



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
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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
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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
Adverse event, serious fatal	4	-
Stroke more than 7 days after primary stroke	2	6
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
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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
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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
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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
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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
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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
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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
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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)
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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
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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)
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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
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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
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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
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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 lipoproteincholesterol, 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
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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
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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
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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
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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
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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
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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)
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Group A - ESL
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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
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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	0 / 61 (0.00%)	3 / 62 (4.84%)	
occurrences (all)	0	3	
Haemoglobin urine present			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	2 / 61 (3.28%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
High density lipoprotein decreased			
subjects affected / exposed	3 / 61 (4.92%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Lipase increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Muscle enzyme increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Post procedural haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 61 (1.64%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	4 / 61 (6.56%)	3 / 62 (4.84%)	
occurrences (all)	4	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	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	4 / 61 (6.56%)	5 / 62 (8.06%)	
occurrences (all)	4	5	
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Urosepsis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Dehydration			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Diabetes mellitus			
subjects affected / exposed	2 / 61 (3.28%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Dyslipidaemia			
subjects affected / exposed	2 / 61 (3.28%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Fluid overload			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences (all)	1	0	
Folate deficiency			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences (all)	1	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: