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AMG334

Clinical Trial Protocol CAMG334A2304 / NCT03867201

A 12-week phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of once monthly subcutaneous erenumab 70 mg in adult chronic migraine patients

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List of abbreviations

ACE/ARB	Angiotensin-Converting Enzyme inhibitor/Angiotensin-Receptor Blocker
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
BDI-II	Beck Depression Inventory II
BMI	body mass index
BOCF	Baseline observation carried forward
BUN	blood urea nitrogen
CDE	Centre Drug Evaluation
CFR	Code of Federal Regulation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CGRP	Calcitonin Gene-related Peptide
CM	Chronic Migraine
CO	Country Organization
COVID-19	Corona virus Disease 2019
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
COA	Clinical Outcome Assessments
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
eC-SSRS	Electronic Columbia Suicide Severity Rating Scale
EDC	Electronic Data Capture
eDiary	Electronic Diary
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
EM	Episodic Migraine

EMA	European Medicines Agency
eSource	Electronic Source
EU	European Union
FAS	Full Analysis Set
FUP	Follow-Up
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HA	Health Authorities
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	high density lipoprotein
[redacted]	[redacted]
HIV	human immunodeficiency virus
HSV	Herpes Simplex Virus
IA	Interim Analysis
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICHD	Headache Classification Committee of the International Headache Society
IEC	Independent Ethics Committee
IHS	International Headache Society
IN	Investigator Notification
INR	International Normalized Ratio
IPD	Important Protocol Deviation
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra-uterine device
IUS	Intra-uterine system
LDL	low density lipoprotein
LFT	Liver function test
LPLV	Last Patient Last Visit
LLOQ	lower limit of quantification
LSM	Least square means
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MI	Multiple Imputation
MIDAS	Migraine Disability Assessment
MMD	Monthly migraine days
MNAR	Missing not at random
MO	Medication Overuse

[redacted]	[redacted]
[redacted]	[redacted]
NSAID	Nonsteroidal Anti-Inflammatory Drugs
OAS	Open-Label treatment Analysis Set
PD	pharmacodynamic(s)
PFS	Pre-filled syringe
PK	pharmacokinetic(s)
PRN	Pro re nata (Latin=as required)
PRO	Patient Reported Outcomes
PT	Preferred Term
q.m.	every month, here refers to an every 4 weeks.
QMS	Quality Management System
QTcF	QT corrected (Fridericia QT formula)
RBC	red blood cell(s)
RDW	Red cell distribution width
s.c.	Subcutaneous
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SOP	Standard Operating Procedure
SC	Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBIL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TIA	Transient ischemic attack
ULN	upper limit of normal
USA	United States of America
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
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
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 (CRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
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
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, Double-Blind Treatment, Open-Label 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
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 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
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
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.

Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
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 study treatment prior to the defined study treatment completion date
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.
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
Withdrawal of study consent	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

Amendment 02 (26-Jan-2021)

Amendment rationale

Details for potential trial conduct changes due to the COVID-19 pandemic have been incorporated in this protocol amendment. No additional risk for COVID-19 pandemic has been identified, and therefore the benefit risk is unchanged.

In addition, clarification that DMC will conduct regular unblinded reviews of cumulative safety data has been added.

Duration of post-trial access (PTA) in Korea has been updated to June 2021 instead of 'launch in the country', as sponsor no longer plans to launch erenumab in Korea. Other CGRP treatments are expected to be available in Korea in June 2021.

Furthermore, a mistake regarding the urine pregnancy test has been corrected in the assessment schedule and relevant protocol sections.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

List of Abbreviations

Section updated to add one abbreviation and correct the definition of another one.

Section 1.2 Purpose

Section updated to reflect that in Korea post-trial access will no longer be provided until 'launch in the country', but until June 2021.

Section 3 Study design

Section updated to reflect that in Korea post-trial access will no longer be provided until 'launch in the country', but until June 2021. Section updated with a guidance for COVID-19.

Figure 3-1 Study design

Section updated to reflect that in Korea post-trial access will no longer be provided until 'launch in the country', but until June 2021.

Section 4.1 Rationale for study design

Section updated to reflect that in Korea post-trial access will no longer be provided until 'launch in the country', but until June 2021.

Section 4.3 Rationale for choice of control drugs (comparator/placebo)

Title updated as per Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020.

Section 4.5 Risks and benefits

Details from recent studies and from approval of erenumab in several countries have been added.

Section 5 Study Population

Title updated as per Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020.

Section 5.2 Exclusion Criteria

Section updated to correct a typo.

Section 6.1.4 Treatment duration

Section updated to reflect that in Korea post-trial access will no longer be provided until 'launch in the country', but until June 2021.

Section 6.2.1 Concomitant therapy

New prohibited medications have been added.

Section 6.2.2 Prohibited medication

New prohibited medications have been added.

Section 6.2.3 Rescue medication

This section has been updated for clarification.

Section 6.6.1 Treatment compliance

Section updated with a guidance for COVID-19.

Section 6.7.2 Instruction for prescribing and taking study treatment

Section updated with a guidance for COVID-19.

Section 7 Informed consent procedures

Section updated with a guidance for COVID-19.

Section 8 Visit schedule and assessments

Included a guidance section for COVID-19 related to alternatives for conducting study visits with options to use phone calls, virtual visits etc. for patients affected by the pandemic.

Table 8-1 Assessment schedule

Updated to clarify that urine pregnancy test results are only collected in source documents and not in the clinical database.

Section 8.3 Efficacy

Section updated with a guidance for COVID-19 that PRO scales may still be collected using the eDiary for subjects impacted due to the pandemic.

Section 8.4 Safety

Section updated with a guidance for COVID-19 for subjects impacted due the pandemic.

Table 8-2 Safety Assessments

Section updated with a guidance for COVID-19 for subjects impacted due the pandemic.

Section 8.4.1 Laboratory evaluations

Introduced guidance for COVID-19 to indicate that collection of laboratory samples may need to be modified for subjects impacted due to the pandemic. Section also updated to indicate which urine pregnancy test are to be used (central lab or local lab tests).

Section 8.4.2 Electrocardiogram (ECG)

Section updated with a guidance for COVID-19 for subjects impacted due the pandemic.

Section 8.4.3 Pregnancy and assessments of fertility

Section updated with a guidance for COVID-19 for subjects impacted due the pandemic.

Section 8.4.4 Prospective suicidality assessment

Section updated with a guidance for COVID-19 for subjects impacted due the pandemic.

Section 8.5.1 Clinical Outcome Assessments (COAs)

Section updated with a guidance for COVID-19 for subjects impacted due the pandemic.

[redacted]

[redacted]

Section 8.5.5 AMG 334 Antibody testing

Section updated with a guidance for COVID-19 for subjects impacted due the pandemic.

Section 9.1.1 Discontinuation of study treatment

Section updated to reflect that in Korea post-trial access will no longer be provided until 'launch in the country', but until June 2021.

Section 9.2 Study completion and post-study treatment

Section updated to reflect that in Korea post-trial access will no longer be provided until 'launch in the country', but until June 2021.

Section 10 Safety monitoring and reporting

Section updated with a guidance for COVID-19 for subjects impacted due the pandemic.

Section 10.1.4 Pregnancy reporting

Section updated as per Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020.

Section 10.2.1 Liver safety monitoring

Section updated as per Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020, and updated to replace liver CRF with Adverse Events CRF.

Section 10.2.2 Prospective suicidality assessment

Section updated with a guidance for COVID-19 for subjects impacted due the pandemic.

Section 10.2.3 Data Monitoring Committee

Added regular unblinded safety reviews to be performed by the DMC.

[redacted]

Section 12.7 Interim analysis

Clarification added that analysis results will be prepared for regulatory submission in case of positive IA read out with 70% information.

Section 12.8.1 Primary endpoint(s)

Overall power updated from 88 to 90%.

Section 13.2 Responsibilities of the investigator and IRB/IEC

Section updated with a guidance for COVID-19 on home-delivery of study drug for subjects impacted due the pandemic.

Table 16-3 Follow Up Requirement for Liver Events and Laboratory Triggers

Table updated to remove mention of the Complete Liver CRF which is not used on the study.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol can be considered non-substantial. However, due to local regulations in some countries the changes can be considered substantial and require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 01 (19-Sep-2019)

Amendment rationale

The purpose of this amendment is to incorporate an open-label treatment period to allow for the provision of post-trial access for subjects who have completed the double-blind treatment period to ensure continued drug access until erenumab is launched in the country. As of 31 January 2019, approximately 4613 patients with migraine have taken this medicine in clinical studies to date including over 200 patients who had > 4 years of maximum treatment duration. The confirmed good safety and tolerability of erenumab does not suggest increased risks for patients with longer exposure.

Given that the chronic migraine patients eligible for this study have a particular unmet need as they may have failed multiple treatments, and as the available effective treatment options for migraine prophylaxis are limited in the participating countries, it is assumed that many subjects will need to be treated for a longer period of time after the completion of the double-blind treatment period.

Inclusion and exclusion criteria for the open-label treatment period have been added, [redacted]

The analysis plan for the open-label treatment period has been added.

In addition to the changes related to the open-label treatment period, inclusion criterion 7 has been added, i.e. 'History of migraine (with or without aura) for ≥ 12 months prior to screening according to the IHS Classification ICHD-3 based on medical records and/or patient self-report'. The reasons for adding this inclusion criterion are:

- IHS guidelines, recommending 12 months of history of migraine to minimize the inclusion of patients that may experience a spontaneous reduction in the frequency of attacks during the trial (Tassorelli et al 2018).
- Completed global pivotal Chronic Migraine (CM) study (Study 20120295), in which 661/667 enrolled CM patients had ≥ 12 months of migraine history. The individual patient-level response data in the 6/667 patients with <12 months of migraine history showed a greater reduction of Monthly Migraine Day (MMD) from baseline, regardless of treatment arm, at the end of the double-blinded treatment period. Although caution should be exercised when interpreting these limited data, it revealed a trend of quick spontaneous improvement in patients with less than 12 months of migraine history.

The required longer duration of migraine history will reduce the likelihood of spontaneous remission and will improve the homogeneity of the study population.

The **Steering Committee** section has been updated as a Steering Committee will now be included in this study in order to provide guidance to Novartis on scientific conduct and reporting of the study, as well as to serve as the publication committee.

Moreover, **corrections of minor administrative and typographical errors**, identified after the finalization of the original protocol, have been incorporated.

Changes to the protocol

Section 1.1 Background

The section has been updated for the number of patients with migraine who have taken this medicine in migraine trial.

Section 1.2 Purpose

The section has been updated to define the purpose of the open-label treatment period.

[redacted]

Section 3 Study design

Open-label treatment period has been added, and clarifications have been added regarding the other periods, the Interim Analysis and the Clinical Study Reports.

Section 4.1 Rationale for study design

This section has been updated to detail the rationale for adding the open-label treatment period.

Section 4.2 Rationale for dose/regimen and duration of treatment

This section has been updated to detail the dose/regimen of the open-label treatment period.

Section 4.4 Purpose and timing of interim analyses/design adaptations

This section has been updated regarding the Clinical Study Reports.

Section 4.5 Risks and benefits

Details from recent studies and from approval of erenumab in several countries have been added.

Section 5.1 Inclusion criteria

Inclusion criterion number 7 has been added.

Section 5.2 Exclusion criteria

Exclusion criteria number 7, number 16 and number 22 have been updated and clarified.

Section 5.3 Inclusion/Exclusion criteria for the open-label treatment period

Section created to detail the Inclusion/Exclusion criteria specific to the open-label treatment period.

Section 6.1.1 Investigational and control drugs

Information on open-label treatment period study drug has been added.

Table 6-1 Investigational and control drug

Section updated for the investigational drug detail.

Section 6.1.4 Treatment duration

Section updated to detail the duration of the open-label treatment period.

Section 6.2.1 Concomitant therapy

This section has been updated regarding the recording of the Concomitant Therapies during the open-label treatment period.

Section 6.2.2 Prohibited medication

This section has been updated regarding the exclusion of the Prohibited medication during the open-label treatment period.

Section 6.2.3 Rescue medication

This section has been updated regarding the recording of the Rescue medication in the eDiary.

Section 6.4 Treatment blinding

Information has been added regarding the unblinding circumstances and the randomization information availability.

Section 6.6.1 Treatment compliance

Information on open-label treatment period has been added.

Section 6.7 Preparation and dispensation

Information on open-label treatment period has been added.

Section 6.7.1.1 Handling of study treatment

Removal of the return of unused study treatment by the subjects.

Section 6.7.2 Instruction for prescribing and taking study treatment

Information on open-label treatment period study treatment has been added.

Section 7 Informed consent procedures

Removal of sentence related to pregnant female partner of male subject.

Table 8-1 Assessment Schedule

Table updated to incorporate the open-label treatment period assessments.

Section 8.3.1 Migraine Days

Clarifications added to the definition of Migraine Day.

Section 8.3.2 Appropriateness of efficacy assessments

Replaced benefit with clinically meaningful response

Table 8-2 Safety Assessments

Section updated to specify to which visits Vital Signs assessments are applicable.

Section 8.4.1 Laboratory evaluations

Information added regarding the urine pregnancy tests to be performed locally during the open-label treatment period.

Section 8.4.3 Pregnancy and assessments of fertility

Information on open-label treatment period pregnancy tests has been added.

Section 8.4.4 Prospective suicidality assessment

Section updated to specify that this assessment is not applicable during the open-label treatment period.

Section 8.5.1 Clinical Outcome Assessments (COAs)

Information related to the COAs has been updated.

Section 8.5.2 Patient Reported Outcomes (PROs)

Section updated to specify that those assessments are not applicable during the open-label treatment period.

Section 9.1.1 Discontinuation of study treatment

Information on open-label treatment period has been added.

Section 9.2 Study completion and post-study treatment

Information on open-label treatment period has been added.

Section 10.1.1 Adverse events

Update of the CTCAE version to be used

Section 10.1.4 Pregnancy reporting

Removal of sentence related to pregnant female partner of male subject.

Section 10.2.2 Prospective suicidality assessment

Section updated to specify that this assessment is not applicable during the open-label treatment period.

Section 10.2.4 Steering Committee

This section has been updated as there will be a Steering committee for this study.

Section 12 Data analysis and statistical methods

Information on open-label treatment period analysis has been added.

Section 12.1 Analysis sets

Information on open-label treatment period analysis has been added.

Section 12.2 Subject demographics and other baseline characteristics

This section has been updated.

Section 12.3 Treatments

Information on open-label treatment period analysis has been added.

Section 12.4 Analysis of the primary endpoint(s)

This section has been updated regarding the primary endpoint analysis.

Section 12.4.3 Handling of missing values/censoring/discontinuations

Missing at random assumption has been removed.

Section 12.4.4 Sensitivity and Supportive analyses

Missing at random assumption has been removed.

[redacted]

Section 12.7 Interim Analyses

This section has been updated regarding the unblinded interim analyses.

Section 15 References

New Reference added

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CAMG334A2304
Full Title	A 12-week phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of once monthly subcutaneous erenumab 70 mg in adult chronic migraine patients
Brief title	Study of efficacy and safety of erenumab in adult subjects with chronic migraine
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to obtain data from regions not adequately represented in the global chronic migraine (CM) pivotal Study 2012095, and to support registration of 70 mg erenumab in China. It has a similar design to the global pivotal study.
Primary Objective(s)	The primary objective of this study is to evaluate the effect of erenumab compared to placebo by measuring the change in monthly migraine days (MMD) from baseline to the last 4 weeks of the 12-week treatment period.
Secondary Objectives	Objective 1: To evaluate the effect of erenumab compared to placebo on change in migraine-related disability and productivity as measured by the modified Migraine Disability Assessment (mMIDAS) from baseline to the last 4 weeks of the 12-week treatment period Objective 2: To evaluate the effect of erenumab compared to placebo on the proportion of subjects with at least 50% reduction in monthly migraine days from baseline to the last 4 weeks of the 12-week treatment period Objective 3: To evaluate the effect of erenumab compared to placebo on the change in monthly acute headache medication days from baseline to the last 4 weeks of the 12-week treatment period Objective 4: To evaluate the safety and tolerability of erenumab, including adverse events (AEs), clinical laboratory values, vital signs, and anti-AMG 334 antibodies
Study design	This study uses a single-cohort, 2-treatment arms, randomized (1:1 (70 mg: placebo)), double-blind study design in adult subjects with chronic migraine. A screening period of 2 weeks will be used to assess initial eligibility, followed by a 4-week baseline period to assess diary compliance and headache frequency. Eligible patients will then be randomized to either erenumab 70 mg or placebo for 12 weeks, followed by an open-label treatment period to last until launch of erenumab in the country or until June 2021 in Korea. A safety follow-up visit will occur 12 weeks after the last treatment for subjects who discontinue the double-blind treatment or who complete the double-blind treatment period without continuing in the open-label treatment period. An unblinded interim analysis (IA) will be conducted after 70% (385) of subjects have completed the double-blind treatment period (including early withdrawals), to determine whether the study will stop early or continue to the final primary analysis (full sample size). The recruitment continues until the read-out of the unblinded interim analysis.

Study Population	The study population will consist of male and female subjects, ages 18 to 65, with a documented history of chronic migraine as outlined in the inclusion criteria. Approximately 550 subjects will be randomized in China and other Asian countries/regions (approximately 350 Chinese subjects for final analysis or around 250 for the unblinded interim analysis). Assuming a 30% screening failure rate, approximately 790 subjects are anticipated to be screened.
Key Inclusion criteria	• Adults ≥ 18 to ≤ 65 years of age upon entry into screening • History of at least 5 attacks of migraine (with or without aura) based on medical records and/or patient self-report • History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine days per month in each of the 3 months prior to screening • ≥ 15 headache days of which ≥ 8 headache days meet criteria as migraine days during the baseline period based on the electronic Diary (eDiary) calculation (Refer to Section 8.3.1 for definition of migraine day) • Demonstrated at least 80% compliance with the eDiary during the baseline period based on the eDiary calculation • History of migraine (with or without aura) for ≥ 12 months prior to screening according to the IHS Classification based on medical records and/or patient self-report

Key Exclusion criteria	• Older than 50 years of age at migraine onset
	• Taken an opioid and/or opioid-containing analgesic for any indication during more than 4 days within one month prior to the start of the baseline period or during the baseline period
	• Taken a butalbital-containing analgesic for any indication during more than 2 days within one month prior to the start of the baseline period or during the baseline period
	• Prior migraine prophylaxis treatments failure in more than 3 out of the following medication categories:
	  • Category 1: Divalproex sodium, sodium valproate
	  • Category 2: Topiramate
	  • Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
	  • Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
	  • Category 5: Flunarizine, verapamil, cinnarizine
	  • Category 6: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
	  • Category 7: Botulinum toxin
	  • Category 8: lisinopril, candesartan
	  • Category 9: Pregabalin, gabapentin
	  • Category 10: Zonisamide
	  • Category 11: Memantine
	  • Category 12: Pizotifen
	• Use of a prohibited medication for migraine prophylaxis within 5 half-lives, or a device or procedure for migraine prophylaxis within one month prior to the start of the baseline period or throughout the study (Refer to Section 6.2.2 for the list of these excluded therapies)

	• Prior Botulinum toxin A treatment in the head/neck region within 4 months prior to the start of the baseline period or during the baseline period
Study treatment	In the double-blind treatment period: • Erenumab 70 mg/1 mL pre-filled syringe • Matching placebo in 1 mL pre-filled syringe, identical in appearance In the open-label treatment period: • Erenumab 70 mg/1 mL pre-filled syringe
Efficacy assessments	Migraine days
Key safety assessments	• Adverse event monitoring • Physical examination • Vital signs • Laboratory evaluations, including anti-AMG 334 antibody testing • Electrocardiogram (ECG)

Other assessments	• Patient reported outcomes (PROs)
	  • Modified Migraine Disability Assessment Questionnaire (mMIDAS)
	  [redacted]
	  • Beck Depression Inventory-II (BDI-II)
	[redacted]
	• Clinical Outcome Assessments (COAs): eDiary
	[redacted]

Data analysis	The primary efficacy endpoint variable will be analyzed using a generalized linear mixed model based on observed monthly data during the treatment period. The secondary efficacy endpoints will be analyzed using a linear mixed effects model similar to the primary endpoint. The dichotomous endpoints will be analyzed by Cochran-Mantel-Haenszel (CMH) test with subjects who are missing monthly migraine day data during the last 4 weeks of treatment period imputed as non-responders. Nominal 95% confidence intervals and p-values will be reported. Tests of secondary endpoints will be tested at nominal 2-sided significant level 0.05.
Key words	AMG 334, erenumab, migraine, chronic, headache, Chinese

1 Introduction

1.1 Background

Migraine is a common worldwide occurring neurological disorder throughout all regions and ethnicities with a high global prevalence, significant socio-economic burden and substantial impairment and disability of affected patients. It has a global prevalence of 11% in adults (Stovner et al 2007). The first headache epidemiological survey across the China mainland showed that the estimated 1-year prevalence of migraine is 9.3% (Yu et al 2012). It is mainly characterized by recurrent headache lasting 4-72 hours but is usually accompanied by other neurological disturbances, nausea, vomiting and other nonspecific symptoms. The patient burden and disability as well as the societal impact increase with higher attack frequency, which is why the spectrum of migraine disorders is typically described according to frequency of migraine days per month. "Episodic migraine" (EM) is characterized by migraine with fewer than 15 headache days per months, while "Chronic migraine" (CM) is defined as 15 or more headache days per months, at least 8 out of which have to be typical migraine days. According to World Health Organization (WHO), CM is one of the most disabling disorders as it imposes a substantial effect on day-to-day functioning. Compared with individuals with EM, those with CM are much more likely to be unemployed, be divorced, and have psychological comorbidities, suggestive of the burden of the disease on the individual, their families, and society (Buse et al 2013). Based on the high frequency of migraine and effect on quality of life, patients with CM are good candidates for preventive therapy. In general, EM and CM patients share many common features in terms of the clinical presentation, which include the headache pain features and associated symptoms. The distinction between EM and CM is somewhat arbitrary and numerous lines of evidence support that they are a continuum of the same disorder.

Migraineurs are currently being treated for migraine prophylaxis by a variety of drug classes, many of them being used off-label and often based on insufficient or limited evidence. In particular in CM, despite its enormous burden, there are few well-controlled studies for migraine prophylaxis with quality evidence available, only for onabotulinum toxin A and topiramate. Other therapies such as β blockers or amitriptypine are frequently used, despite a lack of evidence in patients with CM. Oral preventive therapies available at present, including topiramate, β blockers, and amitriptyline are often not fully efficacious or are poorly tolerated, which can lead to low adherence rates. Botulinum toxin (Botox®) is approved in many countries for CM use, but not for EM. In China, there is only 1 drug, flunarizine, approved for migraine prophylaxis.

Nontraditional therapies such as herbal medicines, supplements, acupuncture and other therapies also have some role in migraine prophylaxis. While the evidence supporting their use is minimal and often controversial (Gooriah et al 2015), they are very common in the Asian region, and becoming more widespread and increasingly introduced into mainstream Western healthcare.

Based on emerging evidence, Calcitonin Gene-related Peptide (CGRP) is a neuropeptide that prominently contributes to migraine pathophysiology. The potential mechanisms of action of CGRP receptor antagonists involve components of the trigeminal-vascular system and include normalization of CGRP-induced vasodilation, reduction of CGRP-induced neurogenic inflammation, and inhibition of pain transmission at the trigeminal ganglion and trigeminal

nucleus (Wang et al 1995, Zimmermann et al 1996, Durham 2006). CGRP is an attractive target for the development of a migraine-specific prophylactic therapy with the aim of minimizing migraine days and improving patient quality of life in this common and often disabling disorder.

Erenumab (AMG 334) is a fully human monoclonal antibody targeting the CGRP receptor under development for migraine prophylaxis in adults. To date studies have been, or are currently being, conducted in North America, Europe, Japan and some other Asian countries/regions. Erenumab is already approved in United States of America (USA), European Union (EU) and other countries for the preventive treatments of migraine in adults. As of 31 January 2019, approximately 4613 patients with migraine have taken this medicine in clinical studies to date including over 200 patients who had >4 years of maximum treatment duration. The confirmed good safety and tolerability of erenumab does not suggest increased risks for patients with longer exposure.

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. Exposure-response pharmacokinetic (PK) analyses over a large range of PK exposures indicated that 70 mg was the lowest dose resulting in efficacious concentrations and potentially higher efficacy could be achieved with 140 mg. Based on this results, a higher dose of 140 mg was incorporated into the following pivotal studies. Results from the erenumab Phase 2 study (Study 20120295) in patients with chronic migraine also 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 39.9% and 41.2% with 70 mg and 140 mg erenumab respectively compared to 23.5% with placebo. Both doses were also effective across various other endpoints including frequency-related outcomes and functional improvement measured by established Patient Reported Outcome (PRO) scales (Tepper et al 2017).

The results from two completed Phase 3 studies (Studies 20120296, 70 and 140 mg, and 20120297, 70 mg) in patients with episodic migraine, also showed positive outcomes for erenumab. In 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 et al 2018). In study 20120296, patients randomized to the 70 and 140 mg dose groups experienced mean 3.2 and 3.7-day reductions from baseline, respectively compared with a 1.8 days observed in the placebo group over weeks 13-24 (Goadsby et al 2017). Results for both of these studies were statistically significant. Fifty percent responder rates were significantly increased with erenumab compared to placebo in both of the Phase 3 episodic migraine studies. Treatment effects observed with 140 mg in Study 20120296 showed consistently higher values across different parameters and subgroups compared to placebo than the 70 mg group, suggesting additional efficacy in global patients with episodic migraine.

Apart from the global clinical program focused on Caucasian population, a Phase 1 study in Japanese subjects (Study 20120130) and a Phase 2 study (Study 20120309) in Japanese subjects with EM were conducted to support the registration in Japan. The PK of erenumab at 70 mg was similar and there is no ethnic difference between healthy Japanese and Caucasian subjects. Study 20120309 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. A total of 475 subjects were randomized 2:1:2:2 to receive placebo, erenumab 28 mg, 70 mg, or 140 mg during the 24-week double-blind treatment phase. While the results were significant for all 3 doses evaluated, the efficacy on the primary and secondary endpoints for the 28 mg dose were almost 50% lesser in magnitude than the 70 mg dose. Comparable efficacy was seen between 70 mg and 140 mg doses. Besides, the safety profile was similar to placebo and also comparable between Japanese and Caucasian subjects. A multi-regional, three arms (placebo, 70 mg and 140 mg groups), double-blinded, Phase 3 study (Study CAMG334A2302) in the EM population, primarily in Asia is currently ongoing. The purpose of this study is to obtain data from regions not adequately represented in the global pivotal trials, and to support registration in countries or regions requiring local data for regulatory approval (India, Korea, and Taiwan).

The safety and tolerability profile of erenumab was similar to placebo in both treatment groups for all studies. No adverse event (AE) occurred with an incidence of > 6%; the most commonly reported adverse events included injection site pain, infection of the upper respiratory tract and nausea. Based on a pooled analysis across four placebo-controlled trials, the identified adverse drug reactions include injection site reactions, constipation, muscle spasm and pruritus.

In view of limited information on ethnic subgroups, especially Chinese, this trial will provide additional information about erenumab safety and efficacy in CM in a mainly Chinese population and provide local data for regulatory submission.

1.2 Purpose

The purpose of this study is to obtain data from regions not adequately represented in the global Chronic Migraine (CM) pivotal study (Study 20120295), and to support registration of 70 mg erenumab in China. It has a similar design to the global pivotal study in CM (Tepper et al 2017), with the exception of the open-label treatment period.

The purpose of the open-label treatment period is to provide continued drug access to patients who completed the double-blind treatment period, until erenumab is launched in the country or until June 2021 in Korea. [redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the effect of erenumab compared to placebo on the change from baseline in monthly migraine days, in subjects with chronic migraine	• Change from baseline in monthly migraine days during the last 4 weeks of the 12-week treatment period

Objective(s)	Endpoint(s)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect of erenumab compared to placebo on change from baseline in migraine-related disability and productivity as measured by the modified Migraine Disability Assessment (mMIDAS)	• Change from baseline in migraine-related disability and productivity as measured by the mMIDAS during the last 4 weeks of the 12-week treatment period
• To evaluate the effect of erenumab compared to placebo on the proportion of subjects with at least 50% reduction from baseline in monthly migraine days	• Achievement of at least a 50% reduction from baseline in monthly migraine days during the last 4 weeks of the 12-week treatment period
• To evaluate the effect of erenumab compared to placebo on the change from baseline in monthly acute headache medication days	• Change from baseline in monthly acute headache medication days during the last 4 weeks of the 12-week treatment period
• To evaluate the safety and tolerability of erenumab	• Adverse events, clinical laboratory values, vital signs, and anti-AMG 334 antibodies

[redacted]

3 Study design

This study uses a single-cohort, 2-treatment arm, randomized (1:1 (70 mg: placebo)), double-blind study design in adult subjects with chronic migraine (see Figure 3-1), followed by an open-label treatment period.

Subjects with co-existing Medication Overuse (MO) of triptans, ergot-derivatives, analgesics and combination drug use will be allowed in the trial.

MO will be considered present if any of the following criteria are met during baseline period.

- ≥ 15 days of simple analgesics
- ≥ 10 days of triptans
- ≥ 10 days of ergots
- ≥ 10 days of combination therapy intake of any combination of ergots, triptans, combination-analgesic medications or simple analgesics

The following periods are included in the study design, with study visits at 4-week intervals after completion of screening:

- **Screening (up to 2 weeks):** to assess initial eligibility

- **Baseline (4 weeks)** diary compliance and headache frequency will be assessed for a final eligibility assessment prior to randomization and dosing. The maximum duration for the baseline period is 35 days. During the COVID-19 pandemic that limits or prevents on-site study visits, the duration of the baseline visit can be extended up to 50 days.
- Eligible subjects will be randomized 1:1 to once monthly erenumab 70 mg and placebo within each of the 4 strata below:
  - prior prophylactic migraine treatment failure and MO
  - prior prophylactic migraine treatment failure and non-MO
  - non-prior prophylactic migraine treatment failure and MO
  - non-prior prophylactic migraine treatment failure and non-MO
- **Double-blind treatment (12 weeks)**: Eligible subjects will be randomized to one of two treatment arms. At the end of this period (Week 12), the final assessment to address the efficacy-related objectives will occur.
- **Post double-blind treatment follow-up (12 weeks):** for subjects discontinuing treatment during the double-blind treatment period and willing to return for the subsequent scheduled follow-up (FUP) visits, until the Week 12 follow-up visit.
- **Safety follow-up (8 weeks)**: in subjects completing the double-blind treatment period, but not entering into the open-label treatment period, a safety follow-up visit will occur 8 weeks after the Week 12 visit (Week 20). Subjects who discontinue study drug during the double-blind treatment period and who do not remain in the study to follow the assessment schedule until the Week 12 FUP visit, will have the safety follow-up visit 12 weeks after the last dose. For subjects discontinuing double-blind treatment and remaining in the study to follow the assessment schedule until the Week 12 FUP visit, the Safety Follow-Up visit should occur on Week 20 even if the last dose was taken at Day 1. The Safety Follow-Up visit is not required in subjects who discontinue or complete the open-label treatment period.
- **Open-label treatment (until launch of erenumab in the country or until June 2021 in Korea):** all subjects completing the double-blind treatment period on study drug are invited to participate. Eligible subjects who consented to participate in this open-label treatment period will receive erenumab until it is launched in the country, or until June 2021 in Korea, in order to ensure continued drug access.

  Should a treatment gap exist between the two treatment periods due to a delay of HA/EC approvals or other administrative/logistical reasons, the subject may enter the open-label treatment period at a later time provided he or she still meets the eligibility criteria. During this treatment gap, the subject is allowed to use standard of care.

See the assessment schedule in Table 8-1.

Two interim analyses (IA) are planned for this study:

- A **blinded IA**, after approximately 50% (275) of subjects have completed the double-blind treatment period (including early withdrawals), will be conducted to re-estimate the sample size by providing information on the variance for this trial relative to the planned assumptions to account for potential higher variability in general Asian population.

- An **unblinded IA** will be conducted after 70% (385, if no increase of sample size is needed following the blinded IA) of subjects have completed the double-blind treatment period (including early withdrawals), to determine whether the study will stop early or continue to the final primary analysis (full sample size). Study recruitment will continue until unblinded IA read-out.

  If it is decided to stop early due to **success** (positive IA read-out), all subjects ongoing in the double-blind treatment period at the time of the IA read-out will be scheduled for an End of Treatment visit: they will then either enter into the open-label treatment period or enter into the safety follow-up Period (in case the subject does not want to continue in the open-label treatment period).

  In case of a **negative** interim analysis (70%) which is meeting the futility boundary, or in case of a negative primary analysis at the full sample size (100%), the open-label treatment period will be cancelled. All subjects ongoing in the double-blind treatment period at that time will be scheduled for an End of Treatment visit followed by a safety follow-up visit. All subjects ongoing in the open-label treatment period will be scheduled for an End of Treatment Open-Label visit.

  If it is decided to continue until final analysis, the recruitment will continue to full sample size.

  In case of exceptionally fast recruitment the unblinded IA might be cancelled and the full sample size will be analyzed.

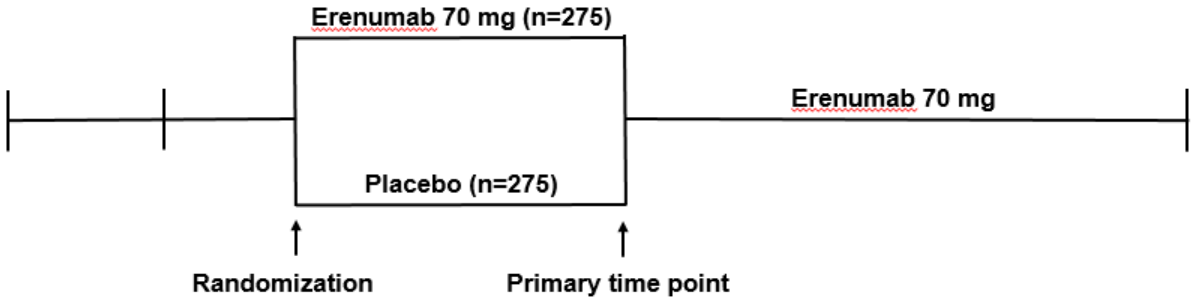
Two clinical study reports (CSR) are planned for this study:

- An **interim CSR** will be prepared for the **primary analysis**, when the last patient completed the double-blind treatment period (including early withdrawals). This might either be after approximately 70% of subjects completed the double-blind treatment period, or when 100% of subjects completed the double-blind treatment period. The CSR will include efficacy and safety data, as well as safety follow-up visit data up to this point. This CSR will be prepared for regulatory submission in China.
- A **final CSR** will be prepared when all subjects have completed their respective last visit (LPLV). In this CSR, all available data not captured in the interim CSR will be included.

In case of a **negative** primary analysis only one CSR will be developed, including all available double-blind, safety follow-up and open-label treatment data.

If the marketing application of erenumab, for the indication in this study, is rejected in a participating country, the subjects in that country will be discontinued from the open-label treatment period. End of Trial will occur when the last subject completes the last visit (Last patient Last Visit (LPLV)) of the trial.

Figure 3-1 Study design



Screening	Baseline	Double-Blind Treatment	Open-Label Treatment (if applicable)
2 weeks	4 weeks	12 weeks	Until launch of erenumab in the country or until June 2021 in Korea

Note: For subjects not entering the Open-Label Treatment period, Safety Follow-Up visit will occur 8 weeks after last visit of the Double-Blind Treatment period

4 Rationale

4.1 Rationale for study design

The subject population will be described in more detail in the Section 5 below.

A parallel-group, placebo-controlled design is a standard way of assessing efficacy and safety of new migraine prophylactic agents. This study design has been chosen in line with erenumab Phase 3 study designs, which were developed in accordance with the guidelines of the International Headache Society (IHS) for controlled trials of preventive treatment of chronic migraine in adults(Tassorelli et al 2018) and the IHS guidelines for Controlled Trials of Drugs in Migraine (Tfelt-Hansen et al 2012). The key design features were also aligned with China Centre Drug Evaluation (CDE) on 5-Sep-2018.

The open-label treatment period is a mechanism to provide **post-trial access** of erenumab until launch, or until June 2021 in Korea, to subjects who completed the double-blind treatment period.

Given that the enrolled chronic migraine subjects have a particular unmet need as they may have failed multiple treatments, and the available treatment choices for migraine prevention are limited after the completion of the double-blind treatment period, it is assumed that many of them will need to be treated for a longer period of time. Besides, subjects in the placebo group will get drug access during the open-label treatment period.

The confirmed good safety and tolerability of erenumab does not suggest increased risks for patients with longer exposure up to 64 weeks (Tepper et al 2017). Interim analysis from an ongoing five-year open-label extension study (Study 20120178), after all patients completed three years in the open-label treatment period, showed that 61.3% of the patients still remained in the study, which demonstrated adherence is favorable with erenumab and may result in positive long-term outcomes (Ashina et al 2019).

Therefore, in order to collect additional [redacted] data in this population of Chinese and Asian patients this open-label treatment period has been added.

4.2 Rationale for dose/regimen and duration of treatment

Dose-finding Phase 2 results for erenumab in EM subjects (Study 20120178) are available for the doses of 7 mg and 21 mg (both of which have proven to be ineffective compared to placebo) and 70 mg. The dose of 70 mg was established as the effective dose. It has shown a statistically significant and clinically relevant reduction in the primary endpoint of monthly migraine days. The PK of erenumab at 70 mg SC were similar for healthy Japanese and white subjects (ratio of geometric means [i.e, Japanese/white] for Cmax, AUClast, and AUCinf = 1.02, 1.12, and 1.12, respectively). Data from PK exposure-response modelling in global population indicated that additional efficacy might be achieved with a higher dose of 140 mg erenumab. The safety profile of erenumab has been investigated up to 280 mg in healthy volunteers in Phase 1 without a difference in safety profile. Based on these considerations, an additional dose of 140 mg s.c. q.m. has been included in global pivotal programs. The two main studies that inform the dosing in the current proposed study in CM population are Study 20120295 and Study 20120309.

One global pivotal study, Study 20120295, was conducted in the CM population (mostly Caucasian subjects). Subjects randomly assigned to either the erenumab 70 mg or erenumab 140 mg group experienced a mean 6.6 days reduction from baseline in monthly migraine days (2.4 days more than subjects receiving placebo). While there was no apparent difference between erenumab doses in primary endpoint, point estimates numerically favored 140 mg over 70 mg at Week 4 and Week 8 for MMD reduction as well as at all timepoints (i.e. weeks 4, 8, and 12) for all 3 secondary endpoints and multiple exploratory endpoints.

A Phase 2 study, Study 20120309, was conducted in Japan in the EM population. While the results were significant for all three doses evaluated (28 mg, 70 mg and 140 mg), the efficacy on the primary endpoint for the 28 mg dose was almost 50% lesser in magnitude than the 70 mg dose. Therefore, the 28 mg dose is not considered a clinically relevant dose given the similar safety profile between three doses. Comparable efficacy was seen between 70 mg and 140 mg doses in primary endpoint and all secondary endpoints, whereas maximal efficacy was observed with the 140 mg dose in the global Study 20120296. This study showed comparable exposure-response characteristics between the overall global and the Japanese population. The clinically relevant dose of 70 mg is consistent with the overall higher exposure associated with lower body mass index BMI/body weight in Japanese population, which likely led to the lack of incremental efficacy benefits in Study 20120309 between the 140 and 70 mg dose that were observed in the overall global population. This difference does not reflect any meaningful differences in ethnic sensitivity.

Similar BMI/body weight was observed between Chinese and Japanese based on prior study results in the same subject population. Since the body-weight was the only important covariate identified with the population PK modeling, we do not expect that other demographic/ethnic factors might be associated with a relevant difference between global and Japanese and/or Chinese population. Consequently, the 70 mg is likely also the appropriate efficacious dose in Chinese population. Although this study was conducted in the EM population, numerous lines of evidence that support they are a continuum of the same disorder (Section 1.1).

The combination of Study 20120295 and Study 20120309 are therefore considered most informative for the dose selection and support the selection of the 70 mg dose in this study.

The 12-weeks double-blind study duration is endorsed by IHS guidelines as a sufficient duration to assess efficacy in prophylactic migraine treatment clinical trials. A longer double-blind trial duration is not considered feasible due to the prolonged placebo exposure.

Subjects will receive either erenumab 70 mg q.m. s.c. or matching placebo for 12 weeks in the double-blind treatment period, followed by erenumab 70 mg q.m. s.c. in the open-label treatment period.

4.3 Rationale for choice of control drugs (comparator/placebo)

The choice of a specific therapy for a migraine headache prophylactic often takes into account individual circumstances, comorbidities and patient preferences. The preventive treatment choices are similar between other countries and China. Patients are currently being treated by a variety of drug classes that were originally developed for other indications, but were repurposed for migraine prophylaxis. Some drugs have been formally approved for migraine prophylaxis in many countries. The most common approved drugs are propranolol, metoprolol, topiramate and flunarizine. For CM patients, the therapeutic options are even more limited, with only onabotulinum toxin (Botox®) being specifically approved in United States, several EU countries and Canada. In China, only one drug, flunarizine, is approved for migraine prophylaxis. However, there is no solid evidence and adequate and well-controlled trial conducted worldwide with flunarizine for migraine prophylaxis. Other drugs, while not formally approved, are considered acceptable alternatives and are recommended within national treatment guidelines. Examples with evidence for migraine headache prophylaxis include other drug classes such as antidepressants (mainly amitriptyline and venlafaxine), Angiotensin-Converting Enzyme inhibitor/Angiotensin-Receptor Blocker (ACE/ARBs) (mainly candesartan and lisinopril) and valproate/divalproex. All of those drugs are occasionally used as migraine prophylactics, but the use is off-label and rests on the individual clinical responsibility of the prescribing physician after an adequate individual benefit-risk assessment.

All of these therapies, regardless if approved or off-label, are commonly associated either with variable migraine efficacy and/or substantial tolerability issues that often lead to treatment discontinuation. The standard of care also varies significantly across different geographies and treatment decisions, particularly in patients that have already failed the standard first line therapies are often made on a case-by-case basis without general consensus on treatment guidelines. Because of the variability of standard of care across different geographies and the potential for functional unblinding due to typical adverse events with any active comparator, placebo was selected as the comparator. The short duration (12 weeks) of placebo treatment, in conjunction with the allowed use of acute migraine treatment, justifies the use of placebo in this study as also suggested in the IHS guidelines (Tfelt-Hansen et al 2012, Tassorelli et al 2018). All patients continue to receive best supportive care in form of acute abortive medications and other non-pharmacological interventions as appropriate.

4.4 Purpose and timing of interim analyses/design adaptations

A blinded interim analysis, after approximately 50% (275) of subjects have completed the treatment period (including early withdrawals), will be conducted to re-estimate the sample size by providing information on the variance for this trial relative to the planned assumptions to account for potential higher variability in general Asian population.

An unblinded interim analysis will be implemented when 70% (385) of subjects have completed the treatment period (including early withdrawals). An independent Data Monitoring Committee (DMC) will conduct this interim analysis.

The main purpose of this unblinded interim analysis is to determine whether the trial will stop early due to success, or will continue to the final analysis with the planned full sample size (100%), based on the result of the primary efficacy assessment. This interim analysis will focus on the primary efficacy endpoint, but the DMC recommendation on whether to stop the trial or not will be based on the evaluation of totality of efficacy and safety data at the time of interim cut-off. The study team will not be unblinded unless the study is stopped early for success.

Refer to Section 12.7 for more information regarding this unblinded IA.

4.5 Risks and benefits

Key risks and benefits are briefly summarized below. For further information, please refer to the current Investigator Brochure (IB).

The safety of erenumab in migraine prophylaxis was assessed from integrated safety analyses of 4817 subjects with migraine who received at least one dose of erenumab (dose level at 7, 21, 70, or 140 mg), representing 4418.3 subject-years of exposure as of data cut-off date 16 May 2019 as per Investigator's Brochure edition 11.1. Overall, the safety and tolerability profile of erenumab was similar between the 140 mg and 70 mg doses and also comparable to placebo. For adverse drug reactions refer to Section 7 (Summary and Data and Guidance for the Investigator) of the IB.

Overall, to date, there is no evidence from nonclinical and clinical data of risk of cardiovascular effects. On the theoretical basis of the mechanism of action of erenumab, CGRP receptor blockade may reduce compensatory vasodilation, particularly under ischemic conditions. To determine the potential impact of erenumab on total exercise time, time to exercise-induced angina, and ST depression during a Treadmill Test in subjects with stable angina, a double-blind, placebo-controlled study conducted and demonstrated that erenumab does not impact exercise tolerance or interfere with homeostatic vasodilatory mechanisms in subjects with chronic myocardial ischemia. However, in this planned study, cardiovascular effects continue to be monitored, and subjects with major cardiovascular disease within 12 months prior to screening will be excluded from participation.

All biologicals, including fully human proteins, have the potential to induce immunogenicity leading to the development of specific anti-drug antibodies. Overall, erenumab treatment is associated with a low incidence of immunogenicity. While the number of anti-AMG 334 antibody-positive subjects is limited, impact analyses suggest that despite a modest reduction in exposure among anti-AMG 334 antibody-positive subjects, there was no impact of anti-AMG 334 antibody development on efficacy or safety. Subjects in clinical studies will continue to be monitored for the development of anti-erenumab antibodies and 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 subjects 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.

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 outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

The need for a regular safety data monitoring committee for this study was assessed and deemed not necessary because the safety profile of erenumab has already been well-characterized from 4 double-blind, placebo-controlled trials in over 2500 subjects. The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and use of rescue medications.

Three pivotal/key Phase 2/3 studies (Goadsby et al 2017, Tepper et al 2017, Dodick et al 2018), including 1 study in CM (study 20120295), have been completed with erenumab, which have established 70 mg and/or 140 mg as being effective and safe in subjects 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 other 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.

Besides, a one-year open-label extension to Study 20120295 in CM subjects was completed to evaluate the long-term efficacy, safety and tolerability of erenumab. Based on results for all dose groups, a long-term persistence of efficacy was observed that the mean (95% CI) change from baseline in MMDs was -8.36 (-8.92, -7.80) days at week 24 and -9.29 (-9.96, -8.62) days at week 52. From the safety aspect, the AE profile with longer exposure up to 1 year were similar to the AE profile in placebo-controlled phase and no additional signals of concern were identified with long-term treatment in global studies.

As of July 2018, two open-label extension studies of erenumab in patients with chronic and episodic migraine were reported (1 and 3 years extension respectively), confirming sustained efficacy and a favorable safety and tolerability profile (Tepper et al 2017, Ashina et al 2019) (Study 20120295 and Study 20120178). Additionally, erenumab has been approved for migraine prophylaxis in adults in the United States of America (USA), the European Union (EU) as well as in other countries since 2018.

Overall, given the characteristics of erenumab and the large experience in clinical trials, the overall benefit-risk assessment is supportive.

5 Study population

The study population will consist of male and female subjects, ages 18 to 65, with a documented history of chronic migraine as outlined in the inclusion criteria.

The goal is to randomize approximately 550 subjects in China and other Asian countries/regions. Approximately 350 Chinese subjects will be recruited, or around 250 subjects for the unblinded IA (when 70% of subjects completed the treatment period (including early withdrawals)). Assuming a 30% screening failure rate, approximately 790 subjects will be screened.

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. Adults ≥ 18 to ≤ 65 years of age upon entry into screening
3. History of at least 5 attacks of migraine without aura and/or migraine with visual, sensory, speech and/or language, retinal or brainstem aura according to the IHS Classification ICHD-3 (Headache Classification Committee of the International Headache Society, 3rd edition 2018) based on medical records and/or patient self-report.
4. History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine days per month in each of the 3 months prior to screening
5. ≥ 15 headache days of which ≥ 8 headache days meet criteria as migraine days during the baseline period based on the eDiary calculation (the detailed definition of migraine day can be found in Section 8.3.1)
6. Demonstrated at least 80% compliance with the eDiary (e.g. must complete eDiary items on at least 23 out of 28 days during the baseline period) based on the eDiary calculation
7. History of migraine (with or without aura) for ≥ 12 months prior to screening according to the IHS Classification (Tassorelli et al 2018) based on medical records and/or patient self-report

5.2 Exclusion criteria

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

1. Older than 50 years of age at migraine onset
2. History of cluster headache or hemiplegic migraine headache
3. Chronic migraine with continuous pain, in which the subject does not experience any pain free periods (of any duration) during the 1 month prior to screening
4. Unable to differentiate migraine from other headaches
5. Taken an opioid and/or opioid-containing analgesic for any indication during more than 4 days within one month prior to the start of the baseline period or during the baseline period
6. Taken a butalbital-containing analgesic for any indication during more than 2 days within one month prior to the start of the baseline period or during the baseline period
7. Prior migraine prophylaxis treatments failure in more than 3 out of the following medication categories:

- Category 1: Divalproex sodium, sodium valproate
- Category 2: Topiramate
- Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
- Category 5: Flunarizine, verapamil, cinnarizine
- Category 6: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- Category 7: Botulinum toxin
- Category 8: Lisinopril, candesartan
- Category 9: Pregabalin, gabapentin
- Category 10: Zonisamide
- Category 11: Memantine
- Category 12: Pizotifen

Prior migraine prophylaxis treatments failure is defined as efficacy failure or tolerability failure.

- Efficacy failure is defined as "no meaningful reduction in headache frequency after administration of the respective medication for at least 6 weeks at generally accepted therapeutic dose(s) based on the investigator's assessment within the last 5 years prior to screening."
- Tolerability failure is defined as "documented discontinuation due to adverse events of the respective medication at any previous time."

8. Use of a prohibited medication **for migraine prophylaxis** within 5 half-lives, or a device or procedure for migraine prophylaxis (e.g. transcranial magnetic stimulation, greater occipital nerve block, invasive or non-invasive neuromodulation) within one month prior to the start of the baseline period or throughout the study (Refer to Section 6.2.2 for the list of these excluded medications, devices and procedures for migraine prophylaxis)

   Note: use of other non-pharmacological treatments and traditional techniques such as acupuncture, traditional and herbal medicine, etc. is in general allowed if the dose/regimen is stable for at least 1 month prior to the start of the baseline phase and also stable throughout the study.
9. Prior Botulinum toxin A treatment in the head/neck region within 4 months prior to the start of the baseline period or during the baseline period
10. Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain)
11. History of major psychiatric disorder (such as schizophrenia or other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder), or current evidence of depression based on a Beck Depression Inventory (BDI)-II total score > 24 at Screening. Subjects with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable and are taking no more than one medication for each disorder. Subjects must have been on a stable dose within the 3 months prior to the start of the baseline period.

12. History of seizure disorder or other significant neurological conditions other than migraine. (note: A single childhood febrile seizure is not exclusionary)
13. 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.
14. History or evidence of any other unstable or clinically significant medical condition, that in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion
15. Human immunodeficiency virus (HIV) infection by history
16. Evidence of pre-existing liver condition as defined as any of the following:
    - Total bilirubin (TBIL) ≥ 2.0 × upper limit of normal (ULN) or alanine transaminase (ALT) or aspartate aminotransferase (AST) ≥ 3.0 x ULN, as assessed by the central laboratory at initial screening
    - Known history of acute/active hepatitis B virus (HBV) or hepatitis C virus (HCV) within 3 months prior to screening according to local clinical practice
17. Myocardial infarction (MI), stroke, transient ischemic attach (TIA), unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening
18. Subject has any clinically significant vital sign, laboratory, or electrocardiogram (ECG) abnormality during screening that, in the opinion of the investigator, could pose a risk to subject safety or interfere with the study evaluation
19. Score “yes” on item 4 or item 5 of the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale (C-SSRS), if this ideation occurred in the past 6 months, or “yes” on any item of the Suicidal Behavior section, except for the “Non-Suicidal Self-Injurious Behavior” (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.
20. Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids or barbiturates)
21. Pregnant or nursing (lactating) women
22. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, 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 investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject

- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

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

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.

23. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamics (PD) effect has returned to baseline, whichever is longer.
24. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes
25. Any prior exposure to investigational or marketed products targeting the CGRP pathway, including previous erenumab studies
26. Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures to the best of the subject's and investigator's knowledge. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients

5.3 Inclusion/Exclusion criteria for the open-label treatment period

Inclusion criteria

Subjects eligible for inclusion in the open-label treatment period must meet the following additional criteria:

8. Completed the double-blind treatment period on study drug and did not meet any of the discontinuation criteria
9. Signed informed consent covering the open-label treatment period

Exclusion criteria

Subjects meeting any of the following criteria are not eligible for the open-label treatment period:

27. Local access to launched erenumab

28. Subject developed, during the double-blind treatment period, any contra-indication as per the Investigator's Brochure (IB) Edition 9.1 Appendix A section 4.3, or any unstable or clinically significant medical condition, laboratory or ECG abnormality that in the opinion of the investigator would pose a risk to subject safety. Note: Any ECG abnormality noted by the central reader must be evaluated by the investigator and discussed with the sponsor as deemed necessary to determine if the ECG finding is representative of an unstable or clinically significant medical condition

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Novartis will supply the investigational product listed below in Table 6-1.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
AMG334 70 mg/1 mL	Solution for injection	Subcutaneous Use	Double Blind supply; pre-filled syringe	Sponsor global
Matching placebo 1 mL	Solution for injection	Subcutaneous Use	Double Blind supply; pre-filled syringe	Sponsor global
AMG334 70 mg/1 mL	Solution for injection	Subcutaneous Use	Open Label supply; pre-filled syringe	Sponsor global

The matching placebo to AMG334 70 mg/1 mL pre-filled syringe will have the same appearance as the investigational drug. Each syringe will be packaged individually in double-blinded fashion for the double-blind treatment period. The study treatments will be labeled as AMG334 70 mg/1 mL/Placebo.

For the open-label treatment period each pre-filled syringe will be packaged individually in open-label fashion. This open-label study treatment will be labeled as AMG334 70 mg.

6.1.2 Additional study treatments

No additional treatment beyond investigational drug and control drug are included in this trial. Rescue medication is allowed as outlined in Section 6.2.3.

6.1.3 Treatment arms/group

Subjects will be assigned to either erenumab 70 mg, or placebo at the Randomization Visit (Visit Day 1), in a 1:1 ratio, stratified by prior prophylactic migraine medication treatment failure and medication overuse status.

Study medication will be provided as follows:

- Placebo: One pre-filled 1 mL syringes (PFS) containing placebo identical in appearance to erenumab
- AMG334 70 mg: One PFS containing 70 mg/1 mL of erenumab

6.1.4 Treatment duration

The planned duration of double-blind treatment is 12 weeks. Subjects who complete the double-blind treatment period may be eligible to participate in the open-label treatment period until the drug is launched in the country or until June 2021 in Korea.

Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the subject.

6.2 Other treatment(s)

6.2.1 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 in the appropriate Case Report Form (CRF) or eDiary for the double-blind treatment period and in the CRF only for the open-label treatment period.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing 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.

Use of concomitant therapies for indications other than migraine prevention is allowed throughout the course of the study. Medications with possible migraine prophylactic effects (the list of relevant medications can be found in Section 6.2.2) for **indications other than migraine prevention** (e.g. beta blockers used for anti-hypertension, SNRIs used for major depressive disorder) are permitted in the study if they are considered by the investigator to be stable and are taking no more than 1 medication for each indication. Subjects must have been on a stable dose within the 3 months prior to the start of the baseline period. The dose level must be stable throughout the study.

Use of other non-pharmacological treatments and traditional techniques such as acupuncture, traditional and herbal medicine, etc. is in general allowed if the dose/regimen is stable for at least 1 month prior to the start of the baseline period and also stable throughout the study (with the exception of Cao Wu Jia Su Pian, Du Liang Ruan Jiao Nang that shall not be administered at least 2 weeks prior to the start of the baseline period and throughout the study).

6.2.2 Prohibited medication

1. The following medications **used for migraine prophylaxis** are excluded within 5 half-lives prior to the start of the baseline period and throughout the study, including the open-label treatment period:
    - Antiepileptics (e.g. divalproex sodium, sodium valproate, topiramate, carbamazepine, gabapentin, pregabalin, zonisamide)

- Beta blockers (e.g. atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- Tricyclic antidepressants (e.g. amitriptyline, nortriptyline, protriptyline)
- Serotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- Calcium channel blockers (e.g. flunarizine, verapamil, cinnarizine)
- Others: Lisinopril, candesartan, cyproheptadine, pizotifen, memantine, butterbur, feverfew, magnesium (> 600 mg/day), riboflavin (> 100 mg/day)
- Cao Wu Jia Su Pian, Du Liang Ruan Jiao Nang

2. Botulinum toxin A (in the head and/or neck region) is excluded within 4 months prior to the start of the baseline period and throughout the study.
3. Ergotamine-derivatives, steroids and triptans used for migraine prophylaxis are excluded within 2 months prior to the start of the baseline period and throughout the study.
4. Devices and procedures used for migraine prophylaxis (e.g. nerve stimulators, transcranial magnetic stimulation, greater occipital nerve block, invasive or non-invasive neuromodulation, pulsed radiofrequency) are excluded within 1 month prior to the start of the baseline period and throughout the study.
5. Investigational medications, devices, and procedures, unless specifically allowed as per above, are excluded throughout the study.

6.2.3 Rescue medication

Subjects can continue to use “best supportive care” as rescue medication. This can include both pharmacologic interventions (i.e., abortive treatments for acute attacks) and non-pharmacologic interventions (e.g. biofeedback, psychotherapy, acupuncture or other locally accepted and endorsed interventions for migraine). Traditional medications (e.g. herbal medicines) are allowed as determined by the investigator, as long as the regimen is not likely to interfere with headache assessments. Chronically administered “best supportive care” is recommended to be in a stable regimen for at least 1 month prior to the start of baseline period.

During or before the screening period, the subject and investigator are to agree on the medications for the acute treatment of headache pain and the appropriate dose(s) that the subject may take on an as-needed basis (Pro re nata, PRN) throughout the study. Medications for acute treatment of headache pain include: simple analgesics, combination analgesics, triptans, ergot-derivatives. Opioid-containing and butalbital-containing analgesics are not allowed during the study. To avoid confounding the study results, new acute medications for treatment of headache pain should not be introduced after the start of baseline visit (in double blind treatment period) and addition of daily medication that fall into the categories of simple analgesics, combination analgesics, triptans, and ergot-derivatives should be avoided, even if the medication is used for indications other than headache.

Site staff will pre-specify the name, dose strength, and route of administration of the subject’s acute headache (rescue) medications in the subject’s eDiary (double-blind treatment period only). If the subject takes an acute headache medication during aura or to treat a migraine or non-migraine headache, they will select one of the pre-specified medications (or “other” medication) and enter the date of administration, the number of times the medication was taken

on that date and number of units taken. Use of rescue medication must be recorded in the eDiary during the double-blind treatment period only. Relevant non-drug therapies as part of "best supportive care" use should also be recorded in appropriate CRF.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At Day 1, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the subject. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supplies using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by prior prophylactic migraine treatment failure (Yes vs. No) and presence of medication overuse (Yes vs. No) during baseline according to the planned randomization ratio within each stratum. The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Group.

6.4 Treatment blinding

Subjects, investigator staff, persons performing the assessments, and clinical trial team (CTT) will remain blind to the identity of the treatment from the time of randomization using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
    - PK/anti-AMG 334 antibody analysts who will keep PK/anti-AMG 334 antibody results confidential until data base lock

- DMC members and unblinded statisticians and programmers in charge of the outputs of unblinded IA (including statisticians from external vendors involved in data analyses)

2. The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding will occur in the case of subject emergencies (see Section 6.6.2) and at the conclusion of the primary analysis. Randomization information will be available to the investigator when the clinical study report for the primary analysis has been finalized.

Table 6-2 Blinding levels

Role	Time or Event		
	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis & dose escalation
Subjects/Patients	B	UI	B
Site staff	B	UI	B
Independent committees used for assessing interim results	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	B

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

The starting dose for erenumab is 70 mg/1 mL and matching placebo is 1 mL. Subjects will keep this dose throughout the study. Study treatment dose adjustments are not permitted. For subjects who are unable to tolerate the protocol-specified dosing scheme, dose interruptions of study treatment are permitted in order to keep the subject on study drug. These changes must be recorded on the appropriate CRF.

6.5.2 Follow-up for toxicities

6.5.2.1 Follow up on potential drug-induced liver injury cases

Subjects with transaminase increase combined with TBIL increase may be indicative of potential DILI and should be considered as clinically important events.

The threshold for potential drug-induced liver injury (DILI) may depend on the subject's baseline AST/ALT and TBIL value; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2.0 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2.0 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as alkaline phosphatase (ALP) elevation > 2.0 x ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis.
Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

In the absence of cholestasis, these subjects should be immediately discontinued from study treatment, and repeat Liver Function Test (LFT) testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, Gamma-glutamyl transferase (GGT), prothrombin time (PT)/ International Normalized Ratio (INR), and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant” and thus, meet the definition of Serious Adverse Event (SAE) and should be reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

During both the double-blind treatment and the open-label treatment period, the study medication is administered by the investigator or designated study staff at each visit. This information should be captured in the source documents and the CRF at each visit. All study treatment administered must be recorded in the Drug Accountability Log. Information regarding treatment during the COVID-19 pandemic can be found in Section 13.2.

Site staff will review eDiary compliance with the subject at each visit during the double-blind treatment period.

6.6.2 Emergency breaking of assigned treatment code

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

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

- protocol number
- study drug name
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit(s) to the subject, site personnel will detach the outer part of the label(s) from the packaging and affix it to the source document.

During both the double-blind treatment as well as the open-label treatment period, one medication kit will be dispensed per visit by the IRT system. The medication is administered by the investigator or designated study staff at each visit.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure (IB). Clinical supplies are

to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They 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.

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 Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Subcutaneous (s.c.) injections are to be administered in the clinic by qualified staff at drug dispensing visit.

For purposes of study treatment dosing, "q.m." refers to an every 4 weeks injection regimen. The study drug administration date should be in 4-week increments (± 5 days) from the first dose of study drug. Any dose administrations that may occur greater than ± 5 days from the 4-week timepoint (e.g. subject unavailability) should be discussed with the Sponsor prior to dosing. The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen; the location of the injection sites should be documented in the source document.

One injection will be administered by qualified study staff at each dosing visit during the 12-week treatment period (i.e. at Day 1 and Weeks 4 and 8). Subjects will be administered one of the following, depending on their randomization:

- 70 mg erenumab: one 70 mg erenumab syringe
- Placebo: one placebo syringe

One injection of 70 mg erenumab will be administered by qualified study staff at each visit during the open-label treatment period.

The investigator must promote compliance administering the study treatment exactly as prescribed. The investigational product dose is fixed and will not be adjusted for individual subjects during the study. There are no temporal restrictions for study drug administration (eg, proximity to meals, sleep or activity).

All kits of study treatment assigned will be recorded in the IRT, both for the double-blind treatment and the open-label treatment period. Novartis monitors will reconcile treatment assigned vs treatment administered and ensure that the information is congruent during their monitoring visits.

During the COVID-19 pandemic:

During the **COVID-19 pandemic** that limits or prevents on-site study visits, delivery of study drug directly to a subject's home is generally permitted in the event the Investigator has decided that an on-site visit by the subject is no longer appropriate or possible, and that it is in the interest of the subject's health to administer (e.g., self-injection or study staff administration at subjects' home) the study treatment even without performing an on-site visit. Implementation will need to be discussed with Novartis (see section 7 for required training process). The dispatch of study drug from the site to the subject's home remains under the accountability of the investigator. Each shipment/provisioning will be for a maximum of 1 month supply. In this case, regular phone calls or virtual contacts (at the time of every scheduled visit, or more frequently if needed) will occur between the site and the subject for instructional purposes, safety monitoring, and discussion of the subject's health status until the subjects can again visit the site.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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 Investigator's Brochure (IB). 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 between IB updates will be communicated as appropriate, for example, via an Investigator Notification (IN) 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.

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

During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate informed consent form by subject and person obtaining informed consent, etc...).

During the **COVID-19 pandemic** the investigator should also discuss the home-delivery of study drug, and should provide detailed step by step instructions for the proper method for self-administration of study drug including: 1) the correct handling, 2) self-administration procedure, and 3) storage of study drug. This training may be done in person or videoconference or by telephone if subject visits to site are not possible. This training process needs to be documented in the subject chart with the subject's verbal/e-mail/ or chat function agreement. Written informed consent must be obtained once protocol amendment 2 is approved at the site.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments 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 End of Treatment visit will be performed. At this visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

If the **COVID-19 pandemic** limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff to the subject's home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the subject to visit the site again (see Section 8.3 Efficacy, Section 8.4 Safety, Section 8.4.1 Laboratory evaluations, Section 8.4.2 Electrocardiogram (ECG), Section 8.4.3 Pregnancy and assessments of fertility, Section 8.4.4 Prospective suicidality assessment, [redacted], Section 8.5.5 AMG 334 Antibody testing, Section 10 Safety monitoring and reporting, Section 10.2.2 Prospective suicidality assessment and Section 13.2 Responsibilities of the Investigator and IRB/IEC for further COVID-19 guidance).

Table 8-1 Assessment Schedule

Period	Screening		Double-Blind Treatment[1,2]				Post Double-Blind Treatment Follow-Up[1]				Open-Label Treatment[1]				
Visit Name	**Screening**	**Baseline**	**Day 1**	**Week 4**	**Week 8**	**End of Treatment (EOT)**	**Week 4 FUP[3]**	**Week 8 FUP[3]**	**Week 12 FUP[3]**	**Safety Follow -Up[4,5]**	**Week 12**	**Week 16, 20, 28, 32, 40, 44...**	**Week 24**	**Week 36, 48, and every 12 weeks**	**End of treatment Open-label**
Days	**-42**	**-28**	**Day 1**	**28**	**56**	**84**	**28**	**56**	**84**	**140**	**84**	**112, 140, 196, 224, 280, 308...**	**168**	**252, 336...**	
Weeks	**-6**	**-4**	**1**	**4**	**8**	**12**	**4**	**8**	**12**	**20**	**12**	**16, 20, 28, 32, 40, 44...**	**24**	**36, 48...**	
Informed consent	X										X				
IRT contact[6]	X	X	X	X	X	X					X	X	X	X	X
Randomization			X												
Demography	X														
Inclusion/Exclusion criteria	X	X									X				
Medical history/current medical conditions[7]	X														
Complete Physical Examination	S					S				S					
Brief Physical Examination		S	S	S	S		S	S	S						
Electrocardiogram (ECG)	X		X	X		X									

Period	Screening		Double-Blind Treatment[1,2]				Post Double-Blind Treatment Follow-Up[1]				Open-Label Treatment[1]				
Visit Name	**Screening**	**Baseline**	**Day 1**	**Week 4**	**Week 8**	**End of Treatment (EOT)**	**Week 4 FUP[3]**	**Week 8 FUP[3]**	**Week 12 FUP[3]**	**Safety Follow -Up[4,5]**	**Week 12**	**Week 16, 20, 28, 32, 40, 44...**	**Week 24**	**Week 36, 48, and every 12 weeks**	**End of treatment Open-label**
Days	**-42**	**-28**	**Day 1**	**28**	**56**	**84**	**28**	**56**	**84**	**140**	**84**	**112, 140, 196, 224, 280, 308...**	**168**	**252, 336...**	
Weeks	**-6**	**-4**	**1**	**4**	**8**	**12**	**4**	**8**	**12**	**20**	**12**	**16, 20, 28, 32, 40, 44...**	**24**	**36, 48...**	
Vital signs and body measurements[8]	X	X	X	X	X	X	X	X	X	X					
Chemistry	X		X			X				X			X		
Hematology	X		X			X				X			X		
Pregnancy Test (serum)	X					X									
Pregnancy test (urine)		S	S	S	S		S	S	S	S			S	S	S
Urine Drug Screen	X														
Anti-AMG 334 antibodies[9]			X			X				X					
eDiary Dispensing		S													
eDiary Return[10]			S	S	S	S	S	S	S						
Clinical Outcome Assessment(s)		X[11]					X[11]								

Period	Screening		Double-Blind Treatment[1,2]				Post Double-Blind Treatment Follow-Up[1]				Open-Label Treatment[1]				
Visit Name	Screening	Baseline	Day 1	Week 4	Week 8	End of Treatment (EOT)	Week 4 FUP[3]	Week 8 FUP[3]	Week 12 FUP[3]	Safety Follow -Up[4,5]	Week 12	Week 16, 20, 28, 32, 40, 44...	Week 24	Week 36, 48, and every 12 weeks	End of treatment Open-label
Days	-42	-28	Day 1	28	56	84	28	56	84	140	84	112, 140, 196, 224, 280, 308...	168	252, 336...	
Weeks	-6	-4	1	4	8	12	4	8	12	20	12	16, 20, 28, 32, 40, 44...	24	36, 48...	
[redacted]															
mMIDAS[13]			X	X	X	X	X	X	X						
Columbia-Suicide Severity Rating Scale (C-SSRS)[13]	X	X	X	X	X	X	X	X	X	X					
Beck Depression Inventory-II (BDI-II)	X[12]														
[redacted]															

Period	Screening		Double-Blind Treatment[1,2]				Post Double-Blind Treatment Follow-Up[1]				Open-Label Treatment[1]				
Visit Name	Screening	Baseline	Day 1	Week 4	Week 8	End of Treatment (EOT)	Week 4 FUP[3]	Week 8 FUP[3]	Week 12 FUP[3]	Safety Follow -Up[4,5]	Week 12	Week 16, 20, 28, 32, 40, 44...	Week 24	Week 36, 48, and every 12 weeks	End of treatment Open-label
Days	-42	-28	Day 1	28	56	84	28	56	84	140	84	112, 140, 196, 224, 280, 308...	168	252, 336...	
Weeks	-6	-4	1	4	8	12	4	8	12	20	12	16, 20, 28, 32, 40, 44...	24	36, 48...	
Concomitant medications	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Adverse Events[14]	X	X	X	X	X	X	X	X	X	X					
Study drug administration[15]			X	X	X						X	X	X	X	
Study Disposition Form						X				X					X

X Assessment to be recorded in the clinical database or received electronically from a vendor

S Assessment to be recorded in the source documentation only

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

[2] Entry (i.e. randomization) into the double-blind treatment period using the IRT System must occur only after the successful completion of all Screening Period requirements and prior to the first dose of study drug (randomization and administration of the first dose must occur on Day 1).

[3] Week 4 FUP, Week 8 FUP, Week 12 FUP are to be performed by discontinued subjects (double-blind treatment period) who are willing to remain on the study to perform regular assessments.

[4] The Safety Follow-Up Visit is required for all subjects who either discontinue study drug in the double-blind treatment period or complete the double-blind treatment period without continuing in the open-label treatment period.[5] Safety Follow-Up Visit is 12 weeks after last dose of study treatment during the double-blind treatment period. For patients discontinuing treatment during the double-blind treatment period and remaining on the study to follow the assessment schedule until Week 12 Follow-Up (FUP) visit, Safety Follow-Up visit should occur on Week 20 even if last dose was taken at Day 1.

[6] Sites will access the Interactive Response Technology (IRT) System to enter the subject into the initial screening period, to randomize an eligible subject into the

double-blind treatment period, to dispense study treatment during the double-blind and open-label treatment periods, and to register study early termination. Subject data will be collected in the IRT System including, but not limited to, reason for screen fail (if applicable). The IRT system will automatically assign study drug when a subject is randomized.

[7] Including prior prophylactic migraine medication

[8] Height collected at Screening visit only. Weight collected at Screening, Baseline, and End Of Treatment (double-blind treatment period) visits. Blood pressure, pulse and body temperature collected at every double-blind treatment period visit.

[9] At Day 1 visit sample should be collected prior to dose administration.

[10] Subject brings the eDiary device to each double-blind treatment visit for use at site.

[11] Subjects will record headache and headache medication information daily, using the provided eDiary device, during the double-blind treatment period.

[12] Completed daily via the eDiary device, during the double-blind treatment period.

[13] To be completed during applicable study visits before study drug administration.

[14] Adverse Events will be collected after Informed Consent signature through the end of the Follow-Up Period (12 weeks after the last dose of study drug) [redacted].

[15] Study drug is administered by study staff, every 4 weeks (± 5 days) during the applicable study visits. One pre-filled syringe will be administered at each visit.

8.1 Screening

The procedures are to be completed during the screening period can be found in Table 8-1.

The duration of the screening period is up to 2 weeks. Certain screening procedures may be repeated during the original screening period. In case a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to baseline period. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study. Novartis may grant an extension to the screening period in rare cases where additional time is required to confirm eligibility.

Investigators may re-screen a subject (screening period only) if the investigator is reasonably certain that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Re-screening after the subject entered the baseline period is not allowed. Reasons to re-screen may include but are not limited to the following:

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

or

- Additional time is required following the subject's last dose of an excluded medication.

Investigators are encouraged to consult with Novartis prior to re-screening subjects for other reasons.

A subject must provide informed re-consent prior to the initiation of any re-screening procedures. A new subject number will be assigned. A subject may be screened up to 2 times (i.e. no more than 1 re-screen).

Near to the end of randomization, sites may be notified when no additional subjects will be screened or re-screened.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for subjects who are found to be ineligible during the Screening visit. No other data will be entered into the clinical database for screen failure subjects, unless the subject experienced a serious adverse event during the Screening period (see SAE section for reporting details). If the subject fails to be randomized, the IRT should be notified within 2 days of the screen fail that the subject was not randomized.

Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: age, sex, race, ethnicity, relevant medical history/current medical condition present before signing informed consent where possible, diagnoses and not symptoms will be recorded.

Prior headache characteristics and previous headache medication history will be collected as part of baseline characteristics.

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

8.3 Efficacy

Efficacy assessments will include:

- Migraine days

The timing and frequency of these assessments are outlined in Table 8-1. Subjects will record the efficacy information using the provided eDiary platform. To aid in compliance, it is recommended that the information be completed at the same time every day that is convenient for the subject. Retroactive completion will be allowed one day prior to the time of completion. Any entries > 2 days old will not be allowed and will be considered missing data.

During the COVID-19 pandemic that limits or prevents on-site study visits, efficacy information including PRO scales may still be collected by using the provided eDiary.

8.3.1 Migraine Days

A migraine day is defined as any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for **≥ 4 continuous hours**, and meeting at least one of the following criteria:

1.≥ 2 of the following pain features:

- Unilateral
- Throbbing
- Moderate to severe
- Exacerbated with exercise/physical activity

2.≥ 1 of the following associated symptoms:

- Nausea and/or vomiting
- Photophobia and phonophobia

If the subject took **ANY acute medication** (simple analgesics [NSAIDs, acetaminophen], combination analgesics, triptans or ergot-derivative) during aura, or to treat a **moderate or severe headache** on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms. A migraine headache event that is lasting less than 24 consecutive hours in duration, regardless whether or not it extends into the prior or next

calendar day for less than 4 hours, should be counted as a single migraine day, even if acute medication is taken on the prior or next calendar day. Opioid-containing analgesic and butalbital-containing analgesics are excluded in allowed acute medication categories.

8.3.2 Appropriateness of efficacy assessments

Monthly migraine days (MMD) is a clinically relevant and commonly accepted primary endpoint in accordance with current standards and guidelines (Tassorelli et al 2018, Tfelt-Hansen et al 2012) for migraine prophylactic studies. The definition of migraine day (Section 8.3.1) in this study is adapted based on the diagnostic criteria of ICHD-3 (3rd edition 2018) and the clinical practice in China. Acute migraine-specific medication (mainly triptan) use is very common in global countries or regions. In global pivotal Study 20120295 in CM population, 75%-79% patients used acute migraine-specific medication during baseline. However, the use of triptan or ergots is extremely low in China (Jiang et al 2016). Almost all of migraine patients in China usually use migraine unspecific analgesics such as NSAIDs or combination analgesics for the acute treatment of migraine. Due to the difference in use pattern of acute migraine-specific medication (mainly triptans) between Chinese and the global migraine population, the criteria of migraine day in ICHD-3 makes this clinical tool less applicable in our clinical setting, and argues for inclusion of other acute migraine-unspecific medications in the definition of migraine day in this study to better illustrate Chinese patients characteristics. This definition of migraine day was also aligned with China CDE. The monthly migraine days will be calculated using migraine day data collected from the eDiary.

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

8.4 Safety

During the COVID-19 pandemic that limits or prevents on-site study visits regular phone or virtual calls will occur (at the time of every scheduled visit or more frequently if needed) for safety monitoring and discussion of the subject´s health status until the subject can again visit the site.

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 Safety Assessments

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, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A brief physical exam, as per local practice, will include the examination of general appearance and will be at all visits starting from Visit Baseline, except where a complete physical examination is required (see above). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History section of the CRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded in the Adverse Event section of the CRF.
Vital sign	Vital signs include blood pressure, pulse and body temperature measurements and will be collected at every visit of the double-blind treatment period [redacted]. Pulse, systolic and diastolic blood pressure will be measured three times when the subject has been sitting for approximately 5 minutes. The repeat sitting measurements should be made at approximately 1 - 2 minute intervals and the mean of the three measurements will be used for analysis purposes. If an automated blood pressure device is used, it should be calibrated according to the manufacturer's guidelines. The method to take temperature should be consistent throughout the study. During the **COVID-19 pandemic** that limits or prevents on-site study visits, the measurements of vital signs may be performed locally.
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. Height will be collected at Screening visit only. Weight will be collected at Screening, Baseline, and End Of Treatment visits.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Central lab will provide urine pregnancy test to be assessed at site during the double-blind treatment period. Site will have to use local pregnancy test during the open-label treatment period. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Section 16.1

During the **COVID-19 pandemic** that limits or prevents on-site study visits, or if visits by site staff to a subject's home are not feasible, the collection of samples may be modified by Novartis and will be communicated to the investigator (e.g., local lab collection of samples).

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Red Blood Cells (RBC), Nucleated RBCs, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, Reticulocytes, Platelets, White Blood Cells (WBCs), WBC differential (Bands/Stabs, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, Myeloblasts, Promyelocytes, Myelocytes, Metamyelocytes, and Atypical Lymphocytes)
Chemistry	Sodium, Potassium, Chloride, Bicarbonate, Total Protein, Albumin, Calcium, Magnesium, Phosphorus, Glucose, BUN/Urea, Bilirubin (Direct and Total), Alkaline Phosphatase, ALT (SGPT), AST (SGOT), Total Cholesterol, HDL, LDL, Triglycerides, CPK, and eGFR.
Drug Screen	Urine Drug test for substances of abuse, at Screening. It can also be performed during the study at the investigator's discretion based on clinical suspicion. If a subject has a positive urine drug screen during the study (except for certain prescribed medications), the investigator should consider discontinuation from the investigational product.
Pregnancy testing	Serum or Urine

8.4.2 Electrocardiogram (ECG)

All ECGs must be recorded as outlined in the central ECG reading manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) as reported by the central reader should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs, printed on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, subject 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. Clinically significant ECG findings at randomization (pre-dose) must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the CRFs as appropriate.

During COVID-19 pandemic, if a subject cannot visit the site to have ECG recorded, or if visits by site staff to a subject's home are not feasible, the ECG may be performed locally and the result reported to the site. If local ECG is an option, each ECG tracing must be recorded as outlined in the central ECG reading manual, be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. A communication process should be established with the patient so that the site is informed of the ECG result if performed locally.

If it is not possible to perform ECG locally, ECG must then be performed at the next on-site visit.

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 Screening and End of Treatment (End of Treatment visit/week 12 being the first visit of the open-label treatment period in case the subject agrees to participate).

Urine pregnancy tests will be performed at the remaining double-blind treatment visits, every three months during the open-label treatment period and at the End of Treatment Open-Label visit. Kits will be provided by the Central Lab only for the double-blind treatment visits assessments.

The specific schedule is outlined in Table 8-1.

For more details about potential deviation in case of local regulations, please refer to Section 5.2 and Exclusion criterion #22.

During COVID-19 pandemic, if a subject cannot visit the site to have pregnancy tests conducted the subject may complete a urine pregnancy test at home and report the result to the site. It is important that subjects are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the subject so that the site is informed of the pregnancy test results.

8.4.4 Prospective suicidality assessment

The C-SSRS is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior. The C-SSRS must be administered at each visit of the double-blind treatment period, including unscheduled visits.

A validated version of the electronic Columbia Suicide Severity Rating Scale eC-SSRS will be used to capture self-reported eC-SSRS data via a web-based interactive response system and via a phone system (both interchangeable). The eC-SSRS uses a detailed branched logic algorithm to perform the eC-SSRS subject interview, evaluating each subject's suicidality ideation and behavior in a consistent manner. At the conclusion of each assessment, a detailed eC-SSRS Findings Report will be available on the vendor portal. If the system assesses the subject as having positive suicidal signs, the investigator will be immediately notified by either email and via telephone.

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

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

All SAEs relating to suicidal behavior must be reviewed by the safety physician.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, the eC-SSRS may still be collected via a web-based interactive response system or via a phone system (both interchangeable). In this latter case, the dialing number will be temporarily kept by the vendor.

8.4.5 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Clinical Outcome assessments (COAs) will be collected by subjects using a handheld electronic diary (eDiary) at various frequencies during the **double-blind treatment period**.

The eDiary will collect the following COAs daily, at home:

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

The eDiary will categorize headache events as migraine days or headache days based on the definitions below:

- Headache Day: Any calendar day in which the subject experiences a qualified migraine or a non-migraine headache (initial onset, continuation, or recurrence of the headache lasting ≥ 4 continuous hours, or a headache of any duration for which acute medication was administered for treatment of headache pain). A headache event that is lasting less than 24 consecutive hours in duration, regardless if it extends into the prior or next calendar day for less than 4 hours even if acute medication is taken on the prior or next calendar day, should be counted as a single headache day.

- Migraine Day: see Section 8.3.1 for details.

The site study staff will train the subject on how to use the eDiary (e.g. turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day during the baseline period and treatment period and to bring the eDiary to every study visit. At the Day 1 study visit, the investigator will use the subject's eDiary device to review all data entered during the baseline period and confirm the relevant inclusion and exclusion criteria. Please refer to the eDiary manual for additional details.

During the COVID-19 pandemic that limits or prevents on-site study visits, COA information may still be collected using the eDiary.

8.5.2 Patient Reported Outcomes (PROs)

The eDiary will collect the following patient-reported outcomes (PRO) until the end of the double-blind treatment period:

- mMIDAS, monthly
- [redacted]
- Beck Depression Inventory, screen

For those PROs that are completed during the site visit, subjects must complete the PROs before any clinical assessments are performed.

Subject questionnaires as well as the COAs should be completed in the language most familiar to the subject. The subject should be given sufficient space and time to complete the PRO measure(s).

The responses (COAs and PROs) stored electronically in the database will be considered the source file.

Site staff will review eDiary compliance with the patient at each applicable visit.

8.5.2.1 Modified Migraine Disability Assessment Questionnaire (mMIDAS)

The modified MIDAS is a 5-item self-administered questionnaire that sums the number of productive days lost over the past month in two settings: the workplace and the home. The MIDAS also assesses disability in family, social, and leisure activities. The MIDAS score is the sum of missed days due to a headache from paid work, housework, and non-work (family, social, leisure) activities; and days at paid work or housework where productivity was reduced by at least half. The analysis will based on total score, subscore of absenteeism (items 1, 3, and 5) and subscore of presenteeism (items 2 and 4).

Subjects will complete the MIDAS at the timepoints outlined in Table 8-1. The recall period is the past one month. The questionnaire takes approximately 5 minutes to complete.

[redacted]

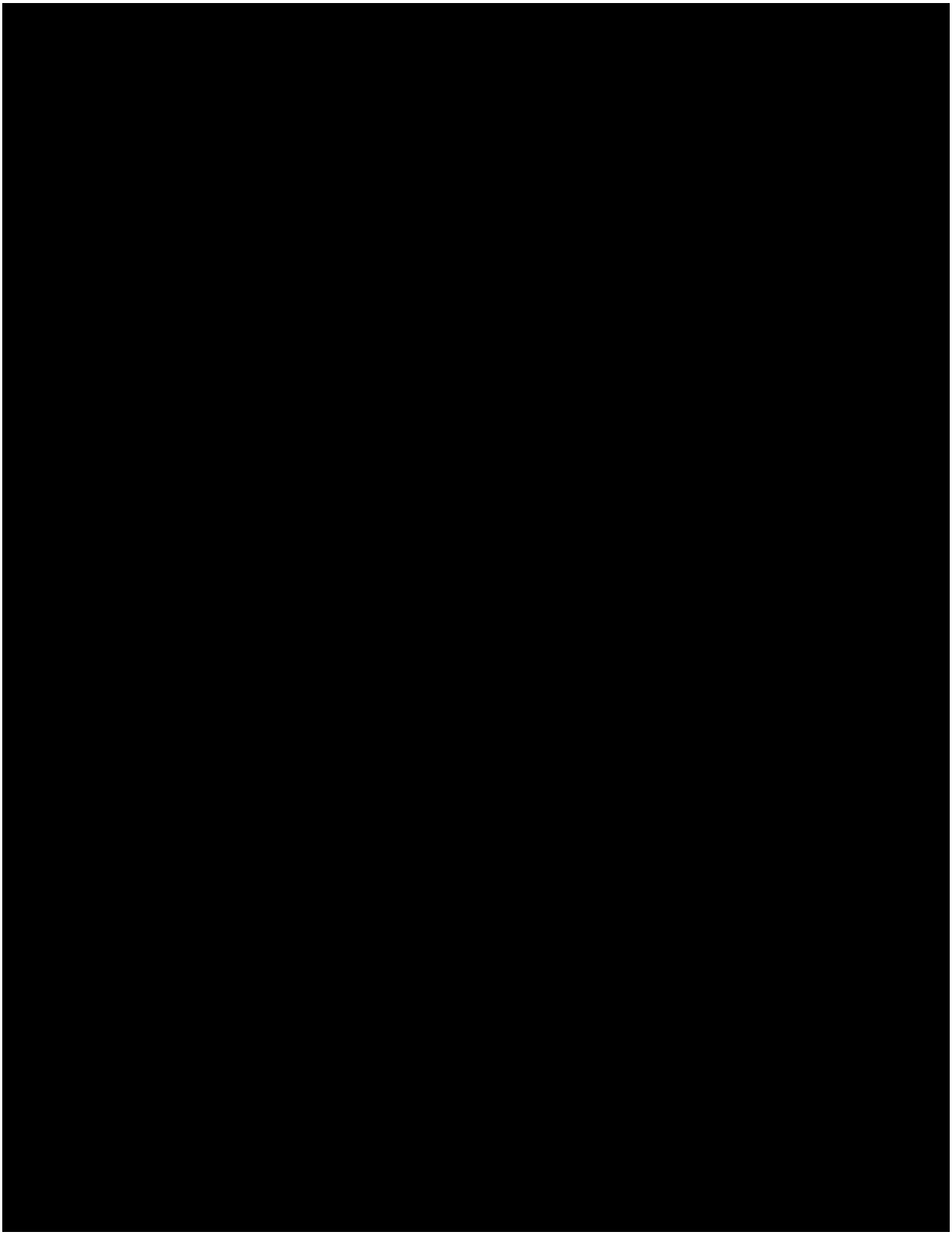
[redacted]

8.5.2.4 Beck Depression Inventory (BDI)-II

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

Subjects will complete the BDI-II at the timepoint outlined in Table 8-1. The recall period is the preceding two weeks, including the day of completion. The questionnaire takes approximately 10 minutes to complete.

[redacted]



8.5.5 AMG 334 Antibody testing

Blood samples for antibody testing are to be collected for the measurement of anti-AMG 334 binding antibodies. Samples will be collected at the timepoints defined in Table 8-1, prior to study drug administration. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity, and presence of immune complexes. Additional blood samples may be obtained for further evaluation of anti-AMG 334 antibodies during the study.

Sites will not be notified of positive neutralizing antibody results to the investigational product for a subject prior to that subject's final scheduled study visit and the subjects with a positive neutralizing antibody response will continue to be dosed during the course of study.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, or if visits by site staff to a subject's home are not feasible, the collection of samples may be modified by Novartis and will be communicated to the investigator.

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 drug is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

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

Study treatment must be discontinued under the following circumstances:

- Subject/Guardian decision
- Pregnancy (See Section 8.4.3)
- Use of prohibited treatment as per recommendations in Section 6.2.2
- 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 subject's overall status, prevents the subject from continuing participation in the study
- Following emergency unblinding (during the double-blind treatment period)

In addition, study treatment should be discontinued under the following circumstances during the open-label treatment period:

- Upon launch of erenumab in the country or in June 2021 in Korea
- Subject is no longer clinically benefitting in the opinion of the investigator

If discontinuation of study treatment occurs during the double-blind or open-label treatment period, the subject should NOT be considered withdrawn from the study (unless the subject specifically withdrew the consent). The Subject should return to the clinic at the time of the next scheduled visit (4-weeks interval), for the 'End of Treatment' or 'End of Treatment Open-Label' visit respectively. Assessments detailed for this visit in Table 8-1 should be completed

and recorded in the appropriate CRF. 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 on the appropriate CRF.

Subjects who discontinue the study treatment in the double-blind treatment period and are willing to return for the subsequent scheduled Follow-Up (FUP) visits should perform the End of Treatment assessments at the time of the next scheduled visit (4-weeks interval). The subject will then continue the subsequent FUP visits as per Table 8-1, including the Safety Follow-Up visit on Week 20.

All subjects ongoing in the treatment period at the time of a positive IA read-out will be scheduled for an End of Treatment visit and then enter directly into the open-label treatment period or into the safety Follow-Up Period (in case the subject does not want to continue in the open-label treatment period) without performing those FUP visits.

Subjects who discontinue the study treatment in the double-blind treatment period and are NOT willing to return for the subsequent FUP visits should perform the assessments according to the End of Treatment visit as soon as possible and the following data should be collected after study treatment discontinuation and until the Safety Follow-Up visit (which should occur 12 weeks after the last dose):

- new / concomitant treatments
- adverse events/Serious Adverse Events

If the subject who discontinued study treatment in the double-blind treatment period cannot or is unwilling to attend the End of Treatment visit or the Safety Follow-Up visit, the site staff should maintain telephone contact with the subject, or with a person pre-designated by the subject.

Subjects who discontinue the treatment during the open-label treatment period and performed the End Of Treatment visit will not be allowed to re-enter the study.

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If study drug discontinuation occurs because the treatment code has been broken, please refer to Section 6.6.2. Subjects who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled subjects.

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 their time of withdrawal) according to applicable law.

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 for any reason.

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 the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible for End of Treatment Visit 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 the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

A subject will be considered to have completed the double-blind treatment period when the subject has completed Week 12. A subject will be considered to have completed the open-label treatment period when the subject remained in the study until erenumab is launched in the country or until June 2021 in Korea.

A subject will be considered to have completed the study when the subject has completed the last visit as per the protocol. The study will be considered completed when the last subject completes their last visit planned in the protocol.

Enrollment will continue at least until the time of the unblinded IA read-out. In case of positive read-out, enrollment will stop. Refer to Section 9.1.1 for details on how to handle ongoing subjects. In case the study does not stop early, enrollment will continue until the full sample size.

10 Safety monitoring and reporting

During the **COVID-19 pandemic** that limits or prevents on-site study visits, regular phone or virtual calls will occur (at the time of every scheduled visit or more frequently if needed) for safety monitoring and discussion of the subject's health status until the subject can again visit the site.

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 in the Adverse Events CRF 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. Adverse events will be assessed and graded according to the most current version of the Common Terminology Criteria for Adverse Events (CTCAEs)
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject

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
- Drug interrupted/withdrawn

6. its outcome (i.e. recovery status or whether it was fatal)

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.

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 Investigator's Brochure (IB).

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 subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1

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 the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Safety 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.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

10.1.4 Pregnancy reporting

Pregnancies

If a female subject becomes pregnant, the study treatment must be stopped, and the subject must be asked to read and sign the pregnancy follow-up consent form to allow the investigator to ask about her pregnancy. 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 Safety. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment for 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 (European Medicines agency (EMA) definition).

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the Study Treatment CRF irrespective of whether or not associated with an AE/SAE and reported to Novartis 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 Dose Administration (DAR) CRF (Yes/No)	Document in AE CRF	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 completion of the standard AE CRF pages

Please refer to Table 16-2 in Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Once a subject is exposed to study treatment, 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 16-3. Repeat liver chemistry tests (i.e. ALT, AST, TBIL, PT/INR, ALP and GGT) 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 reported on the unplanned local laboratory CRF (or liver CRF page).

- 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 the procedures performed must be recorded as appropriate in the AE CRF.

10.2.2 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The C-SSRS must be administered at each visit of the double-blind treatment period, including unplanned visits.

A validated version of the eC-SSRS will be used to capture self-reported eC-SSRS data via an interactive voice response telephone system (eC-SSRS). The eC-SSRS uses a detailed branched logic algorithm to perform the eC-SSRS subject interview, evaluating each subject's suicidality ideation and behavior in a consistent manner. At the conclusion of each assessment, the investigator will receive a detailed eC-SSRS Findings Report via e-mail or fax. If the system assesses the subject as having positive suicidal signs, the investigator will be immediately notified by either fax, email and/or via telephone.

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

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

During the **COVID-19 pandemic** that limits or prevents on-site study visits, the eC-SSRS may still be collected via phone or via the web link.

10.2.3 Data Monitoring Committee

This study will include a DMC which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study.

The DMC will conduct regular unblinded safety reviews of cumulative safety data. In addition, the DMC will assess efficacy and safety data at the pre-defined unblinded interim analysis timepoint (see Section 12.7).

This unblinded IA will be conducted after 70% (385) of subjects have completed the treatment period (including early withdrawals). Although this unblinded IA will focus on the primary efficacy endpoint, the secondary efficacy endpoints and safety data will also be assessed. The DMC recommendation on whether to stop the trial or not will be based on the evaluation of the totality of efficacy and safety data at the interim cut-off. The study team will not be unblinded unless the study is stopped early for success.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.4 Steering Committee

There will be a Steering Committee (SC) for this study. The SC is comprised of a group of external subject matter experts who will provide guidance to Novartis on scientific conduct and reporting of the study, as well as to serve as the publication committee. The SC membership, roles and responsibilities, meeting arrangements and other detailed information will be defined in a separate charter that is established between the sponsor and the SC.

10.2.5 Adjudication committee

Not applicable.

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 (CRF). The CRFs 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 Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the CRFs, 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 CRF) 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 Contract Research Organization (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.

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

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

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 CRFs) 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/CRA 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

The primary analysis will include double-blind treatment data as well as safety follow-up data available at the time of the cut-off. Ongoing subjects at the time of the cut-off will not be included.

Additional analysis will be performed at the end of the study, when all subjects have completed their respective last visit (LPLV). [redacted]

Interim analyses will be performed at planned time points with details defined in Section 12.7.

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

As this study is a China-centric study, the primary and interim analyses (only if early stop for efficacy) will be repeated for Chinese population for primary endpoint, secondary endpoints, [redacted] and important safety evaluations (i.e. adverse events). The consistency of treatment effect of primary endpoint in Chinese population will be evaluated accordingly. [redacted]

12.1 Analysis sets

The following analysis sets are defined for the double-blind treatment period:

The **Full Analysis Set (FAS)** includes all subjects who were randomized in the study. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Tabulations of demographic and baseline characteristics, disposition, important protocol deviations (IPDs), and efficacy analyses will utilize this analysis set.

The **Safety analysis set (SAF)** will consist of all randomized subjects who received at least one dose of investigational product. In SAF, subjects will be analyzed based on actual treatment received. Safety analyses will be performed based on SAF.

The following analysis set is defined for the open-label treatment period:

The **Open-label treatment analysis set (OAS)** will consist of all subjects who consented to enter into the open-label treatment period and who have taken at least one dose of erenumab during the open-label treatment period. This analysis set will be used when summarizing data collected during the open-label treatment period.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group (choose appropriate term as needed, e.g. for all subjects, or by treatment group or dose cohort) for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class (SOC) and preferred term (PT) by treatment group.

12.3 Treatments

The number of investigational drug injections administered will be summarized and the study administration information will be presented in listing for SAF for the double-blind treatment period and for OAS for the open-label treatment period.

In addition, concomitant medications and significant non-drug therapies during the double-blind treatment period, prior to and after the start of the study treatment, will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group for SAF. Prior medications and significant non-drug therapies which were used and ended before start of study treatment will be summarized for FAS. The rescue medications and prohibited medications will be analyzed similarly.

12.4 Analysis of the primary endpoint(s)

The primary objective of the study is to evaluate the effect of erenumab compared to placebo on the reduction of monthly migraine days from baseline. This will be measured by the change from baseline in monthly migraine days at the last 4 weeks of the 12-week treatment period. Primary endpoints will be analyzed for FAS.

12.4.1 Definition of primary endpoint(s)

The primary efficacy endpoint is the change from baseline in monthly migraine days during the last 4 weeks of the 12-week treatment period. The monthly migraine days will be calculated using data collected from the eDiary.

12.4.2 Statistical model, hypothesis, and method of analysis

The null hypothesis is that there is no difference in the change from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period between erenumab group and placebo group versus the alternative hypothesis that there is a difference between the two groups. The null hypothesis will be rejected if the observed p-value for the between-group comparison is less than the significant level adjusted according to the alpha spending function with the O'Brien-Flemming approach. The nominal p-value threshold will be calculated upon the exact information collected in the interim analysis, considering the alpha-level spent at interim analysis and considering the actual correlation among the test statistics, in order to achieve a cumulative type I error smaller than the desired significance level (i.e. smaller than the 5% for a two-sided test). The primary efficacy endpoint variable will be analyzed using a generalized

linear mixed model with treatment, scheduled visit, treatment by visit interaction, and the stratification variables and baseline values as covariates. If applicable, unstructured covariance structure is assumed. Least squares means (LSMs) for treatment groups and its associated 95% confidence intervals, difference of LSMs compared to placebo group and the associated 95% confidence interval of the difference, as well as the nominal two-sided p-values, will be tabulated by visit and treatment.

12.4.3 Handling of missing values/censoring/discontinuations

The method of handling missing data for efficacy endpoints will be described for each set of endpoints. For the primary analysis, missing data will not be imputed, but various sensitivity analyses under missing not at random (MNAR) assumptions will be performed. Missing data will not be imputed for safety endpoints. Details of the missing data handling will be specified in the Statistical Analysis Plan (SAP).

12.4.4 Sensitivity and Supportive analyses

Multiple imputation (MI) techniques applying MNAR approaches will be used to assess the impact of missing values on the interpretation of the results during study. In addition, the baseline observations carried forward (BOCF) method will also be used.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary efficacy variables (all during the 12-week treatment period) are:

- Proportion of subjects who achieve at least a 50% reduction from baseline in monthly migraine days during the last 4 weeks of the 12-week treatment period.
- Change from baseline in monthly acute headache medication days during the last 4 weeks of the 12-week treatment period
- Change from baseline in migraine-related disability and productivity as measured by modified MIDAS during the last 4 weeks of the 12-week treatment period

The above continuous endpoints (i.e. change from baseline) will be analyzed using a generalized linear mixed effects model similar to the primary endpoint. The dichotomous endpoints will be analyzed by Cochran-Mantel-Haenszel (CMH) test with subjects who are missing monthly migraine day data during the last 4 weeks of the treatment period imputed as non-responders. Nominal 95% confidence intervals and p-values will be reported. Tests of secondary endpoints will be tested at nominal 2-sided significant level 0.05.

12.5.2 Safety endpoints

Safety analyses for the double-blind treatment period and the safety follow-up period will be conducted on SAF set. Safety data will be presented by actual treatments. Safety variables for the double-blind treatment and safety follow-up period include:

- Adverse events
- Clinical laboratory values, vital signs, and ECG
- Anti-AMG 334 antibodies

Safety data for the open-label treatment period will be conducted on OAS. [redacted]

Adverse events

The Medical Dictionary for Regulatory Activities will be used to code all adverse events (AEs). A treatment-emergent adverse events (TEAE) is defined as any adverse event that develops after initiation of study treatment until the end of the last study visit or any event already present that worsens following exposure to the study treatment until the end of the last study visit. Subject incidence rates of TEAEs will be tabulated by SOC and PT by treatment group, separately for the double-blind period [redacted]. Tables of TEAE by maximum toxicity grade, fatal AEs, serious AEs, AEs leading to withdrawal from investigational drug, treatment-related AEs, and serious treatment-related AEs will also be presented in a similar format as TEAE. Additionally, a listing of subject with TEAE will be presented. The TEAEs identified as potential risk will be summarized separately.

Laboratory data

The mean and change from baseline values of laboratory data will be summarized over time. Shift tables of the most extreme post-baseline value from baseline will be tabulated.

Vital signs

Vital sign measurements and their change from baseline will be summarized with descriptive statistics (mean, median, standard deviation, min, max) by visit. The number and percentage of subjects with clinical notable vital signs will be presented.

ECG evaluations

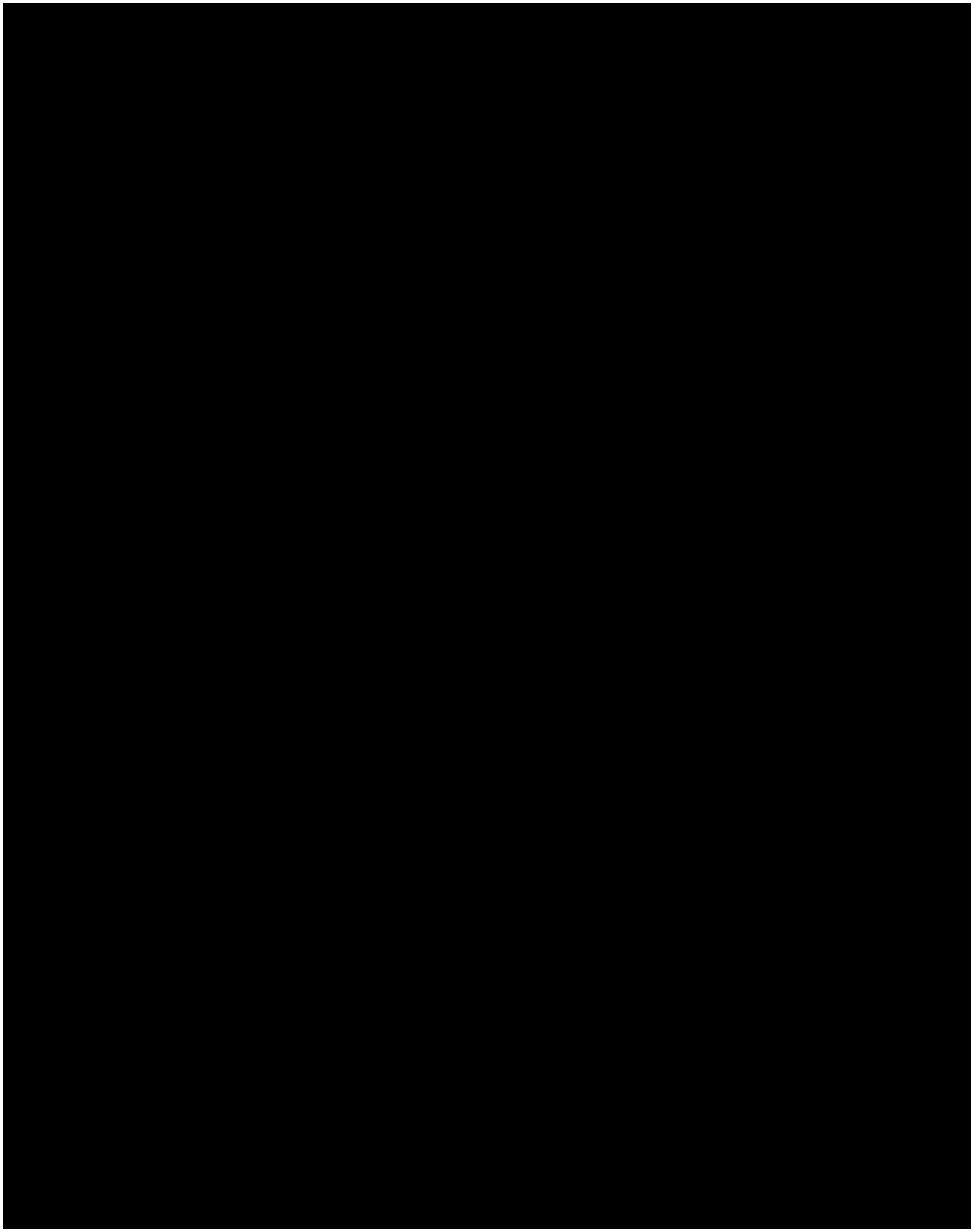
ECG intervals will be summarized by presenting summary statistics for changing from baseline values. The incidence rate of clinically notable ECG abnormalities will be summarized.

Anti-AMG 334 antibodies

The number and percentage of subjects who develop anti-AMG 334 antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

[redacted]

[redacted]



12.7 Interim analyses

To account for potential larger than expected variability during the study, a **blinded** sample size re-estimation is planned after about **50%** (275) subjects finish their treatment or early withdraw. Only the standard deviation of the primary variable, change from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period based on pooled (blinded) data, will be estimated. The sample size will be increased appropriately if the standard deviation is larger than expected. The blinded sample size re-estimation will be conducted by study team.

An **unblinded interim analysis** for potentially stopping the trial early for efficacy will be implemented when approximately **70%** (385, if no increase of sample size is needed following the blinded IA) of subjects finished the double-blind treatment period or discontinued from the study. The significant level will be adjusted using the alpha spending function with the O'Brien-Fleming boundary. An observed two-sided p-value ≤ 0.014 will be required at 70% information. The adjusted significance level based on the actual information included in the interim analysis will be used. If the study proceeds after interim analysis, the hypothesis test will be performed at the end of the double-blind treatment period using the pre-planned final adjusted significance level.

This unblinded analysis will be conducted and reviewed by an independent DMC. Interim results and unblinded data will not be accessible to Novartis personnel who are managing trial operations nor to study investigators and raters. Only DMC members will receive unblinded results. Detailed operating procedures will be specified in a DMC charter, which will define the composition and responsibilities of the DMC members as well as the detailed procedure for handling unblinded data within the DMC and for sharing with Novartis management personnel who is not part of the study team. The interim analysis will focus on the primary efficacy endpoint, but the DMC recommendation on whether to stop the trial or not will be based on the evaluation of totality of efficacy and safety data at interim cut-off. The detailed decision algorithms will be described in the DMC charter.

In case of a positive IA read-out with 70% information, the analysis results will be prepared for regulatory submission. Subjects who are ongoing at the cut-off time of the interim analysis will not be included in the unblinded interim analysis. Their data and all data collected beyond the IA cut-off will be analyzed separately.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The planned total sample size in this proposed China-centric phase 3 study is 550 subjects. The key assumptions in calculating the sample size are based on prior results from erenumab global pivotal study. A treatment difference in terms of change from baseline on MMDs during Week 9-12 (primary endpoint) for erenumab 70 mg vs. placebo is assumed at -2.0 days. The common standard deviation of the primary variable is assumed at 6.8. Given a 1:1 randomization ratio among erenumab 70 mg and placebo, it requires a total of 550 subjects (including 10% drop out rate) to achieve approximate 90% power to demonstrate the treatment difference of erenumab 70 mg compared with placebo under two-sided 0.05 alpha level. The impact of spending alpha at unblinded interim analysis on sample size and power is relatively negligible. Having this interim analysis with alpha spending at 0.014 two-sided, at final analysis an observed p-value

≤ 0.046 two-sided would be required (given that the interim analysis was performed when 70% subject finished treatment or early withdraw). With that said, the overall power will be maintained approximately at 90% with planned sample size.

The sample size for Chinese sub-population will make sure the consistency of treatment effect between Chinese and total population. The methods for consistency assessment is proposed as,

$Pr(D_{china} / D_{overall} > 0.5) > 95\%$,

which means that this China study should have high probability (>95%) to demonstrate consistency where the treatment effect (treatment difference of erenumab compared with placebo) observed in the Chinese population should be as high as at least 50% of the treatment effect observed in the overall study population in the prospective trial, assuming there is no difference between the Chinese population assessed in the trial and the overall population.

To meet the above criteria, approximately 350 (out of 550 for the overall study) Chinese subjects will be recruited.

At the interim analysis, as long as China population takes the majority of the overall population, there should have high likelihood to demonstrate the consistency as well.

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.

As mentioned in Section 7, during the COVID-19 pandemic, the training related to the home-delivery of study drug should be documented in the subject chart.

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 Standard Operating Procedures (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 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

References are available upon request

Ashina M, Goadsby PJ, Reuter U, et al (2019) Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. Cephalalgia 1-10.

Blumenfeld AM, Bloudek LM, Becker WJ, et al (2013) Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). Headache 644-55.

Buse DC, Silberstein SD, Manack AN, et al (2013) Psychiatric comorbidities of episodic and chronic migraine. J. Neurol. 1960-9.

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

Durham PL (2006) Calcitonin gene-related peptide (CGRP) and migraine. Headache S3-8.

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

Gooriah R, Nimeri R, Ahmed F (2015) Evidence-Based Treatments for Adults with Migraine. Pain Res Treat 629382.

Headache Classification Committee of the International Headache Society (IHS) (2018) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 1-211.

Jiang H, Deng Y, Zhang Y, et al (2016) Field testing of the ICHD-3β and expert opinion criteria for chronic migraine. J Headache Pain 85.

Stovner Lj, Hagen K, Jensen R, et al (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 193-210.

Tassorelli C, Diener HC, Dodick DW, et al (2018) Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. Cephalalgia Vol. 38(5) 815-832.

Tepper S, Ashina M, Reuter U, 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 425-434.

Tfelt-Hansen P, Pascual J, Ramadan N, et al (2012) Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia 6-38.

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. U.S.A. 11480-4.

Yu S, Liu R, Zhao G, et al (2012) The prevalence and burden of primary headaches in China: a population-based door-to-door survey. Headache 582-91.

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

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

Table 16-1 Clinically notable laboratory values

Laboratory Variable	Gender (M/F/Both)	Standard Units	SI Units
LIVER FUNCTION AND RELATED VARIABLES			
SGOT (AST)	F	>93 U/L	>93 U/L
SGOT (AST)	M	>111 U/L	>111 U/L
SGPT (ALT)	F	>90 U/L	>90 U/L
SGPT (ALT)	M	>123 U/L	>123 U/L
Total bilirubin	Both	>3.6 mg/dL	>63 mmol/L
Alkaline Phosphatase	F	>832 U/L	>832 U/L
Alkaline Phosphatase	M	>1032 U/L	>1032 U/L
HEMATOLOGY VARIABLES			
Neutrophils	Both	<1.5 x 10^3/uL	<1.5 x10^9/L

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

Table 16-2 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN · 1.5 x ULN < TBIL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBIL > 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 TBIL > 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 TBIL: total bilirubin; ULN: upper limit of normal

Table 16-3 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	ALT, AST, TBIL, Albumin, 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	ALT, AST, TBIL, Albumin, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately	ALT, AST, TBIL, Albumin, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Hospitalize, if clinically appropriate • Establish causality	
> 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	ALT, AST, TBIL, Albumin, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Establish causality • Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBIL, Albumin, 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	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBIL (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	ALT, AST, TBIL, Albumin, 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	ALT, AST, TBIL, Albumin, PT/INR, ALP and GGT until

Criteria	Actions required	Follow-up monitoring
	• Hospitalize the subject • Establish causality	resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBIL > 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.