



Clinical trial results:

Prevention of epilepsy in stroke patients at high risk of developing unprovoked seizures: anti-epileptogenic effects of eslicarbazepine acetate

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2018-002747-29 |
| Trial protocol | ES SE GB PT IT |
| Global end of trial date | 11 September 2023 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 18 January 2025 |
| First version publication date | 18 January 2025 |
| Summary attachment (see zip file) | BIA-2093-213_Synopsis (CTR synopsis_2018-002747-29_BIA-2093-213.pdf) |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | BIA-2093-213 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT06597084 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bial - Portela & Ca, S.A. |
| Sponsor organisation address | À Av. da Siderurgia Nacional, Trofa, Portugal, 4745-457 |
| Public contact | Sponsor, Bial - Portela & Ca, S.A., 00351 22 98661 00, info@bial.com |
| Scientific contact | Head of Clinical Operations, Bial - Portela & Ca, S.A., 00351 229866100, clinical.trials@bial.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 | 22 November 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 September 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess if eslicarbazepine acetate (ESL) treatment (started within 96 hours after stroke occurrence and continued for 30 days) changes the incidence of unprovoked seizures (USs) within the first 6 months after randomisation as compared to placebo.

Protection of trial subjects:

This trial was performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 15 February 2019 |
| 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 | Israel: 6 |
| Country: Number of subjects enrolled | Portugal: 10 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | Sweden: 8 |
| Country: Number of subjects enrolled | United Kingdom: 26 |
| Country: Number of subjects enrolled | Austria: 22 |
| Country: Number of subjects enrolled | Germany: 24 |
| Country: Number of subjects enrolled | Italy: 27 |
| Worldwide total number of subjects | 125 |
| EEA total number of subjects | 93 |

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) | 58 |
| From 65 to 84 years | 59 |
| 85 years and over | 8 |

Subject disposition

Recruitment

Recruitment details:

A total of 129 patients were enrolled at 19 active trial centres in Europe and Israel. Following sponsor's decision, recruitment was closed by the end of February 2022, since due to the unforeseen COVID-19 pandemic circumstances. The recruitment termination was not related to safety issues or other circumstances related to the IMP.

Pre-assignment

Screening details:

4 patients failed screening, 125 patients were randomised. Two did not take the IMP due to withdrawal of consent (patient or patient's family decision). Overall, of 125 patients randomised, 92 (73.6%) patients completed the 6-month period, 86 (68.8%) patients completed the 12-month period, and 84 (66.7.2%) patients completed the 18 month period.

Period 1

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

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group A - ESL |

Arm description:

800 mg ESL tablets for oral administration. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Eslicarbazepine acetate |
| Investigational medicinal product code | BIA 2093 |
| Other name | Zebinix |
| Pharmaceutical forms | Oral suspension, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

At the first visit (screening/baseline, V1a), patients will undergo several examinations to check eligibility. The next visit (V1b) has to be performed within 96 hours after primary stroke occurrence. After eligibility has been confirmed, patients will be randomised (randomisation ratio 1:1) to treatment with ESL 800 mg (Group A) or placebo (Group B). Patients can receive therapies for stroke treatment according to local clinical practice at any time during the trial.

Patients will start treatment with the investigational medicinal product (IMP), i.e. ESL or placebo, within 96 hours after primary stroke occurrence at V1b. They will continue treatment until Day 30 after randomisation and then be tapered off. Thereafter, patients will be followed up until 18 months after randomisation. Patients can concomitantly receive antiepileptic therapies, except commercially available ESL or oxcarbazepine, until Day 30.

| | |
|------------------|-------------------|
| Arm title | Group B - Placebo |
|------------------|-------------------|

Arm description:

Placebo tablets for oral administration, matching the test product. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line.

| | |
|--|-------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

At the first visit (screening/baseline, V1a), patients will undergo several examinations to check eligibility. The next visit (V1b) has to be performed within 96 hours after primary stroke occurrence. After eligibility has been confirmed, patients will be randomised (randomisation ratio 1:1) to treatment with ESL 800 mg (Group A) or placebo (Group B). Patients can receive therapies for stroke treatment according to local clinical practice at any time during the trial.

Patients will start treatment with the investigational medicinal product (IMP), i.e. ESL or placebo, within 96 hours after primary stroke occurrence at V1b. They will continue treatment until Day 30 after randomisation and then be tapered off. Thereafter, patients will be followed up until 18 months after randomisation. Patients can concomitantly receive antiepileptic therapies, except commercially available ESL or oxcarbazepine, until Day 30.

| Number of subjects in period 1 | Group A - ESL | Group B - Placebo |
|---|---------------|-------------------|
| Started | 62 | 63 |
| Completed | 43 | 41 |
| Not completed | 19 | 22 |
| Stroke more than 7 days after primary stroke | 2 | 6 |
| Adverse event, serious fatal | 4 | - |
| Consent withdrawn by subject | 4 | 9 |
| Physician decision | 1 | - |
| Adverse event, non-fatal | 3 | 2 |
| Consent was not given by the patient until V2 | - | 3 |
| Other | 1 | - |
| Lost to follow-up | 4 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Group A - ESL |
|-----------------------|---------------|

Reporting group description:

800 mg ESL tablets for oral administration. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line.

| | |
|-----------------------|-------------------|
| Reporting group title | Group B - Placebo |
|-----------------------|-------------------|

Reporting group description:

Placebo tablets for oral administration, matching the test product. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line.

| Reporting group values | Group A - ESL | Group B - Placebo | Total |
|--|---------------|-------------------|-------|
| Number of subjects | 62 | 63 | 125 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 31 | 28 | 59 |
| From 65-84 years | 25 | 33 | 58 |
| 85 years and over | 6 | 2 | 8 |
| Not recorded | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 66.1 | 65.3 | |
| standard deviation | ± 14.47 | ± 13.94 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 23 | 22 | 45 |
| Male | 39 | 41 | 80 |
| Race | | | |
| Units: Subjects | | | |
| White | 58 | 61 | 119 |
| Black or African American | 3 | 1 | 4 |
| Asian | 1 | 0 | 1 |
| Multiple | 0 | 1 | 1 |

End points

End points reporting groups

| | |
|---|-------------------|
| Reporting group title | Group A - ESL |
| Reporting group description: 800 mg ESL tablets for oral administration. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line. | |
| Reporting group title | Group B - Placebo |
| Reporting group description: Placebo tablets for oral administration, matching the test product. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line. | |

Primary: Proportion of Patients Who Experience the First Unprovoked Seizures (US) Within the First 6 Months After Randomisation (Failure Rate)

| | |
|---|---|
| End point title | Proportion of Patients Who Experience the First Unprovoked Seizures (US) Within the First 6 Months After Randomisation (Failure Rate) |
| End point description: Deaths before the first US or patients without evaluable assessment of the primary endpoint will be counted as treatment failures. To show that ESL (Group A) is superior to placebo (Group B), the primary null hypothesis will be tested against the alternative hypothesis | |
| End point type | Primary |
| End point timeframe: First 6 months after randomisation | |

| End point values | Group A - ESL | Group B - Placebo | | |
|-------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Failures - Unprovoked seizure | 2 | 7 | | |
| Failures - Death | 3 | 0 | | |
| Failures - Withdrawn | 12 | 16 | | |
| Non-failures | 44 | 39 | | |

Statistical analyses

| | |
|----------------------------|-----------------------------------|
| Statistical analysis title | U within 6 Months after Randomis |
| Comparison groups | Group A - ESL v Group B - Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1739 ^[1] |
| Method | Chi-squared corrected |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -0.0801 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1953 |
| upper limit | 0.0301 |

Notes:

[1] - p-value from chi-square test with continuity correction

Secondary: Measure Title Proportion of Patients Who Experience the First US During the First 12 Months After Randomisation

| | |
|-----------------|---|
| End point title | Measure Title Proportion of Patients Who Experience the First US During the First 12 Months After Randomisation |
|-----------------|---|

End point description:

Deaths before the first US or patients without evaluable assessment of the primary endpoint will be counted as treatment failures. To show that ESL (Group A) is superior to placebo (Group B), the primary null hypothesis will be tested against the alternative hypothesis

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 12 months after randomisation

| End point values | Group A - ESL | Group B - Placebo | | |
|-------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Failures - Unprovoked seizure | 3 | 8 | | |
| Failures - Death | 3 | 0 | | |
| Failures - Withdrawn | 13 | 18 | | |
| Non-failures | 42 | 36 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients Who Experience the First US During the Course of the Trial

| | |
|-----------------|---|
| End point title | Proportion of Patients Who Experience the First US During the Course of the Trial |
|-----------------|---|

End point description:

Deaths before the first US or patients without evaluable assessment of the primary endpoint will be

counted as treatment failures. To show that ESL (Group A) is superior to placebo (Group B), the primary null hypothesis will be tested against the alternative hypothesis

| | |
|-------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Until 18 months after randomisation | |

| End point values | Group A - ESL | Group B - Placebo | | |
|-------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Failures - Unprovoked seizure | 5 | 9 | | |
| Failures - Death | 4 | 0 | | |
| Failures - Withdrawn | 14 | 18 | | |
| Non-failures | 38 | 35 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Acute Symptomatic Seizure (ASS)

| | |
|--|---|
| End point title | Number of Acute Symptomatic Seizure (ASS) |
| End point description: | |
| Number of ASSs will be summarised by means of descriptive statistics | |
| End point type | Secondary |
| End point timeframe: | |
| During the first 7 days after stroke | |

| End point values | Group A - ESL | Group B - Placebo | | |
|--------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Patients without an ASS | 51 | 47 | | |
| Patients with at least one ASS | 10 | 15 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First US After Randomisation

| | |
|---|--------------------------------------|
| End point title | Time to First US After Randomisation |
| End point description: The time to first US will be analysed and presented by means of the Kaplan-Meier estimate for the failure time and corresponding simultaneous confidence interval (CI), logrank test as well as estimates for 25% percentile, median, and 75% percentile failure time and corresponding CI. | |
| End point type | Secondary |
| End point timeframe: Over 18 months follow-up period | |

| End point values | Group A - ESL | Group B - Placebo | | |
|--|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |
| KM failure probability estimate at Month 6 (D 182) | 0.0350 | 0.1455 | | |
| KM failure probability estimate at Month 12 (D365) | 0.0574 | 0.1686 | | |
| KM failure probability estimate at Month 18 (D547) | 0.1034 | 0.1917 | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Time to First US After Randomisation |
| Comparison groups | Group A - ESL v Group B - Placebo |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.2081 |
| Method | Logrank |
| Parameter estimate | Percentiles of time to first US |
| Point estimate | 92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 25 |
| upper limit | 95 |

Notes:

[2] - The primary efficacy endpoint was assessed in the FAS by using a Chi-square test with continuity correction on the significance level of 5% (two-sided), which corresponds to one-sided 2.5% to compare the proportion of treatment failures between both arms. The odds ratio for ESL vs. placebo and corresponding 95% Confidence Interval (CI) were provided. The risk difference between ESL and placebo with corresponding 95% continuity-corrected Newcombe CI was also calculated. Additionally, the p-value

Secondary: Barthel Index (BI) Original 10-item Version

| | |
|-----------------|---|
| End point title | Barthel Index (BI) Original 10-item Version |
|-----------------|---|

End point description:

The BI at baseline and post-baseline visits of each patient will be calculated adding the individual scores from each item. Baseline is the value assessed before first IMP intake. Endpoint is the last non-missing value collected after the first IMP intake.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over 18 months follow-up period

| End point values | Group A - ESL | Group B - Placebo | | |
|---------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Points | | | | |
| median (full range (min-max)) | | | | |
| Baseline - Observed Value | 85.0 (0 to 100) | 72.5 (0 to 100) | | |
| Endpoint - Observed Value | 100.0 (0 to 100) | 100.0 (0 to 100) | | |
| Endpoint - Change from Baseline | 5.0 (0 to 100) | 7.5 (0 to 100) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: National Institutes of Health Stroke Scale (NIHSS)

| | |
|-----------------|--|
| End point title | National Institutes of Health Stroke Scale (NIHSS) |
|-----------------|--|

End point description:

The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficits. The stroke scale is valid for predicting lesion size and can serve as a measure of stroke severity on the level of consciousness, extraocular movement, visual fields, facial muscle function, extremity strength, sensory function, coordination (ataxia), language (aphasia), speech (dysarthria), and hemi-inattention (neglect). The sum of all 15 individual scores will provide the patient's total NIHSS score where 0 is "no stroke symptoms" and 42 is "severe stroke". For each patient, the total NIHSS score at baseline and each post-baseline visit will be calculated adding the individual scores from each item.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over 18 months follow-up period

| End point values | Group A - ESL | Group B - Placebo | | |
|----------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Points | | | | |
| median (confidence interval 42%) | | | | |
| Baseline - Observed Value | 22 (0 to 42) | 24 (0 to 42) | | |
| Endpoint - Observed Value | 15 (0 to 42) | 16 (0 to 42) | | |
| Endpoint - Change from Baseline | 5 (0 to 42) | 1 (0 to 42) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Health Questionnaire (PHQ-9)

| | |
|-----------------|--------------------------------------|
| End point title | Patient Health Questionnaire (PHQ-9) |
|-----------------|--------------------------------------|

End point description:

The PHQ-9 can be used for screening, diagnosing and measuring the severity of depression in stroke patients. The patient will rate on a scale from 0 (not at all) to 3 (nearly every day) how often each of the 9 symptoms occurred during the past 2 weeks. The individual scores from each item of the PHQ-9 will be added to calculate the total PHQ-9 score for each time of examination.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over 18 months follow-up period

| End point values | Group A - ESL | Group B - Placebo | | |
|---------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Point | | | | |
| log mean (standard deviation) | | | | |
| Baseline - Observed Value | 3.7 (± 3.34) | 3.4 (± 4.43) | | |
| Endpoint - Observed Value | 4.1 (± 3.96) | 4.3 (± 5.25) | | |
| Endpoint - Change from Baseline | 0.5 (± 4.61) | 0.7 (± 6.13) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Overall survival will be analysed and presented by means of the Kaplan-Meier estimates for the survival rates including pointwise CI, logrank test as well as estimates for 25% percentile, median, and 75% percentile survival time and corresponding CI

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over 18 months follow-up period

| End point values | Group A - ESL | Group B - Placebo | | |
|--|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |
| KM death probability estimate at Month 6 (Day 182) | 0.0564 | 0.000 | | |
| KM death probability estimate at Month 12 (Day365) | 0.0564 | 0.000 | | |
| KM death probability estimate at Month 18 (Day547) | 0.0774 | 0.000 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Electrocardiogram (ECG)

| | |
|--|-------------------------|
| End point title | Electrocardiogram (ECG) |
| End point description: | |
| Safety endpoint: The ECG equipment is to be calibrated to 1 cm/mV and recording is to be done at 25 mm/sec and performed for a minimum of 10 sec. At V1a the investigator should examine the ECG for signs of cardiac disease that should exclude the patient from the trial. An assessment of normal or abnormal will be recorded and if the ECG abnormality is considered clinically significant, the abnormality will be documented in the eCRF. If an ECG was done after primary stroke, the results should be used and the examination does not need to be repeated at V1a. After each recording of a simultaneous 12-lead resting ECG, a copy of the originally printed ECG records will be printed, assessed and filed by the investigator, in order to ensure that maintenance of the data will not be affected by thermolability of the paper. | |
| End point type | Secondary |
| End point timeframe: | |
| Over 18 months follow-up period | |

| End point values | Group A - ESL | Group B - Placebo | | |
|---|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 ^[3] | 62 ^[4] | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Baseline - Clinically Significant abnormal | 9 | 8 | | |
| V2 - Clinically Significant abnormal | 4 | 3 | | |
| V3 - Clinically Significant abnormal | 4 | 3 | | |
| Early disconti. visit - Clinically Signific abnorm | 0 | 0 | | |
| Endpoint | 4 | 3 | | |

Notes:

[3] - 1^a Category: Group A - 60 participan.

2^a Cat: A - 43

3^a Cat: A - 34

4^a Cat: A - 4

4^a Cat: A - 47

[4] - 1^a Category: Group B - 62 participan.
 2^a Cat: B - 37
 3^a Cat: B - 32
 4^a Cat: B - 1
 4^a Cat: B - 41

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Treatment Emergent Adverse Events (TEAEs) Incl. Findings From Physical and Neurological Examinations

| | |
|---|--|
| End point title | Treatment Emergent Adverse Events (TEAEs) Incl. Findings From Physical and Neurological Examinations |
| End point description: | |
| Safety endpoint: | |
| AEs not considered treatment-emergent according to this definition or with missing data will be medically reviewed during the data review meeting and will be considered treatment emergent if appropriate. | |
| TEAE: Adverse Event with onset or worsening after first IMP intake until 14 days after last IMP intake. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Over 18 months follow-up period | |

| End point values | Group A - ESL | Group B - Placebo | | |
|--|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| TEAE | 50 | 51 | | |
| Non-serious TEAE | 50 | 48 | | |
| Serious TEAE | 12 | 13 | | |
| Related TEAE | 23 | 12 | | |
| Serious related TEAE | 3 | 0 | | |
| Severe TEAE | 9 | 8 | | |
| TEAE leading to discontinuation of IMP | 16 | 6 | | |
| TEAE leading to dose reduction | 0 | 2 | | |
| TEAE requiring medication | 36 | 46 | | |
| TEAE leading to death | 2 | 0 | | |
| Ongoing TEAE at the end of the trial | 31 | 30 | | |
| TEAE leading to study discontinuation | 4 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinically Significant Haematology Abnormalities

| | |
|--|--|
| End point title | Clinically Significant Haematology Abnormalities |
| End point description: | |
| Safety endpoint: Based on haemoglobin, haematocrit, red blood cell count (RBC), white blood cell count (WBC), differential - neutrophils, eosinophils, lymphocytes, monocytes and basophils, and platelet count. All laboratory values will be classified as normal or abnormal according to the laboratories normal ranges and as clinically significant according to the assessment of the investigator. For these tests, approximately 12 mL of blood will be collected at each blood withdrawal. Shifts of Haematology Parameters from Normal or Abnormal to Clinically Significant Abnormal at Endpoint | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Over 18 months follow-up period | |

| End point values | Group A - ESL | Group B - Placebo | | |
|-----------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Eosinophils - Low to CS high | 1 | 0 | | |
| Eosinophils abs. - Low to CS high | 1 | 0 | | |
| Lymphocytes - Low to CS low | 1 | 0 | | |
| Lymphocytes abs - Low to CS low | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinically Significant Biochemistry Abnormalities, Including eGFR (Estimated Glomerular Filtration Rate) and Coagulation

| | |
|--|--|
| End point title | Clinically Significant Biochemistry Abnormalities, Including eGFR (Estimated Glomerular Filtration Rate) and Coagulation |
| End point description: | |
| Safety endpoint The biochemistry analysis is based on sodium (will be monitored for signs of hyponatraemia), potassium, chloride, calcium, phosphate, blood urea nitrogen, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase, creatine phosphokinase (CPK), creatinine, glucose, C-reactive protein, albumin, total protein, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides, and total bilirubin (bilirubin will be fractionated direct/indirect if elevated). eGFR will be estimated based on serum creatinine value using the according CKD-EPI formula using age, sex and race. Coagulation is based on international normalised ratio and activated partial thromboplastin time (aPTT). All laboratory values will be classified as normal or abnormal according to the laboratories normal ranges and as clinically significant according to the assessment of the invest | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Over 18 months follow-up period | |

| End point values | Group A - ESL | Group B - Placebo | | |
|---|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Sodium - Normal to CS low | 1 | 0 | | |
| Potassium - Normal to CS low | 1 | 0 | | |
| Potassium - Normal to CS high | 1 | 0 | | |
| Potassium - Missing to CS high | 1 | 0 | | |
| Blood urea nitrogen - Missing to CS high | 1 | 0 | | |
| Aspartate transaminase - Normal to CS high | 1 | 0 | | |
| Alanine transaminase - Normal to CS high | 1 | 0 | | |
| Alanine transaminase - High to CS high | 1 | 0 | | |
| Gamma-glutamyl transferase - Normal to CS high | 3 | 0 | | |
| Lactate dehydrogenase - Low to CS high | 1 | 0 | | |
| Alkaline phosphatase - Normal to CS high | 2 | 1 | | |
| Creatinine - Normal to CS high | 1 | 1 | | |
| Creatinine - Missing to CS high | 1 | 0 | | |
| C-reactive protein - High to CS high | 2 | 0 | | |
| LDL-cholesterol - Normal to CS high | 1 | 0 | | |
| HDL-cholesterol - Normal to CS low | 2 | 0 | | |
| Triglycerides - Normal to CS high | 0 | 1 | | |
| Total bilirubin - Normal to CS high | 1 | 0 | | |
| Bilirubin direct - Missing to CS high | 1 | 0 | | |
| Glomerular filtration rate - Normal to CS low | 1 | 0 | | |
| International normalised ratio - High to CS high | 1 | 0 | | |
| Activated partial thromboplastin time - Normal to | 2 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinically Significant Urinalysis Abnormalities - Urinalysis

| | |
|--|--|
| End point title | Clinically Significant Urinalysis Abnormalities - Urinalysis |
| End point description: | |
| Safety endpoint: | |
| The urinalysis is based on pH, specific gravity, protein, blood, glucose, ketones, bilirubin, urobilinogen (local dipstick). Microscopy and other appropriate tests (as needed) will be performed if dipstick indicates any significant abnormality. All laboratory values will be classified as normal or abnormal according to the laboratories normal ranges and as clinically significant according to the assessment of the investigator. | |
| The number analyzed are patients with data available. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Over 18 months follow-up period | |

| End point values | Group A - ESL | Group B - Placebo | | |
|--|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 ^[5] | 62 ^[6] | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Clinically Significant abnormality - Baseline - No | 46 | 42 | | |
| Clinically Significant abnormality - Baseline-Yes | 14 | 14 | | |
| Clinically Significant abnormality - Endpoint - No | 36 | 34 | | |
| Clinically Significant abnormality - Endpoint-Yes | 13 | 9 | | |

Notes:

[5] - 1^a Category: Group A - 60 participants

2^a Categ: A - 60

3^a Categ: A - 49

4^a Categ: A - 49

[6] - 1^a Category: Group B - 56 participants

2^a Categ: A - 56

3^a Categ: A - 43

4^a Categ: A - 43

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinically Significant Vital Sign Abnormalities: Blood Pressure

| | |
|-----------------|---|
| End point title | Clinically Significant Vital Sign Abnormalities: Blood Pressure |
|-----------------|---|

End point description:

Safety endpoint:

The systolic and diastolic blood pressure (mmHg) were to be measured after the patient had rested for at least 5 minutes. Painful procedures, like drawing blood, had to be performed after vital signs measurements (not before). The analyses of variables for vital sign parameters will focus on the evaluation of the change from baseline to the scheduled time points after baseline. Descriptive statistics of the time course and of changes from baseline to each post-baseline time point will be presented by treatment group.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Over 18 months follow-up period

| End point values | Group A - ESL | Group B - Placebo | | |
|---|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Systolic BP [mmHg] - Baseline - CS high | 1 | 3 | | |
| Diastolic BP [mmHg] - Baseline - CS low | 0 | 0 | | |

| | | | | |
|--|---|---|--|--|
| Diastolic BP [mmHg] - Baseline - CS high | 0 | 1 | | |
| Systolic BP [mmHg] - Endpoint - CS high | 1 | 1 | | |
| Diastolic BP [mmHg] - Endpoint - CS low | 0 | 1 | | |
| Diastolic BP [mmHg] - Endpoint - CS high | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinically Significant Vital Sign Abnormalities: Heart Rate

| | |
|-----------------|---|
| End point title | Clinically Significant Vital Sign Abnormalities: Heart Rate |
|-----------------|---|

End point description:

Safety endpoint:

The Heart Rate (bpm) were to be measured after the patient had rested for at least 5 minutes. Painful procedures, like drawing blood, had to be performed after vital signs measurements (not before). The analyses of variables for vital sign parameters will focus on the evaluation of the change from baseline to the scheduled time points after baseline. Descriptive statistics of the time course and of changes from baseline to each post-baseline time point will be presented by treatment group.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Over 18 months follow-up period

| End point values | Group A - ESL | Group B - Placebo | | |
|---------------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Pulse rate [bpm] - Baseline - CS high | 0 | 0 | | |
| Pulse rate [bpm] - Endpoint - CS high | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Suicidal Ideation and Behaviour, Assessed by PHQ-9 (Question 9)

| | |
|-----------------|---|
| End point title | Suicidal Ideation and Behaviour, Assessed by PHQ-9 (Question 9) |
|-----------------|---|

End point description:

Safety endpoint:

Suicidal ideation and suicidal behaviour as assessed by the PHQ-9 question 9 will be presented for each time of assessment by the number and frequency of patients in each response category by treatment group. The individual scores from each item of the PHQ-9 will be added to calculate the total PHQ-9

score for each time of examination. The PHQ-9 score and its change from baseline will be summarised by means of descriptive statistics and differences between the treatment groups will be evaluated exploratively using the Wilcoxon-Mann-Whitney Test and Hodge-Lehmann CIs. Cumulative incidence curves of USs vs. the PHQ-9 score will be displayed graphically by time of examination and treatment group.

| | |
|---------------------------------|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| Over 18 months follow-up period | |

| End point values | Group A - ESL | Group B - Placebo | | |
|--|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 62 | | |
| Units: Points | | | | |
| log mean (standard deviation) | | | | |
| Baseline - Observed Value | 0 (± 0) | 0.1 (± 0.45) | | |
| V3 - Observed Value | 0.1 (± 0.47) | 0.1 (± 0.39) | | |
| V3 - Change from Baseline | 0 (± 0.20) | 0 (± 0.66) | | |
| V5 - Observed Value | 0.1 (± 0.56) | 0.1 (± 0.29) | | |
| V5 - Change from Baseline | 0.1 (± 0.47) | 0 (± 0.60) | | |
| V7 - Observed Value | 0 (± 0) | 0 (± 0) | | |
| V7 - Change from Baseline | 0 (± 0) | -0.1 (± 0.55) | | |
| Early discontinuation visit - Observed Value | 0 (± 0) | 0 (± 0) | | |
| Early discontinuation visit - Change from Baseline | 0 (± 0) | 0 (± 0) | | |
| End of trial visit - Observed Value | 0.1 (± 0.23) | 0.1 (± 0.52) | | |
| End of trial visit - Change from Baseline | 0 (± 0.16) | 0 (± 0.77) | | |
| Endpoint - Observed Value | 0.1 (± 0.45) | 0.1 (± 0.45) | | |
| Endpoint - Change from Baseline | 0.1 (± 0.44) | 0 (± 0.69) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events with the first onset or worsening after the first IMP intake until 14 days after the last IMP intake.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Group A - ESL |
|-----------------------|---------------|

Reporting group description:

800 mg ESL tablets for oral administration. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line.

| | |
|-----------------------|-------------------|
| Reporting group title | Group B - Placebo |
|-----------------------|-------------------|

Reporting group description:

Placebo tablets for oral administration, matching the test product. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line.

| Serious adverse events | Group A - ESL | Group B - Placebo | |
|---|------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 61 (19.67%) | 13 / 62 (20.97%) | |
| number of deaths (all causes) | 2 | 0 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Benign neoplasm of bladder | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney angiomyolipoma | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Cardiac disorders | | | |
| Cardiac valve disease | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nodal arrhythmia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Basal ganglia infarction | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral vasoconstriction | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thalamic infarction | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic abscess | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Urinary tract infection pseudomonal | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Group A - ESL | Group B - Placebo | |
|---|------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 50 / 61 (81.97%) | 48 / 62 (77.42%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Benign neoplasm of bladder | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Kidney angiomyolipoma | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Blood pressure inadequately controlled | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) | |
| occurrences (all) | 1 | 1 | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertension | | | |
| subjects affected / exposed | 10 / 61 (16.39%) | 13 / 62 (20.97%) | |
| occurrences (all) | 10 | 13 | |
| Hypotension | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 0 / 62 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Feeling of body temperature change | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) | |
| occurrences (all) | 1 | 1 | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 2 / 62 (3.23%) | |
| occurrences (all) | 1 | 2 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 62 (1.61%) | |
| occurrences (all) | 2 | 1 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Hypertransaminasaemia | | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Asthma-chronic obstructive pulmonary disease overlap syndrome | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) | |
| occurrences (all) | 1 | 1 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---------------------|---------------------|--|
| Pulmonary embolism subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Sleep apnoea syndrome subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Psychiatric disorders | | | |
| Agitation subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 2 / 62 (3.23%) 3 | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 3 / 62 (4.84%) 3 | |
| Anxiety disorder subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Delirium subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Depressed mood subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Depression subjects affected / exposed occurrences (all) | 3 / 61 (4.92%) 3 | 4 / 62 (6.45%) 4 | |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 61 (6.56%) 4 | 5 / 62 (8.06%) 5 | |
| Major depression subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 62 (1.61%) 1 | |
| Mood swings subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Nightmare | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Post stroke depression | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) | |
| occurrences (all) | 1 | 1 | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 62 (3.23%) | |
| occurrences (all) | 0 | 2 | |
| Sleep disorder | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 62 (1.61%) | |
| occurrences (all) | 2 | 1 | |
| Sleep disorder due to general medical condition, insomnia type | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Sopor | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 62 (1.61%) | |
| occurrences (all) | 2 | 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 62 (1.61%) | |
| occurrences (all) | 3 | 1 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 62 (3.23%) | |
| occurrences (all) | 0 | 2 | |
| Blood glucose increased | | | |

| | | |
|---------------------------------------|----------------|----------------|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 2 | 0 |
| Blood lactate dehydrogenase increased | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood magnesium decreased | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| Blood potassium increased | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood triglycerides increased | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood urea increased | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood uric acid increased | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| C-reactive protein increased | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Electrocardiogram QT prolonged | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 62 (3.23%) |
| occurrences (all) | 0 | 2 |
| Eosinophil count increased | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 62 (1.61%) |
| occurrences (all) | 2 | 1 |
| Glomerular filtration rate decreased | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 3 / 62 (4.84%) 3 | |
| Haemoglobin urine present subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Hepatic enzyme increased subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 1 / 62 (1.61%) 1 | |
| High density lipoprotein decreased subjects affected / exposed occurrences (all) | 3 / 61 (4.92%) 3 | 0 / 62 (0.00%) 0 | |
| Lipase increased subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Muscle enzyme increased subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Post procedural haemorrhage subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Congenital, familial and genetic disorders Atrial septal defect subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 62 (1.61%) 1 | |
| Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 4 / 61 (6.56%) 4 | 3 / 62 (4.84%) 3 | |
| Atrioventricular block first degree | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) | |
| occurrences (all) | 1 | 1 | |
| Cardiac valve disease | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Intracardiac thrombus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Nodal arrhythmia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Basal ganglia infarction | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | |
|-----------------------------|----------------|-----------------|
| Cerebral vasoconstriction | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| Cerebrovascular accident | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) |
| occurrences (all) | 1 | 1 |
| Diabetic neuropathy | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| Disturbance in attention | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 62 (1.61%) |
| occurrences (all) | 2 | 1 |
| Dizziness | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 0 / 62 (0.00%) |
| occurrences (all) | 4 | 0 |
| Dysarthria | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| Dysgeusia | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Headache | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 8 / 62 (12.90%) |
| occurrences (all) | 4 | 8 |
| Hemiparesis | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 62 (3.23%) |
| occurrences (all) | 0 | 3 |
| Loss of consciousness | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Memory impairment | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Muscle spasticity | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |

| | | |
|-----------------------------|----------------|----------------|
| Neuralgia | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 3 / 62 (4.84%) |
| occurrences (all) | 0 | 3 |
| Paraesthesia | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 62 (1.61%) |
| occurrences (all) | 2 | 1 |
| Partial seizures | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Polyneuropathy | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Presyncope | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Psychomotor hyperactivity | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Restless legs syndrome | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Seizure | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 2 / 62 (3.23%) |
| occurrences (all) | 1 | 2 |
| Sensory loss | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Somnolence | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) |
| occurrences (all) | 1 | 1 |
| Status epilepticus | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) |
| occurrences (all) | 1 | 1 |
| Thalamic infarction | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|--|---------------------|---------------------|--|
| Tremor subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 2 | 0 / 62 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Anaemia macrocytic subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Eosinophilia subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Leukocytosis subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Lymphopenia subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 0 / 62 (0.00%) 0 | |
| Ear and labyrinth disorders | | | |
| Tinnitus subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Eye disorders | | | |
| Cataract subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Vision blurred subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 62 (1.61%) 1 | |
| Visual impairment subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Gastrointestinal disorders | | | |

| | | |
|-----------------------------|----------------|----------------|
| Abdominal pain upper | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| Anal incontinence | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Constipation | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 6 / 62 (9.68%) |
| occurrences (all) | 3 | 6 |
| Diarrhoea | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 0 / 62 (0.00%) |
| occurrences (all) | 3 | 0 |
| Dry mouth | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| Duodenal ulcer | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Flatulence | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) |
| occurrences (all) | 2 | 1 |
| Gastritis erosive | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 |
| Haemorrhoids | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| Nausea | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 3 / 62 (4.84%) |
| occurrences (all) | 3 | 3 |
| Pancreatitis chronic | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| Rectal haemorrhage | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |

| | | | |
|--|---------------------|---------------------|--|
| Rectal polyp subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 2 / 62 (3.23%) 2 | |
| Hepatobiliary disorders Hepatic failure subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Eczema subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 0 | 0 / 62 (0.00%) 1 | |
| Erythema subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Rash subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 2 / 62 (3.23%) 2 | |
| Rash erythematous subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Rash generalised subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Haematuria | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Hypertonic bladder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Ketonuria | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Polyuria | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 62 (3.23%) | |
| occurrences (all) | 0 | 2 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 62 (1.61%) | |
| occurrences (all) | 2 | 1 | |
| Back pain | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) | |
| occurrences (all) | 1 | 1 | |
| Infections and infestations | | | |
| Candida infection | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 62 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) | |
| occurrences (all) | 1 | 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 62 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 62 (1.61%) | |
| occurrences (all) | 1 | 1 | |
| Prostatic abscess | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---------------------|---------------------|--|
| Pulmonary sepsis subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 4 / 61 (6.56%) 4 | 5 / 62 (8.06%) 5 | |
| Urinary tract infection pseudomonal subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Urosepsis subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 62 (1.61%) 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 4 | 0 / 62 (0.00%) 0 | |
| Dyslipidaemia subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 1 / 62 (1.61%) 1 | |
| Fluid overload subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Folate deficiency subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 62 (0.00%) 0 | |
| Hypercholesterolaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 62 (3.23%) | |
| occurrences (all) | 0 | 2 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 62 (1.61%) | |
| occurrences (all) | 0 | 1 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 3 / 62 (4.84%) | |
| occurrences (all) | 5 | 4 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 6 / 61 (9.84%) | 1 / 62 (1.61%) | |
| occurrences (all) | 7 | 1 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 62 (0.00%) | |
| occurrences (all) | 2 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 24 October 2018 | Version 2.0: Updated study design; first version for submission to authorities. |
| 20 January 2020 | Version 3.0: Global Amendment #1, dated 20-JAN-2020: Adjustments of inclusion and exclusion criteria for specification of patient population in accordance with the discussions with the investigators that are participating in the study. |

Notes:

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.

Recruitment was closed by the end of February 2022, due to the unforeseen COVID-19 pandemic circumstances, recruitment had not progressed as initially estimated. This decision was not based on safety concerns or circumstances related to the IMP.

Notes: