Clinical Trial Protocol CHERUB01

Efficacy of erenumab in chronic cluster headache: A 10-week double-blind, randomized, placebo-controlled, multicentric trial.

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List of abbreviations

AE	Adverse Event
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
CGRP	Calcitonin Gene-related Peptide
CH	Cluster Headache
CQA	Compliance Quality Assurance
CRA	Clinical Research Associate
CRF	Case Report/Record Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBTE	Double-Blind Treatment Epoch
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
HIT	Headache Impact Test
HRQoL	Health-Related Quality of Life
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICHD	International Classification of Headache Disorders
ID	Identification
IEC	Independent Ethics Committee
IHS	International Headache Society
IP	Investigational Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention to Treat
IUD/IUS	Intrauterine Device/System
LFT	Liver function test
MAR	Missing at Random
MMRM	Mixed Model for Repeated Measurements
MNAR	Missing not at Random

PRO	Patient-reported Outcome
PSD	Premature subject discontinuation
PT	Prothrombin Time
q.m.	once a month
QM	Quality Management
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SF-12	Medical Outcome Short Form Health Survey
s.c.	Subcutaneous
SGOT	Serum Glutamic Oxaloacetic Transaminase (Aspartate Aminotransferase)
SGPT	Serum Glutamic Pyruvic Transaminase (Alanine Aminotransferase)
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total Bilirubin
TD	Treatment Discontinuation
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization
WoC	Withdrawal of Consent
γGT	Gamma-Glutamyltransferase

Glossary of terms

Calendar month	A calendar month is the period from a particular date in one month to the same date in the next month.
Cohort	A specific group of patients fulfilling certain criteria
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
eDiary	Handheld device for recording patient reported measures for each headache attack.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study, which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Medication pack number	A unique identifier on the label of each investigational drug package
Patient ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug.
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CHERUB01
Title	Efficacy of erenumab in chronic cluster headache: A 10-week double-blind, randomized, placebo-controlled, multicentric trial. (CHERUB)
Brief title	A 10-week double-blind, randomized, multicenter trial comparing the efficacy of erenumab (280mg loading dose at day 1, 140mg after 4 weeks) against placebo in adult patients with chronic cluster headache.
Sponsor and Clinical Phase	Charité Universitätsmedizin Berlin, Department of Neurology, Phase II
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the efficacy of erenumab in a loading dose of 280mg followed by 140mg after 4 weeks compared to placebo as a prophylactic treatment in patients with chronic cluster headache. Data from this study will provide important information if the blockade of the CGRP receptor with erenumab is an efficacious principle for the treatment of chronic cluster headache
Primary Objective	The primary objective of this study is to test the hypothesis that erenumab is superior to placebo in the reduction of weekly CH attacks in weeks 5 and 6 (days 29-42) in the erenumab group compared to placebo versus baseline.
Secondary Objectives	1. To evaluate the effect of erenumab compared to placebo on the proportion of patients with at least a 50% reduction from baseline in weekly CH attacks at week 5 and 6 (days 29-42). 2. To evaluate the effect of erenumab compared to placebo on the change from baseline in the GPI-Scale at week 6.
Study design	This study has a 6-week 2-arm, randomized, double-blind, parallel-group, placebo-controlled design.
Population	The patient population will compromise of 118 male and female patients with chronic cluster headache between the ages of 18 and <65, inclusive.
Key Inclusion criteria	<u>During the Screening Epoch</u> - Documented history of chronic cluster headache (cCH) for ≥ 12 months prior to screening based on the International Classification of Headache Disorders, 3rd Edition (ICHD-3) - Sufficient acute attack treatment with triptans or oxygen or both based on the patient´s history - Age between 18 and <65 years - Insufficient efficacy or tolerability or contraindications of approved cluster headache prophylactic medications. Insufficient efficacy and tolerability as determined by the patient <u>During the Baseline Epoch</u> - At least 9 cluster headache attacks (based on ICHD-3 criteria) in 7 days during the Baseline Epoch, confirmed by eDiary - Attacks must have occurred on at least 50% of days (≥50% of days). - ≥ 90% eDiary compliance during the Baseline Epoch

Key Exclusion criteria	- Diagnosis or history of other primary headache diseases including the diagnosis of episodic cluster headache according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3), excluding episodic tension type headache. - Use of a prophylactic cluster headache prophylaxis medication within 5 half-lives prior to the start of the baseline phase. (specified in Table 5.1) - Parallel use of an SPG stimulator or parallel use of a device for the acute/preventive treatment of cCH; - Significant comorbidities or psychiatric disorders, drug abuse or opioid use - Diagnosis or history of severe psychiatric or personality disorder - Concurrent use of other therapeutic monoclonal antibodies - Diagnosis of chronic or active hepatitis
Study treatment	Treatment arms: erenumab (280mg loading dose, 140mg after 4 weeks) and placebo. The investigational product is administered as a subcutaneous injection once per month.
Efficacy assessments	- CH attacks per week - Frequency, duration and intensity of CH attacks - Use of Rescue medication
Key safety assessments	- AE-related treatment discontinuations - Adverse event monitoring - Physical exams and vital signs - ECG monitoring - Monitoring of laboratory markers in blood - C-SSRS
Other assessments	Patient-reported outcomes: HIT-6, SF-12, PGI-I
Data analysis	For the analysis of this Proof-of-Concept study we will apply Bayesian methods. The methods used were suggested by Fisch et al.(Fisch et al., 2015). Using non-informative prior distributions, we will obtain samples from the posterior distribution of the differences in change from baseline between erenumab and placebo. For sampling from the posterior distribution, we will use the STAN software with the default, non-informative prior. A mixed effects model approach will be used to account for possible center-effects and baseline differences. A reduction of 3 attacks per week is considered as the threshold for clinical relevance, i.e. the smallest effect difference to placebo. Using the posterior distribution, we will calculate the proportion of samples that exceed this value, which is the posterior probability of erenumab having an effect larger than the relevance threshold. Further, the proportion of samples from the posterior distribution that exceed 0 will be calculated, which is the posterior probability of erenumab having any effect compared to placebo. This study will suggest to continue the development of erenumab in cluster headache, if the posterior probability of any effect is at least 90% (significance criterion) and if the posterior probability of a relevant effect (>3 reduction of attacks per week) is at least 50% (relevance criterion). In case of missing data, multiple imputation will be applied and the missing at random assumption will be assessed via sensitivity analysis.

	The population used for efficacy analyses will be the ITT population including all patients receiving at least one dose of active drug or placebo with at least one post-baseline efficacy assessment. Safety analyses will be performed on the safety population including all patients receiving at least one dose of active drug or placebo, In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they were randomized.
Key words	Cluster Headache, Chronic Cluster Headache, prophylactic treatment, monoclonal antibody, CGRP, Calcitonin Gene-related Peptide

1 Introduction

1.1 Background

Cluster headache is a primary headache disorder affecting about 100,000 people, mostly men (70%) in Germany. About 30% of all cluster headache patients suffer from chronic cluster, i.e. in one year, they are not experiencing more than 3 months without cluster headache attacks. In many cases chronic cluster headache develops from episodic cluster headache. Cluster headache attacks are characterized by a strictly unilateral, excruciating headache attacks with a duration of 15-180 minutes. Up to 8 attacks can occur during a day. Headache is necessarily associated with ipsilateral autonomic symptoms such as lacrimation, facial redness, unilateral sweating, ptosis, nasal congestion, or a runny nose. Chronic cluster is considered difficult to treat and many patients are not attack-free despite combination therapy for prophylaxis. Verapamil, Lithium, Topiramate or intermittent corticosteroids are used for prophylaxis alone or in combination, among which only lithium has regulatory approval. Their mechanism of action is unclear, but most of these substances interfere with CGRP. For the acute treatment of cluster headache sumatriptan s.c. or zolmitriptan nasal spray can be used. Both substances inhibit CGRP release from trigeminal afferent neurons and lead to the abortion of acute attacks in over 70% of patients within 30 minutes (Law et al., 2013). Oxygen 100%, with a flow rate of 7-12l/minute, is also commonly used for treating the acute cluster headache attacks (Dirkx et al., 2018).

Calcitonin Gene-Related Peptide (CGRP) is a potent endogenous vasodilator and neurotransmitter, which is involved in the pathophysiology of cluster headache. In 1991 Goadsby and Edvinsson were able to demonstrate the release of CGRP during cluster headache attacks. Our own work shows that treatment with steroids in patients in episodic cluster headache bouts reduces CGRP levels in jugular vein blood (Neeb et al., 2015). Nitroglycerin-induced cluster attacks lead to a measurable increase in CGRP in the blood.(Fanciullacci et al., 1995) In animal experiments, it has been shown that the activation of the ganglion trigeminal leads to the release of CGRP.(Limmroth et al., 2001). Activation of the trigeminal nervous system forms the experimental correlate of unilateral migraine or cluster headache.

The two CGRP monoclonal antibodies (mAbs) galcanezumab and fremanezumab have failed to show efficacy in double-blind placebo control studies in the prophylaxis of chronic cluster headache. In episodic cluster headache prevention galcanezumab was superior to placebo. (Goadsby et al., 2019) However, fremanezumab also failed to show superiority in eCH. Several reasons may apply for the failure of these trials. About 80% of study participants remained on stable prevention in these trials, which may lead to the lowering of CGRP levels. From a pathophysiological view, it is more difficult to achieve a significant difference to further lower CGRP levels by using a monoclonal antibody vs. placebo, which may lead to these negative study findings. Finally, there is also the possibility that blocking CGRP is not sufficient to block cluster headache attacks while blocking the CGRP receptor could lead to different findings. The CGRP receptor expression is constant and turnover is slow, while CGRP bursts seem to happen during cluster attacks in a significantly faster timely manner than in migraine. Therefore, a constant blockade of the CGRP receptor might be beneficial over the blockade of rapidly fluctuating ligand levels. The monoclonal antibody erenumab is a highly selective antagonist at the canonical CGRR receptor. Erenumab has been approved by the EMA in 2018

for the prevention of migraine in patients with at least 4 monthly migraine days (see medical product professional information). It is the aim of this study to investigate the preventive effects of erenumab monotherapy on cCH attack frequency compared to placebo.

The safety and tolerability profile of erenumab was similar to placebo in both treatment groups for all studies in migraine. A dose dependent increase of adverse events was not observed across trials. Most commonly reported AEs (≥3% in any group) include hypersensitivity, nasopharyngitis, fatigue, constipation, headache, back pain and influenza. Constipation has also been reported in post market real world studies and has been included into the SMPC.

There were no clinically significant changes in laboratory values, vital signs and electrocardiograms. For doses of 70mg and 140mg, the rate of adverse events is similar to what was seen with placebo (Goadsby et al., 2017). The overall safety and tolerability profile is similar to placebo for all doses across the phase 2 and 3 study for migraine. To date no clinical significant dose related tolerability concerns have been established (Dodick et al., 2018; Goadsby et al., 2017; Reuter et al., 2018).

In order to reach maximal efficacy and early steady state of active drug, we will use erenumab in a loading dose of 280mg s.c. followed by one single dose of 140mg s.c. after 4 weeks (and equal amounts of placebo). A dose of 280mg erenumab has been studied in a Phase I trial followed by 210mg s.c (multi-dose study; Hoon et al., 2018). We estimate that in the cluster headache population patients obtain an additional benefit from a loading with a faster reach of drug steady state. This may translate into earlier CH attack freedom and also will prevent a wearing off phenomenon in the last week of the 4-week treatment cycle (i.e. prior to the second injection of erenumab). Based on simulations from the manufacturer of erenumab (Novartis Pharma) the loading dose of 280mg in this trial will lead to a steady-state exposure equivalent to 140mg every 2nd week and comfortably maintain the exposure in a broad population above the saturation level and can expect a low placebo response due to fewer visits and contacts with the study sites than with a biweekly injection.

To minimize a placebo response we will not offer an open-label extension period after this study. Stable preventive co-medication are possible confounding factors and are therefore also excluded. In contrast, all approved acute medications (e.g. triptans and oxygen) to abort acute CH attacks are permitted.

Cardiac safety was no concern in all prior trials. However, ECG monitoring, arterial blood pressure monitoring and heart rate will be performed prior to all drug administrations.

Severe constipation, defined as less than 3 bowel movements /week not adequately manageable by routine medical treatment, within 3 months prior to screening, is an exclusion criterion. This is based on the IB (Investigators Brochure) stating constipation as an adverse reaction and the usage of a loading dose in this trial. Many of the cases of constipation with serious complications were reported for patients who have a history of constipation.

1.2 Purpose

The purpose of this study is to determine the efficacy of erenumab compared to placebo as a prophylactic treatment for patients with chronic cluster headache. Data from this study will provide proof of principle that blocking the CGRP receptor with erenumab is a suitable mechanism to reduce cluster headache frequency. In addition, this data will give insight in the pathophysiology of chronic cluster headache and the relevance of the CGRP receptor in this disease.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Primary **Objective**	**Endpoint**
To test the hypothesis that erenumab is superior to placebo in the reduction of weekly CH attacks in week 5 (days 29-35) and week 6 (36-42) versus baseline	Reduction from baseline (averaged per 7 days) in weekly CH attacks averaged for 7 days over the last 2 weeks (days 29-42) of the double-blind epoch.

Secondary **Objective**	**Endpoint**
To evaluate the effect of erenumab compared to placebo on the proportion of patients with at least a 50% reduction from baseline in weekly CH attacks at week 5 and 6 (days 29-42).	Number of patients achieving at least a 50% reduction from baseline in weekly CH attacks averaged over the last 2 weeks (days 29-42) of the double-blind epoch.
To evaluate the effect of erenumab compared to placebo in the PGI-I Scale at week 6.	Patient Global Impression of Improvement (PGI-I) at week 6 (day 42).

Exploratory **Objective**	**Endpoint**
To evaluate the effect of erenumab compared to placebo in the reduction of CH attacks from baseline in each of the 2 last week of the double blind period (week 5/week 6)	Reduction from baseline in the number of CH attacks in each of the last 2 weeks of the double blind epoch.
To evaluate the effect of erenumab compared to placebo in total reduction of CH attacks over the entire double-blind trial period (6 weeks).	Reduction from baseline in the number of CH attacks over the entire double-blind trial period (day 1-42).

To compare the safety and tolerability of erenumab with placebo in patients with chronic CH.	Number of AEs, TEAEs, SAEs, and number of patients discontinue study participation stratified for treatment and non-treatment related discontinuation.
To compare erenumab with placebo in reduction of frequency and intensity of CH attacks assessed by the rate of patients discontinuing the study due to intolerable attack frequency or severity.	Discontinuation of the study due to intolerable attack frequency or severity during the double-blind epoch of the study.
To compare erenumab with placebo with respect to 30% response rate at week 5 -6 (days 29-42) from baseline.	Number of patients achieving at least a 30% reduction from baseline in weekly CH attacks averaged over the last 2 weeks (days 29-42) of the double-blind epoch.
To compare erenumab with placebo with respect to 70% response rate at week 5 -6 (days 29-42) from baseline.	Number of patients achieving at least a 70 % reduction from baseline in weekly CH attacks averaged over the last 2 weeks (days 29-42) of the double-blind epoch.
To evaluate the effect of erenumab compared to placebo on generic health-related quality of life, as measured by the Short Form-12.	a) Change from baseline in SF-12 quality of life at week 6 (day 42). B) Difference between erenumab and placebo scores at week 6
To evaluate the effect of erenumab compared to placebo on headache impact on quality of life, as measured by the HIT-6.	a) Change from baseline in HIT-6 quality of life at week 6 (day 42). B) Difference between erenumab and placebo scores at week 6
To compare erenumab with placebo in reduction of duration of CH attacks.	Change from baseline in average duration in minutes of recorded attacks over week 5 and 6 (days 29-42).
To compare erenumab with placebo in reduction of intensity of CH attacks.	Change from baseline in average intensity in average numerical pain rating scale value of recorded attacks over week 5 and 6 (days 29-42).
To compare erenumab with placebo in reduction of use of acute medication.	Change from baseline in count of times acute medication was used weekly averaged over week 5 and 6 (days 29-42).
To evaluate tolerability of erenumab compared to placebo assessed by the rate of patients discontinuing treatment due to all-cause treatment discontinuations during the double-blind epoch of the study.	Discontinuation of treatment due to all-cause during the double-blind epoch of the study

3 Investigational plan

3.1 Study design

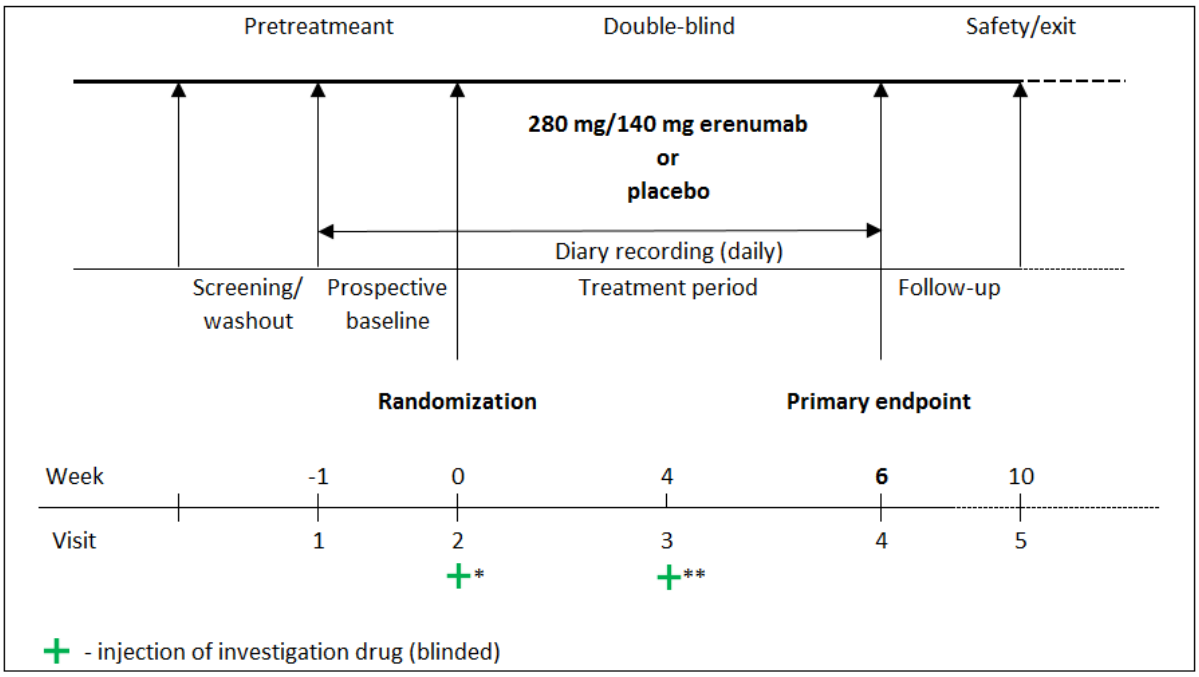
This study is a multicenter, randomized, double-blind, parallel group, placebo-controlled study of erenumab in patients who meet the International Classification of Headache Disorders (ICHD-3) criteria for a diagnosis of chronic cluster headache. The study will be conducted at up to 12 sites in Germany. Patients will be stratified to into groups according to trial site and their number of weekly headache attacks during the baseline epoch. The study has 4 periods, including a pre-treatment baseline period to determine patient eligibility and 5 visits.

The following epochs are included in the study design:

- **SP1 - Screening Epoch (0 – 2 weeks) –** Required for all patients to assess eligibility.
- **SP2 - Baseline Epoch (1 week) –** All patients fulfilling eligibility criteria for screening epoch successfully completing the Screening Epoch are invited to participate. Eligibility for randomization will be assessed based on weekly headache attack frequency and diary compliance during this epoch.
- **SP3 - Double-blind Treatment Epoch (DBTE, 6 weeks) –** All patients completing the Baseline Epoch and fulfilling baseline eligibility criteria are invited to participate. Eligible patients will be randomized in a 1:1 ratio to receive placebo or erenumab (280mg loading dose, 140mg after 4 weeks). The investigational product is administered as a subcutaneous injection at two time points (week 0 and week 4).
- **SP4 - Follow-Up Epoch (4 weeks) –**A Follow-Up Visit 4 weeks after last study visit (or 6 weeks after last IMP injection for discontinued patients) will be required as part of routine safety monitoring. The primary analysis will be triggered when all patients have completed their respective last visit of the double-blind treatment epoch.

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

Figure 1 | Study design



*: 280 mg of erenumab or placebo s.c. ; **: 140 mg of erenumab or placebo s.c.

3.2 Rationale for study design

A parallel-group, double-blind design is a standard way of assessing efficacy and safety of new agents. Erenumab, a novel antibody therapy already approved by the European Commission, for the prophylaxis of migraine in patients with ≥4 migraine days/month, is administered according to current product information every 4 weeks s.c. with a dose of 140mg s.c.; however we start with a loading dose of 280mg erenumab s.c. in order to reach rapid activity. Of note, the effective dose of galcanezumab in episodic cluster headache prevention is 300mg/month s.c. (approved by the FDA). This is more than double of the recommended monthly dose of galcanezumab (120mg s.c.) for the preventive treatment of migraine.

Erenumab is a fully human monoclonal antibody that selectively targets the CGRP receptor and has been identified for clinical development in pain conditions relevant to the CGRP pathway such as migraine. The pathophysiological similarities between migraine and cluster headache as primarily unilateral trigeminal headache disorders, the role of CGRP in both disorders and the clinical efficacy observed with erenumab to date for the prevention of migraine support the evaluation of erenumab for the treatment of cluster headache. Chronic cluster headache has a significantly higher unmet therapeutic need than episodic cluster headache. Therefore, it is the aim of this study to assess the efficacy of erenumab in the prevention of chronic cluster headache.

The proposed duration of the randomized, double-blind treatment phase is 6 weeks, with the primary endpoint assessed during weeks 5 and 6 after the second IP dose.

This duration and use of a placebo-control is consistent with current published International Headache Society guidelines (IHS 1995), in which a duration of at least 2 weeks is recommended when assessing cluster headache prophylaxis treatment.

The study will allow the use of specific abortive treatments (those initiated at the start of a cluster headache attack to shorten overall attack duration) for cluster headache attacks, but will require exclusion of all preventive therapies to directly assess the superiority of erenumab over placebo as a preventive treatment. This approach is mainly based on the lack of approved substances for cCH prevention. We are keen to avoid prophylactic treatments without approval for CH in this trial. In addition, we do not have any evidence that a CGRP mAb has any additional effect when use in combination with SoC medications (in migraine) than as monotherapy.

Most currently used cluster preventive treatments are not approved for this disease. The placebo design in this study can also be severely affected by the permission of stable prophylaxis co-medication. Prevention can be effective, partially effective or non-effective, which we can hamper the outcome of the trial. The current designs allows to directly compare the superiority of erenumab over placebo as a preventive treatment in chronic cluster headache. Hence, the discontinuation rates in the placebo group may be higher due to lack of efficacy. Therefore, treatment discontinuation rate due to intolerable attack frequency or attack severity during the double-blind epoch of the study has been chosen as an exploratory endpoint. However, abortive attack therapy is allowed and necessary.

The specifics of population and treatment requirements were designed based on feedback from clinical experts and consultations with Novartis.

