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

Summary

EudraCT number	2020-004399-16
Trial protocol	DE
Global end of trial date	27 September 2023

Results information

Result version number	v1 (current)
This version publication date	17 November 2024
First version publication date	17 November 2024

Trial information

Trial identification

Sponsor protocol code	CHERUB01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04970355
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité- Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Projectmanager, Charité - Universitätsmedizin Berlin, +49 30450 660 139, ma.lorenz@charite.de
Scientific contact	Projectmanager, Charité - Universitätsmedizin Berlin, +49 30450 660 139, ma.lorenz@charite.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2023
Global end of trial reached?	Yes
Global end of trial date	27 September 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The conduct of this study met all legal and regulatory requirements and in accordance with ethical principles of the Declaration of Helsinki.

Background therapy:

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. . Erenumab has a marketing authorization for the prophylactic treatment of adult patients with diagnosed migraine (70mg/140mg). It is and was not authorized for the prophylaxis and/or treatment of chronic cluster headache. Two other CGRG monoclonal antibodies (galcanezumab / fremanezumab) were investigated in different double-blind placebo controlled clinical trials, but failed to show any efficacy in the prophylaxis of chronic cluster headache. Only Lithium has a regulatory approval for the prophylaxis of cCH, but other treatments such as Verapamil, Topiramate and Corticosteroids are currently used (off-label) alone or in combination. For treatment of acute headache attacks, treatments such as sumatriptan s.c. or zolmitriptan nasal spray can be used. Furthermore, Oxygen is also used by patients.
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. This study was conducted with a CGRP (Calcitonin Gene-Related Peptide) monoclonal antibody named erenumab (Aimovig®).
Prophylactic pharmacological treatments of chronic cluster headache (cCH) are limited. Blocking the Calcitonin Gene-Related Peptide (CGRP) receptor might represent a specific new treatment based on pathophysiological evidence. This proof-of-concept study assessed the efficacy and tolerability of the CGRP receptor antibody erenumab in cCH.

Evidence for comparator: -	
Actual start date of recruitment	02 December 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 81
Worldwide total number of subjects	81
EEA total number of subjects	81

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	81
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 11 study centers in Germany, between 02/12/2021 and 27/09/2023.

Pre-assignment

Screening details:

101 patients were screened according the inclusion criteria (at least 9 cluster attacks as defined by ICHD-3 in 7 days during the baseline epoch (SPII), Attacks must have occurred on more than 50% of days of the baseline epoch, ≥ 90% patient-reported eDiary compliance during the Baseline epoch)
81 of whom were randomized.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum

Arm description:

Erenumab is a monoclonal antibody (mab) that blocks the CGRP receptor. The dosage of 280mg s.c. erenumab as a loading dose and a continuing dosage of
140mg s.c. erenumab after 28 days was 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 and onset of efficacy might be observed. The estimation was that the cluster headache population obtain an additional benefit from a loading dose with a faster reach of drug steady state.

Arm type	Experimental
Investigational medicinal product name	Erenumab
Investigational medicinal product code	
Other name	Aimovig®
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

280mg s.c. loading dose at Visit 2 (week 0) in 4x pre-filled syringes of 1 ml each with 70mg Erenumab
140mg s.c. at Visit 3 (4 weeks after first application) with 2x pre-filled syringes á 70mg/1ml

6 weeks, with two dose applications at Visit 2 (week 0) and Visit 4 (week 4)

Arm title	Placebo

Arm description:

Trial medication (IMP and Placebo) was provided by the Funder Novartis. The pre-filled syringes of IMP and Placebo were completely identical. There were no differences regarding look, smell or other factors.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0mg s.c. loading dose at Visit 2 (week 0) with 4x pre-filled syringes of 1 ml each.
0mg s.c. at Visit 3 (4 weeks after first application) with 2x pre-filled syringes of 1 ml each

6 weeks, with two dose applications at Visit 2 (week 0) and Visit 4 (week 4)

Number of subjects in period 1	Verum	Placebo
Started	41	40
Completed	35	35
Not completed	6	5
Adverse event, non-fatal	1	-
Lost to follow-up	2	-
Protocol deviation	3	5

Baseline characteristics

Reporting groups	
Reporting group title	Verum

Reporting group description:

Erenumab is a monoclonal antibody (mab) that blocks the CGRP receptor. The dosage of 280mg s.c. erenumab as a loading dose and a continuing dosage of
140mg s.c. erenumab after 28 days was 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 and onset of efficacy might be observed. The estimation was that the cluster headache population obtain an additional benefit from a loading dose with a faster reach of drug steady state.

Reporting group title	Placebo

Reporting group description:

Trial medication (IMP and Placebo) was provided by the Funder Novartis. The pre-filled syringes of IMP and Placebo were completely identical. There were no differences regarding look, smell or other factors.

Reporting group values	Verum	Placebo	Total
Number of subjects	41	40	81
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	48.3	49.6	
standard deviation	± 10.7	± 10.3	-
Gender categorical Units: Subjects			
Female	11	10	21
Male	30	30	60
Weight Units: kg			
arithmetic mean	83.8	78.5	
standard deviation	± 21.4	± 16.6	-
Duration of CH Units: years			
arithmetic mean	7.6	9.0	
standard deviation	± 7.0	± 7.3	-
Baseline weekly CH attacks Units: number			
arithmetic mean	21.2	21.7	

standard deviation	± 8.95	± 10.6	-

End points

End points reporting groups

Reporting group title	Verum

Reporting group description:

Erenumab is a monoclonal antibody (mab) that blocks the CGRP receptor. The dosage of 280mg s.c. erenumab as a loading dose and a continuing dosage of
140mg s.c. erenumab after 28 days was 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 and onset of efficacy might be observed. The estimation was that the cluster headache population obtain an additional benefit from a loading dose with a faster reach of drug steady state.

Reporting group title	Placebo

Reporting group description:

Trial medication (IMP and Placebo) was provided by the Funder Novartis. The pre-filled syringes of IMP and Placebo were completely identical. There were no differences regarding look, smell or other factors.

Primary: Reduction in number of weekly CH attacks

End point title	Reduction in number of weekly CH attacks

End point description:

End point type	Primary

End point timeframe:

from baseline up to 42 days (5/6 weeks)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: cluster headache attacks				
arithmetic mean (standard deviation)	-7.3 (± 8.65)	-5.9 (± 10.5)		

Statistical analyses

Statistical analysis title	Change of weekly cluster headache attacks

Statistical analysis description:

Bayesian method used for this Proof of Concept. Methods used was suggested by Fish et al. (Fish et al., 2015); Using non-informative prior distributions,
we obtained samples from the posterior distribution of the differences in change from baseline between erenumab and placebo. For sampling from the posterior distribution, we used the STAN software with the default, weakly informative prior.

Comparison groups	Verum v Placebo

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Odds ratio (OR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.5
Variability estimate	Standard deviation

Notes:

[1] - PerProtocol Effect estimates PE with imputation

Secondary: participants with a ≥50% reduction of weekly CH attacks

End point title	participants with a ≥50% reduction of weekly CH attacks

End point description:

End point type	Secondary

End point timeframe:

from baseline to weeks 5/6

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: subjects				
Yes	13	18		
No	28	22		

Statistical analyses

Statistical analysis title	difference of participants with a ≥50% reduction

Statistical analysis description:

Percent of participants with a ≥50% reduction of weekly CH attacks from baseline to weeks 5/6

Comparison groups	Verum v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Bayesian
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.3

Secondary: PGI-I at 6 week

End point title	PGI-I at 6 week

End point description:

End point type	Secondary

End point timeframe:
at week 6

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: subjects				
Missing	1	4		
PGI-I = 1-2	15	14		
PGI-I >2	25	22		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: overall trial	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0
Reporting groups	
Reporting group title	Verum
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Verum	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 41 (4.88%)	0 / 40 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial flutter	Additional description: On admission at hospital sigmoid diverticulitis Type 1b was also diagnosed.		
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression	Additional description: worsening of Cluster Headache attacks		
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Verum	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 41 (65.85%)	15 / 40 (37.50%)	
Vascular disorders			

Hypertension			
subjects affected / exposed	3 / 41 (7.32%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Flu like symptoms	Additional description: including common cold		
subjects affected / exposed	3 / 41 (7.32%)	1 / 40 (2.50%)	
occurrences (all)	4	2	
Pain			
subjects affected / exposed	2 / 41 (4.88%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Mental Tension			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Investigations			
iincreased potassium			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased (ALAT)			

subjects affected / exposed	3 / 41 (7.32%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
increased GPT			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Increased GOT			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Increased CK			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Exerbation of Clusterattacks			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 41 (2.44%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Dizziness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	1 / 41 (2.44%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	4 / 41 (9.76%)	0 / 40 (0.00%)	
occurrences (all)	4	0	
Diarrhoea			
subjects affected / exposed	1 / 41 (2.44%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Anal stenosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Vomiting/ Emesis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Simoid Diverticulitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
skin and other subcutaneous tissue disorders-other	Additional description: Hidradenitis suppurativa in left axilla and Decubitus (Coccyx)		
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscular pain in upper body			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Mucosal infection			

subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Rhinitis infection			
subjects affected / exposed	2 / 41 (4.88%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
SARS-CoV-2 test positive			
subjects affected / exposed	2 / 41 (4.88%)	2 / 40 (5.00%)	
occurrences (all)	2	3	
Pharyngitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Brochial infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Hepatitis E			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Hypercholesterteroemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2021	Update: CT application form, Labelling, Trial protocol (V02, 15-3-2021) Changes in conduct or management of the trial (SARS-CoV-2 Antigen testing, Discontinuation of study treatment by new onset of SARS-CoV-2 Infection as determined at any of the study visits, remote-Site monitoring during pandemic)
13 June 2022	Update: CT application form, trial protocol and synopsis (V03,30-04-2022), Patient information (ICF V03), SmPc Aimovig 12/21, Changes in safety or integrity of trial subjects, Changes in conduct or management of the trial
28 February 2023	Update: CT application form, trial protocol and synopsis (V04, 18-01-23); Changes in safety or integrity of trial subjects, Changes in conduct or management of the trial

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

We did not find a sufficient number of patients in the allocated time period and therefore stopped recruitment prematurely. The result is very clearly negative and the addition of the missing subjects would not have changed anything to results.

Notes: