharmacological treatment 3 months prior to baseline.

Patients discontinued from study drug may only use rescue treatments for their migraine attacks as described above.

Site staff will pre-specify the name, dose strength, and route of administration of the patient's acute headache (rescue) medications in the patient's eDiary. If the patient takes an acute headache medication during aura or to treat a migraine or non-migraine headache, they will select one of the pre-specified medications (or "other" medication) and enter the date of administration, the number of times the medication was taken on that date and number of units taken.

Use of rescue medication must be recorded in the eDiary. The acute headache medications reported in the eDiary also will be collected on the Concomitant medications/Significant non-drug therapies eCRF, but data will include only the drug name, indication, and start and stop dates of overall use (i.e., not the individual administration dates). Relevant non-drug therapies as part of "best supportive care" use should also be recorded in the eCRF.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after enrolling into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications/ significant non-drug therapies eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. Potential interactions of each concomitant drug with topiramate, according to SmPC section 4.5, must be individually assessed as additional clinical monitoring of defined parameters might be necessary (e.g., adequate control of diabetic disease state). If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

5.5.8 Prohibited treatments

Use of the treatments displayed in Table 5-1 is NOT allowed as designated due to the potential confounding of efficacy assessments unless in the context of a different pre-existing condition in stable doses for at least 3 months prior to baseline.

Table 5-1 Prohibited Treatments

Treatment	Prohibition period
All prophylactic treatments targeting the CGRP pathway	Any time before study start and throughout the study
Topiramate	Any time before study start
Valproate/Divalproex	Any time before study start and throughout the study
All oral beta blockers	Within 5 half-lives of the start of the baseline epoch and throughout the study
Flunarizine	
Antidepressants (amitriptyline, venlafaxine, desvenlafaxine)	
Antiepileptics (e.g. gabapentin)	
ACE/ARB (lisinopril, candesartan)	
Botulinum toxin (in the head and/or neck region) for medical treatment	Any time before study start and throughout the study
Botulinum toxin (in the head and/or neck region) for cosmetic treatment	Within 4 months of the start of the baseline epoch and throughout the study
Invasive interventions (e.g., nerve blocks, occipital nerve stimulators, transcranial magnetic stimulation)	Within 1 month of the start of the baseline epoch and throughout the study

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or e-mail confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)

- patient number

In addition, oral and written information to the patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time. If a code break occurs, the patient has to discontinue the study.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the double-blind treatment epoch when the patient has completed Visit 199 in the protocol.

The patient's completion status will be recorded on the appropriate Study Phase Completion eCRF pages.

For all patients tapering off Control-IMP after study completion, an unscheduled visit has to be conducted after finishing the tapering off phase. At this visit, information about Control-IMP compliance, AEs, SAEs and concomitant medications have to be collected.

For all patients a safety follow-up visit (visit 201) should be conducted 4 weeks after the last visit or 8 weeks after the last IMP injection. The information to be collected at this follow up visit is outlined in Table 6-1.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.6 and Section 7.5)
- Use of prohibited treatment as per recommendations in Table 5-1
- Any situation in which study treatment might result in a safety risk to the patient
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study, and should continue recording in the eDiary as per protocol. Also, patients who discontinued treatment from the double-blind treatment epoch will follow the abbreviated visit schedule until the follow up visit (week 28) is reached (Table 6-2). These visits should be performed with all assessments outlined in Table 6-2. At a minimum, the following data should be collected at clinic visits or via telephone visits:

- new/concomitant treatments
- adverse events / serious adverse events

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (Visit 199) will be performed. At this final visit, the adverse event and concomitant medications should be reconciled on the eCRF. Patients will return for a follow-up visit approximately 8 weeks after their last dose of study medication, and perform the study procedures outlined in Table 6-1.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment. If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9. Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.All patients receiving a daily dose of 75 mg or 100 mg topiramate (for at least one week) should perform a taper off phase for one week after discontinuation of study treatment. After the taper off phase an unscheduled visit should be performed to record control-IMP compliance, AEs, SAEs and concomitant medications.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore, and
- Does not want any further visits or assessments, and
- Does not want any further study related contacts, and

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table below.

5.6.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone

calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit-risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board / Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 and Table 6-2 list all of the assessments and indicate with an "X" when the visits are performed.

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

During visits 102 to visit 107, intervals between visits must not exceed 7 +/- 1 day calculated from Visit 101 (Day1), to ensure continuous supply regarding oral medication.

During visits 108 to visit 199, intervals between visits should not exceed 28 +/- 4 days calculated from Visit 101 (Day 1). If the visit has to be scheduled outside this window, an approval from the sponsor has to be collected to ensure continues supply of oral medication and patient safety regarding s.c. medication.

Table 6-1 Assessment Schedule: Double – Blind Treatment

	Screen	Baseline	Double – Blind Treatment Epoch (Titration)						Double – Blind Treatment Epoch (Maintenance)						Follow Up[2]
Visit number[1]	**0**	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**199**	**201**
End of Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**	**28**
Day	**-42**	**-28**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**57**	**85**	**113**	**141**	**169**	**197**
Obtain informed consent	x														
Randomization			x												
Demography	x														
Medical history, prior medication[3]	x														
Complete Physical Exam	S													S	S
Brief Physical Exam		S	S	S	S	S	S	S	S	S	S	S	S		
Height	x														
Weight	x		x											x	x
Vital Signs[4]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x													x	
Chemistry/ Hematology[12]	x		x							x				x	x
Serum Pregnancy	x													x	
Urine pregnancy[13]		x	x	x	x	x	x	x	x	x	x	x	x		x

	Screen	Baseline	Double – Blind Treatment Epoch (Titration)						Double – Blind Treatment Epoch (Maintenance)						Follow Up[2]
Visit number[1]	**0**	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**199**	**201**
End of Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**	**28**
Day	**-42**	**-28**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**57**	**85**	**113**	**141**	**169**	**197**
eDiary dispensing		S													
eDiary return[5]			S	S	S	S	S	S	S	S	S	S	S	S	
Clinical Outcomes (eDiary)		Daily eDiary starting at -4 (baseline Epoch) throughout DBTE (daily migraine attacks, duration, severity, rescue medication)													
SF-36 [6] (eDiary)			X				x			x	x	x	x	x	
HIT-6 [6] (eDiary)			X				x			x	x	x	x	x	
[redacted]															
C-SSRS [6,7]	x	x	X	x	x	x	x	x	X	x	x	x	x	x	x
BDI-II[6]	x														
Concomitant Medications		x	X	x	x	x	x	x	X	x	x	x	x	x	x
Adverse Events[8]			X	x	x	x	x	x	X	x	x	x	x	x	x
Serious Adverse Events[8]	x	x	X	x	x	x	x	x	X	x	x	x	x	x	x
Study Drug Administration PFS[9]			X				x			x	x	x	x		
Oral Study Drug Dispensing[10]			X	x	x	x	x	x	X	x	x	x	x		
Contact IRT[11]	x	x	X	x	x	x	x	x	X	x	x	x	x	x	

	Screen	Baseline	Double – Blind Treatment Epoch (Titration)						Double – Blind Treatment Epoch (Maintenance)						Follow Up[2]
Visit number[1]	**0**	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**199**	**201**
End of Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**20**	**24**	**28**
Day	**-42**	**-28**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**57**	**85**	**113**	**141**	**169**	**197**
Baseline Phase Completion form		x													
Double-Blind Treatment Phase Completion form														x	
Follow-Up Phase Completion form															x

1 – All study visit target dates are to be calculated from the Day 1 visit date and all study procedures for a given visit should be completed on the same day.

2 – The Follow-Up Visit is required 8 weeks after last IMP injection (erenumab / corresponding Placebo) for patients who discontinue the study or 4 weeks after V199 for patients who complete the study. The Follow-Up visit can be skipped if any other safety follow up visit occurred 8 weeks after last IMP injection.

3 – Including prior prophylactic medication.

4 – Includes blood pressure, pulse and temperature.

5 – Patient brings to each visit for use at site

6 – To be completed during applicable study visits before study drug administration, where applicable.

7 – Should also be performed at unscheduled visits.

8 – SAEs will be collected after signing of the informed consent through the end of the Follow-Up Epoch (8 weeks after the last IMP injection). Non-serious AEs will be collected after randomization (Visit 101) through the end of the Follow-Up Epoch (8 weeks after the last IMP injection).

9 – Study drug is administered by study staff, during the applicable study visits, q.m., s.c..

10 – Oral study drug will be dispensed to the patient at the center during the applicable study visit for home application.

11 – Sites will access the Interactive Response Technology (IRT) System to register study early termination.

12 – Should be additionally performed at any visit if deemed necessary by the investigator due to AEs.

13 – Should be performed/registered by the investigator prior to dosing during DBTE.

TD = Treatment discontinuation; PFS = Prefilled syringe; PSD = Premature subject discontinuation; X = Assessment to be recorded in the source documents and the clinical data base; S = Assessment to be recorded as source documentation only.

Table 6-2 Abbreviated schedule of assessments (ASA) for patients with Treatment Discontinuation (TD)

Visit number	V105-ASA	V108-ASA	V109-ASA	V110-ASA	V111-ASA	V199-ASA	V201-ASA[2]
End of Week[1]	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Complete Physical Exam						S	
Brief Physical Exam	S	S	S	S	S		
Weight						x	x
Vital Signs[3]	X	x	x	x	x	x	x
Chemistry/Hematology[12]		x				x	x
Serum Pregnancy						x	
Urine pregnancy	S	S	S	S	S		x
ECG						x	
Clinical Outcomes (eDiary)	eDiary should be maintained						
SF-36[4](eDiary)	X	x	x	x	x	x	
HIT-6[4] (eDiary)	X	x	x	x	x	x	
C-SSRS	X	x	x	x	x	x	
Concomitant Medications	X	x	x	x	x	x	x
Adverse Events[5]	X	x	x	x	x	x	x
Serious Adverse Events[5]	X	x	x	x	x	x	x
Follow Up Phase Completion form							x

1 – All study visit target dates are to be calculated from the Day 1 visit date, and all study procedures for a given visit should be completed in the same day.

2 – The Follow-Up Visit is required for all patients who discontinue study drug early. or complete the study and do not continue commercial drug (if locally available). The Follow-Up visit can be skipped if any other safety follow up visit occurred 4 weeks after V199-ASA or the patient continues commercial drug (if locally available). For assessments please refer to table 6-2.

3 – Includes blood pressure, pulse and temperature.

4 – To be completed during applicable study visits before study drug administration, where applicable

5 – SAEs will be collected after signing of the informed consent through the end of the Follow-Up Epoch. Non-serious AEs will be collected after randomization (Visit 101) through the end of the Follow-Up Epoch (V201-ASA).

12 – Should additionally be performed at any visit if deemed necessary by the investigator due to AEs.
TD = Study treatment discontinuation; PSD = Premature patient discontinuation; X = Assessment to be recorded in the source documents and the clinical data base;
S = Assessment to be recorded as source documentation only.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the Screening Epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients include: year of birth, age, sex, race, source of patient referral, relevant medical history/current medical condition present before signing informed consent. Where possible, diagnoses not symptoms will be recorded.

Prior headache characteristics and previous headache medication history, including information on the suitability for migraine prophylactics will be collected as part of baseline characteristics.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

Study medication is administered at the site (test-IMP) or dispensed to the patient (control-IMP) by the investigator or designated study staff as outlined in Table 6-1. This information should be captured in the source document and the eCRF at each visit. All study treatments dispensed and returned must be recorded in the Drug Accountability Log. Site staff will review eDiary compliance and control-IMP compliance (topiramate) with the patient at each visit.

6.4 Efficacy

Efficacy assessments will include:

- Migraine days

The timing and frequency of these assessments are outlined in Table 6-1. Patients will record the efficacy information using the provided eDiary platform. To aid in compliance, it is recommended that the information be completed at the same time every day that is convenient for the patient. Retroactive completion will be allowed up to 48hours prior to the time of completion. Any entries >48 hours will not be allowed and will be considered missing data. Data collected in the eDiary will be normalized to a 28 day period.

6.4.1 Migraine Days

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). 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:

1. ≥2 of the following pain features:
   - Unilateral
   - Throbbing
   - Moderate to severe
   - Exacerbated with exercise/physical activity
2. ≥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.

To further characterize a migraine day, the following information will be collected:

- Date and time of start of headache (i.e., migraine or non-migraine headache)
- Date and time of end of headache
- Worst pain severity per headache
- Pain features (e.g., one-sided, throbbing, worsens with exercise/physical activity)
- Symptoms (e.g., aura, nausea, vomiting, photophobia, phonophobia)
- Use of acute headache medications (medication name (from pre-entered list), date of dosing, number of times taken of each date, number of units taken)

6.4.2 Appropriateness of efficacy assessments

The definition of migraine day (Section 6.4.1) is consistent with the diagnostic criteria of migraine and probable migraine according to the International Classification of Headache Disorder (ICHD-3). The MMD will be calculated using migraine day data collected from the eDiary. Migraine days are commonly used as an endpoint in pivotal trials as acknowledged in the IHS guidelines for controlled trials of drugs in migraine (Tfelt-Hansen 2012).

The mean change in MMD however describes a population-based measure and, given the natural variability in migraine trials, often is associated with small effect sizes. Thus, a clinically important complementary information is the proportion of patients that achieve a certain clinical benefit, which is usually described with achieving at least a 50% reduction of migraine days compared to the individual baseline ("50% responder rate"). In pivotal trials, 50% (or higher) responder rates are usually included as secondary or key secondary outcomes.

[redacted] Additional PRO scales were included to gather information on functional impact of headache (HIT-6, SF-36).

6.5 Safety

Safety assessments will include:

- Treatment discontinuations due to AEs
- Adverse events (Section 7.1)
- Physical examination
- Vital signs
- ECG
- Height/weight
- Laboratory evaluations
- Pregnancy testing (females of childbearing potential)
- Columbia Suicide Severity Rating Scale (C-SSRS) (Section 7.6)

The timing and frequency of these assessments are outlined in Table 6-1 and Table 6-2.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, as well as vascular and neurological examination. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A brief physical exam will include the examination of general appearance and will be at all visits starting from Visit 2, except where a complete physical examination is required (see above).

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to randomization must be included in the Medical History part of the eCRF. Significant findings made after first administration of investigational drug, which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.

6.5.2 Vital signs

Vital signs include blood pressure, pulse and temperature measurements. After the patient has been sitting for approximately five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using a validated device, with an appropriately sized cuff. The repeat sitting measurements should be made at approximately 1 – 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. The method to take temperature should be consistent throughout the study.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be measured.

6.5.4.2 Clinical chemistry

Bilirubin (total, direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT), GGT, creatinine and estimated creatinine clearance (GFR) will be measured. Clinical chemistry assessment will be performed at Screening (Visit 0), begin of DBTE (Visit 101), during DBTE two weeks after topiramate titration phase (Visit 108), at the end of DBTE (Visit 199) and at follow up (Visit 201).

6.5.5 Electrocardiogram (ECG)

ECGs must be recorded as outlined in the central ECG reading manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) as reported by the central reader should be used for clinical decisions. Single 12 lead ECGs are collected. The original ECGs, printed on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site. Each ECG tracing must be labeled with study number, subject number, date and time, and filed in the study site source documents. For any ECGs with patient safety concerns, two additional ECGs must be performed to confirm the safety finding and forwarded to the central ECG laboratory for assessment. Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRFs as appropriate.

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Serum pregnancy tests will be performed at the beginning and end of the study, with urine pregnancy tests performed at the remaining visits. Pregnancy tests during DBTE should be performed/registered by the investigator prior to dosing. The specific schedule is outlined in Table 6-1 and Table 6-2.

6.5.7 Appropriateness of safety measurements

The safety assessments have been selected based upon the safety profile of the drug as reported in the Investigator Brochure and are standard for this patient population and drug class.

6.6 Other assessments

- Headache Impact Test (HIT-6)
- SF-36 V2
- Beck Depression Inventory (BDI)-II
- [redacted]

The timing and frequency of these assessments are outlined in Table 6-1 and Table 6-2.

6.6.1 Patient Reported Outcomes (PROs)

Patients will complete all Patient Reported Outcome (PRO) questionnaires using the provided eDiary platform. For those questionnaires that are completed in-clinic, during visits, completion should occur before any other assessments are performed.

All questionnaires will be completed in German, at the scheduled study visit prior to the patient seeing the investigator for any clinical assessment or evaluation. The site staff should check the responses to the questionnaire for completeness and encourage the patient to complete any missing responses.

Patients should be given sufficient space and time to complete all study PROs. If patients experience any difficulties with submission after they complete the PROs, the study staff should assist them with submitting their PRO responses. Attempts should be made to collect responses to all PROs for all patients, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if patients refuse to complete PROs, this should be documented in study source records.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

6.6.1.1 Headache Impact Test (HIT-6)

The HIT-6 is a short-form self-administered questionnaire based on the internet-HIT question pool (Kosinski 2003). 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 items assess the frequency of pain severity, headaches limiting 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 headaches limiting ability to concentrate

or work on daily activities. Each of the 6 questions is responded to using 1 of 5 response categories: “never,” “rarely,” “sometimes,” “very often,” or “always.”

For each HIT-6 item, 6, 8, 10, 11, or 13 points, respectively, are assigned to the response provided. These points are summed to produce a total HIT-6 score that ranges from 36 to 78. HIT-6 scores are categorized into 4 grades, representing little or no impact (49 or less), some impact (50 – 55), substantial impact (56 – 59), and 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. Patients will complete this in their eDiary during their scheduled clinic visit, at the frequency outlined in Table 6-1 and Table 6-2.

6.6.1.2 Medical Outcome Short Form Health Survey (SF-36) Version 2 (4-week recall period)

The SF-36 is a widely used and extensively studied instrument to measure 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, and Mental Health (Ware 1993). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (Ware 1994). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual subjects. The purpose of the SF-36 in this study is to assess the HRQoL of subjects. Given the nature of this disease and the 4-weekly assessment, the SF-36 version 2, with a 4-week recall period, will be used in this study.

6.6.1.3 Beck Depression Inventory (BDI)-II

The BDI-II is a 21-item questionnaire that assesses severity of depression. Each item is scored from 0 to 3. The total score is categorized into 4 severity grades: minimal depression (0 – 13), mild depression (14 – 19), moderate depression (20 – 28), and severe depression (29 – 63) (Beck 1996).

The questionnaire takes approximately 10 minutes to complete. Patients will be asked to complete this in their eDiary during their scheduled clinic visit, at the frequency outlined in Table 6-1. The recall period is the preceding two weeks, including the day of completion.

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient from randomization (Visit 101) until the end of study visit (16 weeks after the last IMP injection). Any events occurring during the Screening and Baseline Epochs and conditions that were already present at the time of informed consent should be documented as medical history. An AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
  - Yes
  - No

- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment

If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, e.g., via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above .

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until the completion of the Follow-Up Epoch (8 weeks after the

last IMP injection) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the completion of the Follow-Up Epoch should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Migraine days including migraine-related events (underlying disease) which meet SAE-definition (e.g. hospitalization) should be reported on the relevant eCRF pages instead of SAE form unless, in the judgement of the investigator, a migraine attack is unusually severe or unexpected and warrants specific notification as an SAE.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities/adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter

- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver eCRF pages

Please refer to Table 13-1-Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 13-1-Appendix 2 should be followed up by the investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in Table 13-2-Appendix 2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver eCRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease. All follow-up information, and the procedures performed must be recorded on appropriate eCRF pages, including the liver event overview eCRF pages.

7.4 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

Table 7-1 Guidance for Capturing the Study Treatment Errors Including Misuse/Abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.5 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported as an SAE.

7.6 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior (Posner 2011). The C-SSRS must be administered at each visit, including unscheduled visits.

A validated version of the C-SSRS will be used to capture self-reported C-SSRS data via web-based interactive response system (eC-SSRS). The eC-SSRS uses a detailed branched logic algorithm to perform the C-SSRS patient interview, evaluating each patient's suicidality ideation and behavior in a consistent manner. At the conclusion of each assessment, the investigator will receive a detailed eC-SSRS Findings Report via e-mail or fax. If the system

assesses the patient as having positive suicidal signs, the investigator will be immediately notified by either fax, e-mail and/or via telephone.

If, at any time after screening and/or baseline, the score is "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS or "yes" on any item of the Suicidal Behavior section, the patient must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the patient is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a patient answers "yes" to one of the questions in the Suicidal Behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the Suicidal Behavior section) should be reported as AEs and assigned the appropriate severity grade.

All SAEs relating to suicidal behavior must be reviewed by the Safety Management Team or early project teams.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. This central analytics organization may also analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation

of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the EDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Prior/concomitant medications and procedures as well as significant non-drug therapies entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and medical history possibly contributing to liver dysfunction as well as adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally in Germany and the results will be sent electronically to Novartis (or a designated CRO in Germany).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The first analysis will be conducted on all patient data when the double-blind treatment epoch of the trial ends. The data will be analyzed by Novartis and/or by the designated CRO.

Analysis sets

The Randomized Analysis Set (RAS) 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 double-blind 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 investigational product and will be analyzed based on actual treatment received.

9.1 Patient demographics and other baseline characteristics

Demographic variables and other baseline characteristics including previous migraine treatments will be summarized. Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables for each treatment group and for all participants (total). The number and percentage of participants in each category will be presented for categorical variables for each treatment group and all participants (total).
In addition, all relevant medical history will be summarized following the same strategy. Any condition entered as medical history or current medical conditions at baseline will be coded using the MedDRA dictionary. Medical history will be summarized by system organ class and preferred term in the MedDRA dictionary. Summaries for migraine specific medical history will be provided as well.

9.2 Treatments

The analysis of study treatment data will be based on the safety set. A data listing and a summary of the investigational drug injections and pill counts (erenumab or topiramate) administered will be provided. Dose levels achieved and no. /percentage of patients titration per visit will be presented for topiramate or matching placebo. The duration of exposure to study treatment will be summarized by treatment group. In addition, the number and percentage of participants receiving rescue medications, concomitant medications, and significant non-drug therapy will be summarized by preferred term (coded by WHO Anatomic Therapeutic Chemical classification [ATC]) and by treatment arm, and be listed.

9.3 Analysis of the primary variable(s)

9.3.1 Variable(s)

The analysis of the primary variable will be based on the following estimand:

- Population – Safety Analysis Set (SAF)
- Variable of Interest: The primary endpoint is the rate of patients discontinuing the allocated study treatment due to an adverse event (AE) during the double-blind treatment epoch.
- Intervention effect – effect between erenumab versus topiramate during double-blind treatment regardless of adherence to randomized treatment.
- Summary measure – odds ratio

9.3.2 Statistical model, hypothesis, and method of analysis.

The null hypothesis to be rejected is that the odds of AE-related treatment discontinuations are equal in both treatment groups. The corresponding alternative hypothesis is that the odds are not equal under erenumab compared to topiramate.

Let pj denote the proportion of AE-related treatment discontinuations for treatment group j, j=0, 1, where

- 0 corresponds to erenumab
- 1 corresponds to topiramate

The following hypotheses will be tested:

H0: (p1 / (1- p1)) / (p0 / (1- p0)) = 1 versus HA: (p1 / (1- p1)) / (p0 / (1- p0)) $\neq$ 1In other words:

H0: The odds ratio of AE-related treatment discontinuations for erenumab vs topiramate is equal to 1, meaning no difference on AE-related treatment discontinuations between the two treatments. HA: The odds ratio of AE-related treatment discontinuations for erenumab vs topiramate is different from 1.

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment and stratification factor (migraine days during the baseline epoch). The odds ratio and its 95% confidence interval

(CI) and p-value will be given. The null hypothesis of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor "treatment" is <0.05; however, superiority of erenumab will be claimed only if the direction is correct, i.e. if the odds of response are lower under erenumab compared to topiramate.

9.3.3 Handling of missing values/censoring/discontinuations

For every patient, it can be determined whether he/she discontinued for AE-related reasons. Non-AE-related discontinuations or losses to follow up will not be counted as AE-related discontinuations. AE-related discontinuations are counted as events, discontinuation due to other reasons are not counted as events.

[redacted]

9.4 Analysis of secondary variables

The secondary variable is the achievement of at least a 50% reduction from baseline in monthly migraine days (MMD) over the last 3 months (months 4, 5, and 6) of the double-blind treatment period.

The analysis of the primary variable will be based on the following estimand:

- Population – Full Analysis Set (FAS)
- Variable of Interest: number of patients with at least 50% reduction from baseline in monthly migraine days (MMD)
- Intercurrent event: discontinuation of study medication – effect between erenumab versus topiramate assuming to evaluate treatment policy
- Intercurrent event: discontinuation of study or lost to follow up – effect between erenumab versus topiramate assuming no response could be achieved
- Summary measure – odds ratio

All the subjects' data collected regarding 50% response of MMD will be used in the analysis regardless whether subjects complete the study drug or not. Subjects with missing response information on this endpoint will be imputed as non-response (non-responder imputation). A logistic regression model including treatment group, baseline value, and stratification factor will be used to perform the treatment comparison (erenumab vs. topiramate) at end of the DBTE. Additional to the odds ratio obtained from the logistic regression, estimates for the risk ratio and the risk difference (with corresponding confidence intervals and p-values) will be calculated for the secondary endpoint.

9.5 Analysis of exploratory variables

Exploratory variables are the patient reported outcomes (PROs) HIT-6 and SF-36 [redacted] The analysis of PROs [redacted] will be described in detail in the statistical analysis plan (SAP).

9.5.1 Safety variables

9.5.1.1 Adverse events

Treatment emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a patient reported more than one adverse event with the same preferred term, 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. Serious adverse events will also be summarized.

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

9.5.1.2 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from Baseline to each study visit will be presented.

These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from Baseline will only be summarized for patients with both Baseline and Post-Baseline assessments.

For each parameter, the maximum change from Baseline within each study period will be analyzed analogously.

9.5.1.3 Vital signs

Analysis of the vital sign measurements using summary statistics for the change from Baseline for each Post-Baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from Baseline will only be summarized for patients with both Baseline and Post-Baseline values.

9.5.2 Resource utilization

9.5.3 Not applicable. PK/PD

Not applicable.

9.5.4 DNA

Not applicable.

9.5.5 Blood Biomarkers

Not applicable.

9.6 Interim analyses

Not applicable.

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC-approved informed consent. The patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before

conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide a proposed informed consent form to investigators that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 must be followed.

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13 Appendices

Appendix 1: Clinically notable laboratory values

Only selected lab parameters which have potential to be sensitive to erenumab exposure are listed.

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	<1.5x 10^3/uL	<1.5x10^9/L

Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 13-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT/AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

Table 13-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Complete liver CRF	
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.