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

The dosage of 280mg s.c. erenumab as a loading dose and a continuing dosage of 140mg s.c. erenumab after 28 days is based on the pharmacodynamical considerations of the Novartis pharmacological experts. PK-exposure response modelling suggests that with higher doses, a potential additional benefit in terms of efficacy might be observed. The safety profile of erenumab has been investigated up to 280mg in healthy volunteers in Phase 1 without a difference in safety profile (Hoon et al., 2018). A monthly dose of 140mg erenumab is approved for the prevention of migraine.

PK-exposure response modelling shows steady-state exposure equivalent to 140mg QM after one 280mg loading dose and suggest that the exposure in a broad population above the saturation level is maintained. A lower placebo response due to fewer visits in study sites can be expected with the loading dose than with biweekly injections. For these reasons, a loading dose of 280mg was introduced into this trial.

3.4 Purpose and timing of interim analyses/design adaptations

The primary analysis will occur when the last patient completes the double-blind epoch prior to the follow-up epoch. No interim analysis is planned.

3.5 Risks and benefits

Erenumab has been developed for migraine prophylaxis in a large clinical development program including more than 3.000 patients and has shown efficacy across the migraine spectrum. Key risks and benefits are briefly summarized below. For further information, please refer to the most recent IB (Investigators Brochure). Toxicology studies with erenumab do not show results that would predict a risk to human patients. There were no significant findings on electrocardiogram (ECG) parameters, blood pressure or respiration rate in the single dose cardiovascular study in cynomolgus monkeys (up to a dose of 30mg/kg or twice monthly 150 mg).

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

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

A theoretical cardiovascular safety risk with CGRP receptor blockade is the lack of compensatory vasodilation, particularly in the context of the coronary circulation during ischemic-related conditions. Overall, to date, there is no evidence from nonclinical and clinical data of an increased risk of cardiovascular effects with CGRP or a CGRP receptor mAb. However, cardiovascular monitoring in this clinical trial will be applied in order to assess cardiovascular effects in this specific patient population with cCH.

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

Adverse reactions for erenumab include injection site reactions, constipation, muscle spasm, pruritus and allergic reaction (common frequency, ≥1/100 to <1/10). Injection Site Reactions includes multiple preferred terms, such as injection site pain and injection site erythema. Pruritus includes preferred terms of generalized pruritus, pruritus, and pruritic rash. Allergic reaction includes preferred terms of anaphylaxis, angioedema, rash, swelling/edema and urticaria. Since the approval of erenumab in May 2018, severe allergic reactions have been observed in patients prescribed erenumab. Severe allergic reactions can cause drowsiness, severe skin reactions, swelling, shortness of breath or difficulty swallowing, as well as a drop in blood pressure, and can become life-threatening. These reactions can occur within minutes,

but some may occur more than a week after treatment. The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, a follow-up visit and use of rescue medications.

4 Population

The patient population will consist of 118 male and female patients with a diagnosis of chronic cluster headache patients according to the ICHD-3 between the age of 18 and < 65 years. All patients must meet the following selection criteria. Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical examination, clinical laboratory tests, ECG, and cluster headache history during SP I and SP II, as described in the Inclusion and Exclusion Criteria sections below. The nature of any co-morbid conditions present at the time of the physical examination and any pre-existing conditions must be documented. Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreen once, for selected criteria, with approval from Medical Monitor. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

4.1 Inclusion criteria

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

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

1) Patient is capable of understanding the nature, significance and implications of the clinical trial .Written informed consent must be obtained before any assessment is performed
2) Adult's ≥18 and < 65 years of age upon entry into screening.
3) Documented history of chronic cluster headache for ≥12 months prior to screening according to the International Classification of Headache Disorders-3rd Edition (ICHD-3) listed below.
4) Insufficient efficacy OR tolerability OR contraindications of approved cluster headache prophylactic medications. Insufficient efficacy and tolerability as determined by the patient.
5) Sufficient acute attack treatment with triptans or oxygen based on the patient´s history
6) The patient is able to distinguish cluster headache attacks from other headaches (i.e. tension-type headaches).

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

7) **<u>This inclusion criteria should not be shared with potential patients:</u>**

At least 9 cluster headache attacks as defined by the ICHD-3 in 7 days during the baseline epoch (SPII), confirmed by patient-reported eDiary entries. Attacks must have occurred on more than 50% of days of the baseline epoch (SPII).

8) ≥ 90% patient-reported eDiary compliance during the Baseline epoch, compliance is measured as interacting with e-Diary at least once a day.

ICHD-3 diagnostic criteria for Cluster Headache:

A. At least five attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)[1]
C. Either or both of the following:
    1. at least one of the following symptoms or signs, ipsilateral to the headache:
        - conjunctival injection and/or lacrimation
        - nasal congestion and/or rhinorrhoea
        - eyelid oedema
        - forehead and facial sweating
        - miosis and/or ptosis
    2. a sense of restlessness or agitation
D. Occurring with a frequency between one every other day and 8 per day[2]
E. Not better accounted for by another ICHD-3 diagnosis.

ICHD-3 diagnostic criteria for Chronic Cluster Headache:

A. Attacks fulfilling criteria for 3.1 *Cluster headache*, and criterion B below
B. Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year.

4.2 Exclusion criteria

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

1. Diagnosis or history of other primary headache diseases according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3), excluding episodic tension type headache.
2. Unable to differentiate cluster headache attacks from other headaches
3. Use of a prophylactic cluster headache medication within 5 half-lives prior to the start of the baseline phase; (see Table 5.1: Prohibited treatments)
4. Parallel use of an SPG stimulator, deep brain stimulation or parallel use of a device for the acute/preventive treatment of chronic cluster headache
5. Administration of botulinum toxin type A or B in the head or neck area, within 4 months of baseline (SP II) for treatment of cluster headache or other disorders, or for cosmetic use

6. Concurrent use of other therapeutic monoclonal antibodies. Prior use of other therapeutic antibodies is allowed if an adequate wash-out has occurred (≥5 half-lives) prior to baseline (SP II)
7. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer
8. Evidence of drug, opioid or alcohol abuse or dependence within 12 months prior to screening, based on medical records or patient self-report
9. History of use of cannabis, cannabinoids, psilocybin (mushrooms), LSD, MDMA or 2-bromo-LSD within 2 months prior to baseline (SPII)
10. Have a positive urine drug screen (UDS) for any substances of abuse prior to randomization. A retest is applicable if, in judgment of the investigator, there is a reasonable explanation for the positive result. A negative result in the retest is obligatory for entering baseline (SPII)
11. Diagnosis or history of significant active or unstable psychiatric disease, such as bipolar disorder, schizophrenia, personality disorders, or other serious mood or anxiety disorders. Patients with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable and are taking no more than one medication per disorder. Patients must have been on a stable dose within the 3 months prior to the start of the baseline phase.
12. 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 month, 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 3 months. Patients who do not meet this criterion, but who are considered by the judgment of the investigator to be at significant risk for suicide, must be excluded.
13. Active chronic pain syndromes (e.g., fibromyalgia or chronic pelvic pain)
14. History or current evidence of major psychiatric disorder (such as schizophrenia, bipolar disorder or type B personality disorder that might interfere with the ability to properly report clinical outcomes)
15. History or current severe coronary artery disease, myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedures within 12 months prior to screening
16. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study
17. 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
18. Hepatic disease by history or total bilirubin ≥2×ULN or ALT or AST ≥3xULN as assessed by central laboratory at initial screening
19. History of severe constipation, defined as less than 3 bowel movements /week not adequately manageable by routine medical treatment, within 3 months prior to screening.
20. Acute SARS-CoV2 Infection within 2 weeks prior to screening

21. Pregnant or nursing women
22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 110 days after stopping of study medication. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient and should have received medical assessment of surgical success.
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), e.g. hormone vaginal ring or transdermal hormone contraception
    - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
23. Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to erenumab or to any of the inactive ingredients.
24. Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (e.g., independent completion of electronic diary items) to the best of the patient's and investigator's knowledge.
25. Prior treatment with a CGRP receptor mAb or a CGRP mAb.
26. Patients who may be dependent on the sponsor or investigator
27. Patients who are in custody of an institution due to governmental authority decision or court order

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The investigational medicinal products (IMP) listed below will be supplied in a placebo controlled setting:

Verum:

Test-IMP:

4x Erenumab 70mg/1mL (280mg), in pre-filled syringe, administered at week 0;

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

Placebo:

4x Erenumab matching placebo, in pre-filled syringe, administered at week 0;

2x Erenumab matching placebo, in pre-filled syringes, administered at week 4;

5.1.2 Additional treatment

No additional treatment beyond IMP and matching placebo is included in this trial.

5.2 Treatment arms

Patients will be assigned to either erenumab or placebo at the Randomization Visit (V2), in a 1:1 ratio,

5.3 Treatment assignment and randomization

At visit 2 (V2), all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the two treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first packages of study drug to be dispensed to the patient. Randomization will be stratified by study site and weekly CH attack frequency using a 1:1 stratified permuted block (block size will be randomly either 4 or 6). The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers stratified by study site and weekly CH attack frequency (9-19 attacks per week during the Baseline Epoch vs >19 attacks per week during the Baseline Epoch). These randomization numbers are linked to the

different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and Charité personnel and their delegates will remain blinded to the identity of the treatment from the time of randomization until the conclusion of the double-blind treatment epoch and primary analysis. Following methods will be used: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the randomization office, (2) the identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.8). Randomization information will be available to the investigator when the study report has been finalized.

5.5 Treating the patient

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

5.5.1 Patient numbering

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

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

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

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

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

Only one re-screening is allowed per patient. Patients who had <9 weekly CH attacks during Baseline Phase cannot be re-screened.

5.5.2 Application of the study drug

Each study site will be supplied with study drug in packaging of identical appearance.
The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number. Study Sites will be supplied with an initial shipment of study drug /placebo. One Kit will contain 2 syringes/vials = 140mg. The medication (kit) number will be placed on the kit and on each single syringe/vial. For visit (V2), the IRT will dispense 2 kits á 2 syringes, which equals 4 vials altogether for administration of 280mg study drug/placebo.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

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

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

The investigational product´s dose is 280mg at randomization and 140mg four weeks later.

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

280mg and 140mg erenumab or respective placebos will be administered by qualified study staff at each dosing visit during the 6 week double-blind treatment epoch (i.e., at Day 1 and Week 4). Subcutaneous (s.c.) injections are to be given for each investigational product administration. The second study drug administration date should 4 weeks (+/ – 2 days) from the first dose of study drug. Any dose administrations that may occur greater than +/ – 2 days from the 4 week time point (e.g., patient unavailability) should be discussed with the Sponsor prior to dosing. The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen; the location of the injection site should be documented in the source document. The injections should be divided up between at least two different locations to reduce injection site reactions (e.g. 2 injections in the left upper arm and 2 injections in the abdomen). In order to reduce irritation at the injection site, the investigational product should be stored at room temperature for 30 minutes prior to the administration.

5.5.5 Rescue treatments

Patients can continue to use acute CH medication as rescue treatments. These may include pharmacologic interventions (i.e., treatments for acute attacks such as triptans and oxygen).

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

Site staff will pre-specify the name, dose strength, and route of administration of the patient's acute headache (rescue) medications in the patient's eDiary. If the patient takes an acute headache medication to treat a headache attack, they will select one of the pre-specified medications (or "other" medication) and enter the time of administration and number of units taken in that attack (or "minutes" for oxygen treatment).

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

5.5.6 Concomitant medication

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the medical monitor before randomizing a patient or allowing a new medication to be started.

5.5.7 Prohibited treatments

Use of the treatments displayed in Table 5-1 is NOT allowed as designated due to the potential confounding of efficacy assessments.

Table 5-1 Prohibited Treatments

Treatment	**Prohibition period**
Verapamil Lithium Corticosteroids Dihydroergotamine Topiramate Valproate Gabapentin Civamide Melatonin Opioids and Cannabinoids All other prophylactic treatments specifically targeting the CGRP pathway (e.g. gepants and CGRP monoclonal antibodies)	Within ≥5 half-lives prior to the start of the baseline epoch and throughout the entire study period.
Botulinum toxin (in the head and/or neck region) for medical or cosmetic treatment	Within 4 months of the start of the baseline epoch and throughout the study
Noninvasive interventions (e.g., vagus nerve stimulation)	Within 1 month of the start of the baseline epoch and throughout the study
Invasive interventions (e.g., nerve blocks, occipital nerve stimulators, SPG stimulators, deep-brain stimulation, transcranial magnetic stimulation)	Within 1 month of the start of the baseline epoch and throughout the study

5.5.8 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or e-mail confirming this information. The system will automatically inform the monitor for the site and the study team that the code has been broken. The unblinding process via IRT is available 24/7. The detailed process will be described in the IRT User manual.

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

- protocol number
- study drug name (if available)
- patient number

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

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the double-blind treatment epoch when the patient has completed Visit 4 in the protocol.

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

For all patients a safety follow-up visit (visit 5) should be conducted 4 weeks after the last visit or 6 weeks after the last IP injection for patients discontinuing after the first application. The information to be collected at this follow up visit is outlined in Table 6-1.

5.6.2 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.6 and Section 7.5)
- Use of prohibited treatment as per Table 5-1

- Any situation in which study treatment might result in a safety risk to the patient
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study
- New onset of SARS-CoV-2 Infection as determined at any of the study visits 1,2,3 or 4 or at any time during the trial under the condition that a study visit cannot be conducted ±2 days of the scheduled study visit due to quarantine regulations by local health authorities. If due to these restrictions the patient is unable to continue in the trial within the normal regimen, the abbreviated visits (4-A, 5-A) should still be conducted if applicable and possible.

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

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

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

Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (V4-A) will be performed. At this final visit, the adverse event and concomitant medications should be reconciled on the eCRF. Patients will return for a follow-up visit (V5-A) approximately 6 weeks after their last dose of study medication, and perform the study procedures outlined in Table 6-2.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment. If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.8

5.6.3 Withdrawal of informed consent

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

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

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

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

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

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

5.6.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

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

The study will also be terminated if the requisitions for inclusion of patients do not exist any longer and if the approval of the ethic committee or approval of the responsible national competent authority are withdrawn (§42a Abs.1 S.3 Nr. 2 AMG). If new scientific evidence appears during the conduction of the trial, which will make the scientific evidence for this trial obsolete, we will terminate the study prematurely. Other reasons for early termination will be the appearance of SUSARs in a frequency of more than 4 %. We will also terminate the study if we see an increased number of serious adverse events compared to the migraine population related to the AE constipation or SAEs related to vascular or cardiac disease.

6 Visit schedule and assessments

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

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

During visits intervals and allowed time windows calculated from V2 (day 1) are specified in the assessment schedule (Table 6-1)

The screening visit (V1) is the start of the baseline and must take place at least 7 and at most 12 days before the V2 visit to allow for the required 7-12 days to be recorded in the baseline epoch.

If a visit has to be scheduled outside these windows, an approval from the sponsor has to be collected to ensure patient safety regarding s.c. medication.

Table 6-1 Assessment Schedule:

Epoch	Screening	End of Baseline	Double-Blind- Treatment		Follow-Up	Notes
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	
Day and allowed time windows	**Day -7 (+5 days)**	**Day 1**	**28 (±2)**	**42 (±2)**	**70 (±3)**	
Obtain Informed Consent	**X**					
Randomization		**X**				
Demography	**X**					
Medical & Medication History	**X**					**Including prior prophylaxis medication for Cluster Headaches**
Registration of prophylaxis washout	**X**					
Complete Physical Exam	**X**			**X**	**X**	
Brief Physical Exam		**X**	**X**			
Height, Weight	**X**				**X**	
SARS-CoV-2 Antigen Test	**X**	**X**	**X**	**X**	**X**	
Clinical chemistry and Hematology	**X**			**X**		
Vital Signs	**X**	**X**	**X**	**X**	**X**	
Urinary drug screening	**X**	**X**	**X**	**X**	**X**	
Urine pregnancy test		**X**	**X**		**X**	
Serum pregnancy test	**X**			**X**		
ECG	**X**	**X**	**X**	**X**		

Provide eDiary	**X**					**Recording: (attacks, duration, severity, rescue medication)**
eDiary Return				**X**		**Patients brings eDiary to each visit for use at site**
SF-12 (eDiary)	**X**	**X**		**X**		
HIT-6 (eDiary)	**X**	**X**		**X**		
PGI-I				**X**		
C-SSRS/SHSF	**X**	**X**	**X**	**X**	**X**	
Concomitant Medications	**X**	**X**	**X**	**X**	**X**	
Adverse Events		**X**	**X**	**X**	**X**	
Serious Adverse Events		**X**	**X**	**X**	**X**	
Injection s.c. of erenumab 280mg / placebo		**X**				
Injection s.c. of erenumab 140mg / placebo			**X**			
Vital signs (only 1x RR & Pulse) 15 min. after erenumab / placebo injection		**X**	**X**			

Table 6-2 Abbreviated Assessment Schedule for patients with Treatment Discontinuation:

Visit number	V4-A	V5-A
Day and allowed time windows	Immediately after discontinuation	42 days after last injection (±3 days)
Complete Physical Exam	X	X
Brief Physical Exam		
Height, Weight		X
Clinical chemistry and hematology	X	
Vital Signs	X	X
Urinary drug screening	X	X
Urine pregnancy test		X
Serum pregnancy test	X	
ECG	X	
eDiary Return	X	
SF-12 (eDiary)	X	
HIT-6 (eDiary)	X	
PGI-I	X	
C-SSRS/SHSF	X	X
Concomitant Medications	X	X
Adverse Events	X	X
Serious Adverse Events	X	X

6.1 Information to be collected on screening failures

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

6.2 Patient demographics/other baseline characteristics

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

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

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

6.3 Treatment exposure and compliance

Study medication is administered at the site (IP) by the investigator or designated study staff as outlined in Table 6-1. This information should be captured in the source document and the eCRF at each visit. Site staff will review eDiary compliance with the patient at each visit.
For eDiary compliance at least one daily interaction with the eDiary is considered compliant.

6.4 Efficacy

Efficacy assessments will include:

- Weekly CH attacks

The timing and frequency of these assessments are outlined in Table 6-1 and 6-2. Patients will record the efficacy information using the provided eDiary platform.

The information can be completed after each attack or on a daily reminder questionnaire for up to 24 hours after the last completed reminder questionnaire.

Any entries >24 hours after the last completed reminder questionnaire will not be allowed and will be considered missing data. Data collected in the eDiary will be normalized to a 7 day period (week).

6.4.1 Weekly CH attacks

A CH attack is defined as each episode in which the patient experiences a qualified Cluster headache attack. Weekly CH attacks are calculated from CH attacks during a 7 day period. A qualified CH attack is defined as a Cluster headache attack when it is meeting both of the following criteria:

A. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes

B. Either or both of the following:

   a. at least one of the following symptoms or signs, ipsilateral to the headache:

      i. conjunctival injection and/or lacrimation

      ii. nasal congestion and/or rhinorrhoea

      iii. eyelid edema

      iv. forehead and facial sweating

      v. miosis and/or ptosis

   b. a sense of restlessness or agitation

If the patient took a cluster headache-specific medication (i.e., triptans or oxygen) to treat a headache, then it will be counted as a CH attack regardless of the duration and pain features/associated symptoms. However, pain (at any intensity) must be experienced.

To further characterize a CH attack, the following information will be collected:

- Date and time of start of headache
- Duration of headache
- Worst pain severity per headache
- Use of acute headache medications (medication name (from pre-entered list))

6.4.2 Appropriateness of efficacy assessments

The definition of CH attack (Section 6.4.1) is consistent with the diagnostic criteria of Cluster headache according to the International Classification of Headache Disorder (ICHD-3). The weekly CH attacks will be calculated using CH attacks data collected from the eDiary. Weekly CH attacks are commonly used as an endpoint in pivotal trials for CH.

The mean change in weekly CH attacks however describes a population-based measure and, given the natural variability in CH trials, often is associated with small effect sizes. Thus, a clinically important complementary information is the proportion of patients that achieve a certain clinical benefit, which is usually described with achieving at least a 50% reduction of weekly CH 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.

The Patient Global Impression of Improvement (PGI-I) is a patient reported outcome measure commonly used in CH trials for assessing the subjective benefit.

The exploratory endpoints are in line with standard CH trials and include additional responder rates. Additional PRO scales were included to gather information on functional impact of headache (HIT-6, SF-12).

6.5 Safety

Safety assessments will include:

- Treatment discontinuations due to AEs
- Adverse events (Section 7.1)
- Physical examination
- Vital signs
- ECG
- Height/weight
- Laboratory evaluations
- SARS-CoV-2 Antigen test
- Pregnancy testing (females of childbearing potential)
- Columbia Suicide Severity Rating Scale (C-SSRS) (Section 7.6)

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

6.5.1 Physical examination

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

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

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

6.5.2 Vital signs

Vital signs include blood pressure, pulse and temperature measurements. After the patient has been sitting for approximately five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three (3) times using a validated device, with an appropriately sized cuff. The repeat sitting measurements should be made at approximately 1 – 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. The method to take temperature should be consistent throughout the study. Fifteen minutes after study drug injection (V2/V3) blood pressure and pulse will again be measured.

6.5.3 Height and weight

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

6.5.4 Laboratory evaluations

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

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

Hemoglobin, hematocrit, erythrocyte count, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count will be measured.

6.5.4.2 Clinical chemistry

Serum concentrations of sodium, potassium, bilirubin (total, direct and indirect), ALT (SGPT), AST (SGOT), creatinine and estimated creatinine clearance (GFR) will be measured. Clinical chemistry assessment will be performed at Screening (V1) and at the end of DBTE (V4).

6.5.5 Electrocardiogram (ECG)

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

6.5.6 Pregnancy and assessments of fertility

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

6.5.7 Appropriateness of safety measurements

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

6.5.8 COVID testing (SARS-CoV-2 Infection)

A SARS-CoV-2 Antigen test will be conducted on each study visit at the study site. The sites will be provided with an approved SARS-CoV- 2 antigen rapid test. The rapid test will be performed by the local study staff. A positive antigen test at visits 1,2,3 and 4 will lead to study exclusion of the patient, unless an immediately following PCR confirmation test is negative and Infection with SARS-CoV-2 is ruled out.

6.6 Other assessments

- Headache Impact Test (HIT-6)
- SF-12
- PGI-I

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

6.6.1 Patient Reported Outcomes (PROs)

Patients will complete all Patient Reported Outcome (PRO) questionnaires using the provided eDiary platform. The PRO questionnaires, that are completed in-clinic during visits, must be performed/completed as the first task after registering with the study nurse at randomization (Week 0; Visit 2) and at the endpoint assessment visit (Week 6; Visit 4).

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

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

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

6.6.1.1 Headache Impact Test (HIT-6)

The HIT-6 is a short-form self-administered questionnaire based on the internet-HIT question pool (Kosinski et al., 2003).The HIT-6 was developed as a global measure of adverse headache impact to assess headache severity in the previous month and change in a patient's clinical status over a short period of time. Six items assess the frequency of pain severity, headaches limiting daily activity (household, work, school, and social), wanting to lie down when headache is experienced, feeling too tired to work or do daily activities because of headache, feeling "fed up" or irritated because of headache, and headaches limiting ability to concentrate or work on daily activities. Each of the 6 questions is responded to using 1 of 5 response categories: "never," "rarely," "sometimes," "very often," or "always."

For each HIT-6 item, 6, 8, 10, 11, or 13 points, respectively, are assigned to the response provided. These points are summed to produce a total HIT-6 score that ranges from 36 to 78. HIT-6 scores are categorized into 4 grades, representing little or no impact (49 or less), some impact (50 – 55), substantial impact (56 – 59), and severe impact (60 – 78) due to headache.

No recall period is specified for the first 3 items. The recall period is the past 4 weeks for the last 3 items. Patients will complete this in their eDiary during their scheduled clinic visit, at the frequency outlined in Table 6-1 and Table 6-2.

6.6.1.2 Medical Outcome Short Form Health Survey (SF-12) (4-week recall period)

The SF-12 is a widely used and extensively studied instrument to measure health-related quality of life (HRQoL) among healthy subjects and patients with acute and chronic conditions. (Ware et al., 1998). The SF-12 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual subjects. The purpose of the SF-12 in this study is to assess the HRQoL of subjects. Given the nature of this disease and the assessment schedule, the SF-12, with a 4-week recall period, will be used in this study.

6.6.1.3 Patient Global Impression of Improvement (PGI-I)

The PGI-I is an instrument that assesses dimensions of patients' experiences with their medication. The general nature of the instrument provides a way of evaluating and comparing patients' impression of improvement. The PGI-I has a 1-question format and uses a balanced Likert scale that allows to assess how much the patient's condition has improved or worsened relative to his or her baseline state. For this study, the PGI-I asks the patient to mark the box that best describes the cluster headache condition since starting the study treatment and the response scale ranges from 1-7, with 1 being very much improved and 7 being very much worse.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient from randomization (V2) until the end of study visit (10 weeks after the first IP injection). Any events occurring during the Screening and Baseline Epochs and conditions that were already present at the time of informed consent should be documented as medical history. An AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

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

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

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

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

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

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

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

- changes in study drug treatment (drug interrupted)
- starting or stopping concomitant treatments
- medically required intervention

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

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

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

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Charité (please see section 7.2.3).

Adverse Reactions

Adverse reactions are all untoward and unintended responses to an investigational medicinal product related to any dose administered.

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

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

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

An SAE which is a harmful and undesired reaction to the investigational medicinal product and therefore the causality is given is defined as a Serious Adverse Reaction (SAR).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately

life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

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

7.2.2

Serious adverse events must be reported on the SAE report form under the signs, symptoms or diagnosis associated with them.

It is the responsibility of the investigator to make a determination of severity and whether or not a relationship to study treatment is suspected. As far as possible, each SAE should be evaluated to determine:

1. the severity grade (assessment of intensity)
2. its relationship to the study treatment (assessment of causality)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; hospitalization)
5. whether it constitutes a serious adverse event (assessment of SAE criteria)

Assessment of intensity:
The intensity should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

- Grade 1 mild
- Grade 2 moderate
- Grade 3 severe
- Grade 4 life-threatening
- Grade 5 death

Assessment of causality:
To assess causality between administration of the investigational product and the Serious Adverse Event the following definitions apply:

Not related	An adverse event that is not related to the use of the drug.
Unlikely	An adverse event for which an alternative explanation is more likely, e.g. concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
Possible	An adverse event that might be due to the use of the drug. An alternative explanation, e.g. concomitant drug(s), concomitant disease(s), is

	inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
Probable	An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely, e.g. concomitant drug(s), concomitant disease(s).
Certain/ related	An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).
Not assessable	Cannot be judged because information is insufficient or contradictory.

Assessment of SAE criteria: The assessment of seriousness shall be determined according to the SAE definition above (please see section 7.2.1).

7.2.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until the completion of the Follow-Up Epoch (10 weeks after the first IP injection) must be reported to Charité Universitätsmedizin Berlin within 24 hours of learning of its occurrence. Any SAEs experienced after the completion of the Follow-Up Epoch should only be reported to Charité if the investigator suspects a causal relationship to study treatment.

This notification will be sent via fax or email to:

Clinical Trial Office (CTO) Charité - Pharmacovigilance
Charité - Universitätsmedizin Berlin
Email: pharmacovigilance-kks@charite.de
Fax: +49 30 / 450 7553 856

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

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

Follow-up information is submitted as instructed in the investigator folder. Each change, 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.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any suspected adverse reaction related to the study treatment that is both serious and unexpected. “Unexpected” means that the nature and severity of the adverse reaction are not consistent with the information about the study medication in question set out in the reference safety information.

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 the Charité 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 as well as to all Investigators involved in the trial in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries. In case of a fatal or life-threatening SUSAR, the sponsor will report all information relevant for judging the event immediately, at the latest 7 days after the event becomes known. After a further 8 days all further relevant information must be available. All other suspicious cases of suspected unexpected serious adverse reactions (SUSARs) will be reported at the latest 15 days after it becomes known.

The sponsor will immediately, at the latest 15 days after it becomes known, report all circumstances that require a revision of the risk-benefit analysis to the relevant ethics committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory. This especially includes:

- Singular cases of expected severe adverse events with an unexpected outcome.
- Increased incidence of expected severe adverse events that are judged as being clinically relevant.
- SUSARs which occur after termination of the clinical trial until end of follow-up
- Events related to study procedures or development of the study medication, which could affect a subject’s safety.

All person-related data will always be transmitted pseudonymized.

7.3 Development Safety Update Report

Once a year during the trial, or on request, the sponsor shall submit to the competent ethics committee, the national competent authority and the competent authorities of other Member States of the European Union and other Contracting States to the Agreement on the European Economic Area in whose territory the clinical trial is being conducted, a list of all suspected cases of serious adverse reactions occurring during the trial, as well as a report on the safety of the trial subjects. The report shall be created in accordance with guideline ICH Topic E2F - Development Safety Update Report (DSUR). The Sponsor will quarterly submit a list of all occurred SUSARS to the responsible EC in charge.

7.4 Liver safety monitoring

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

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

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver eCRF pages

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

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

For the liver laboratory trigger:

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

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

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

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate

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

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

7.5 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, patient or consumer (EMA definition).

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

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

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

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

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

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

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Charité within 24 hours of learning of its occurrence. The pregnancy should be

followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

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

7.7 Prospective suicidality assessment

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

A validated version of the C-SSRS will be used to evaluate each patient's suicidality ideation and behavior in a consistent manner.

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

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

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Charité representative will review the protocol and CRFs with the investigators and their staff. The study will be monitored at appropriate intervals to assure compliance to the protocol, Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The study monitor will visit the site to check the completeness of patient records, the accuracy of entries in the eCRF, 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 study monitor during these visits. Edit checks and reports of the eCRF Database can be used to identify

recruitment status and documentation status. These statistical reports can help CRA to prepare upcoming Monitoring visit and have an overview about documentation from each site.

The investigator must maintain source documents for each patient in the study, consisting of signed informed consent 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 in eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The study monitor will have direct access to source data for data verification provided by investigator or study team. Source Data verification (SDV) will be conducted by comparing the data entered into the eCRF with source data. The study monitor will verify the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and data that will be used for all primary variables. Further details of the content of monitoring are described in the monitoring manual. No information in source documents about the identity of the patients will be disclosed.

If on-site monitoring visits cannot be performed due to the ongoing SARS-CoV-2 pandemic and restrictions by local health authorities, remote monitoring visits will be performed instead. On-Site monitoring during pandemic will be planned carefully and performed according to current hygiene standards and in accordance with government restrictions.

8.2 Data collection

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

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

8.3 Database management and quality control

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

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

adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally in Germany and the results will be sent electronically to Charité (or the Charité CTO). ECG readings will be processed centrally and the results will be sent electronically to Charité (or the Charité CTO)

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

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

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 Charité.

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

The processing of the collected data will be performed by the data management of the CTO. Data clearing will follow the data validation plan, which has to be approved by the study team. Found abnormalities will be controlled via data management queries. The corrected data base will be the foundation for the data transferred to the biometrics department. The alignment and format will be set up according to the instructions from the biometricians.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The first analysis will be conducted on all patient data when the double-blind treatment epoch of the trial ends. The data will be analyzed by Charité staff, and/or by the Charité CTO.

Analysis sets

The population used for efficacy analyses will be the modified ITT population including all patients receiving at least one dose of active drug or placebo with at least one post-baseline efficacy assessment.

Safety analyses will be performed on the safety population including all patients receiving at least one dose of investigational product. In this population, treatment will be assigned based

upon the treatment patients actually receive, regardless of the treatment to which they were randomized.

9.1 Patient demographics and other baseline characteristics

Demographic variables and other baseline characteristics including previous Cluster headache treatments will be summarized. Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables for each group and for all participants (total). The number and percentage of participants in each category will be presented for categorical variables for each group and all participants (total).
In addition, all relevant medical history will be summarized following the same strategy.
Summaries for Cluster headache specific medical history will be provided as well.

9.2 Analysis of the primary variable(s)

9.2.1 Variable(s)

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

- Population – modified ITT population including all patients receiving at least one dose of active drug or placebo with at least one post-baseline efficacy assessment.
- Variable of Interest: The primary endpoint is the change from baseline in weekly headache attacks over last 2 weeks (days 29-42) of the double-blind epoch.

9.2.2 Statistical model, hypothesis, and method of analysis.

For the analysis of the Proof-of-Concept study we will apply Bayesian methods. The methods used was suggested by Fisch et al.(Fisch et al., 2015). Using non-informative prior distributions, we will obtain samples from the posterior distribution of the differences in change from baseline between erenumab and placebo. For sampling from the posterior distribution, we will use the STAN software with the default, weakly informative prior. A mixed effects model approach will be used to account for possible center-effects and baseline differences.

A reduction of 3 attacks per week is considered as the threshold for clinical relevance, i.e. the smallest effect difference to placebo below which the drug would not be worth promoting into further development. Using the posterior distribution, we will calculate the proportion of samples that exceed this value, which is the posterior probability of erenumab having an effect larger than the relevance threshold. Further, the proportion of samples from the posterior distribution that exceed 0 will be calculated, which is the posterior probability of erenumab having any effect compared to placebo. This study will suggest to continue the development of erenumab in cluster headache, if the posterior probability of any effect is at least 90% (significance criterion) and if the posterior probability of a relevant effect (>3 reduction of attacks per week) is at least 50% (relevance criterion).

9.3 Analysis of secondary variables

The first secondary variable is the achievement of at least a 50% reduction from baseline in weekly CH attacks averaged over the last 2 weeks (days 29-42) of the double-blind epoch.

A Bayesian logistic regression model will be used to assess the posterior distribution of the odds ratio of having a 50% reduction from baseline comparing erenumab to placebo. Center effects and baseline measurements will be taken into account by applying a mixed effects approach. The significance criterion will be reached if the posterior probability of any effect, i.e. odds ratio larger than 1, is at least 90%. The relevance criterion will be reached if the posterior probability of an odds ratio of at least 2 is larger than 50%.

The second secondary variable is the change from baseline measured with the Patient Global Impression of Improvement (PGI-I) assessed on the end of the double-blind epoch (V4).

The analysis of the variable will be based on the following estimates:

- Population – modified ITT population including all patients receiving at least one dose of active drug or placebo with at least one post-baseline efficacy assessment.
- Variable of Interest: proportion of patients with Score of the Patient Global Impression of Improvement (PGI-I) of 1 (“very much better”) or 2 (“much better”) assessed on the end of the double-blind epoch (V4).

A Bayesian logistic regression model will be used to assess the posterior distribution of the odds ratio of having a PGI-I score of 1 or 2 comparing erenumab to placebo. Center effects and baseline measurements will be taken into account by applying a mixed effects approach. The significance criterion will be reached if the posterior probability of any effect, i.e. odds ratio larger than 1, is at least 90%. The relevance criterion will be reached if the posterior probability of an odds ratio of at least 2 is larger than 50%.

9.4 Analysis of exploratory variables

Exploratory variables are the patient reported outcomes (PROs) HIT-6, SF-12 and the reduction in weekly CH attacks. The analysis of PROs and the reduction in weekly CH attacks will be described in detail in the statistical analysis plan (SAP).

9.4.1 Safety variables

9.4.1.1 Adverse events

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

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

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

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

9.4.1.2 Laboratory data

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

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

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

9.4.1.3 Vital signs

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

9.4.2 DNA

Not applicable.

9.4.3 Blood Biomarkers

Not applicable.

9.5 Interim analyses

Not applicable.

9.6 Sample size calculation

The study aims to recruit 118 patients. Patients will be randomized stratified by center and attack frequency in a 1:1-ratio into the erenumab or into the placebo arm, therefore there will be 47 patients per arm. In a similar study investigating the effect of galcanezumab on the number of attacks per week in cluster headache patients (Dodick et al., 2020), the difference in the placebo group from baseline was at average -4.6 attacks per week, and the difference in the treatment group was -5.4 (SD about 8.65 in each).

For this study, we assume a treatment effect with erenumab of doubling the placebo effect, i.e. a difference of -9.2 attacks per week. An effect of similar magnitude was reported by Goadsby et al. (Goadsby et al., 2019) who studied the effect of galcanezumab in a phase II study. The treatment effect will be estimated using Bayesian methods.
Using R, we simulated 1000 data sets with the planned sample size, assuming normal distributions for the reduction from baseline with mean of 4.6 for placebo (SD of 8.65) and mean of 9.2 for erenumab (SD of 8.65). STAN and its default weakly informative prior was used to obtain the samples from the posterior distribution, which was then analyzed in R. Based on these simulations, this trial will have approximately 90% probability of meeting the significance criterion and 81% probability of meeting the relevance criterion. We expect approximately 20% of patients to drop-out during the study, therefore we plan to recruit 118 patients in total.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC-approved informed consent. The patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

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

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

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol,

written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Charité assigned monitors, auditors, designated agents of Charité, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Charité immediately that this request has been made.

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

Audits of investigator sites, vendors, and used systems are performed by the Charité CRO, from a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs.

11 Protocol adherence

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

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

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Charité, health authorities where required, and the IRB/IEC prior to

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

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13 Appendices

Appendix 1: Clinically notable laboratory values

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

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

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

Table 13-1 Liver Event and Laboratory Trigger Definitions

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

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

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

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

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

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

Signature Pages

Clinical Trial Protocol CHERUB01

Efficacy of erenumab in chronic cluster headache: A 10-week double-blind, randomized, placebo-controlled, multicentric trial.

Document type: Protocol Version *No.02*

Charité approval signatures for:
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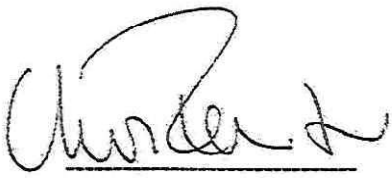
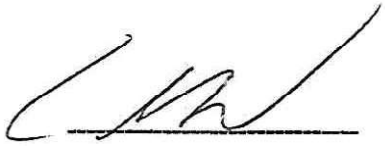
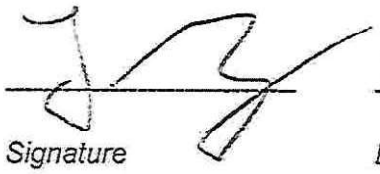
Prof. Dr. Uwe Reuter		21-03-2021
Coordinating Investigator	Signature	Date
PD Dr. Lars Neeb		23-03-2021
#1Deputy Coordinating Investigator	Signature	Date
Jasper Mecklenburg		22-03-2021
#2 Deputy Coordinating Investigator	*Signature*	*Date*

Investigator approval signatures for:

Protocol Version No.02 to Clinical trial Protocol CHERUB01

Investigator signature

I have read the protocol version and agree to conduct this trial in accordance with all stipulation of the protocol, with applicable laws and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki.

| --- | --- | --- |
| Principal Investigator | Signature | Date |