# 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<br>Units: | | | |
| Between 18 and 65 years | 61 | 61 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 45.4 | | |
| standard deviation | ± 9.94 | - | |
| Sex: Female, Male<br>Units: | | | |
| Female | 53 | 53 | |
| Male | 8 | 8 | |
| Race/Ethnicity, Customized<br>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<br>occurrences (all) | 1 / 57 (1.75%)<br>1 | 0 / 59 (0.00%)<br>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: