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Erenumab

Clinical Trial Protocol AMG334ADE03 / NCT04084314

Protocol Title

Assessment of Prolonged safety and tOLerability of erenumab in migraine patients in a Long-term OpeN-label study (APOLLON)

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List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
b.i.d.	bis in die/twice a day
BMI	Body Mass Index
BLRM	Bayesian Logistic Regression Model
BUN	Blood Urea Nitrogen
CDP	Clinical Development Plan
CD-ROM	Compact Disc – Read Only Memory
CDS	Core Data Sheet
CK	Creatinine Kinase
ClinRO	Clinician Reported Outcomes
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcome Assessment
CO_2	carbon dioxide
CRF	Case Report/Record Form (paper or electronic)
CO	Country Organization
CQA	Clinical Quality Assurance
CRO	Contract Research Organization
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTC	Common Terminology Criteria
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DIN	Drug Inducted Nephrotoxicity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DQF	Data Query Form
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOI	End of Infusion
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	Hour
HbsAg	Hepatitis B surface antigen

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human Equivalent Dose
HEOR	Health Economics & Outcomes Research
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
i.v.	intravenous
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRSD	Maximum Recommended Starting Dose
MTD	Maximum Tolerated Dose
Nab	Neutralizing antibody
NCDS	Novartis Clinical Data Standards
NOVDD	Novartis Data Dictionary
ObsRO	Observer Reported Outcomes
PA	posteroanterior
PC	Personal Computer
PD	Pharmacodynamic(s)
PerfO	Performance Outcomes
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic(s)
p.o.	oral(ly)
PRO	Patient Reported Outcomes
PSD	Premature Subject Discontinuation
PT	prothrombin time
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RAP	Report and Analysis Plan
RBC	red blood cell(s)
RDC	Remote Data Capture
RDE	Recommended dose for expansion

REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RoW	Rest of World
RP2D	Recommended phase two dose
R Value	ALT/ALP x ULN
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
s.c.	subcutaneous
sCR	serum creatinine
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
TD	Study Treatment Discontinuation
[redacted]	[redacted]
ULN	upper limit of normal
ULQ	upper limit of quantification
UTI	Urinary Tract Infection
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

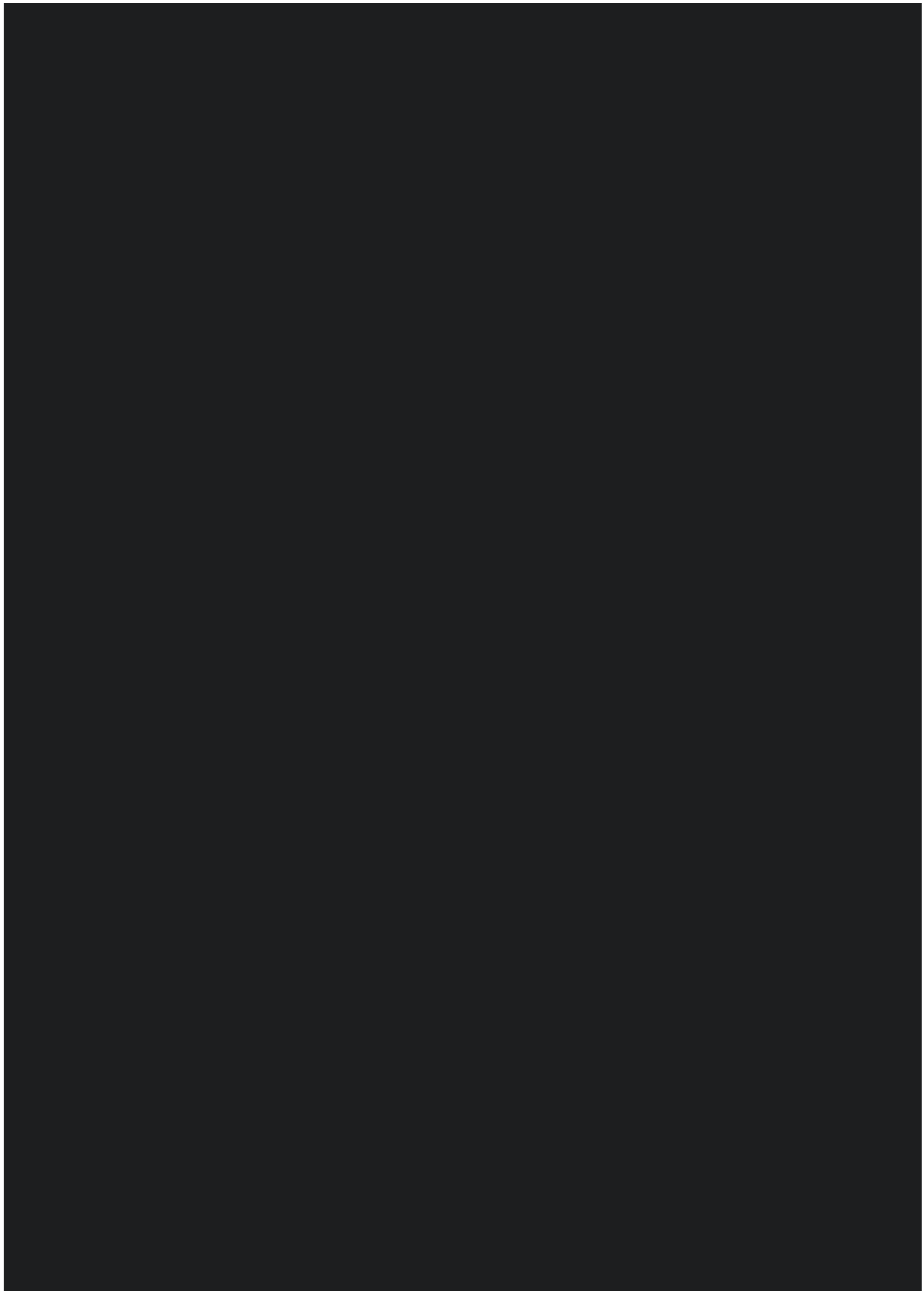
Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) 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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.

Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject
Run-in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's intervention or other treatment)
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject.
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Victim drug	The drug that is affected by the drug-drug interaction
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

Protocol summary

Protocol number	CAMG334ADE03
[redacted]	



Amendment 1

The protocol is being amended to include patients with chronic migraine and to restrict the transition from the trial CAMG334ADE01 to this study to 3 months.

Further, some minor linguistic changes have been introduced to clarify certain criteria and procedures in the protocol.

Changes to the protocol

- Objectives were updated to include chronic migraine patients.
- The description of the study population has been adjusted to include all female and male patients that are 18 years or older with a documented history of episodic (4 – 14 baseline migraine days) or chronic migraine (≥15 baseline headache days), who were successfully randomized to clinical trial CAMG334ADE01.
- The inclusion criteria have been adjusted to define 3 months after the V199 visit as the latest time point at which patients can be included in the study
- The exclusion criteria have been updated to exclude patients that have terminated the trial CAMG334ADE01 due to a safety event.
- The sample size calculation was updated considering the inclusion of chronic migraine patients and resulted in a sample size increase from 700 to 750 patients including up to 70 patients with ≥ 15 monthly migraine days.Mentions of an eDiary were replaced by paper-based migraine diary.

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.

A novel class of drugs for the prophylactic treatment of migraine is based on the discovery of calcitonin-gene-related peptide (CGRP) being involved in the pathogenesis of migraine. Currently, several monoclonal antibodies directly targeting CGRP are either under development or already approved. Erenumab (AMG334) as the only monoclonal antibody targeting the CGRP receptor itself was approved by EMA and FDA in 2018 as the first compound specifically developed for the prophylactic treatment of migraine patients.

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.

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 (DGN 2018) 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 erenumab treated 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 a positive 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 but long term data on safety and tolerability in a large group of patients is still limited.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective	**Endpoint for primary objective**
• To evaluate the long-term safety of 70 and 140 mg erenumab in patients with episodic or chronic migraine.	• Exposure adjusted incidence rate of AE during Open-label Treatment Epoch per 100 subject years
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the long-term tolerability of 70 and 140 mg erenumab in patients with episodic or chronic migraine.	• Proportion of patients discontinuing open-label Treatment Epoch due to AE • Proportion of patients discontinuing open-label Treatment Epoch due to non-AE reasons

3 Study design

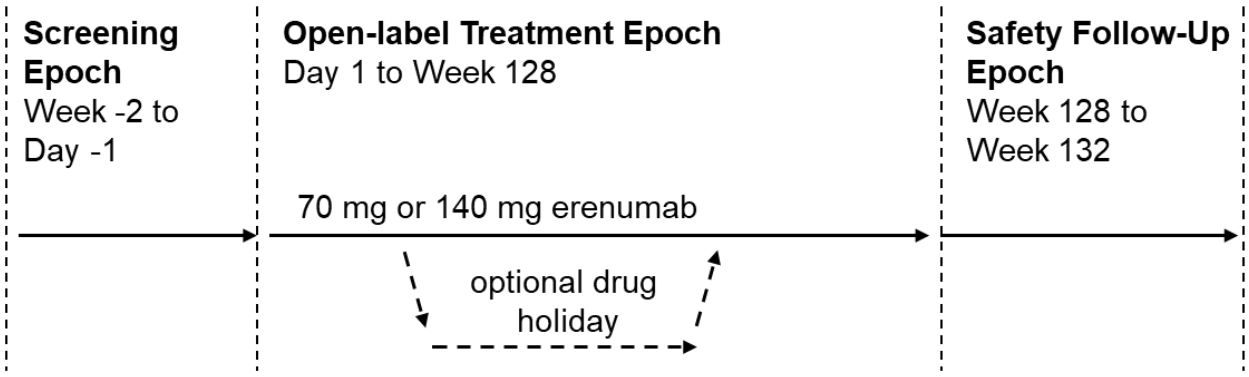
This is an open-label, multi center, single arm study with flexible dosing allowing both dose adjustment and one drug holiday per patient.

The study design consists of 3 parts:

- **Screening Epoch (0 - 2 weeks):** required for all patients to assess initial eligibility.
- **Open-label Treatment Epoch (128 weeks):** Individual patients are treated for 128 weeks in the open-label treatment phase. During this open-label Treatment Epoch the erenumab dose may be adjusted from 70 mg to 140 mg or vice versa by discretion of the physician at any scheduled study visit. Additionally, a voluntary single treatment interruption ('drug holiday') of up to 24 weeks (approximately six months) may be introduced after at least 12 weeks of treatment in the open-label Treatment Epoch.
- **Follow-up Epoch (4 weeks):** A Follow-Up Visit 4 weeks after the last regular study visit (8 weeks after last IMP application) will be required as part of routine safety monitoring.

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

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

Until now long-term safety and tolerability data of erenumab in a large group of patients are still limited. This 128-week open-label study will provide further treatment to patients still blinded for the randomization of the study CAMG334ADE01 (Eudract number:2019 -

002201 - 22) and will provide data about the long-term safety and tolerability of Erenumab and patients' quality of life during long-term treatment. The regular assessments in a controlled trial allows a close observation of safety parameters during long-term treatment with erenumab. Furthermore, while regular reviews of treatment outcome and drug holidays are routine in migraine prophylaxis and also recommended in the German S1 guideline (DGN 2018), there are no data regarding erenumab treatment yet. Besides options to adjust the dose, an optional drug holiday is therefore included in this open-label study and the effects of a treatment interruption on safety, tolerability, efficacy and quality of life will be investigated.

4.2 Rationale for dose/regimen and duration of treatment

Dosing and route of administration are in accordance with the Summary of Product Characteristics (SmPC, version Mai 2019) either 70 mg or 140 mg erenumab at the discretion of the physician. Erenumab will be injected s.c. by the well trained patient at home in 28-day intervals.

The starting dose of erenumab in the open-label trial is matched to the last dose received (either as erenumab verum or placebo) during the head-to-head clinical trial CAMG334ADE01 from which all patients are recruited. In CAMG334ADE01 patients have received either erenumab verum at 70/140 mg and topiramate placebo OR erenumab placebo at 70/140 mg and topiramate verum for 24 weeks. While patients and physicians are still blinded at study start of CAMG334DE03 to the identity of verum/placebo in CAMG334ADE01 the dose is known as 70 mg erenumab/placebo were delivered in one pre-filled syringe and 140 mg erenumab/placebo was injected by two pre-filled syringes. Accordingly, patients who have received 70 mg erenumab/placebo injections as last dose in CAMG334ADE01 will also receive 70 mg erenumab as starting dose in this open-label study. Patients who have received 140 mg erenumab/placebo as last dose in CAMG334ADE01 will receive 140 mg erenumab as starting dose in this open-label extension study. Evidently, patients who received topiramate during trial CAMG334ADE01 will be switched to erenumab in this study.

Subsequently, physicians may adjust the erenumab dose during the open-label study at any planned study visit during the open-label Treatment Epoch at their discretion. Furthermore, one voluntary treatment interruption ('drug holiday') may be performed earliest 12 weeks after first dose in the open-label study with a duration of no more than 24 weeks before returning to the dosing regimen.

A treatment duration of 128 weeks was chosen for the long-term assessment of erenumab treatment. In comparison in oral migraine prophylaxis trials almost 50% of patients discontinued the study after six months of treatment (Hepp 2014). The chosen treatment duration for the open-label study is therefore five times longer and thus assessed to be suitable to analyze the long-term tolerability and safety of erenumab treatment and sustained study compliance of subjects.

4.3 Risks and benefits

Erenumab was 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 SmPC.

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.

As of June 2018, the safety of erenumab in migraine prophylaxis was assessed from integrated safety analyses of 2537 migraine patients exposed to at least one dose of erenumab, with a cumulative exposure of 2310.3 subject-years (SY). Overall, the safety and tolerability profile of erenumab was similar between the 140 mg and 70 mg doses and comparable to placebo. Adverse drug reactions include injection site reactions, constipation, muscle spasms, and pruritus. The majority were mild or moderate in severity and rarely led to treatment discontinuation. To date, no important risk has been identified for erenumab.

Overall, to date, there is no evidence from non-clinical and clinical data of risk of cardiovascular effects. On the theoretical basis of the mechanism of action of erenumab, CGRP receptor blockade might reduce compensatory vasodilation, particularly under ischemic conditions. Therefore, cardiovascular effects continue to be monitored.

All biologicals, including fully human proteins, have the potential to induce immunogenicity leading to the development of specific anti-drug antibodies. So far, the development of antierenumab antibodies has only been observed with low incidence and was not associated with specific adverse events or a clinically relevant reduction in erenumab plasma levels. In most cases, subjects with a positive anti-erenumab antibody status reverted to antibody negative with continued follow-up. Subjects in clinical studies will continue to be monitored for the development of anti-erenumab antibodies and possible associated clinical sequelae.

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.

An external data monitoring committee was established to review the erenumab safety data for Phase 2b and Phase 3a studies, and based on these data, recommended continuation of the program. The need for a data monitoring committee (DMC) for this study was assessed, and deemed not necessary because erenumab was approved by FDA and EMA for migraine prophylaxis and the safety profile of erenumab was well characterized in 4 double-blind, placebo-controlled trials in over 2500 patients. The risk to patients in this trial will be minimized

by compliance with the eligibility criteria, close clinical monitoring, and allowance of acute rescue medications.

Initial benefits for erenumab as a migraine prophylactic have been demonstrated in a Phase 2b trial (Amgen Study 20120178), in which 70 mg was established as the minimally effective dose in EM (Sun et al 2016) with a significant placebo-corrected reduction of 1.1 monthly migraine days compared to baseline, as well as positive results on most secondary endpoints, including 50% responder rate.

Three additional Phase 2/3 studies, including 2 studies in EM, have been completed with erenumab, which have established 70 mg and 140 mg as being effective and safe in patients with EM or CM, with a favorable benefit/risk profile. Positive treatment effects in general were observed in a robust way across typical migraine endpoints such as change in mean monthly migraine days, > 50% (and higher) responder rates, change in migraine-specific medication use and functional improvement by established PRO scales. Results were in general highly statistically significant and clinically meaningful. Retention rates observed in clinical trials were very high (~95% with active treatment after 3 months and ~90% after 6 months with only minimal discontinuations attributed to adverse events). This feature is important, as discontinuation rates are high for current migraine prophylaxis treatments, with the main drivers of discontinuation being either lack of efficacy or tolerability issues (Blumenfeld et al 2013). As such, there is a high unmet need for a therapy that is well-tolerated, has sustained response rates and excellent compliance.

As of July 2018, two open-label extension studies (OLE) of erenumab in patients with chronic (1 year) and episodic migraine (3 years) were reported confirming sustained efficacy and a favorable safety and tolerability profile. Overall, given the characteristics of erenumab and the large experience in clinical trials, the overall benefit-risk assessment is supportive.

5 Population

The study population will consist of female and male patients that are 18 years or older with a documented history of episodic (4 – 14 baseline migraine days) or chronic migraine (≥15 baseline headache days), who were successfully randomized to clinical trial CAMG334ADE01. Patients can only be enrolled to the study from two weeks after their end of study visit (V199 at week 24) in CAMG334ADE01 until three months after their end of study visit (V199). For patients terminating CAMG334ADE01 earlier than planned as per protocol,the planned end of study date (V199) at 26 weeks after randomization to CAMG334ADE01 is applicable (see inclusion criteria 4 below).

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Patient is capable of understanding the nature, significance and implications of the clinical trial.
3. Adults ≥18 years of age upon entry into screening

4. Earliest time point for inclusion to this open-label study is 26 weeks after randomization to trial CAMG334ADE01:
   a) Subjects who completed visit V199 in trial CAMG334ADE01 have to wait additional 2 weeks for down-titration of topiramate (doses 75 and 100 mg) and total elimination for topiramate (equals 26 weeks after randomization)
   b) Subjects who discontinued their participation in CAMG334ADE01 before V199 have to wait until the planned V199 visit date and additional 2 weeks (26 weeks after randomization).
5. Latest time point for inclusion to this open-label study is 3 months after visit V199 in trial CAMG334ADE01. For subjects who discontinued their participation in trial CAMG334ADE01 the theoretical V199 is applicable.
6. Subjects who are deemed by the investigator to benefit from erenumab therapy.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Patients who had to terminate the trial CAMG334ADE01 due to a safety event.
2. Use of a prophylactic migraine medication within five plasma clearance half-lives, or a device or procedure within one month prior to the start of the Open-label Treatment Epoch. This exclusion criteria does not apply to erenumab or topiramate administered within clinical trial CAMG334ADE01
3. Any prior exposure to (investigational) prophylactic migraine products targeting the CGRP pathway, other than erenumab.
4. Use of the following for any indication one month prior to the start of the Open-label Treatment Epoch:
   a. Opioid- or butalbital-containing analgesics ≥4 days/month
5. Anticipated to require any excluded medication device or procedure (e.g., occipital nerve stimulators, transcranial magnetic stimulation,) during the study
6. Active chronic pain syndromes (e.g., fibromyalgia or chronic pelvic pain)
7. 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
8. Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records or patient self-report
9. Myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedures within 12 months prior to screening
10. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study

11. 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
12. Pregnant or nursing (lactating) women
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 110 days after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). 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 six weeks before taking study treatment. 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 subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - 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%), for example, 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 study treatment

    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 six weeks ago.

    If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF)
14. Use of any other investigational drug outside of CAMG334ADE01 since randomization to the CAMG334ADE01 trial.
15. Simultaneous participation in a study that includes administration of any investigational drug or procedure in the indication migraine and simultaneous participation in a non-interventional study.
16. History of hypersensitivity to the study drug or its excipients including latex

17. 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 diary items) to the best of the patient's and investigator's knowledge
18. Patients who may be dependent on the sponsor or investigator
19. Patient has not been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities

6 Treatment

6.1 Study treatment

Novartis will supply the market sourced investigational medicinal product erenumab in pre-filled autoinjectors containing 70 mg or 140 mg erenumab.

6.1.1 Investigational drug

Table 6-1 Investigational drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration
AMG334 70mg	Solution	Subcutaneous use
AMG334 140mg	Solution	Subcutaneous use

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.3 Treatment arms/group

This is a single arm study. All subjects will continue to receive the same dose of erenumab that was administered (either as erenumab verum or placebo) on the last visit in clinical trial CAMG334ADE01.

6.1.4 Treatment duration

The planned duration of treatment is 128 weeks for individual patients. However, each patient is eligible to one voluntary treatment interruption of up to 24 weeks (approximately 6 months) after an initial treatment duration of at least 12 weeks. After such a voluntary treatment interruption within the 128 weeks of the Treatment Epoch patients may return to the treatment schedule.

Subjects can be discontinued from treatment earlier due to unacceptable adverse events and/or at the discretion of the investigator or the subject.

6.1.5 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis Medical Advisor before including a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.1.6 Prohibited medication

Only prophylactic migraine (Erenumab) monotherapy is allowed. If a subject is taking a migraine prophylactic for a different pre-existing condition (not for migraine prophylaxis), this will be allowed as long as the subject is on stable dose for at least 3 months prior to baseline visit and the pre-existing condition and corresponding treatment is documented in the source and eCRF. No other concomitant prophylactics for migraine should be used.

Use of the treatments displayed in Table 6-2 is NOT allowed unless in the context of a different pre-existing condition in stable doses for at least 3 months prior to baseline visit.

Table 6-2 Prohibited medication

Treatment	Prohibition period
All prophylactic treatments targeting the CGRP pathway	Any time before study start and throughout the study
Valproate/Divalproex	Any time before study start and throughout the study
All oral beta blockers Flunarizine Antidepressants (amitriptyline, venlafaxine, desvenlafaxine) Antiepileptics (e.g. gabapentin) ACE/ARB (lisinopril, candesartan)	Within 5 half-lives of the start and throughout the study
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	Any time before study start 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 visit and throughout the study

6.1.7 Rescue medication

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 the patient has been stable dose 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.

Use of rescue medication should be noted and documented in the eCRF. Data will include the drug name, indication and the individual administration dates.

Relevant non-drug therapies should also be recorded in the eCRF.

6.2 Subject numbering, treatment assignment, randomization

6.2.1 Subject numbering

Upon signing the informed consent form for the study CAMG334AD01, each patient was assigned a unique identification number by the investigator using a combination of the study center number and patient number. The same unique patient identification numbers used in the study CAMG334AD01 will be retained for the identification of patients participating in the study CAMG334AD03.

6.2.2 Treatment assignment, randomization

This is a single arm study. All patients will receive Erenumab. No randomization is required. At study start, subjects will be assigned to the latest choice of dose (either as erenumab verum or placebo) in the CAMG334ADE01 trial and can be adjusted at any following visit throughout the Open-label Treatment Epoch.

6.3 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the CTT.

6.4 Dose escalation and dose modification

At study start, the subjects will be assigned to the latest administered dose of CAMG334ADE01 trial regardless of verum or placebo. Dose modification can be performed at the discretion of the physician at any of the following visits throughout the Open-label Treatment Epoch of the study according to the SmPC.

Dose modifications include dose escalation from 70 mg to 140 mg erenumab or dose reduction from 140 mg to 70 mg erenumab. One voluntary treatment interruption (drug holiday) per patient may be conducted but earliest after 12 weeks of treatment and for up to 24 weeks during the open-label treatment Epoch. Afterwards, patients may return to treatment.

6.4.1 Dose escalation guidelines

There is no dose escalation guideline other than the SmPC. In clinical studies there was no clear dose-dependent safety signal combined with a comparable overall efficacy trend between 70 mg and 140 mg erenumab. Both 70 mg and 140 mg erenumab are considered to offer an optimal benefit-risk ratio for patients with some patients obtaining an additional benefit from the 140 mg dose.

6.4.1.1 Starting dose

The starting dose of erenumab in the open-label trial is matched to the last dose received (either as erenumab verum or placebo) during clinical trial CAMG334ADE01 from which all patients are recruited. In CAMG334ADE01 patients have received either erenumab verum at 70/140 mg and topiramate placebo OR erenumab placebo at 70/140 mg and topiramate verum. While patients and physicians were blinded to the identity of verum/placebo in CAMG334ADE01 the dose is known as 70 mg erenumab/placebo were delivered in one pre-filled syringe and 140 mg erenumab/placebo was injected by two pre-filled syringes. Accordingly, patients who have received 70 mg erenumab/placebo injections as last dose in CAMG334ADE01 will also receive 70 mg erenumab as starting dose in this open-label study. Patients who have received 140 mg erenumab/placebo as last dose in CAMG334ADE01 will receive 140 mg erenumab as starting dose in this open-label extension study.

As CAMG334ADE01 will still be ongoing at patient inclusion into the open-label study CAMG334ADE03 un-blinding cannot be performed and neither patients nor physicians will know at this point which medication was received during CAMG334ADE01.

6.4.2 Dose modifications

See Section 6.4 above.

6.4.3 Follow-up for toxicities

Not applicable.

6.5 Additional treatment guidance

6.5.1 Treatment compliance

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit and based on information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.5.2 Emergency breaking of assigned treatment code

Not applicable as this is an open label study.

6.6 Preparation and dispensation

Each study site will be supplied with study drug in in packaging.

6.6.1 Handling of study treatment

Erenumab 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 designated site personnel have access.

Erenumab must be stored according to the instructions specified on the label and in the prescribing information/package insert. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (CPO) Quality Assurance. Medication labels will include storage conditions for the study treatment but no information about the subject 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. Subjects will be asked to return all unused study treatment and packaging 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 will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Sponsor address provided in the investigator folder at each site.

6.6.2 Instruction 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 up-titration 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

The dose may also be reduced from 140 mg to 70 mg. Possible reasons for down-titration could be, but are not limited to:

- complete response as deemed by physician and/or patient
- suspected treatment dependent adverse events

A dose adjustment can be performed at any scheduled study visit during the open-label Treatment Epoch.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing, IRB/IEC-approved informed consent.

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 subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the prescribing information/package insert/CDS. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

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 requirements.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all assessments and when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects 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 will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

In table 8-1 all assessments are shown and "X" indicate when the visits are performed.

During visits 101 to visit 199, intervals between visits should not exceed 84 +/- 7 days. If the visit has to be scheduled outside this window, an approval from the sponsor has to be collected to ensure patient safety.

Table 8-1 Assessment Schedule

	Screen	Open-label Treatment Epoch												During drug holiday	First visit after drug holiday	Follow up[2]
Visit number[1]	**0**	**Baseline**	**V101**	**V102**	**V103**	**V104**	**V105**	**V106**	**V107**	**V108**	**V109**	**V110**	**V199**	**V201 – V20X**	**V101B**	**V301**
End of week	**-2 to 0**	**0**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**128**	**Every 12 weeks**	**NA**	**132**
Obtain informed consent	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		S
Height	X															
Weight	X												X		X	
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X														X	
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Screen	Open-label Treatment Epoch												During drug holiday	First visit after drug holiday	Follow up[2]
Visit number[1]	**0**	**Baseline**	**V101**	**V102**	**V103**	**V104**	**V105**	**V106**	**V107**	**V108**	**V109**	**V110**	**V199**	**V201 – V20X**	**V101B**	**V301**
End of week	**-2 to 0**	**0**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**128**	**Every 12 weeks**	**NA**	**132**
Adverse Events[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug dispensing[6]		X	X	X	X	X	X	X	X	X	X	X			X	
[redacted]																
Chemistry/Hematology[8]	X														X	X
Urine pregnancy[9]		X	X	X	X	X	X	X	X	X	X	X	X			
Serum Pregnancy	X														X	X
[redacted]																

	Screen	Open-label Treatment Epoch												During drug holiday	First visit after drug holiday	Follow up[2]
Visit number[1]	**0**	**Baseline**	**V101**	**V102**	**V103**	**V104**	**V105**	**V106**	**V107**	**V108**	**V109**	**V110**	**V199**	**V201 – V20X**	**V101B**	**V301**
End of week	**-2 to 0**	**0**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**128**	**Every 12 weeks**	**NA**	**132**
Open-label 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). The Follow-Up visit can be skipped if any other safety follow up visit occurred 4 weeks after last study visit.
3 – Including prior prophylactic medication.
4 – Includes blood pressure, pulse and temperature.
5 – SAEs will be collected after signing of the informed consent through the end of the Follow-Up Epoch end of study. Non-serious AEs will be collected starting at Baseline Visit through the end of the Follow-Up Epoch.
6 – Study drug erenumab will be dispensed to the patient at the center during the applicable study visit for home application. Last study drug application will be at week 124.
[redacted]
8 – Should be additionally performed at any visit if deemed necessary by the investigator due to AEs
9 Should be performed/registered by the investigator prior to dosing during DBTE.
[redacted]
X = Assessment to be recorded in the source documents and the clinical data base; S = Assessment to be recorded as source documentation only.

8.1 Screening

At the screening visit, all study subjects must be thoroughly informed about all aspects of the study, including the study treatment, visit schedule, required evaluations, and all regulatory requirements for informed consent. For details of screening assessments, refer to Assessment schedule in Table 8-1. Assessments cannot be performed prior to signature of the informed consent. If the subject does not fulfill all inclusion/exclusion criteria, he/she must be documented as a screening failure (Section 8.1.1).

It is permissible to re-screen a subject if he/she fails the initial screening criteria. If the subject is re-screened, a new ICF must be obtained and re-screening will be documented in the subject's source documents. A new subject number will be allocated and the site will record data in a new CRF.

8.1.1 Information to be collected on screening failures

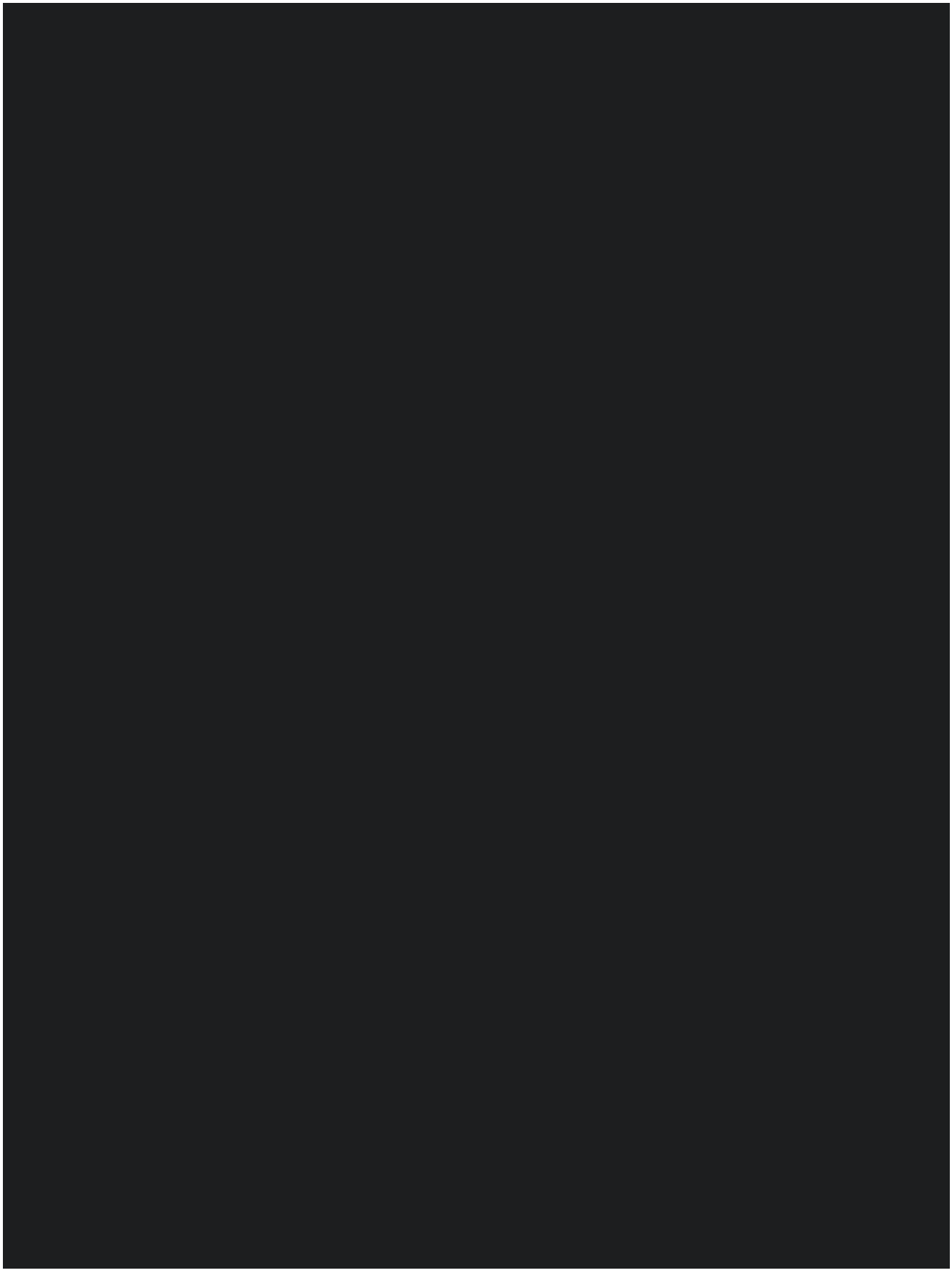
All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening Epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected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

8.2 Subject demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients including: year of birth, age, sex, race, source of patient referral, relevant medical history/current medical condition present before signing informed consent for trial CAMG334ADE01 (HER-MES). Where possible, diagnoses not symptoms will be recorded.

Prior headache characteristics and previous headache medication history prior to treatment in trial CAMG334ADE01 (HER-MES), 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.



8.4 Safety/Tolerability

Safety assessments will include:

- Treatment discontinuations due to AEs
- Adverse events (Section 10.1)
- Physical examination
- Vital signs
- ECG
- Height/weight
- Laboratory evaluations
- Pregnancy testing (females of childbearing potential)

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-2 Assessments & Specifications

Assessment	Specification
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 baseline visit, 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 at screening 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.

Assessment	Specification
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 increased blood pressure is recorded (systolic/diastolic) measurements have to be repeated at the end of the study visit for validation. 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.
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.

8.4.1 Laboratory evaluations

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), Platelets
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN)
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Pregnancy Test	Urine pregnancy test
	Serum pregnancy test

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (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. The Fridericia QT correction formula (QTcF) 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, patient initials, subject number, date and time, and filed in the study site source documents.

For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding and forwarded to the central ECG laboratory for assessment. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 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 8-1.

8.4.4 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.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than defined in the protocol and not for a planned "drug-holiday", and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the subject
- 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 investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events/Serious Adverse Events

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject'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 subject 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 subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision. A subject will be considered to have completed the study when the subject has completed the last visit planned in the protocol.

After study completion, post-trial access to erenumab will be offered to the study participants as needed.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 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 subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events. Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

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

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. 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
2. its relationship to the study treatment.
   - Yes
   - No
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment. 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
6. its outcome
   a. not recovered/not resolved;
   b. recovered/resolved;
   c. recovered/resolved with sequelae;
   d. fatal; or unknown.

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

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. Adverse event monitoring should be continued for at least eight weeks following the last dose of study treatment.

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

Information about adverse drug reactions for the investigational drug can be found in the SmPC. 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 SmPC 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.

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.

10.1.2 Serious adverse events

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:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject 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 the ICH-E2D Guidelines).

- 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
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - 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
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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 subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". 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 the ICH-E2D Guidelines).

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until completion of the Follow-Up Epoch (8 weeks after last IMP injection). must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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.

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.

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 CMO & PS 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.

Any SAEs experienced after completion of the Follow-Up Epoch (8 weeks after last IMP injection) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject 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 should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 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, subject 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 recorded on the appropriate CRF 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.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject 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 AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 16-2 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
-
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate

- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
  - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; 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 procedures performed must be recorded as appropriate in the eCRF.

11 Data collection and database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused supplies to Novartis.

Once all the necessary 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. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, 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 organization. Additionally, a central analytics organization may analyze data & identify risks & 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 subject 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 CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. 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 subjects will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Safety Set comprises all subjects who received at least one dose of study treatment in the open-label treatment epoch of CAMG334ADE03.

The Full Analysis Set is equivalent to the safety set.

12.2 Subject demographics and other baseline characteristics

Demographic, medical history and other baseline data including previous migraine treatments will be listed and summarized descriptively for all subjects.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

In addition, all relevant medical history will be summarized by system organ class and preferred term, for all subjects.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

A data listing and a summary of erenumab administered will be provided. Unless otherwise specified, patients assigned to 70 mg or 140 mg erenumab dose will be analyzed together under one treatment arm erenumab. The analysis by dose will be detailed in SAP as needed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

A data listing and summary of rescue medications will be provided.

The duration of exposure to erenumab will be summarized by means of descriptive statistics using the safety set. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary aim of the study is to evaluate the long-term safety of 70 and 140 mg erenumab in patients with episodic or chronic migraine. The primary endpoint variable is the exposure adjusted incidence rate of AEs during the open-label treatment epoch per 100 subject years.Statistical model, hypothesis, and method of analysis

The primary analyses will be conducted dividing the number of AEs by the time under treatment and standardizing it per 100 person-years. Exact Pearson-Clopper confidence intervals for single proportions will be calculated in order to evaluate the precision of the estimated parameter. No formal hypotheses testing will be conducted.

12.4.2 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.

12.4.3 Sensitivity analyses

Sensitivity analyses

The primary analysis will also be conducted within the subgroups defined by sex, disease severity and prior treatment failure status (naïve vs. prior treatment failures). The primary analysis will also be repeated for all- cause treatment discontinuations (instead of AE-related).

Supportive analyses

12.5 Analysis of secondary endpoints

To evaluate the long-term tolerability of 70 and 140 mg erenumab in patients with episodic or chronic migraine.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

- Proportion of patients discontinuing open-label treatment epoch due to AE
- Proportion of patients discontinuing open-label treatment epoch due to non-AE reasons

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 112 days after the date of the last actual administration of study treatment.

Adverse events

All information obtained on adverse events will be displayed and subject.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by primary system organ class and preferred term.
- by primary system organ class, preferred term and maximum severity
- by Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

The number (and proportion) of subjects with adverse events of special interest will be summarized.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by subject, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by visit/time.

12-lead ECG

All ECG data will be listed by subject and visit/time, abnormalities will be flagged. Summary statistics will be provided.

Clinical laboratory evaluations

All laboratory data will be listed by subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by visit/time. Shift tables using the low/normal/high/ (low and high) *(or project specific)* classification will be used to compare baseline to the worst on-treatment value.

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

In general, the 750 subjects randomized for clinical trial CAMG334ADE01 will be eligible for participation in the open-label study. It is estimated that approximately 75% to 85% of the study population meaning 563~638 subjects will enroll in the open-label study thus allowing the collection of long-term safety, efficacy and quality of life data of a large group of patients.

12.8.1 Primary endpoint(s)

In the three-year open-label phase II study 20120178 the proportion of patients reporting at least one AE was 87%. Based on this finding the following event rates and precisions were calculated for the proposed 128-week trial for the primary endpoint in Table 1.

Table 1: Proportion of event and precision primary endpoint: Any AE

Sample size	Proportion any AE	Precision (+/-)
500	70%	4.0%
	80%	3.5%
	85%	3.1%
	90%	2.6%

In conclusion a study population of at least 500 patients was found to be sufficient for the primary endpoint with an adequate range in precision.

12.8.2 Secondary endpoint(s)

The calculation of effect size and precision for the secondary endpoints is based on the proportion of study discontinuation rates in the three-year open-label phase II study 2012017. 4.2% of 383 patients discontinued this trial due to adverse events. Table 2 shows the effect size and precision for the proposed study with at least 500 patients.

Table 2: Proportion of event and precision secondary endpoint: AE-related discontinuation

Sample size	Proportion any AE	Precision (+/-)
500	5%	1.9%
	10%	2.6%
	15%	3.1%

Among the non-AE related study discontinuations the group 'upon patient request' was particularly high at the time point of erenumab marketing authorization. 68 patients requested study discontinuation in the first two years of the open-label study overlapping with marketing authorization. In the following 12 months 8 patients requested study discontinuation. In order to use more realistic number as basis for the effect calculations of the proposed study patient discontinuation rates after marketing authorization were utilized. This number was multiplied by three to account for the longer duration of the first part of the study and to add an additional buffer for uncertainty. This means, 24 patient requests for study discontinuation in the first two years and 8 requests in the third year were included in the calculation. Overall, this results in a discontinuation rate due to any non-AE reasons of 22.2%. Table 3 shows the estimated event rates and precisions for this secondary endpoint.

Table 3: Proportion of event and precision secondary endpoint: non AE-related discontinuation

Sample size	Proportion any AE	Precision (+/-)
500	15%	3.1%
	20%	3.5%
	25%	3.8%

In conclusion a study population of at least 500 patients was found to be sufficient for the secondary endpoints with an adequate range in precision.

13 Ethical considerations and administrative procedures

13.1 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 with the ethical principles laid down in the Declaration of Helsinki.

13.2 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, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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

14 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 subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs

under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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.

14.1 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 where required prior to implementation.

Only amendments that are required for subject safety 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

[redacted]

Deutsche Gesellschaft für Neurologie (DGN), Deutsche Migräne und Kopfschmerzgesellschaft (DMKG) (2018) Leitlinien für Diagnostik und Therapie in der Neurologie. Therapie der Migräne. Available from:

https://www.dgn.org/images/red_leitlinien/LL_2018/PDFs_Download/030057_LL_Migrane_2018.pdf

Dodick DW, Ashina M, Brandes JL, et al. (2018) ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia; 38(6):1026-1037.

Durham PL (2006) Calcitonin gene-related peptide (CGRP) and migraine. Headache; 46 (Suppl 1):S3-S8.

EPAR RMP summary, https://www.ema.europa.eu/documents/rmp-summary/aimovig-epar-risk-management-plan-summary_en.pdf, accessed 15-Feb-2019

Goadsby PJ, Reuter U, Hallström Y, et al (2017a) A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med; 377: 2123-2132.

Goadsby PJ, et al., (2017b) IHC Oral Abstracts: Efficacy of Erenumab in Subjects with Episodic Migraine with Prior Preventive Treatment Failure(s). Cephalalgia; 37(1_suppl): 13.

Hepp Z, Bloudek LM, Varon SF Systematic review of migraine prophylaxis adherence and persistence. J Manag Care Pharm. 2014 Jan;20(1):22-33.

[redacted]

Pascual, Treatment of migraine in the year 2020, Med Clin (Barc). 2018 Nov 24. pii: S0025-7753(18)30638-9.

Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, Klatt J.: Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study.Lancet. 2018 Nov 24;392(10161):2280-2287. doi: 10.1016/S0140-6736(18)32534-0. Epub 2018 Oct 22.

Tepper S, Ashina M, Reuter U, Brandes JL, et al (2017) Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol;16(6):425-434

Wang X, Yue TL, Barone FC, et al (1995) Discovery of adrenomedullin in rat ischemic cortex and evidence for its role in exacerbating focal brain ischemic damage. Proc Natl Acad Sci USA; 92:11480-84.

Zimmermann U, Fischer JA, Frei K, et al (1996) Identification of adrenomedullin receptors in cultured rat astrocytes and in neuroblastoma x glioma hybrid cells (NG108-15). Brain Res; 724:238-45.

16 Appendices

16.1 Laboratory values and vital signs

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

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/d L	>63 mmol/L
Alkaline Phosphatase	F	>832 U/L	>832 U/L
Alkaline Phosphatase	M	>1032 U/L	>1032 U/L

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

Table 16-1 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 TBL: total bilirubin; ULN: upper limit of normal	

Table 16-2 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 • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	
> 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 • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	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 • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate 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 • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate 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.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.