Clinical trial results:
Interventional, Randomized, Double-blind, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy and Safety of Eptinezumab for the Preventive Treatment of Migraine in Patients with a Dual Diagnosis of Migraine and Medication Overuse Headache

Summary

EudraCT number	2020-001669-35
Trial protocol	ES
Global end of trial date	30 September 2022

Results information

Result version number	v1 (current)
This version publication date	01 October 2023
First version publication date	01 October 2023

Trial information

Trial identification

Sponsor protocol code	19139A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04772742
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
Public contact	H. Lundbeck A/S, LundbeckClinicalTrials@lundbeck.com, +45 36301311, LundbeckClinicalTrials@lundbeck.com
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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	30 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of eptinezumab for the prevention of migraine and medication overuse headache.

Protection of trial subjects:

This study 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	17 February 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 128
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Georgia: 9
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Taiwan: 10
Worldwide total number of subjects	193
EEA total number of subjects	28

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)	184
From 65 to 84 years	9

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study included 2 periods: Placebo-controlled Period - 12-week double-blind treatment period with placebo or eptinezumab 100mg followed by an Open-label Period - 12-week period with eptinezumab 100mg. A safety follow-up visit was conducted 20 weeks after the last investigational medicinal product administration.

Pre-assignment

Screening details:

193 participants were enrolled at sites in 5 countries.

Period 1

Period 1 title	Placebo-controlled (Weeks 1-12)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Eptinezumab

Arm description:

Participants received 100 mg eptinezumab by intravenous (IV) infusion at Baseline (Day 0)

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

Dosage and administration details:

100mg at Baseline (Day 0)

Arm title	Placebo

Arm description:

Participants received matching placebo by IV infusion at Baseline (Day 0)

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mL 0.9% saline solution administered at Baseline (Day 0)

Number of subjects in period 1	Eptinezumab	Placebo
Started	93	100
Received at least 1 dose of study drug	93	100
Completed	81	83
Not completed	12	17
Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	1
Other reasons	10	14

Period 2	
Period 2 title	Open-label (Weeks 12-24)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Eptinezumab

Arm description:

Participants received 100 mg eptinezumab by IV infusion at Primary Outcome Visit (Week 12)

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

Dosage and administration details:

100mg at Primary Outcome Visit (Week 12)

Number of subjects in period 2	Eptinezumab
Started	164
Received at least 1 dose of study drug	162
Completed	137
Not completed	27
Consent withdrawn by subject	5
Adverse event, non-fatal	2
Other reasons	13
Lost to follow-up	2
Lack of efficacy	3

Not treated	2

Baseline characteristics

Reporting groups	
Reporting group title	Eptinezumab
Reporting group description:	
Participants received 100 mg eptinezumab by intravenous (IV) infusion at Baseline (Day 0)	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo by IV infusion at Baseline (Day 0)	

Reporting group values	Eptinezumab	Placebo	Total
Number of subjects	93	100	193
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	87	97	184
From 65-84 years	6	3	9
85 years and over	0	0	0
Age Continuous Units: years			
median	44	43.5	
full range (min-max)	19 to 70	19 to 71	-
Gender Categorical Units: Subjects			
Female	69	82	151
Male	24	18	42
Monthly Migraine Days (MMDs)			
The Full Analysis Set (FAS, n=190) included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.			
Units: days			
arithmetic mean	19.5	19.7	
standard deviation	± 3.6	± 3.8	-

End points

End points reporting groups

Reporting group title	Eptinezumab
Reporting group description:	
Participants received 100 mg eptinezumab by intravenous (IV) infusion at Baseline (Day 0)	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo by IV infusion at Baseline (Day 0)	
Reporting group title	Eptinezumab
Reporting group description:	
Participants received 100 mg eptinezumab by IV infusion at Primary Outcome Visit (Week 12)	

Primary: Change from Baseline in Number of Monthly Migraine Days (MMDs)

End point title	Change from Baseline in Number of Monthly Migraine Days (MMDs)

End point description:

The Migraine Day definition was based on the International Headache Society (IHS) guidelines for controlled trials of preventive treatment of chronic migraine in adults and was defined as any day the participant reported a headache that met criterion A, B, or C:
• Criterion A (all of the following criteria):
– lasted ≥4 hours
– had ≥2 of the following: unilateral location; pulsating quality; moderate/severe pain intensity; aggravation by or avoidance of routine physical activity
– was accompanied by: nausea; vomiting; photophobia or phonophobia
• Criterion B:
– lasted ≥30 minutes and the participant had an aura
• Criterion C: a day with a headache believed by the participant to be a migraine and for which he/she took migraine-specific acute medication (such as triptan, ergotamine, or other migraine-specific acute medication)

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Primary

End point timeframe:

Baseline, Weeks 1-12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	100		
Units: days				
arithmetic mean (standard error)	-7.2 (± 0.73)	-5.9 (± 0.68)		

Statistical analyses

Statistical analysis title	Mean Difference from Placebo
Comparison groups	Eptinezumab v Placebo

Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1484
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.86

Secondary: Percentage of Participants with At Least 50% Reduction in MMDs

End point title	Percentage of Participants with At Least 50% Reduction in MMDs

End point description:

The Migraine Day definition was based on the International Headache Society (IHS) guidelines for controlled trials of preventive treatment of chronic migraine in adults and was defined as any day the participant reported a headache that met criterion A, B, or C:
• Criterion A (all of the following criteria):
– lasted ≥4 hours
– had ≥2 of the following: unilateral location; pulsating quality; moderate/severe pain intensity; aggravation by or avoidance of routine physical activity
– was accompanied by: nausea; vomiting; photophobia or phonophobia
• Criterion B:
– lasted ≥30 minutes and the participant had an aura
• Criterion C: a day with a headache believed by the participant to be a migraine and for which he/she took migraine-specific acute medication (such as triptan, ergotamine, or other migraine-specific acute medication)

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Secondary

End point timeframe:

Weeks 1-12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	100		
Units: percentage of participants				
number (not applicable)	31.1	24.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MMDs With Use of Acute Medication

End point title	Change from Baseline in MMDs With Use of Acute Medication

End point description:

The Migraine Day definition was based on the International Headache Society (IHS) guidelines for controlled trials of preventive treatment of chronic migraine in adults and was defined as any day the participant reported a headache that met criterion A, B, or C:
• Criterion A (all of the following criteria):
– lasted ≥4 hours
– had ≥2 of the following: unilateral location; pulsating quality; moderate/severe pain intensity; aggravation by or avoidance of routine physical activity
– was accompanied by: nausea; vomiting; photophobia or phonophobia
• Criterion B:
– lasted ≥30 minutes and the participant had an aura
• Criterion C: a day with a headache believed by the participant to be a migraine and for which he/she took migraine-specific acute medication (such as triptan, ergotamine, or other migraine-specific acute medication)

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1-12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	100		
Units: days				
arithmetic mean (standard error)	-7.5 (± 0.73)	-6.2 (± 0.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Migraine on the Day After First Dosing

End point title	Percentage of Participants with Migraine on the Day After First Dosing

End point description:

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12. Here, number of subjects analyzed refers to the number of participants in the analysis at the relevant timepoint.

End point type	Secondary

End point timeframe:

Day 1

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	99		
Units: percentage of participants				
number (not applicable)	44.2	59.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with At Least 75% Reduction in MMDs (Weeks 1-4)

End point title	Percentage of Participants with At Least 75% Reduction in MMDs (Weeks 1-4)

End point description:

The Migraine Day definition was based on the International Headache Society (IHS) guidelines for controlled trials of preventive treatment of chronic migraine in adults and was defined as any day the participant reported a headache that met criterion A, B, or C:
• Criterion A (all of the following criteria):
– lasted ≥4 hours
– had ≥2 of the following: unilateral location; pulsating quality; moderate/severe pain intensity; aggravation by or avoidance of routine physical activity
– was accompanied by: nausea; vomiting; photophobia or phonophobia
• Criterion B:
– lasted ≥30 minutes and the participant had an aura
• Criterion C: a day with a headache believed by the participant to be a migraine and for which he/she took migraine-specific acute medication (such as triptan, ergotamine, or other migraine-specific acute medication)

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Secondary

End point timeframe:

Weeks 1-4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	99		
Units: percentage of participants				
number (not applicable)	17.8	1.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Number of Monthly Headache Days (MHDs)

End point title	Change from Baseline in Number of Monthly Headache Days (MHDs)

End point description:

A Headache Day was defined as a day with a headache of a minimum 30 minutes or a Migraine Day.

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Secondary

End point timeframe:

Weeks 1-12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	100		
Units: days				
arithmetic mean (standard error)	-7.1 (± 0.70)	-5.9 (± 0.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with At Least 75% Reduction in MMDs (Weeks 1-12)

End point title	Percentage of Participants with At Least 75% Reduction in MMDs (Weeks 1-12)

End point description:

The Migraine Day definition was based on the International Headache Society (IHS) guidelines for controlled trials of preventive treatment of chronic migraine in adults and was defined as any day the participant reported a headache that met criterion A, B, or C:
• Criterion A (all of the following criteria):
– lasted ≥4 hours
– had ≥2 of the following: unilateral location; pulsating quality; moderate/severe pain intensity; aggravation by or avoidance of routine physical activity
– was accompanied by: nausea; vomiting; photophobia or phonophobia
• Criterion B:
– lasted ≥30 minutes and the participant had an aura
• Criterion C: a day with a headache believed by the participant to be a migraine and for which he/she took migraine-specific acute medication (such as triptan, ergotamine, or other migraine-specific acute medication)

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Secondary

End point timeframe:

Weeks 1-12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	100		
Units: percentage of participants				
number (not applicable)	16.7	2.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with At Least 75% Reduction in MHDs (Weeks 1-12)

End point title	Percentage of Participants with At Least 75% Reduction in MHDs (Weeks 1-12)

End point description:

A Headache Day was defined as a day with a headache of a minimum 30 minutes or a Migraine Day.

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Secondary

End point timeframe:

Weeks 1-12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	100		
Units: percentage of participants				
number (not applicable)	13.3	1.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with At Least 75% Reduction in MHDs (Weeks 1-4)

End point title	Percentage of Participants with At Least 75% Reduction in MHDs (Weeks 1-4)

End point description:

A Headache Day was defined as a day with a headache of a minimum 30 minutes or a Migraine Day.

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12. Here, number of subjects analyzed refers to the number of participants in the analysis at the relevant timepoint.

End point type	Secondary

End point timeframe:

Weeks 1-4

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	99		
Units: percentage of participants				
number (not applicable)	10.0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Percentage of Migraine Attacks with Severe Pain Intensity

End point title	Change from Baseline in Percentage of Migraine Attacks with Severe Pain Intensity

End point description:

A migraine, occurring on a single day or lasting more days, that fulfils the criteria for a migraine, was also referred to as a Migraine Attack.

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1-12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	100		
Units: percentage of migraine attacks				
arithmetic mean (standard error)	-7.4 (± 2.25)	-5.8 (± 2.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MHDs With Use of Acute Medication

End point title	Change from Baseline in MHDs With Use of Acute Medication

End point description:

A Headache Day was defined as a day with a headache of a minimum 30 minutes or a Migraine Day.

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Secondary

End point timeframe:
Baseline, Weeks 1-12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	100		
Units: days				
arithmetic mean (standard error)	-7.6 (± 0.71)	-6.3 (± 0.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC) Score at Week 12

End point title	Patient Global Impression of Change (PGIC) Score at Week 12

End point description:

The PGIC is a single patient-reported item reflecting the participant's impression of change in their disease status since the start of the study (that is, in relation to activity limitations, symptoms, emotions, and overall quality of life). The item is rated on a 7-point scale, where a high score indicates improvement (very much improved; much improved; minimally improved; no change; minimally worse; much worse; very much worse).

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12. Here, number of subjects analyzed refers to the number of participants in the analysis at the relevant timepoint.

End point type	Secondary

End point timeframe:
Week 12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	96		
Units: score on a scale				
arithmetic mean (standard error)	2.6 (± 0.14)	3.1 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Percentage of Headache Episodes with Severe Pain Intensity

End point title	Change from Baseline in Percentage of Headache Episodes with Severe Pain Intensity

End point description:

A headache, occurring on a single day or lasting more days, that either lasts at least 30 minutes or qualifies as a migraine, was also referred to as a Headache Episode.

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1-12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	100		
Units: percentage of headache episodes				
arithmetic mean (standard error)	-8.2 (± 2.09)	-6.0 (± 1.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Screening at Week 12 in Most Bothersome Symptom (MBS) Score

End point title	Change from Screening at Week 12 in Most Bothersome Symptom (MBS) Score

End point description:

The Investigator verbally obtained the most bothersome symptom associated with the participant's migraines during the Screening Visit. Participants were asked to rate the improvement in this symptom from screening on a 7-point scale where a high score indicates improvement (very much improved; much improved; minimally improved; no change; minimally worse; much worse; very much worse). The MBS areas include: nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, and other.

The FAS included all participants who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12. Here, number of subjects analyzed refers to the number of participants in the analysis at the relevant timepoint.

End point type	Secondary

End point timeframe:

Screening, Week 12

End point values	Eptinezumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	96		
Units: score on a scale				
arithmetic mean (standard error)	2.7 (± 0.14)	3.2 (± 0.14)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 32 Weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Eptinezumab
Reporting group description: Placebo-controlled period (Weeks 1-12)	
Reporting group title	Placebo to eptinezumab (Open-label period)
Reporting group description: Open-label period (Weeks 12-24) Participants received placebo during the placebo-controlled period and eptinezumab in the open-label period.	
Reporting group title	Eptinezumab to eptinezumab (Open-label)
Reporting group description: Open-label period (Weeks 12-24) Participants received eptinezumab in both the placebo-controlled and open-label periods	
Reporting group title	Placebo
Reporting group description: Placebo-controlled period (Weeks 1-12)	

Serious adverse events	Eptinezumab	Placebo to eptinezumab (Open-label period)	Eptinezumab to eptinezumab (Open-label)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 93 (2.15%)	0 / 81 (0.00%)	4 / 81 (4.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Rib fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 93 (1.08%)	0 / 81 (0.00%)	0 / 81 (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
Cardiac disorders			
Acute myocardial infarction			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 93 (1.08%)	0 / 81 (0.00%)	0 / 81 (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
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermal cyst			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 93 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
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		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Rib fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermal cyst			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (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	Eptinezumab	Placebo to eptinezumab (Open-label period)	Eptinezumab to eptinezumab (Open-label)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 93 (21.51%)	24 / 81 (29.63%)	20 / 81 (24.69%)
Investigations			
Protein urine present			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 93 (2.15%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences (all)	2	0	0
Glycosylated haemoglobin increased			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 93 (2.15%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences (all)	2	0	1
Nervous system disorders			
Migraine			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 93 (1.08%)	1 / 81 (1.23%)	5 / 81 (6.17%)
occurrences (all)	1	1	5
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 93 (2.15%)	3 / 81 (3.70%)	1 / 81 (1.23%)
occurrences (all)	2	3	1
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	2 / 81 (2.47%)	0 / 81 (0.00%)
occurrences (all)	0	2	0
Influenza like illness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 93 (1.08%)	1 / 81 (1.23%)	0 / 81 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 93 (1.08%)	0 / 81 (0.00%)	3 / 81 (3.70%)
occurrences (all)	1	0	3
Gastrointestinal disorders			
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 93 (1.08%)	2 / 81 (2.47%)	0 / 81 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 93 (2.15%)	2 / 81 (2.47%)	0 / 81 (0.00%)
occurrences (all)	2	2	0
Nausea			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 93 (2.15%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences (all)	2	0	1
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 93 (2.15%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Proteinuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	2 / 81 (2.47%)	0 / 81 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 93 (2.15%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences (all)	2	0	0
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	1 / 81 (1.23%)	2 / 81 (2.47%)
occurrences (all)	0	1	2
Infections and infestations			
Urinary tract infection bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	1 / 81 (1.23%)	0 / 81 (0.00%)
occurrences (all)	0	1	0
COVID-19			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	3 / 81 (3.70%)	3 / 81 (3.70%)
occurrences (all)	0	3	3
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 93 (2.15%)	1 / 81 (1.23%)	1 / 81 (1.23%)
occurrences (all)	3	2	1
Pharyngotonsillitis			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 81 (0.00%)	2 / 81 (2.47%)
occurrences (all)	0	0	2
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 93 (3.23%)	11 / 81 (13.58%)	0 / 81 (0.00%)
occurrences (all)	3	14	0
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 93 (2.15%)	0 / 81 (0.00%)	3 / 81 (3.70%)
occurrences (all)	2	0	3
Metabolism and nutrition disorders			
Hyperlipidaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	3 / 81 (3.70%)	0 / 81 (0.00%)
occurrences (all)	0	3	0
Glucose tolerance impaired			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 81 (0.00%)	2 / 81 (2.47%)
occurrences (all)	0	0	2

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 100 (17.00%)		
Investigations			
Protein urine present			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences (all)	0		
Glycosylated haemoglobin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Nervous system disorders			
Migraine			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	5		
Influenza like illness			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			

Dermatitis atopic alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 100 (0.00%) 0		
Renal and urinary disorders Proteinuria alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 100 (0.00%) 0		
Musculoskeletal and connective tissue disorders Muscle spasms alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 100 (0.00%) 0		
Myalgia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Infections and infestations Urinary tract infection bacterial alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 100 (3.00%) 3		
COVID-19 alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Nasopharyngitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 100 (0.00%) 0		
Pharyngotonsillitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 100 (0.00%) 0		

Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperlipidaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Glucose tolerance impaired			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2020	Deleted: the maximum number of White patients
25 January 2021	Deleted: exit interviews Made changes to the statistical methodology: • added: efficacy analyses will be based on the FAS • included estimands Added: • withdrawal criteria for patients who have anaphylactic reactions or other severe and/or serious hypersensitivity reactions • information on how to manage anaphylactic/hypersensitivity reactions • the possibility to collect additional blood specimens using immune response laboratory kits • follow-up of patients with elevated AST or ALT values Clarified: • the acute medication allowed • the possibility for re-screening of patients affected by COVID-19
23 April 2021	Added that, per investigator judgement, it can be considered to perform additional immune response tests in accordance with local clinical practice, such as histamine, tryptase, immunoglobulin E, and complement components C3 and C4
29 October 2021	Updated the definition of a migraine day Made changes to the statistical methodology: • updated: the definition of the FAS to reflect an update in the statistical methodology • primary analysis: updated to include estimands • exploratory analysis: replaced ANCOVA with MMRM, replaced the CMH test with logistic regression

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported