Clinical trial results:
A Randomized, double-blind, cross-over study to assess erenumab effect on brain networks function and structure in comparison to placebo in episodic migraine patients (RESET BRAIN)

Summary

EudraCT number	2018-004875-11
Trial protocol	IT
Global end of trial date	05 July 2021

Results information

Result version number	v1 (current)
This version publication date	16 July 2022
First version publication date	16 July 2022

Trial information

Trial identification

Sponsor protocol code	CAMG334AIT03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03977649
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG , 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG , 41 613241111, Novartis.email@Novartis.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 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to evaluate whether the prophylactic treatment of a cohort of episodic migraine patients for 3 months with erenumab was able to produce significant changes versus placebo in the functional recruitment and connectivity of multisensory processing areas and, as such, modulate the dysfunctional pain network (chosen as primary area of interest) in the CNS of these patients.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2017
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	Italy: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	61
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There were 70 participants screened for the trial and 61 randomized.

Period 1

Period 1 title	Overall Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Erenumab Sequence 1

Arm description:

Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL)

Arm type	Experimental
Investigational medicinal product name	erenumab
Investigational medicinal product code	AMG334
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

140 mg administered monthly as 2 syringes of 70mg/mL

Arm title	Placebo Sequence 1

Arm description:

Matching placebo every 4 weeks for 12 weeks

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	AMG334
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo administered monthly as 2 syringes

Arm title	Erenumab - Sequence 1 and 2

Arm description:

All participants who received erenumab in either sequence

Arm type	Experimental
Investigational medicinal product name	erenumab
Investigational medicinal product code	AMG334
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

140 mg administered monthly as 2 syringes of 70mg/mL

Arm title	Placebo - Sequence 1 and 2

Arm description:

All participants who received placebo in either sequence

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	AMG334
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo administered monthly as 2 syringes

Number of subjects in period 1	Erenumab Sequence 1	Placebo Sequence 1	Erenumab - Sequence 1 and 2
Started	30	31	59
Completed	26	28	59
Not completed	4	3	0
COVID-19 pandemic	2	-	-
Adverse event, non-fatal	1	1	-
Subject/Guardian Decision	1	2	-

Number of subjects in period 1	Placebo - Sequence 1 and 2
Started	57
Completed	57
Not completed	0
COVID-19 pandemic	-
Adverse event, non-fatal	-
Subject/Guardian Decision	-

Period 2

Period 2 title	Sequence 1
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	No
Arm title	Erenumab Sequence 1

Arm description:

Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL)

Arm type	Experimental
Investigational medicinal product name	erenumab
Investigational medicinal product code	AMG334
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

140 mg administered monthly as 2 syringes of 70mg/mL

Arm title	Placebo Sequence 1

Arm description:

Matching placebo every 4 weeks for 12 weeks

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	AMG334
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo administered monthly as 2 syringes

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is also included in the Overall Period

Number of subjects in period 2	Erenumab Sequence 1	Placebo Sequence 1
Started	30	31
Completed	26	28
Not completed	4	3
COVID-19 pandemic	2	-
Adverse event, non-fatal	1	1
Subject/Guardian Decision	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Sequence 1

Reporting group description: -

Reporting group values	Sequence 1	Total	
Number of subjects	61	61	
Age Categorical Units:			
Between 18 and 65 years	61	61	
Age Continuous Units: years			
arithmetic mean	45.4		
standard deviation	± 9.94	-	
Sex: Female, Male Units:			
Female	53	53	
Male	8	8	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	60	60	
Pacific Islander	1	1	

End points

End points reporting groups

Reporting group title	Erenumab Sequence 1
Reporting group description: Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL)	
Reporting group title	Placebo Sequence 1
Reporting group description: Matching placebo every 4 weeks for 12 weeks	
Reporting group title	Erenumab - Sequence 1 and 2
Reporting group description: All participants who received erenumab in either sequence	
Reporting group title	Placebo - Sequence 1 and 2
Reporting group description: All participants who received placebo in either sequence	
Reporting group title	Erenumab Sequence 1
Reporting group description: Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL)	
Reporting group title	Placebo Sequence 1
Reporting group description: Matching placebo every 4 weeks for 12 weeks	
Subject analysis set title	Erenumab – Sequence 1
Subject analysis set type	Full analysis
Subject analysis set description: Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL)	
Subject analysis set title	Placebo - Sequence 1
Subject analysis set type	Full analysis
Subject analysis set description: Matching placebo every 4 weeks for 12 week	
Subject analysis set title	Placebo - Sequence 1
Subject analysis set type	Full analysis
Subject analysis set description: Matching placebo to erenumab every 4 weeks for 12 weeks	
Subject analysis set title	Erenumab - Sequence 1
Subject analysis set type	Full analysis
Subject analysis set description: Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL)	
Subject analysis set title	Difference between Responder and Non-Responder - erenumab
Subject analysis set type	Full analysis
Subject analysis set description: Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL)	
Subject analysis set title	Difference between Responder and Non-Responder - placebo
Subject analysis set type	Full analysis
Subject analysis set description: Matching placebo every 4 weeks for 12 weeks	
Subject analysis set title	All Patients
Subject analysis set type	Per protocol
Subject analysis set description: Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL) or matching placebo	
Subject analysis set title	Erenumab – Period 1

Subject analysis set type	Safety analysis
Subject analysis set description:	
Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL)	
Subject analysis set title	Placebo - Sequence 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
Matching placebo every 4 weeks for 12 weeks	
Subject analysis set title	Erenumab + Placebo Sequence 1 Total
Subject analysis set type	Full analysis
Subject analysis set description:	
Erenumab and placebo arms combined to analyze differences in increase of RS FCs	
Subject analysis set title	Placebo + erenumab Sequence 1 Total
Subject analysis set type	Full analysis
Subject analysis set description:	
Erenumab and placebo arms combined to analyze differences in increase of RS FCs	
Subject analysis set title	Erenumab + Pacebo Sequence 1 Total
Subject analysis set type	Full analysis
Subject analysis set description:	
Erenumab and placebo arms combined to analyze differences in increase of RS FC	
Subject analysis set title	Placebo + erenumab Sequence 1 Total
Subject analysis set type	Full analysis
Subject analysis set description:	
Erenumab and placebo arms combined to analyze differences in increase of RS FC	
Subject analysis set title	Erenumab + Placebo Sequence 1 Total
Subject analysis set type	Full analysis
Subject analysis set description:	
Erenumab and placebo arms combined to analyze differences in increase of RS FC	
Subject analysis set title	Erenumab – Sequence 1
Subject analysis set type	Per protocol
Subject analysis set description:	
Erenumab 140 mg administered subcutaneously every 4 weeks for 12 weeks (2 syringes/70mg/mL)	

Primary: Significant resting state functional connectivity (RS FC) changes in the functional networks as measured by Magnetic Resonance Imaging (MRI)

End point title	Significant resting state functional connectivity (RS FC) changes in the functional networks as measured by Magnetic Resonance Imaging (MRI)[1]

End point description:

FC is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of FC for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of FC. Increased or decreased in the category description indicates an increase or decrease from baseline. FC maps were constructed starting from RS fMRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, L=left, R=right, Cere=cerebellar(um), MFG=middle frontal gyrus, SMFG=superior medial frontal gyrus, DMN=Default mode network, ACC=anterior cingulate cortex, PCG=precentral gyrus, SMA=supplementary motor area,

End point type	Primary

End point timeframe:

Baseline to Month 3

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Resting state (RS) functional Magnetic Resonance Imaging (fMRI) data from each study scan were pre-processed using the CONN toolbox. RS fMRI images were analyzed and reported using classical methodology used for fMR

End point values	Erenumab – Sequence 1			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: voxels				
Cerebellar N, Decreased RS FC, R Cere crus II	73			
DMN, Increased RS FC in R MFG	53			
DMN, Increased RS FC in L MFG	95			
ault mode network II, Decreased RS FC in L ACC	95			
Sec Vis network I, Increased RS FC in L PCG	73			
L PAG network, Increased RS FC in L SMA	90			
L pontine network, Increased RS FC in L Cere	194			
L pontine network, Increased RS FC in R Cere	72			
R PAG network, Increased RS FC in L Cere (crus I)	154			
R pontine N, Increased RS FC in L Cere (crus I)	113			
R thalamic network, Decreased RS FC in R insula	58			

Statistical analyses

No statistical analyses for this end point

Primary: Significant resting state functional connectivity (RS FC) changes in the functional networks for placebo

End point title	Significant resting state functional connectivity (RS FC) changes in the functional networks for placebo[2]

End point description:

FC is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network (FN). In total, 22 FNs were constructed for this study. A voxel is a single 3-dimensional unit that embeds the strength of FC for each element of the image (brain). Larger numbers of voxel indicate wider regions of the brain showing differences of FC. Increased or decreased in the category description indicates increase or decrease from baseline. FC maps were constructed starting from RS fMRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbrev: DMN=Default mode network, L=left, R=right, MTG=middle temporal gyrus, SFG=superior frontal gyrus, ECN=Executive control network, IFG=Inferior frontal gyrus, SuMG=supramarginal gyrus, Prim vis=Primary visual network. STG= superior temporal gyrus, PIG= parietal inferior gyrus, LPN= L pontine network, LTN=L thalamic network, RPN=Right pontine network.

End point type	Primary

End point timeframe:

Baseline to Month 3

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Resting state (RS) functional Magnetic Resonance Imaging (fMRI) data from each study scan were pre-processed using the CONN toolbox. RS fMRI images were analyzed and reported using classical methodology used for fMR

End point values	Placebo - Sequence 1			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: voxels				
DMN II, decreased RS FC in L MTG BA=21	95			
DMN II, decreased RS FC in R MTG BA=21	140			
Default mode N II, decreased RS FC in L MTG BA=21	56			
Default mode N II, decreased RS FC in R MTG BA=21	55			
DMN II, decreased RS FC in R Precuneus	53			
DMN II, decreased RS FC in R SFG	53			
ECN, decreased RS FC in L precuneus	129			
ECN, decreased RS FC in R IFG	50			
Auditory network, increased RS FC in R SuMG	55			
Auditory network, decreased RS FC in R cere	53			
Auditory network, decreased RS FC in L cerebellum	61			
Prim vis network, decreased RS FC in L hippocampus	114			
Secondary visual network, decreased RS FC in L STG	187			
Salience N, decreased RS FC in R lingual gyrus	380			
Salience N, decreased RS FC in L calcarine	71			
Salience N, decreased RS FC in L PIG	64			
Left PAG network, decreased RS FC in R cerebellum	185			
LPN, decreased RS FC in L angular gyrus	77			
LPN, decreased RS FC in R angular gyrus	76			
LPN, decreased RS FC in L middle frontal gyrus	63			
LPN, decreased RS FC in L inferior parietal gyrus	55			
LTN, decreased RS FC in L angular gyrus	693			
LTN, decreased RS FC, Left precuneus	210			
R hypothal network, decreased RS FC in L cuneus	119			
RPN, decreased RS FC in R cerebellum	79			
RPN, decreased RS FC in L middle cingulum	52			
R thalamic N, decreased RS FC in L precuneus	133			
R thalamic N, decreased RS FC in L calcarine	214			

Statistical analyses

No statistical analyses for this end point

Primary: Significant resting state functional connectivity (RS FC) differences in the functional networks as measured by Magnetic Resonance Imaging (MRI) between erenumab and placebo

End point title	Significant resting state functional connectivity (RS FC) differences in the functional networks as measured by Magnetic Resonance Imaging (MRI) between erenumab and placebo[3]

End point description:

FC is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network (FN). In total, 22 FNs were constructed for this study. A voxel is a single 3-dimensional unit that embeds the strength of FC for each element of the image (brain). Larger numbers of voxel indicate wider regions of the brain showing differences of FC. Increased or decreased in the category description indicates an increase or decrease in the placebo vs the erenumab group. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired.

End point type	Primary

End point timeframe:

Baseline to Month 3

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Resting state (RS) functional Magnetic Resonance Imaging (fMRI) data from each study scan were pre-processed using the CONN toolbox. RS fMRI images were analyzed and reported using classical methodology used for fMR

End point values	Erenumab - Sequence 1			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
Cere network, increased RS FC in R and L precuneus	299			
L PAG N, increased RS FC in Cere vermis and R cere	178			
Left STN N, increased RS FC in L thalamus	54			
RPN, increased RS FC in L cerebellum (crus I)	99			
RPN, increased RS FC in R inferior parietal gyrus	58			
RPN, increased RS FC in R cerebellum	72			

Statistical analyses

No statistical analyses for this end point

Primary: Significant resting state functional connectivity (RS FC) differences between clinical response groups of participants in the functional networks for erenumab

End point title	Significant resting state functional connectivity (RS FC) differences between clinical response groups of participants in the functional networks for erenumab[4]

End point description:

A clinical response is defined as a reduction of 50% in monthly migraine days (MMD) from baseline to month 3. FC is the strength with which every area of the brain is connected with a reference area,

constituting the seed region of the functional network (FN). In total, 22 FNs were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of FC for each element of the image (the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of FC. Increased or decreased in the category description indicates an increase or decrease from baseline. FC maps were constructed starting from RS fMRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired.

End point type	Primary

End point timeframe:

Baseline to Month 3

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Resting state (RS) functional Magnetic Resonance Imaging (fMRI) data from each study scan were pre-processed using the CONN toolbox. RS fMRI images were analyzed and reported using classical methodology used for fMR

End point values	Difference between Responder and Non-Responder - erenumab			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: voxels				
Default mode network II, Left cerebellum (crus II)	62			
Primary visual network, Right cuneus	188			
Secondary visual network II, Right lingual gyrus	78			
Left thalamic network, Right lingual gyrus BA=17	153			
Left thalamic network, Left lingual gyrus	205			
Left thalamic network, Right precuneus	51			

Statistical analyses

No statistical analyses for this end point

Primary: Significant resting state functional connectivity (RS FC) differences between clinical response groups of participants in the functional networks for placebo

End point title	Significant resting state functional connectivity (RS FC) differences between clinical response groups of participants in the functional networks for placebo[5]

End point description:

A clinical response is defined as a reduction of 50% in monthly migraine days (MMD) from baseline to month 3. FC is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network (FN). In total, 22 FNs were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of FC for each element of the image (the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of FC. Increased or decreased in the category description indicates an increase or decrease from baseline. FC maps were constructed starting from RS fMRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired.

End point type	Primary

End point timeframe:

Baseline to Month 3

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Resting state (RS) functional Magnetic Resonance Imaging (fMRI) data from each study scan were pre-processed using the CONN toolbox. RS fMRI images were analyzed and reported using classical methodology used for fMR

End point values	Difference between Responder and Non-Responder - placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: voxels	105			

Statistical analyses

No statistical analyses for this end point

Primary: Significant differences in resting state functional connectivity (RS FC) changes over time between erenumab and placebo in the ICA-like networks

End point title	Significant differences in resting state functional connectivity (RS FC) changes over time between erenumab and placebo in the ICA-like networks[6]

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase or decrease in the placebo vs the erenumab group. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: ECN=Executive control network, R=right, L= left, IFG=inferior frontal gyrus, SFG=superior frontal gyrus.

End point type	Primary

End point timeframe:

Baseline to Month 3

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Resting state (RS) functional Magnetic Resonance Imaging (fMRI) data from each study scan were pre-processed using the CONN toolbox. RS fMRI images were analyzed and reported using classical methodology used for fMR

End point values	Placebo - Sequence 1			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
ECN, increased RS FC in R IFG	112			
R thalamic network, increased RS FC in R SFG	110			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation between changes in the ICA-like and seed-based RS functional connectivity (FC) strength over 3 months and concomitant patients' clinical response in all patients

End point title	Correlation between changes in the ICA-like and seed-based RS functional connectivity (FC) strength over 3 months and concomitant patients' clinical response in all patients

End point description:

Clinical outcomes: percentage of change in monthly migraine, reduction in monthly average severity of migraine pain, percentage of reduction in monthly number of days with use of acute treatments, change in HIT-6 score. Abbreviations: MMDs= Monthly migraine days, Prim Vis=Primary visual, N=Network, R=right, SFG=superior frontal gyrus, Calc=Calcarine cortex

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	All Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: voxels				
MMDs, Prim Vis N, R calcarine cortex	5			
MMDs, Prim Vis N, R thalamic network	5			
HIT-6 score, R thalamic network, R SFG	13			
Severity of migraine pain, Prim Vis N, R calc	29			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation between changes in the ICA-like and seed-based RS functional connectivity (FC) strength over 3 months and concomitant patients' clinical response in erenumab

End point title	Correlation between changes in the ICA-like and seed-based RS functional connectivity (FC) strength over 3 months and concomitant patients' clinical response in erenumab

End point description:

Clinical outcomes: the percentage of change in monthly migraine days, the change in HIT-6 score, the severity of migraine pain

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab Sequence 1			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: voxels	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation between the changes of RS FC in brain regions mediating allodynia and changes in the ASC-12 score. Abbreviations: R=right, L= left, SFG=superior frontal gyrus.

End point title	Correlation between the changes of RS FC in brain regions mediating allodynia and changes in the ASC-12 score. Abbreviations: R=right, L= left, SFG=superior frontal gyrus.

End point description:

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	All Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: voxels				
ASC-12 score, R thalamic Network, L SFG	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline functional MRI markers predictive of good clinical response to erenumab

End point title	Baseline functional MRI markers predictive of good clinical response to erenumab

End point description:

The predictive value of the baseline RS FC of the regions of interest were investigated for treatment clinical response, defined by the achievement of at least

50% reduction of monthly migraine days at month 3 versus baseline.

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab – Sequence 1			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Z score				
number (confidence interval 95%)	.95 (0.92 to 0.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in monthly migraine days (MMD)

End point title	Change from baseline in monthly migraine days (MMD)

End point description:

Monthly migraine days are the number of days with a qualified migraine divided by the number of days of observations, multiplied by 30.

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab – Period 1	Placebo - Sequence 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	31		
Units: days				
least squares mean (confidence interval 95%)	-4.985 (-6.385 to -3.585)	-1.067 (-2.441 to 0.307)		

Statistical analyses

Statistical analysis title	MMD
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-3.918
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.88
upper limit	-1.956

Secondary: Change from baseline in migraine pain

End point title	Change from baseline in migraine pain

End point description:

The monthly average severity of migraine pain at each visit is calculated as the mean of the pain scores reported in the diary during the previous month. Scoring was from 1 to 10 with the higher scores indicating greater pain.

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab – Period 1	Placebo - Sequence 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	31		
Units: scores on a scale				
least squares mean (confidence interval 95%)	-0.604 (-1.198 to -0.009)	-0.014 (-0.608 to 0.580)		

Statistical analyses

Statistical analysis title	Pain
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1665
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-0.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.433
upper limit	0.254

Secondary: Change from Baseline in number of days of acute treatments

End point title	Change from Baseline in number of days of acute treatments
End point description:	
Acute treatments were recorded in participants diary and included: xxxx	
End point type	Secondary
End point timeframe:	
Baseline up to Month 3	

End point values	Erenumab – Period 1	Placebo - Sequence 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	31		
Units: days				
least squares mean (confidence interval 95%)	-4.087 (-5.458 to -2.717)	0.089 (-1.255 to 1.434)		

Statistical analyses

Statistical analysis title	Days acute tx
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-4.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.097
upper limit	-2.257

Secondary: Change from Baseline in Headache Impact Test (HIT-6) score

End point title	Change from Baseline in Headache Impact Test (HIT-6) score

End point description:

The HIT-6 is a self-administered questionnaire which measures adverse headache impact to assess headache severity in the previous month (frequency of pain severity, headaches limiting daily activity, wanting to lie down during a headache) and change in a patient's clinical status over a short period of time (feeling too tired to work or do daily activities because of a headache, feeling "fed up" or irritated because of headaches, and headaches limiting ability to concentrate or work on daily activities). Each of the 6 questions had 5 responses: never, rarely, sometimes, very often, or always. Total possible scores ranged from 36 to 78.
Scores were categorized into 4 grades: little or no impact (49 or less), some impact (50-55), substantial impact (56-59), and severe impact (60-78). Patients completed the HIT-6 in their diary during their scheduled visit.

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab – Period 1	Placebo - Sequence 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	31		
Units: scores on a scale				
least squares mean (confidence interval 95%)	-11.822 (-14.833 to -8.810)	-4.764 (-7.719 to -1.809)		

Statistical analyses

Statistical analysis title	HIT-6
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0016
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-7.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.29
upper limit	-2.82

Secondary: Change from Baseline in Allodynia Symptom checklist -12 (ASC-12)

End point title	Change from Baseline in Allodynia Symptom checklist -12 (ASC-12)

End point description:

The ASC-12 measures overall allodynia (sensory hypersensitivity) and subtypes and has 12 questions about the frequency of allodynia symptoms associated with headache attacks. For individuals with more than one type of headache, questions were directed to the "most severe type of headache" based on the

prior evidence indicating that the most severe type was likely to be migraine. The response categories were scored as; 0=never, rarely, less than half the time, and half the time or more, does not apply to me; 1=less than half the time; and 2=half the time or more; and total score ranged from 0 to 24. Scores indicated: <=2 allodynia was not present, 3-5=mild allodynia; 6-8=moderate allodynia; and >=9=severe allodynia. Patients completed this questionnaire during their scheduled visits.

End point type	Secondary
End point timeframe:	
Baseline up to Month 3	

End point values	Erenumab – Period 1	Placebo - Sequence 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	31		
Units: scores on a scale				
least squares mean (confidence interval 95%)	-11.822 (-14.833 to -8.810)	-4.764 (-7.719 to -1.809)		

Statistical analyses

Statistical analysis title	ASC-12
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0016
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-7.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.29
upper limit	-2.82

Secondary: Change from Baseline in Number of days of clinical symptoms during migraine attacks

End point title	Change from Baseline in Number of days of clinical symptoms during migraine attacks
End point description:	
Clinical outcome symptoms were collected by patients at home using a paper diary. The recall period was the past 24 hours.	
End point type	Secondary
End point timeframe:	
Baseline up to Month 3	

End point values	Erenumab – Period 1	Placebo - Sequence 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	31		
Units: days				
least squares mean (confidence interval 95%)				
Aura during migraine attack	-0.383 (-0.551 to -0.216)	-0.578 (-0.745 to -0.410)		
Nausea during migraine attack	-2.433 (-3.453 to -1.414)	-1.614 (-2.634 to -0.595)		
Vomiting during migraine attack	-0.233 (-0.891 to 0.425)	-0.119 (-0.777 to 0.539)		
Photophobia during migraine attack	-3.898 (-5.126 to -2.670)	-0.416 (-1.621 to 0.789)		
Phonophobia during migraine attack	-3.898 (-5.126 to -2.670)	-0.416 (-1.621 to 0.789)		
Photophobia and Phonophobia during migraine attack	-3.336 (-4.558 to -2.115)	-0.351 (-1.549 to 0.848)		

Statistical analyses

Statistical analysis title	Aura
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0155
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-5.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.161
upper limit	-1.119

Statistical analysis title	Nausea
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1053
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	0.195

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.431

Statistical analysis title	Vomiting
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0155
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-5.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.161
upper limit	-1.119

Statistical analysis title	Photophobia
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0035
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-2.692
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.456
upper limit	-0.928

Statistical analysis title	Phonophobia
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-3.482
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.222
upper limit	-1.743

Statistical analysis title	Photophobia and phonophobia
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0011
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-2.986
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.712
upper limit	-1.26

Secondary: Change from Baseline in Number of days of clinical symptoms during migraine attacks

End point title	Change from Baseline in Number of days of clinical symptoms during migraine attacks

End point description:

Clinical outcome symptoms were collected by patients at home using a paper diary. The recall period was the past 24 hours.

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab – Period 1	Placebo - Sequence 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	31		
Units: days				
least squares mean (confidence interval 95%)				
Aura	-0.383 (-0.551 to -0.216)	-0.578 (-0.745 to -0.410)		
Nausea	-2.433 (-3.453 to -1.414)	-1.614 (-2.634 to -0.595)		
Vomiting	-0.233 (-0.891 to 0.425)	-0.119 (-0.777 to 0.539)		
Photophobia	-3.898 (-5.126 to -2.670)	-0.416 (-1.621 to 0.789)		
Phonophobia	-3.898 (-5.126 to -2.670)	-0.416 (-1.621 to 0.789)		
Photophobia and Phonophobia	-3.336 (-4.558 to -2.115)	-0.351 (-1.549 to 0.848)		

Statistical analyses

Statistical analysis title	Aura
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0155
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-5.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.161
upper limit	-1.119

Statistical analysis title	Nausea
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1053
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	0.195

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.431

Statistical analysis title	Vomiting
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0155
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-5.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.161
upper limit	-1.119

Statistical analysis title	Photophobia
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0035
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-2.692
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.456
upper limit	-0.928

Statistical analysis title	Phonophobia
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-3.482
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.222
upper limit	-1.743

Secondary: Change from Baseline in Hospital Anxiety and Depression Scale (HADS) scores

End point title	Change from Baseline in Hospital Anxiety and Depression Scale (HADS) scores

End point description:

The HADS is a fourteen-item scale. Seven of the items relate to anxiety (HSD-A) and seven to depression (HAD-D).
Calculations of scores: each of the 14 items is rated on a 4-point scale (0 to 3). All items except 7 and 10 are scored as Yes, definitely=3 to No, not at all=0. Items 7 and 10 are scored as: Yes, definitely=0 to No, not at all=3. The HAD-A and HAD-D sub-scores range from 0 to 21 points; scores ≥11 indicate the presence of anxious or depressive disorders; scores between 8-10 points are borderline abnormal, and scores ≤7 indicate that the disorder is not present. Patients completed this questionnaire during their scheduled visit.

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab – Period 1	Placebo - Sequence 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	31		
Units: scores on a scale				
least squares mean (confidence interval 95%)				
HAD-Anxiety	-2.284 (-3.183 to -1.385)	-1.060 (-1.942 to -0.178)		
HAD-Depression	-2.241 (-3.230 to -1.252)	-1.249 (-2.220 to -0.278)		

Statistical analyses

Statistical analysis title	HAD-Anxiety
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0572
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-1.224
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.487
upper limit	0.039

Statistical analysis title	HAD-Depression
Comparison groups	Erenumab – Period 1 v Placebo - Sequence 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.157
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	-0.992
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.378
upper limit	0.395

Secondary: RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in allodynia

End point title	RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in allodynia

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase of connectivity in erenumab vs placebo patients. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, R=right, L=left, DMN=Default mode network

End point type	Secondary

End point timeframe:

Baseline up Month 3

End point values	Erenumab + Placebo Sequence 1 Total			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
Cerebellar N, increased RS FC, L and R precuneus	74			
DMN II, increased RS FC, R cerebellum	62			
L PAG N, increased RS FC, R cerebellum	72			

Statistical analyses

No statistical analyses for this end point

Secondary: RS FC increase, from baseline to month 3 of treatment, in placebo patients compared to erenumab in brain regions involved in allodynia

End point title	RS FC increase, from baseline to month 3 of treatment, in placebo patients compared to erenumab in brain regions involved in allodynia

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase of connectivity in placebo vs erenumab patients. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, R=right, L=left, SFG= superior frontal gyrus, ACC=anterior cingulate cortex.

End point type	Secondary

End point timeframe:

Baseline up Month 3

End point values	Placebo + erenumab Sequence 1 Total			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
R thalamic N, increased RS FC in R SFG	327			
R thalamic N, increased RS FS in L SFG	60			
R thalamic N, increased RS FC in R and L ACC	56			

Statistical analyses

No statistical analyses for this end point

Secondary: RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in photophobia

End point title	RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in photophobia

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase of connectivity in erenumab vs placebo patients. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, R=right, L=left, DMN=Default mode network, Prim Vis=Primary visual, Sec Vis=Secondary visual.

End point type	Secondary

End point timeframe:

Baseline up Month 3

End point values	Erenumab + Placebo Sequence 1 Total			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
Cerebellar N, increased RS FC, L and R precuneus	74			
DMN II, increased RS FC, R cerebellum	62			
Prim Vis N, increased RS FC, R calcarine cortex	119			
Prim Vis N, increased RS FC, L postcentral gyrus	92			
Sec Vis N II, increased RS FC, L precentral gyus	52			
L PAG N, increased RS FC, R cerebellum	72			

Statistical analyses

No statistical analyses for this end point

Secondary: RS FC increase, from baseline to month 3 of treatment, in placebo patients compared to erenumab in brain regions involved in photophobia

End point title	RS FC increase, from baseline to month 3 of treatment, in placebo patients compared to erenumab in brain regions involved in photophobia

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase of connectivity in placebo vs erenumab patients. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, R=right, L=left, SFG= superior frontal gyrus, ACC=anterior cingulate cortex.

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Placebo + erenumab Sequence 1 Total			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
R thalamic N, increased RS FC in R SFG	327			
R thalamic N, increased RS FC in L SFG	60			
R thalamic N,,increased RS FC in R and L ACC	56			

Statistical analyses

No statistical analyses for this end point

Secondary: RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in phonophobia

End point title	RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in phonophobia

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase of connectivity in erenumab vs placebo patients. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, R=right, L=left, DMN=Default mode network.

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab + Pacebo Sequence 1 Total			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
Cerebellar N, increased RS FC in L and R precuneus	74			
DMN II, increased RS FC in R cerebellum	62			
L PAG N, increased RS FC in R cerebellum	72			

Statistical analyses

No statistical analyses for this end point

Secondary: RS FC increase, from baseline to month 3 of treatment, in placebo patients compared to erenumab in brain regions involved in phonophobia

End point title	RS FC increase, from baseline to month 3 of treatment, in placebo patients compared to erenumab in brain regions involved in phonophobia

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase of connectivity in placebo vs erenumab patients. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, R=right, L=left, SFG= superior frontal gyrus, ACC=anterior cingulate cortex.

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Placebo + erenumab Sequence 1 Total			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
R thalamic N, increased RS FC in L SFG	327			
R thalamic N, increased RS FC in R SFG	60			

R thalamic N, increased RS FC in R and L ACC	56			

Statistical analyses

No statistical analyses for this end point

Secondary: RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in nausea

End point title	RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in nausea

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase of connectivity in erenumab vs placebo patients. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, R=right, L=left

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab + Placebo Sequence 1 Total			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
Cerebellar N, increased RS FC in L and R precuneus	74			
L PAG N, increased RS FC in R cerebellum	72			

Statistical analyses

No statistical analyses for this end point

Secondary: RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in the emotional control of pain

End point title	RS FC increase, from baseline to month 3 of treatment, in erenumab patients compared to placebo in brain regions involved in the emotional control of pain

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase of connectivity in erenumab vs placebo patients. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, R=right, L=left

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Erenumab + Placebo Sequence 1 Total			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
Cerebellar N, increased RS FC in L and R precuneus	74			
L PAG N, increased RS FC in R cerebellum	62			

Statistical analyses

No statistical analyses for this end point

Secondary: RS FC increase, from baseline to month 3 of treatment, in placebo patients compared to erenumab in brain regions involved in the emotional control of pain

End point title	RS FC increase, from baseline to month 3 of treatment, in placebo patients compared to erenumab in brain regions involved in the emotional control of pain

End point description:

Functional connectivity is the strength with which every area of the brain is connected with a reference area, constituting the seed region of the functional network. In total, 22 functional networks were constructed for this study. A voxel is the single 3-dimensional unit that embeds the strength of functional connectivity for each element of the image (in our case, of the brain). Larger numbers of voxel indicate wider regions of the brain showing differences of functional connectivity. Increased in the category description indicates an increase of connectivity in placebo vs erenumab patients. Functional connectivity maps were constructed starting from resting state (RS) functional MRI sequences. Structural MRI sequences (FLAIR, T2 and 3D T1 weighted scans) were also acquired. Abbreviations: N=Network, R=right, L=left, SFG= superior frontal gyrus, ACC=anterior cingulate cortex

End point type	Secondary

End point timeframe:

Baseline up to Month 3

End point values	Placebo + erenumab Sequence 1 Total			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: voxels				
R thalamic N, increased RS FC in R SFG	327			
R thalamic N, increased RS FC in L SFG	60			
R thalamic N, increased RS FC in R and L ACC	56			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment for a maximum of 136 days plus a 30 day post treatment follow-up for a maximum duration of 166 days.

Adverse event reporting additional description:

All participants received erenumab and also received placebo. All participants are counted in both arms.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Erenumab

Reporting group description:

Erenumab

Serious adverse events	Placebo	Erenumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Erenumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 57 (29.82%)	28 / 59 (47.46%)	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 57 (1.75%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Injection site erythema			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Fibrocystic breast disease			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Genital tract inflammation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Menopausal symptoms			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Menstruation delayed			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Pelvic fluid collection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Vaginal haemorrhage			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 57 (1.75%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Oropharyngeal pain			

subjects affected / exposed	2 / 57 (3.51%)	1 / 59 (1.69%)	
occurrences (all)	2	1	
Productive cough			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Epicondylitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Wrist fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			

subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Abdominal pain lower			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 57 (0.00%)	8 / 59 (13.56%)	
occurrences (all)	0	8	
Diarrhoea			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Alopecia			

subjects affected / exposed	1 / 57 (1.75%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Hyperhidrosis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 57 (1.75%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	1 / 57 (1.75%)	2 / 59 (3.39%)	
occurrences (all)	1	2	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Glycosuria			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Tendon disorder			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Infections and infestations			

COVID-19			
subjects affected / exposed	2 / 57 (3.51%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Candida infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	2 / 57 (3.51%)	1 / 59 (1.69%)	
occurrences (all)	2	1	
Omphalitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Suspected COVID-19			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 57 (1.75%)	4 / 59 (6.78%)	
occurrences (all)	1	6	
Urinary tract infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Hypercalcaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			

subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 59 (0.00%) 0	

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

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

Cross-over without washout between sequences (SEQ). Analysis determined there was a carry-over effect (C-O E); analysis was changed to parallel with SEQ 1 used for efficacy and both SEQs for safety; some AEs in placebo group may be due to C-O E.

Notes: