Clinical trial results:
Interventional, randomized, double-blind, parallel-group, placebo-controlled delayed-start study to evaluate the efficacy and safety of eptinezumab in patients with episodic Cluster Headache

Summary

EudraCT number	2020-001969-37
Trial protocol	NO DK DE SE CZ PT FR BE NL FI GR IT
Global end of trial date	05 October 2023

Results information

Result version number	v1 (current)
This version publication date	29 September 2024
First version publication date	29 September 2024

Trial information

Trial identification

Sponsor protocol code	19386A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04688775
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
Public contact	Email contact via H. Lundbeck A/S, H. Lundbeck A/S, +45 36301311, LundbeckClinicalTrials@Lundbeck.com
Scientific contact	Email contact via H. Lundbeck A/S, H. Lundbeck A/S, +45 36301311, LundbeckClinicalTrials@Lundbeck.com

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	05 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy of eptinezumab in participants with episodic Cluster Headache (eCH).

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice and in accordance with the ethical principles described in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 December 2020
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	Belgium: 4
Country: Number of subjects enrolled	Czechia: 29
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Georgia: 27
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	231
EEA total number of subjects	177

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)	223
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 231 participants were enrolled in 18 countries.

Period 1

Period 1 title	Placebo-controlled period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Eptinezumab

Arm description:

Participants received a single intravenous (IV) infusion of eptinezumab 400 milligrams (mg) in 100 milliliters (mL) 0.9% saline solution.

Arm type	Experimental
Investigational medicinal product name	Eptinezumab
Investigational medicinal product code	
Other name	Vyepti
Pharmaceutical forms	Solution for infusion, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eptinezumab was administered per schedule specified in the arm description.

Arm title	Placebo

Arm description:

Participants received a single IV infusion of 0.9% saline solution as matching placebo for eptinezumab.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was administered per schedule specified in the arm description.

Number of subjects in period 1	Eptinezumab	Placebo
Started	113	118
Received at least 1 dose of study drug	112	117
Completed	108	107
Not completed	5	11

Consent withdrawn by subject	1	6
Adverse event, non-fatal	2	-
Other reasons	-	1
Randomized, not treated	1	1
Lack of efficacy	1	2
Protocol deviation	-	1

Period 2

Period 2 title	Delayed start period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Delayed Start Period: Placebo to Eptinezumab

Arm description:

Participants who received placebo in the placebo-controlled period received a single IV infusion of eptinezumab 400mg in 100 mL 0.9% saline solution.

Arm type	Experimental
Investigational medicinal product name	Eptinezumab
Investigational medicinal product code	
Other name	Vyepti
Pharmaceutical forms	Solution for infusion, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eptinezumab was administered per schedule specified in the arm description.

Arm title	Delayed Start Period: Eptinezumab to Placebo

Arm description:

Participants who received eptinezumab in the placebo-controlled period received a single IV infusion of 0.9% saline solution as matching placebo for eptinezumab.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was administered per schedule specified in the arm description.

Number of subjects in period 2	Delayed Start Period: Placebo to Eptinezumab	Delayed Start Period: Eptinezumab to Placebo
Started	107	108
Received at least 1 dose of study drug	107	108
Completed	101	100
Not completed	6	8
Consent withdrawn by subject	2	4
Adverse event, non-fatal	1	-
Other reasons	1	-
Lost to follow-up	2	1
Lack of efficacy	-	3

Baseline characteristics

Reporting groups

Reporting group title	Placebo-controlled period

Reporting group description: -

Reporting group values	Placebo-controlled period	Total	
Number of subjects	231	231	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	223	223	
From 65-84 years	8	8	
85 years and over	0	0	
Sex: Female, Male Units: Participants			
Female	51	51	
Male	180	180	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	8	8	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	202	202	
Other	3	3	
Unknown or Not Reported	17	17	
Number of Weekly Cluster Headache (CH) Attacks Units: Number of Weekly Attacks			
arithmetic mean	15.4		
standard deviation	± 8.17	-	

End points

End points reporting groups

Reporting group title	Eptinezumab
Reporting group description:	
Participants received a single intravenous (IV) infusion of eptinezumab 400 milligrams (mg) in 100 milliliters (mL) 0.9% saline solution.	
Reporting group title	Placebo
Reporting group description:	
Participants received a single IV infusion of 0.9% saline solution as matching placebo for eptinezumab.	
Reporting group title	Delayed Start Period: Placebo to Eptinezumab
Reporting group description:	
Participants who received placebo in the placebo-controlled period received a single IV infusion of eptinezumab 400mg in 100 mL 0.9% saline solution.	
Reporting group title	Delayed Start Period: Eptinezumab to Placebo
Reporting group description:	
Participants who received eptinezumab in the placebo-controlled period received a single IV infusion of 0.9% saline solution as matching placebo for eptinezumab.	

Primary: Change From Baseline in the Number of Weekly Cluster Headache (CH) Attacks, Averaged Over Weeks 1-2

End point title	Change From Baseline in the Number of Weekly Cluster Headache (CH) Attacks, Averaged Over Weeks 1-2
End point description:	
The participant completed a CH eDiary, daily, and recorded for each day/week whether he/she had any CH attacks. For each CH attack, the start date and time was collected. The participant recorded further daily information regarding CH characteristics and intake of acute medication for CH. CH items were assessed with a yes/no response. The APRS included all randomized participants.	
End point type	Primary
End point timeframe:	
Baseline (Week 0), Weeks 1-2	

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	118		
Units: Number of Weekly Attacks				
least squares mean (standard error)	-4.0 (± 0.93)	-4.6 (± 0.89)		

Statistical analyses

Statistical analysis title	Number of Weekly Attacks: Eptinezumab vs. Placebo
Comparison groups	Eptinezumab v Placebo

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5048
Method	Mixed Models Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	2.6

Secondary: Change From Baseline in the Number of Weekly Times an Abortive Medication Was Used, Averaged Over Weeks 1-2

End point title	Change From Baseline in the Number of Weekly Times an Abortive Medication Was Used, Averaged Over Weeks 1-2

End point description:

Abortive medications included the use of triptans or oxygen (O2).

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 1-2

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: Abortive therapy use per week				
least squares mean (standard error)	-2.54 (± 0.98)	-3.55 (± 0.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With ≥50% Reduction From Baseline in Number of Weekly Attacks Over Weeks 1-2

End point title	Number of Participants With ≥50% Reduction From Baseline in Number of Weekly Attacks Over Weeks 1-2

End point description:

The APRS included all randomized participants.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 1-2

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	118		
Units: participants	44	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Number of Daily Attacks, Averaged Over Days 1-3

End point title	Change From Baseline in the Number of Daily Attacks, Averaged Over Days 1-3

End point description:

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Days 1-3

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	115		
Units: Attacks per day				
least squares mean (standard error)	-0.22 (± 0.16)	-0.35 (± 0.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Number of Days With <3 Attacks Per Day, Averaged Over Weeks 1-2

End point title	Change From Baseline in the Number of Days With <3 Attacks Per Day, Averaged Over Weeks 1-2

End point description:

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 1-2

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: Days				
least squares mean (standard error)	0.60 (± 0.20)	0.82 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Number of Attacks Starting ≤24 Hours After the Start of the First Infusion of IMP

End point title	Change from Baseline in Number of Attacks Starting ≤24 Hours After the Start of the First Infusion of IMP

End point description:

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From first infusion in the placebo-controlled period (Baseline, Day 0) to 24-hours after the first infusion in the placebo-controlled period

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	110		
Units: Number of attacks				
least squares mean (standard error)	2.07 (± 0.18)	1.96 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time From First Infusion of IMP to Resolution of Cluster Headache Bout Within the First 4 Weeks

End point title	Time From First Infusion of IMP to Resolution of Cluster Headache Bout Within the First 4 Weeks

End point description:

Presented here is the result of the analysis of time from first infusion of IMP to resolution of cluster headache bout. The hazard ratio estimate is an estimate from the Cox model of time to resolution.

The APRS included all randomized participants.

"99999" = Data Not Reported. Median and 95% CI could not be calculated due to insufficient number of events.

End point type	Secondary

End point timeframe:

From first infusion (Baseline, Day 0) to 4 weeks

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	117		
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Time From First Infusion to Resolution
Comparison groups	Eptinezumab v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0772
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	2.17

Secondary: Change From Baseline to Week 1 in the Number of Weekly Attacks

End point title	Change From Baseline to Week 1 in the Number of Weekly Attacks

End point description:

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 1

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: Attacks per week				
least squares mean (standard error)	-2.62 (± 0.95)	-3.71 (± 0.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Daily Mean Score on 5-Point Self-Rating Pain Severity Scale, Averaged Over Days 1-3

End point title	Change From Baseline in the Daily Mean Score on 5-Point Self-Rating Pain Severity Scale, Averaged Over Days 1-3

End point description:

The severity of pain was rated on an ordinal scale that ranged from 0 to 4 with higher scores indicating more headache pain (headache pain ratings: 0 = none/barely any pain; 1 = mild; 2 = moderate; 3 = severe; 4 = excruciating).

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Days 1-3

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	112		
Units: score on a scale				
least squares mean (standard error)	-0.30 (± 0.10)	-0.18 (± 0.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 2 in the Number of Weekly Attacks

End point title	Change From Baseline to Week 2 in the Number of Weekly Attacks

End point description:

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome

measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 2

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	110		
Units: Attacks per week				
least squares mean (standard error)	-5.44 (± 1.00)	-5.64 (± 0.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With ≥50% Reduction From Baseline in Number of Weekly Attacks in Week 1

End point title	Number of Participants With ≥50% Reduction From Baseline in Number of Weekly Attacks in Week 1

End point description:

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 1

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: participants	36	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With ≥30% Reduction From Baseline in Number of Weekly Attacks in Week 1

End point title	Number of Participants With ≥30% Reduction From Baseline in Number of Weekly Attacks in Week 1

End point description:

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the

number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 1

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: participants	48	50		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 1 in Weekly Integrated Measure of Frequency and Intensity of Pain

End point title	Change From Baseline to Week 1 in Weekly Integrated Measure of Frequency and Intensity of Pain

End point description:

The weekly integrated measure of frequency and intensity of pain calculates a singular numerical value for frequency and intensity of pain by adding the intensity rating (Worst pain on a 5-point Self-rating pain severity scale) for each attack during that week. The intensity of pain for each attack was rated on an ordinal scale that ranged from 0 to 4 with higher scores indicating more headache pain (0 = none/barely any pain; 1 = mild; 2 = moderate; 3 = severe; 4 = excruciating). The total weekly score could range from 0 (no attacks and/or no pain) to no specified upper limit, with lower scores representing better outcomes.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 1

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: score on a scale				
least squares mean (standard error)	-10.58 (± 2.55)	-11.96 (± 2.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Integrated Measure of Frequency and Intensity of pain, Averaged Over Weeks 1-2

End point title	Change From Baseline in Weekly Integrated Measure of Frequency and Intensity of pain, Averaged Over Weeks 1-2

End point description:

The weekly integrated measure of frequency and intensity of pain calculates a singular numerical value for frequency and intensity of pain by adding the intensity rating (Worst pain on a 5-point Self-rating pain severity scale) for each attack during that week. The intensity of pain for each attack was rated on an ordinal scale that ranged from 0 to 4 with higher scores indicating more headache pain (0 = none/barely any pain; 1 = mild; 2 = moderate; 3 = severe; 4 = excruciating). The total weekly score could range from 0 (no attacks and/or no pain) to no specified upper limit, with lower scores representing better outcomes.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 1-2

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: score on a scale				
least squares mean (standard error)	-13.39 (± 2.56)	-14.46 (± 2.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With ≥30% Reduction from Baseline in Number of Weekly Attacks Over Weeks 1-2

End point title	Number of Participants With ≥30% Reduction from Baseline in Number of Weekly Attacks Over Weeks 1-2

End point description:

The APRS included all randomized participants.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 1-2

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	118		
Units: participants	59	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 2 in Weekly Integrated Measure of Frequency and Intensity of Pain

End point title	Change From Baseline to Week 2 in Weekly Integrated Measure of Frequency and Intensity of Pain

End point description:

The weekly integrated measure of frequency and intensity of pain calculates a singular numerical value for frequency and intensity of pain by adding the intensity rating (Worst pain on a 5-point Self-rating pain severity scale) for each attack during that week. The intensity of pain for each attack was rated on an ordinal scale that ranged from 0 to 4 with higher scores indicating more headache pain (0 = none/barely any pain; 1 = mild; 2 = moderate; 3 = severe; 4 = excruciating). The total weekly score could range from 0 (no attacks and/or no pain) to no specified upper limit, with lower scores representing better outcomes.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 2

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	110		
Units: score on a scale				
least squares mean (standard error)	-16.20 (± 2.73)	-16.95 (± 2.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Mean Score on 5-Point Self-Rating Pain Severity Scale (Average Per Attack Over a Week) for Weeks 1, 2, 3, and 4

End point title	Change From Baseline in the Mean Score on 5-Point Self-Rating Pain Severity Scale (Average Per Attack Over a Week) for Weeks 1, 2, 3, and 4

End point description:

The severity of pain for each attack was rated on an ordinal scale that ranged from 0 to 4 with higher scores indicating more headache pain (headache pain ratings: 0 = none/barely any pain; 1 = mild; 2 =

moderate; 3 = severe; 4 = excruciating).

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome
measure and "Number Analyzed" is the number of participants evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 1, 2, 3, and 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	116		
Units: score on a scale				
least squares mean (standard error)				
Week 1 (n=101,116)	-0.33 (± 0.09)	-0.24 (± 0.08)		
Week 2 (n=91,100)	-0.46 (± 0.10)	-0.35 (± 0.09)		
Week 3 (n=80,97)	-0.56 (± 0.11)	-0.31 (± 0.10)		
Week 4 (n=70,86)	-0.51 (± 0.11)	-0.42 (± 0.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Integrated Measure of Frequency and Intensity of Pain, Averaged Over Weeks 1-4

End point title	Change From Baseline in Weekly Integrated Measure of Frequency and Intensity of Pain, Averaged Over Weeks 1-4

End point description:

The weekly integrated measure of frequency and intensity of pain score calculates a singular numerical value for frequency and intensity of pain by adding the intensity rating (Worst pain on a 5-point Self-rating pain severity scale) for each attack during that week. The intensity of pain for each attack was rated on an ordinal scale that ranged from 0 to 4 with higher scores indicating more headache pain (0 = none/barely any pain; 1 = mild; 2 = moderate; 3 = severe; 4 = excruciating). The total weekly score could range from 0 (no attacks and/or no pain) to no specified upper limit, with lower scores representing better outcomes.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome
measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 1-4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: score on a scale				
least squares mean (standard error)	-17.81 (± 2.50)	-16.81 (± 2.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Number of Weekly Attacks, Averaged Over Weeks 1-4

End point title	Change From Baseline in the Number of Weekly Attacks, Averaged Over Weeks 1-4

End point description:

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 1-4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	116		
Units: Attacks per week				
least squares mean (standard error)	-5.95 (± 0.92)	-5.78 (± 0.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Number of Weekly Attacks for Each of Weeks 3 and 4

End point title	Change from Baseline in the Number of Weekly Attacks for Each of Weeks 3 and 4

End point description:

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure and "Number Analyzed" is the number of participants evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 3-4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	112		
Units: Attacks per week				
least squares mean (standard error)				
Week 3 (n=104,112)	-7.35 (± 0.98)	-6.60 (± 0.94)		
Week 4 (n=102,107)	-8.37 (± 1.11)	-7.15 (± 1.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC) Score at Weeks 1, 2, and 4

End point title	Patient Global Impression of Change (PGIC) Score at Weeks 1, 2, and 4

End point description:

The PGIC is a patient-reported measure of improvement in pain sensation and quality of life scored on a scale from 1 (very much improved) to 7 (very much worse). Lower scores indicate better health status.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome
measure and "Number Analyzed" is the number of participants evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Weeks 1, 2, and 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	106		
Units: score on a scale				
least squares mean (standard error)				
Week 1 (n=102,96)	3.19 (± 0.16)	3.55 (± 0.15)		
Week 2 (n=95,93)	2.92 (± 0.17)	3.44 (± 0.16)		
Week 4 (n=104,106)	2.85 (± 0.18)	3.23 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sleep Impact Scale (SIS) Domain Scores at Weeks 2 and 4

End point title	Change From Baseline in Sleep Impact Scale (SIS) Domain Scores at Weeks 2 and 4

End point description:

The SIS is a patient-reported clinical outcome assessment used to assess quality of life resulting from sleep disturbance. The SIS questionnaire includes 35 items belonging to 7 domains to assess sleep impact on: daily activities; emotional well-being; emotional impact; energy/fatigue; social well-being; mental fatigue; and satisfaction with sleep. Each item, for 6 out of the 7 domains, is rated on a 5-point scale ranging from 1 (always or all of the time) to 5 (never or none of the time), whereas satisfaction with sleep is rated on a 5-point scale ranging from 1 (very satisfied) to 5 (very dissatisfied). Each domain yields a score ranging from 0 to 100, which is presented here. A higher score for Daily Activities, Emotional Well-being, Emotional Impact, Energy/Fatigue, Social Well-being, and Mental Fatigue indicates better quality of life. A lower score for Satisfaction with Sleep indicates a higher quality of life.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 2 and 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: score on a scale				
least squares mean (standard error)				
Daily Activities - Week 2 (n=91,84)	16.83 (± 3.08)	8.93 (± 3.06)		
Daily Activities - Week 4 (n=100,102)	24.82 (± 3.19)	13.97 (± 3.08)		
Emotional Well-being - Week 2 (n=91,84)	14.85 (± 2.84)	6.04 (± 2.81)		
Emotional Well-being - Week 4 (n=100,102)	22.77 (± 3.07)	12.22 (± 2.97)		
Energy/Fatigue - Week 2 (n=91,84)	18.16 (± 3.23)	8.03 (± 3.19)		
Energy/Fatigue - Week 4 (n=100,102)	24.16 (± 3.47)	14.68 (± 3.36)		
Mental Fatigue - Week 2 (n=91,84)	9.04 (± 2.66)	4.15 (± 2.64)		
Mental Fatigue - Week 4 (n=100,102)	15.15 (± 2.91)	8.00 (± 2.81)		
Emotional Impact - Week 2 (n=91,84)	14.39 (± 3.02)	6.00 (± 3.00)		
Emotional Impact - Week 4 (n=100,102)	23.09 (± 3.29)	13.36 (± 3.18)		
Social Well-being - Week 2 (n=91,84)	15.22 (± 3.37)	6.92 (± 3.35)		
Social Well-being - Week 4 (n=100,102)	23.74 (± 3.46)	13.91 (± 3.35)		
Satisfaction with Sleep - Week 2 (n=91,84)	-11.41 (± 2.75)	-6.06 (± 2.73)		
Satisfaction with Sleep - Week 4 (n=100,102)	-19.60 (± 2.88)	-9.63 (± 2.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Euroqol 5-Dimension 5-Levels (EQ-5D-5L) Visual Analogue Scale (VAS) at Weeks 2 and 4

End point title	Change From Baseline in Euroqol 5-Dimension 5-Levels (EQ-5D-5L) Visual Analogue Scale (VAS) at Weeks 2 and 4

End point description:

The EQ-5D-5L VAS is a participant-reported assessment designed to measure the participant's well-

being and ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome
measure and "Number Analyzed" is the number of participants evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 2 and 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	80		
Units: score on a scale				
least squares mean (standard error)				
Week 2 (n=70,63)	8.21 (± 2.79)	3.47 (± 2.86)		
Week 4 (n=76,80)	13.49 (± 2.80)	5.73 (± 2.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Care Resource Utilization (HCRU) Score: Number of Visits to a Family Doctor/General Practitioner

End point title	Health Care Resource Utilization (HCRU) Score: Number of Visits to a Family Doctor/General Practitioner

End point description:

Number of participants who visited a family doctor/general practitioner has been reported.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome
measure at the specified time point.

End point type	Secondary

End point timeframe:

Week 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	104		
Units: participants				
0 visits	85	85		
1 visit	9	10		
2 visits	1	6		
3 visits	3	1		
5 visits	1	1		
6 visits	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: HCRU Score: Number of Visits to a Specialist

End point title	HCRU Score: Number of Visits to a Specialist

End point description:

Number of participants who visited a specialist has been reported.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure at the specified time point.

End point type	Secondary

End point timeframe:

Week 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	104		
Units: participants				
0 visits	77	68		
1 visit	11	18		
2 visits	6	14		
3 visits	4	2		
4 visits	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: HCRU Score: Number of Emergency Department Visits Due to Cluster Headache

End point title	HCRU Score: Number of Emergency Department Visits Due to Cluster Headache

End point description:

Number of participants who visited an emergency department due to CH was reported.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure at the specified time point.

End point type	Secondary

End point timeframe:

Week 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	104		
Units: participants				
0 visits	98	99		
1 visit	1	2		
2 visits	1	2		
3 visits	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: HCRU Score: Number of Hospital Admissions Due to Cluster Headache

End point title	HCRU Score: Number of Hospital Admissions Due to Cluster Headache

End point description:

Number of participants who were admitted to a hospital due to CH was reported.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome measure at the specified time point.

End point type	Secondary

End point timeframe:

Week 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	104		
Units: participants				
0 admissions	97	102		
1 admission	1	0		
2 admissions	2	1		
3 admissions	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: HCRU Score: Number of Overnight Hospital Stays Due to Cluster Headache

End point title	HCRU Score: Number of Overnight Hospital Stays Due to Cluster Headache

End point description:

Number of participants who stayed overnight in a hospital due to CH was reported.

The APRS included all randomized participants. Here, "Overall Number of Participants Analyzed" is the number of participants evaluable for this outcome
measure at the specified time point.

End point type	Secondary

End point timeframe:

Week 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	104		
Units: participants				
0 overnight hospital stays	99	104		
5 overnight hospital stays	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Work Productivity Activity Impairment (WPAI) Questionnaire Subscores at Week 4

End point title	Change From Baseline in the Work Productivity Activity Impairment (WPAI) Questionnaire Subscores at Week 4

End point description:

The WPAI:GH2.0 is a patient self-rated clinical outcome assessment designed to provide a quantitative measure of the work productivity and activity impairment due to a health condition. The WPAI:GH2.0 assesses activities over the preceding 7 days and consists of 6 items: 1 item assesses employment (yes/no); 3 items assess the number of hours worked, the number of hours missed from work due to the participant’s condition, or due to other reasons; and 2 visual numerical scales assess how much the participant’s condition affects his/her productivity at work and his/her ability to complete normal daily activities. Each item (Absenteeism, Presenteeism, Work Productivity Loss, Activity Impairment) was calculated into an impairment percentage ranging from 0 to 100%, with higher numbers indicating greater impairment and less productivity (i.e. worse outcomes). Change from baseline for each item is shown here.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	95		
Units: score on a scale				
least squares mean (standard error)				
Absenteeism	-13.71 (± 3.95)	-4.37 (± 3.74)		
Presenteeism	-19.29 (± 4.81)	-11.03 (± 4.68)		
Work productivity loss	-23.59 (± 5.34)	-13.68 (± 5.20)		
Activity impairment	-25.84 (± 3.70)	-15.82 (± 3.58)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From date of first dose of IMP to 20 weeks after last dose (up to 24 weeks)	
Adverse event reporting additional description:	
The APTS included all randomized participants in the who received infusion with double-blind IMP.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Placebo-controlled Period: Eptinezumab
Reporting group description:	
Participants received a single IV infusion of eptinezumab 400mg in 100 mL 0.9% saline solution.	
Reporting group title	Delayed Start Period: Placebo to Eptinezumab
Reporting group description:	
Participants who received placebo in the placebo-controlled period received a single IV infusion of eptinezumab 400mg in 100 mL 0.9% saline solution.	
Reporting group title	Delayed Start Period: Eptinezumab to Placebo
Reporting group description:	
Participants who received eptinezumab in the placebo-controlled period received a single IV infusion of 0.9% saline solution as matching placebo for eptinezumab.	
Reporting group title	Placebo-controlled Period: Placebo
Reporting group description:	
Participants received a single IV infusion of 0.9% saline solution as matching placebo for eptinezumab.	

Serious adverse events	Placebo-controlled Period: Eptinezumab	Delayed Start Period: Placebo to Eptinezumab	Delayed Start Period: Eptinezumab to Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 112 (1.79%)	1 / 107 (0.93%)	2 / 108 (1.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 112 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	0 / 112 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	1 / 112 (0.89%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	1 / 112 (0.89%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 112 (0.89%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Meningitis enteroviral			
subjects affected / exposed	0 / 112 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo-controlled Period: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 117 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			

Anaphylactic reaction			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Meningitis enteroviral			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo-controlled Period: Eptinezumab	Delayed Start Period: Placebo to Eptinezumab	Delayed Start Period: Eptinezumab to Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 112 (8.93%)	9 / 107 (8.41%)	13 / 108 (12.04%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 112 (3.57%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences (all)	4	1	0
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	4 / 112 (3.57%)	0 / 107 (0.00%)	3 / 108 (2.78%)
occurrences (all)	4	0	4
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 112 (0.89%)	2 / 107 (1.87%)	7 / 108 (6.48%)
occurrences (all)	1	3	7
Nasopharyngitis			
subjects affected / exposed	2 / 112 (1.79%)	6 / 107 (5.61%)	2 / 108 (1.85%)
occurrences (all)	2	6	2
Urinary tract infection			
subjects affected / exposed	0 / 112 (0.00%)	0 / 107 (0.00%)	3 / 108 (2.78%)
occurrences (all)	0	0	3

Non-serious adverse events	Placebo-controlled Period: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 117 (7.69%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences (all)	3		
Infections and infestations			
COVID-19			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported