

**Clinical trial results:****Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as monotherapy for patients with newly diagnosed partial-onset seizures: a double-blind, randomized, active-controlled, parallel-group, multicenter clinical study — Open-label ESL extension —****Summary**

| | |
|--------------------------|---|
| EudraCT number | 2015-001243-36 |
| Trial protocol | DE GB HU LT CZ LV PT BE FR ES SE EE AT BG SK FI HR IT |
| Global end of trial date | 19 March 2019 |

Results information

| | |
|-----------------------------------|---------------------------------------|
| Result version number | v1 (current) |
| This version publication date | 04 October 2019 |
| First version publication date | 04 October 2019 |
| Summary attachment (see zip file) | BIA-2093-311/EXT (STUDY SYNOPSIS.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|------------------|
| Sponsor protocol code | BIA-2093-311/EXT |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02484001 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | BIAL - Portela & Ca, S.A. |
| Sponsor organisation address | À Av. Siderurgia Nacional, Coronado, Portugal, 4745-457 |
| Public contact | Helena Gama, BIAL - Portela & Ca, S.A., 00351 229866100, helena.gama@bial.com |
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 September 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 March 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary: To confirm maintenance of efficacy of eslicarbazepine acetate (ESL, 800 mg to 1600 mg once daily [QD]) monotherapy during long-term treatment in adults (≥ 18 years) with recently diagnosed epilepsy experiencing partial-onset seizures.

Protection of trial subjects:

This study was conducted in compliance with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice, including the archiving of essential documents.

Background therapy:

Concomitant AED therapy (1 or 2 AEDs).

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 21 March 2016 |
| 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 | Argentina: 6 |
| Country: Number of subjects enrolled | Australia: 2 |
| Country: Number of subjects enrolled | Bulgaria: 11 |
| Country: Number of subjects enrolled | Brazil: 3 |
| Country: Number of subjects enrolled | Chile: 2 |
| Country: Number of subjects enrolled | Czech Republic: 15 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Estonia: 3 |
| Country: Number of subjects enrolled | Finland: 8 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Croatia: 1 |
| Country: Number of subjects enrolled | Hungary: 14 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Lithuania: 2 |
| Country: Number of subjects enrolled | Latvia: 13 |
| Country: Number of subjects enrolled | Peru: 5 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 3 |
| Country: Number of subjects enrolled | Portugal: 3 |
| Country: Number of subjects enrolled | Romania: 19 |
| Country: Number of subjects enrolled | Russian Federation: 54 |
| Country: Number of subjects enrolled | Serbia: 11 |
| Country: Number of subjects enrolled | Slovakia: 6 |
| Country: Number of subjects enrolled | Ukraine: 13 |
| Worldwide total number of subjects | 207 |
| EEA total number of subjects | 111 |

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) | 186 |
| From 65 to 84 years | 21 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Adults (≥ 18 years) with recently diagnosed epilepsy experiencing partial-onset seizures who were under treatment in the double-blind study BIA-2093-311.

Pre-assignment

Screening details:

Subjects who met all inclusion criteria and none of the exclusion criteria. 207 subjects were enrolled to the trial and 1 subject was a screening failure.

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 207 |
| Number of subjects completed | 206 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|------------------|
| Reason: Number of subjects | Ineligibility: 1 |
|----------------------------|------------------|

Period 1

| | |
|------------------------------|---|
| Period 1 title | Open-label ESL extension (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|-------------|
| Arm title | Overall ESL |
|-----------|-------------|

Arm description:

Subjects already treated with ESL continued with their last evaluated dose (ESL 800 mg, 1200 mg or 1600 mg QD).

Subjects previously treated with CBZ-CR started with ESL 400 mg QD for one week followed by up-titration to the ESL target dose which was equivalent to the last evaluated CBZ-CR dose level (i.e. CBZ-CR 200 mg BID -> ESL 800 mg QD; CBZ-CR 400 mg BID -> ESL 1200 mg QD; CBZ-CR 600 mg BID -> ESL 1600 mg QD) in steps of 400 mg dose increase per week.

| | |
|--|-------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Eslicarbazepine acetate |
| Investigational medicinal product code | ESL |
| Other name | |
| Pharmaceutical forms | Tablet, Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects already treated with ESL will continue with their last evaluated dose (ESL 800 mg, 1200 mg or 1600 mg QD).

Subjects previously treated with CBZ-CR will start with ESL 400 mg QD for one week followed by up-titration to the ESL target dose which is equivalent to the last evaluated CBZ-CR dose level (i.e. CBZ-CR 200 mg BID -> ESL 800 mg QD; CBZ-CR 400 mg BID -> ESL 1200 mg QD; CBZ-CR 600 mg BID -> ESL 1600 mg QD) in steps of 400 mg dose increase per week.

In case of new seizures, the ESL dose can be increased to a maximum dose of ESL 1600 mg QD [dose level C], depending on the investigator's decision. Any up-titration should be performed in weekly steps of 400 mg.

If deemed necessary by the investigator, e.g. due to occurrence of adverse events, the dose of ESL can be reduced according to investigator's discretion, as long as the dose remains in the range of 800 mg QD to 1600mg QD.

Down-titration of ESL as required should be performed in steps of 400 mg decrease per week.

| Number of subjects in period 1^[1] | Overall ESL |
|---|-------------|
| Started | 206 |
| Completed | 172 |
| Not completed | 34 |
| Adverse event, serious fatal | 2 |
| Consent withdrawn by subject | 9 |
| Physician decision | 3 |
| Hyponatremia <125 mmol/L | 1 |
| Adverse event, non-fatal | 7 |
| Subject non-compliance | 4 |
| Other | 5 |
| Adverse event, serious non-fatal | 2 |
| Lack of efficacy | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline period does not include 1 subject who was a screening failure.

Baseline characteristics

Reporting groups

| | |
|---|-------------|
| Reporting group title | Overall ESL |
| Reporting group description: | |
| Subjects already treated with ESL continued with their last evaluated dose (ESL 800 mg, 1200 mg or 1600 mg QD). | |
| Subjects previously treated with CBZ-CR started with ESL 400 mg QD for one week followed by up-titration to the ESL target dose which was equivalent to the last evaluated CBZ-CR dose level (i.e. CBZ-CR 200 mg BID -> ESL 800 mg QD; CBZ-CR 400 mg BID -> ESL 1200 mg QD; CBZ-CR 600 mg BID -> ESL 1600 mg QD) in steps of 400 mg dose increase per week. | |

| Reporting group values | Overall ESL | Total | |
|--|-------------|-------|--|
| Number of subjects | 206 | 206 | |
| Age Categorical | | | |
| Age Categorical Characteristic | | | |
| Units: Subjects | | | |
| In Utero | 0 | 0 | |
| Preterm newborn- gestational age < 37 wk | 0 | 0 | |
| Newborns (0-27days) | 0 | 0 | |
| Infants and toddlers (28days - 23months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 year) | 0 | 0 | |
| From 18 - 64 years | 185 | 185 | |
| From 65 - 84 years | 21 | 21 | |
| Over 85 years | 0 | 0 | |
| Age Continuous | | | |
| Age Continuous Characteristic | | | |
| Units: Years | | | |
| arithmetic mean | 42.6 | | |
| standard deviation | ± 15.89 | - | |
| Gender Categorical | | | |
| Gender Categorical Characteristic | | | |
| Units: Subjects | | | |
| Female | 98 | 98 | |
| Male | 108 | 108 | |

End points

End points reporting groups

| | |
|--|-----------------------------------|
| Reporting group title | Overall ESL |
| Reporting group description: Subjects already treated with ESL continued with their last evaluated dose (ESL 800 mg, 1200 mg or 1600 mg QD). Subjects previously treated with CBZ-CR started with ESL 400 mg QD for one week followed by up-titration to the ESL target dose which was equivalent to the last evaluated CBZ-CR dose level (i.e. CBZ-CR 200 mg BID -> ESL 800 mg QD; CBZ-CR 400 mg BID -> ESL 1200 mg QD; CBZ-CR 600 mg BID -> ESL 1600 mg QD) in steps of 400 mg dose increase per week. | |
| Subject analysis set title | Overall ESL x Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects enrolled who received at least 1 dose of ESL during the open-label extension study. | |
| Subject analysis set title | Overall ESL x FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects enrolled and treated with at least 1 dose of ESL during the open-label extension study and date of withdrawal of ESL or last day of ESL intake available allowing to calculate the derived variables "time to treatment failure" or "treatment retention time" including censoring. | |
| Subject analysis set title | Overall ESL x Per Protocol |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects in the OL FAS without any major protocol deviation. Subjects will be excluded from the PP set for the following reasons: -Treated with ESL outside the range of 800-1600 mg QD except of treatment with ESL 400 mg QD during the first week of transition when switching from CBZ-CR treatment. -Intake of prohibited therapies. -Poor compliance for completion of the subject diary (i.e. they do not adequately report seizure information or diaries are not returned). -Poor compliance for taking ESL (i.e. confirmed compliance <80% or >120% of the scheduled total dose). -Other events occur that may have a relevant impact on the efficacy evaluations. Such study conditions, which may or may not represent a protocol deviation or violation, will be identified during the data review meeting. | |
| Subject analysis set title | Overall ESL x Per Protocol Subset |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects of the OL PP set, excluding all subjects switching from CBZ-CR who discontinue the open-label extension study before they have completed CBZ-CR down-titration for any reasons not linked to efficacy. | |

Primary: Monthly failure rates of time to treatment failure (TTF) / treatment retention time (TRT)

| | |
|--|--|
| End point title | Monthly failure rates of time to treatment failure (TTF) / treatment retention time (TRT) ^[1] |
| End point description: Estimates of monthly failure rates of time to treatment failure (TTF) / treatment retention time (TRT). Time to treatment failure (TTF) is defined as the time from OL Baseline (OL Visit 1) until withdrawal of ESL due to AE or lack of efficacy (i.e. inadequate seizure control) in subjects who received ESL already during the DB phase. Treatment retention time (TRT) is defined as the time from OL Baseline (OL Visit 1) until withdrawal of ESL due to AE or lack of efficacy (i.e. inadequate seizure control) in all subjects including those subjects who received CBZ-CR during the DB phase. | |
| End point type | Primary |
| End point timeframe: Visit 1 until the end of open-label ESL extension | |

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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|------------------------------|------------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: Failure Probability | | | | |
| number (confidence interval) | | | | |
| +30 days | 0.0049000000 (0.0007 to 0.0340) | | | |
| +60 days | 0.0146 (0.0047 to 0.0445) | | | |
| +90 days | 0.0194000000 (0.0073 to 0.0509) | | | |
| +120 days | 0.0194000000 (0.0073 to 0.0509) | | | |
| +150 days | 0.0194000000 (0.0073 to 0.0509) | | | |
| +180 days | 0.0194000000 (0.0073 to 0.0509) | | | |
| +210 days | 0.0194000000 (0.0073 to 0.0509) | | | |
| +240 days | 0.0194000000 (0.0073 to 0.0509) | | | |
| +270 days | 0.0194000000 (0.0073 to 0.0509) | | | |
| +300 days | 0.0244000000 (0.0102 to 0.0576) | | | |
| +330 days | 0.0293 (0.0133 to 0.0642) | | | |
| +360 days | 0.0293 (0.0133 to 0.0642) | | | |
| +390 days | 0.0394000000 (0.0199 to 0.0772) | | | |
| +420 days | 0.0394000000 (0.0199 to 0.0772) | | | |
| +450 days | 0.0394000000 (0.0199 to 0.0772) | | | |
| +480 days | 0.0548000000 (0.0307 to 0.0968) | | | |
| +510 days | 0.0548000000 (0.0307 to 0.0968) | | | |

| | | | | |
|-----------|---------------------------------------|--|--|--|
| +540 days | 0.0548000000 (0.0307 to 0.0968) | | | |
| +570 days | 0.0548000000 (0.0307 to 0.0968) | | | |
| +600 days | 0.0548000000 (0.0307 to 0.0968) | | | |
| +630 days | 0.0548000000 (0.0307 to 0.0968) | | | |
| +660 days | 0.0548000000 (0.0307 to 0.0968) | | | |
| +690 days | 0.0548000000 (0.0307 to 0.0968) | | | |
| +720 days | 0.0602000000 (0.0346 to 0.1037) | | | |
| +750 days | 0.0602000000 (0.0346 to 0.1037) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Monthly withdrawal rates of time to withdrawal for any reason TTW

| | |
|-----------------|--|
| End point title | Monthly withdrawal rates of time to withdrawal for any reason TTW ^[2] |
|-----------------|--|

End point description:

Estimates of monthly withdrawal rates of time to withdrawal for any reason is defined as the time from OL Baseline OL Visit 1 until withdrawal of ESL.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Visit 1 until the end of open-label ESL extension

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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: Withdrawal Rate | | | | |
| number (not applicable) | | | | |
| +30 days | 0.0049000000 | | | |
| +60 days | 0.0146 | | | |
| +90 days | 0.0194000000 | | | |
| +120 days | 0.0243000000 | | | |
| +150 days | 0.0291000000 | | | |
| +180 days | 0.0291000000 | | | |

| | | | | |
|-----------|--------------|--|--|--|
| +210 days | 0.0340000000 | | | |
| +240 days | 0.0388000000 | | | |
| +270 days | 0.0388000000 | | | |
| +300 days | 0.0485000000 | | | |
| +330 days | 0.0534000000 | | | |
| +360 days | 0.0583000000 | | | |
| +390 days | 0.0777000000 | | | |
| +420 days | 0.0777000000 | | | |
| +450 days | 0.0825000000 | | | |
| +480 days | 0.1117000000 | | | |
| +510 days | 0.1165000000 | | | |
| +540 days | 0.1262000000 | | | |
| +570 days | 0.1311000000 | | | |
| +600 days | 0.1359000000 | | | |
| +630 days | 0.1359000000 | | | |
| +660 days | 0.1359000000 | | | |
| +690 days | 0.1505000000 | | | |
| +720 days | 0.1553000000 | | | |
| +750 days | 0.1746000000 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Seizure freedom

| | |
|-----------------|--------------------------------|
| End point title | Seizure freedom ^[3] |
|-----------------|--------------------------------|

End point description:

Number of subjects without seizures (seizure freedom) while treated during the open-label extension study.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Visit 1 until the end of open-label ESL extension

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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: Seizure Freedom | | | | |
| number (not applicable) | | | | |
| Seizure Freedom | 167 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Subjects with seizures by seizure type

End point title | Subjects with seizures by seizure type^[4]

End point description:

The number of subjects with seizures while treated during the open-label extension study classified by seizure type.

End point type | Primary

End point timeframe:

Visit 1 until the end of open-label ESL extension

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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|-------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Total seizures | 39 | | | |
| Simple partial | 12 | | | |
| Complex partial | 17 | | | |
| Partial evolving to secondary | 19 | | | |
| Generalized | 2 | | | |
| Unclassifiable | 3 | | | |
| Other seizure type | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Subjects with seizures by seizure duration

End point title | Subjects with seizures by seizure duration^[5]

End point description:

The number of subjects with seizures while treated during the open-label extension study classified by seizure duration.

End point type | Primary

End point timeframe:

Visit 1 until the end of open-label ESL extension

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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| < 30 sec. | 4 | | | |
| ≥ 30 sec. - < 1 min. | 11 | | | |
| ≥ 1 min. - < 5 min. | 26 | | | |
| ≥ 5 min. | 17 | | | |
| Unknown | 1 | | | |
| More than 1 day | 0 | | | |
| Ongoing | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Standardized seizure frequency

| | |
|--|---|
| End point title | Standardized seizure frequency ^[6] |
| End point description: | |
| Standardised seizure frequency (ssf), calculated as 28 days * (number of seizures in interval T/length of T in days) summarised by open-label ESL study. | |
| End point type | Primary |
| End point timeframe: | |
| Visit 1 until the end of open-label ESL extension | |

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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: SSF | | | | |
| number (standard deviation) | | | | |
| OL Baseline | 206 | | | |
| OL Visit 2 | 204 | | | |
| OL Treatment Visit 1 | 201 | | | |
| OL Treatment Visit 2 | 199 | | | |
| OL Treatment Visit 3 | 195 | | | |
| OL Treatment Visit 4 | 191 | | | |
| OL Treatment Visit 5 | 184 | | | |
| OL Treatment Visit 6 | 178 | | | |
| OL Treatment Visit 7 | 178 | | | |
| OL EOS | 172 | | | |
| OL EDV | 26 | | | |
| OL PSV | 193 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of responders

End point title | Number of responders^[7]

End point description:

A responder is defined as a subject with $\geq 50\%$ reduction in seizure frequency compared to the seizure frequency at double blind study Baseline.

End point type | Primary

End point timeframe:

Visit 1 until the end of open-label ESL extension

Notes:

[7] - 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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| OL Baseline | 206 | | | |
| OL Visit 2 | 201 | | | |
| OL Treatment Visit 1 | 195 | | | |
| OL Treatment Visit 2 | 193 | | | |
| OL Treatment Visit 3 | 192 | | | |
| OL Treatment Visit 4 | 191 | | | |
| OL Treatment Visit 5 | 181 | | | |
| OL Treatment Visit 6 | 175 | | | |
| OL Treatment Visit 7 | 174 | | | |
| OL EOS | 171 | | | |
| OL EDV | 24 | | | |
| OL PSV | 186 | | | |
| Overall | 206 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of responders

End point title | Frequency of responders^[8]

End point description:

A responder is defined as a subject with $\geq 50\%$ reduction in seizure frequency compared to the seizure frequency at double blind study Baseline.

End point type Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

[8] - 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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|---------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: Percentage of responders | | | | |
| number (not applicable) | | | | |
| OL Baseline | 100 | | | |
| OL Visit 2 | 97.6 | | | |
| OL Treatment Visit 1 | 94.7 | | | |
| OL Treatment Visit 2 | 93.7 | | | |
| OL Treatment Visit 3 | 93.2 | | | |
| OL Treatment Visit 4 | 92.7 | | | |
| OL Treatment Visit 5 | 87.9 | | | |
| OL Treatment Visit 6 | 85 | | | |
| OL Treatment Visit 7 | 84.5 | | | |
| OL EOS | 83 | | | |
| OL EDV | 11.7 | | | |
| OL PSV | 90.3 | | | |
| Overall | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Quality of life assessed using the QOLIE-31

End point title Quality of life assessed using the QOLIE-31^[9]

End point description:

Score of the Quality of Life in Epilepsy Inventory-31 (QOLIE-31).

End point type Primary

End point timeframe:

Visit 1 untill the end of open-label ESL extension

Notes:

[9] - 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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: QOLIE-31 Score | | | | |
| number (standard deviation) | | | | |
| OL Baseline | 205 | | | |
| OL Visit 2 | 201 | | | |
| OL Treatment Visit 2 | 199 | | | |
| OL Treatment Visit 4 | 191 | | | |
| OL Treatment Visit 6 | 178 | | | |
| OL EOS | 172 | | | |
| OL EDV | 23 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Treatment satisfaction by the Subject

| | |
|-----------------|---|
| End point title | Treatment satisfaction by the Subject ^[10] |
|-----------------|---|

End point description:

Subject rating of treatment satisfaction (assessed on a 4-point-scale).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Visit 1 until the end of open-label ESL extension

Notes:

[10] - 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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: Treatment satisfaction | | | | |
| number (not applicable) | | | | |
| OL Visit 2 x Very good | 118 | | | |
| OL Visit 2 x Good | 79 | | | |
| OL Visit 2 x Fair | 6 | | | |
| OL Visit 2 x Poor | 1 | | | |
| OL Treatment Visit 1 x Very good | 129 | | | |
| OL Treatment Visit 1 x Good | 69 | | | |
| OL Treatment Visit 1 x Fair | 2 | | | |
| OL Treatment Visit 1 x Poor | 0 | | | |
| OL Treatment Visit 1 x Missing | 1 | | | |
| OL Treatment Visit 2 x Very good | 139 | | | |
| OL Treatment Visit 2 x Good | 54 | | | |
| OL Treatment Visit 2 x Fair | 6 | | | |
| OL Treatment Visit 2 x Poor | 0 | | | |
| OL Treatment Visit 3 x Very good | 140 | | | |

| | | | | |
|----------------------------------|-----|--|--|--|
| OL Treatment Visit 3 x Good | 51 | | | |
| OL Treatment Visit 3 x Fair | 4 | | | |
| OL Treatment Visit 3 x Poor | 0 | | | |
| OL Treatment Visit 4 x Very good | 133 | | | |
| OL Treatment Visit 4 x Good | 55 | | | |
| OL Treatment Visit 4 x Fair | 3 | | | |
| OL Treatment Visit 4 x Poor | 0 | | | |
| OL Treatment Visit 5 x Very good | 130 | | | |
| OL Treatment Visit 5 x Good | 50 | | | |
| OL Treatment Visit 5 x Fair | 2 | | | |
| OL Treatment Visit 5 x Poor | 2 | | | |
| OL Treatment Visit 6 x Very good | 126 | | | |
| OL Treatment Visit 6 x Good | 48 | | | |
| OL Treatment Visit 6 x Fair | 4 | | | |
| OL Treatment Visit 6 x Poor | 0 | | | |
| OL Treatment Visit 7 x Very good | 122 | | | |
| OL Treatment Visit 7 x Good | 53 | | | |
| OL Treatment Visit 7 x Fair | 3 | | | |
| OL Treatment Visit 7 x Poor | 0 | | | |
| OL EOS x Very good | 121 | | | |
| OL EOS x Good | 49 | | | |
| OL EOS x Fair | 2 | | | |
| OL EOS x Poor | 0 | | | |
| OL EDV x Very good | 10 | | | |
| OL EDV x Good | 9 | | | |
| OL EDV x Fair | 5 | | | |
| OL EDV x Poor | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Treatment satisfaction by the Investigator

| | |
|-----------------|--|
| End point title | Treatment satisfaction by the Investigator ^[11] |
|-----------------|--|

End point description:

Investigator rating of treatment satisfaction (assessed on a 4-point-scale).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Visit 1 until the end of open-label ESL extension

Notes:

[11] - 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: No statistical analyses have been performed for this primary end point.

| End point values | Overall ESL x FAS | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 206 | | | |
| Units: Treatment satisfaction | | | | |
| number (not applicable) | | | | |
| OL Visit 2 x Very good | 128 | | | |
| OL Visit 2 x Good | 72 | | | |
| OL Visit 2 x Fair | 2 | | | |
| OL Visit 2 x Poor | 2 | | | |
| OL Treatment Visit 1 x Very good | 133 | | | |
| OL Treatment Visit 1 x Good | 64 | | | |
| OL Treatment Visit 1 x Fair | 3 | | | |
| OL Treatment Visit 1 x Poor | 0 | | | |
| OL Treatment Visit 1 x Missing | 1 | | | |
| OL Treatment Visit 2 x Very good | 140 | | | |
| OL Treatment Visit 2 x Good | 54 | | | |
| OL Treatment Visit 2 x Fair | 5 | | | |
| OL Treatment Visit 2 x Poor | 0 | | | |
| OL Treatment Visit 3 x Very good | 139 | | | |
| OL Treatment Visit 3 x Good | 53 | | | |
| OL Treatment Visit 3 x Fair | 3 | | | |
| OL Treatment Visit 3 x Poor | 0 | | | |
| OL Treatment Visit 4 x Very good | 137 | | | |
| OL Treatment Visit 4 x Good | 52 | | | |
| OL Treatment Visit 4 x Fair | 2 | | | |
| OL Treatment Visit 4 x Poor | 0 | | | |
| OL Treatment Visit 5 x Very good | 132 | | | |
| OL Treatment Visit 5 x Good | 49 | | | |
| OL Treatment Visit 5 x Fair | 3 | | | |
| OL Treatment Visit 5 x Poor | 0 | | | |
| OL Treatment Visit 6 x Very good | 130 | | | |
| OL Treatment Visit 6 x Good | 45 | | | |
| OL Treatment Visit 6 x Fair | 3 | | | |
| OL Treatment Visit 6 x Poor | 0 | | | |
| OL Treatment Visit 7 x Very good | 126 | | | |
| OL Treatment Visit 7 x Good | 49 | | | |
| OL Treatment Visit 7 x Fair | 3 | | | |
| OL Treatment Visit 7 x Poor | 0 | | | |
| OL EOS x Very good | 122 | | | |
| OL EOS x Good | 49 | | | |
| OL EOS x Fair | 14 | | | |
| OL EOS x Poor | 0 | | | |
| OL EDV x Very good | 12 | | | |
| OL EDV x Good | 7 | | | |
| OL EDV x Fair | 4 | | | |
| OL EDV x Poor | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Visit 1 until post study visit (4 weeks after OL EOS or OL EDV).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Overall ESL x Safety |
|-----------------------|----------------------|

Reporting group description:

Subjects in the Safety set treated with ESL

| Serious adverse events | Overall ESL x Safety | | |
|---|----------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 206 (8.25%) | | |
| number of deaths (all causes) | 3 | | |
| number of deaths resulting from adverse events | 3 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer recurrent | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Aortic dilatation | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Hypertension | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Partial seizures | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Partial seizures with secondary generalisation | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Seizure | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mesenteric artery thrombosis | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal achalasia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Overall ESL x Safety | | |
|--|----------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 124 / 206 (60.19%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Thyroid neoplasm | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |

| | | | |
|--|---|--|--|
| <p>Vascular disorders</p> <p>Essential hypertension subjects affected / exposed occurrences (all)</p> <p>Arteriosclerosis subjects affected / exposed occurrences (all)</p> <p>Hypertension subjects affected / exposed occurrences (all)</p> | <p>1 / 206 (0.49%) 1</p> <p>1 / 206 (0.49%) 1</p> <p>11 / 206 (5.34%) 11</p> | | |
| <p>General disorders and administration site conditions</p> <p>Gait disturbance subjects affected / exposed occurrences (all)</p> <p>Fatigue subjects affected / exposed occurrences (all)</p> <p>Asthenia subjects affected / exposed occurrences (all)</p> | <p>1 / 206 (0.49%) 1</p> <p>3 / 206 (1.46%) 3</p> <p>5 / 206 (2.43%) 5</p> | | |
| <p>Immune system disorders</p> <p>Drug hypersensitivity subjects affected / exposed occurrences (all)</p> <p>Allergy to plants subjects affected / exposed occurrences (all)</p> <p>Hypersensitivity subjects affected / exposed occurrences (all)</p> <p>Seasonal allergy subjects affected / exposed occurrences (all)</p> | <p>1 / 206 (0.49%) 1</p> <p>1 / 206 (0.49%) 1</p> <p>1 / 206 (0.49%) 1</p> <p>3 / 206 (1.46%) 3</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Asthma</p> | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Cough subjects affected / exposed occurrences (all) | 6 / 206 (2.91%) 6 | | |
| Pleurisy subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 4 / 206 (1.94%) 5 | | |
| Lung disorder subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Sinus polyp subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Psychiatric disorders | | | |
| Acute stress disorder subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Alcohol abuse subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Anxiety subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 2 | | |
| Disorientation subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Depression subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 2 | | |
| Confusional state subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |

| | | | |
|--|------------------|--|--|
| Bradyphrenia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 2 | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 3 | | |
| Irritability | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Mood disorder due to a general medical condition | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Sleep disorder | | | |
| subjects affected / exposed | 3 / 206 (1.46%) | | |
| occurrences (all) | 3 | | |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 4 / 206 (1.94%) | | |
| occurrences (all) | 4 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Blood chloride decreased | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 13 / 206 (6.31%) | | |
| occurrences (all) | 15 | | |
| Blood creatinine decreased | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|-----------------|--|--|
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Blood parathyroid hormone increased | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Blood pressure decreased | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Blood sodium decreased | | | |
| subjects affected / exposed | 3 / 206 (1.46%) | | |
| occurrences (all) | 3 | | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 7 / 206 (3.40%) | | |
| occurrences (all) | 7 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 6 / 206 (2.91%) | | |
| occurrences (all) | 8 | | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 3 / 206 (1.46%) | | |
| occurrences (all) | 3 | | |
| Body mass index increased | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| N-telopeptide | | | |
| subjects affected / exposed | 5 / 206 (2.43%) | | |
| occurrences (all) | 5 | | |
| Osteocalcin decreased | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Thyroid hormones decreased subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 2 | | |
| Thyroxine decreased subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Thyroxine free decreased subjects affected / exposed occurrences (all) | 3 / 206 (1.46%) 3 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 4 / 206 (1.94%) 4 | | |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 4 | | |
| Hand fracture subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Foot fracture subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 2 | | |
| Craniocerebral injury subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Contusion subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Head injury | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Muscle injury | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Overdose | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Tooth fracture | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Tongue injury | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 2 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|----------------------|--|--|
| Left ventricular failure subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Extrasystoles subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Left ventricular hypertrophy subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Supraventricular extrasystoles subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Myocardial infarction subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Ventricular extrasystoles subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 2 | | |
| Nervous system disorders | | | |
| Amnesia subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Ataxia subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 2 | | |
| Balance disorder subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Carpal tunnel syndrome subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Cerebellar syndrome subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Coordination abnormal | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 3 | | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 206 (4.85%) | | |
| occurrences (all) | 12 | | |
| Epilepsy | | | |
| subjects affected / exposed | 4 / 206 (1.94%) | | |
| occurrences (all) | 4 | | |
| Drop attacks | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 10 / 206 (4.85%) | | |
| occurrences (all) | 17 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 3 / 206 (1.46%) | | |
| occurrences (all) | 8 | | |
| Hyporeflexia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Hyperreflexia | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Migraine | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 4 / 206 (1.94%) | | |
| occurrences (all) | 4 | | |
| Morton's neuralgia | | | |

| | | | |
|---|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Migraine without aura subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Parkinson's disease subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Postictal paralysis subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Sciatica subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Seizure subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Somnolence subjects affected / exposed occurrences (all) | 9 / 206 (4.37%) 11 | | |
| Syncope subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 7 | | |
| Tension headache subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 2 | | |
| Eosinopenia subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Leukopenia subjects affected / exposed occurrences (all) | 4 / 206 (1.94%) 4 | | |

| | | | |
|--|--|--|--|
| <p>Ear and labyrinth disorders</p> <p>Vertigo positional subjects affected / exposed occurrences (all)</p> <p>Vertigo subjects affected / exposed occurrences (all)</p> <p>Tinnitus subjects affected / exposed occurrences (all)</p> | <p>1 / 206 (0.49%) 1</p> <p>3 / 206 (1.46%) 4</p> <p>1 / 206 (0.49%) 1</p> | | |
| <p>Eye disorders</p> <p>Blepharospasm subjects affected / exposed occurrences (all)</p> <p>Conjunctivitis allergic subjects affected / exposed occurrences (all)</p> <p>Dry age-related macular degeneration subjects affected / exposed occurrences (all)</p> <p>Pterygium subjects affected / exposed occurrences (all)</p> <p>Myopia subjects affected / exposed occurrences (all)</p> <p>Eyelid dermatochalasis subjects affected / exposed occurrences (all)</p> <p>Vision blurred subjects affected / exposed occurrences (all)</p> <p>Visual impairment subjects affected / exposed occurrences (all)</p> | <p>2 / 206 (0.97%) 2</p> <p>1 / 206 (0.49%) 1</p> <p>1 / 206 (0.49%) 1</p> <p>1 / 206 (0.49%) 1</p> <p>1 / 206 (0.49%) 1</p> <p>1 / 206 (0.49%) 2</p> <p>1 / 206 (0.49%) 1</p> <p>3 / 206 (1.46%) 3</p> <p>2 / 206 (0.97%) 2</p> | | |
| Gastrointestinal disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Constipation | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 2 | | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Gastritis | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Duodenogastric reflux | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 2 | | |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 4 / 206 (1.94%) | | |
| occurrences (all) | 6 | | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |

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|--|----------------------|--|--|
| Salivary gland mucocoele subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 2 | | |
| Hepatobiliary disorders Biliary dyskinesia subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Cholelithiasis subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Steatohepatitis subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Rash erythematous subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Skin depigmentation subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Skin exfoliation subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Renal and urinary disorders Chromaturia subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Chronic kidney disease subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Haematuria | | | |

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|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Renal artery thrombosis subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Renal cyst subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Urinary incontinence subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Endocrine disorders | | | |
| Autoimmune thyroiditis subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Primary hypothyroidism subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Back pain subjects affected / exposed occurrences (all) | 11 / 206 (5.34%) 11 | | |
| Intervertebral disc protrusion subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Muscle spasms subjects affected / exposed occurrences (all) | 3 / 206 (1.46%) 3 | | |
| Musculoskeletal pain | | | |

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|------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Posture abnormal | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 4 / 206 (1.94%) | | |
| occurrences (all) | 4 | | |
| Bronchitis | | | |
| subjects affected / exposed | 7 / 206 (3.40%) | | |
| occurrences (all) | 8 | | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Gingivitis | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 4 / 206 (1.94%) | | |
| occurrences (all) | 5 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Influenza | | | |
| subjects affected / exposed | 13 / 206 (6.31%) | | |
| occurrences (all) | 19 | | |

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|-------------------------------|------------------|--|--|
| Laryngitis | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Labyrinthitis | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Nasal herpes | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Otitis media acute | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 12 / 206 (5.83%) | | |
| occurrences (all) | 14 | | |
| Ophthalmic herpes zoster | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 206 (1.46%) | | |
| occurrences (all) | 3 | | |
| Pharyngitis bacterial | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Pulpitis dental | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |

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| Respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Respiratory tract infection viral subjects affected / exposed occurrences (all) | 4 / 206 (1.94%) 5 | | |
| Sinusitis subjects affected / exposed occurrences (all) | 3 / 206 (1.46%) 4 | | |
| Tooth infection subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 2 | | |
| Tonsillitis subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Tinea cruris subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Viral infection subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 206 (0.97%) 2 | | |
| Tracheitis subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all) | 1 / 206 (0.49%) 1 | | |
| Diabetes mellitus | | | |

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|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Dyslipidaemia | | | |
| subjects affected / exposed | 2 / 206 (0.97%) | | |
| occurrences (all) | 2 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 206 (1.46%) | | |
| occurrences (all) | 3 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Obesity | | | |
| subjects affected / exposed | 3 / 206 (1.46%) | | |
| occurrences (all) | 3 | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Vitamin C deficiency | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |
| Zinc deficiency | | | |
| subjects affected / exposed | 1 / 206 (0.49%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported