Clinical trial results:
Randomized Efficacy and Safety Trial with Oral S 44819 after Recent ischemic cerebral Event. International, multi-centre, randomized, double-blind placebo-controlled phase II study.

Summary

EudraCT number	2016-001005-16
Trial protocol	HU GB SE DE BE NL ES PL CZ SI IT
Global end of trial date	10 March 2019

Results information

Result version number	v1 (current)
This version publication date	16 November 2019
First version publication date	16 November 2019

Trial information

Trial identification

Sponsor protocol code	CL2-44819-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1180-8991

Notes:

Sponsors

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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2019
Global end of trial reached?	Yes
Global end of trial date	10 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the superiority of at least one of the two doses of S44819 versus placebo on functional recovery from ischemic stroke measured with the modified Rankin Scale (mRS) after 90 days of treatment.
The secondary objectives were:
- To assess the efficacy of the two doses of S44819 versus placebo in stroke recovery using neurological evaluation (NIHSS), activities of daily living test (BI), and cognitive performance tests (Moca, TMT).
- To assess the safety and tolerability of S44819.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 40
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Brazil: 34
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 52
Country: Number of subjects enrolled	Germany: 33

Country: Number of subjects enrolled	Hungary: 101
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 58
Country: Number of subjects enrolled	Spain: 121
Country: Number of subjects enrolled	United Kingdom: 72
Worldwide total number of subjects	585
EEA total number of subjects	477

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)	211
From 65 to 84 years	363
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

The investigators and/or coordinators were Neurologists.

Pre-assignment

Screening details:

Patients, aged 18-85 years (both inclusive), with a recent [between 72 hours (or 3 days) and 192 hours (or 8 days)] cortical or combined cortical-subcortical ischaemic stroke, with NIHSS 7-20 (both inclusive) and with no previous disability (i.e. neither physical nor pre-stroke cognitive impairment).

Period 1

Period 1 title	Overall period (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	S44819 150mg bid

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S44819
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Dosage form: S44819 – sachet of 150 mg twice a day.
Mode of administration: The study medication was administered in the morning and in the evening (during or within 30 minutes following the meal). The interval between two intakes of the study treatment was to be at least 8 hours. Three methods of sachet administration were possible:
- With a glass of water.
- With thickened water, yoghurt, stewed fruit or mashed food.
- Through a nasogastric tube or a percutaneous feeding tube.

Arm title	S44819 300mg bid

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S44819
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Dosage form: S44819 – 300 mg: sachets of 150 mg twice a day.
Mode of administration: The study medication was administered in the morning and in the evening (during or within 30 minutes following the meal). The interval between two intakes of the study treatment was to be at least 8 hours. Three methods of sachet administration were possible:
- With a glass of water.
- With thickened water, yoghurt, stewed fruit or mashed food.
- Through a nasogastric tube or a percutaneous feeding tube.

Arm title	Placebo

Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Dosage form: Placebo: sachets twice a day.
Mode of administration: The study medication was administered in the morning and in the evening (during or within 30 minutes following the meal). The interval between two intakes of the study treatment was to be at least 8 hours. Three methods of sachet administration were possible:
- With a glass of water.
- With thickened water, yoghurt, stewed fruit or mashed food.
- Through a nasogastric tube or a percutaneous feeding tube.

Number of subjects in period 1	S44819 150mg bid	S44819 300mg bid	Placebo
Started	197	195	193
Completed	153	159	154
Not completed	44	36	39
Adverse event, serious fatal	7	9	5
Non medical reason	16	17	11
Adverse event, non-fatal	11	7	20
Lack of efficacy	1	-	-
Protocol deviation	9	3	3

Baseline characteristics

Reporting groups	
Reporting group title	S44819 150mg bid
Reporting group description: -	
Reporting group title	S44819 300mg bid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	S44819 150mg bid	S44819 300mg bid	Placebo
Number of subjects	197	195	193
Age categorical Units: Subjects			
Adults (18-64 years)	75	57	79
From 65-84 years	117	135	111
85 years and over	5	3	3
Age continuous Units: years			
arithmetic mean	66.9	68.5	66.2
standard deviation	± 11.2	± 11.5	± 12.4
Gender categorical Units: Subjects			
Female	91	93	80
Male	106	102	113

Reporting group values	Total		
Number of subjects	585		
Age categorical Units: Subjects			
Adults (18-64 years)	211		
From 65-84 years	363		
85 years and over	11		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	264		
Male	321		

End points

End points reporting groups	
Reporting group title	S44819 150mg bid
Reporting group description: -	
Reporting group title	S44819 300mg bid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
In accordance with the intention-to-treat principle and the Section 5.2.1 of ICH E9 guideline, all patients of the RS having taken at least one dose of IMP and having at least a value of the primary efficacy endpoint after D5 (excluded). Of note, patients deceased after D5 are included in the FAS.	

Primary: Modified Rankin Scale score at D90	
End point title	Modified Rankin Scale score at D90
End point description:	
The modified Rankin Scale (mRS) assigns a subjective grading of disability from 0 (No symptom) to 6 (Dead) with reference to pre-stroke activities rather than on observed performance of specific tasks. This scale had to be administered by a trained and certified rater whether he/she is a medical doctor or not. The rater was to have previous clinical experience with stroke patients and with this scale.	
End point type	Primary
End point timeframe:	
The mRS was assessed at visits D5, D30, D60, D90 and D105 (follow-up visit) and in case of premature withdrawal.	

End point values	S44819 150mg bid	S44819 300mg bid	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	189	188	191	
Units: No unit	189	188	191	

Statistical analyses

Statistical analysis title	Comparison S44819 150mg bid to Placebo
Comparison groups	S44819 150mg bid v Placebo
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.31

Notes:

[1] - Two-sided adjusted p-value taking into account Holm adjustment (to be compared to 0.05).

Statistical analysis title	Comparison S44819 300mg bid to Placebo
Comparison groups	S44819 300mg bid v Placebo
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.67

Notes:

[2] - Two-sided adjusted p-value taking into account Holm adjustment (to be compared to 0.05)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All emergent adverse events that occurred or worsened or became serious between the first intake and last IMP intake + 3 days (both included)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	S44819 150mg bid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	S44819 300mg bid

Reporting group description: -

Serious adverse events	S44819 150mg bid	Placebo	S44819 300mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 195 (36.41%)	65 / 193 (33.68%)	56 / 194 (28.87%)
number of deaths (all causes)	7	4	9
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 195 (0.51%)	4 / 193 (2.07%)	6 / 194 (3.09%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	4 / 195 (2.05%)	2 / 193 (1.04%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asthma			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 195 (0.00%)	2 / 193 (1.04%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 195 (0.00%)	2 / 193 (1.04%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 195 (0.51%)	3 / 193 (1.55%)	4 / 194 (2.06%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	2 / 195 (1.03%)	6 / 193 (3.11%)	4 / 194 (2.06%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary hypertension			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sputum retention			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Anxiety			
subjects affected / exposed	1 / 195 (0.51%)	2 / 193 (1.04%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Apathy			

subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	2 / 195 (1.03%)	0 / 193 (0.00%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed mood			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	3 / 195 (1.54%)	2 / 193 (1.04%)	3 / 194 (1.55%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, visual			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post stroke depression			

subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 195 (0.51%)	2 / 193 (1.04%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 195 (0.00%)	3 / 193 (1.55%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 195 (0.00%)	2 / 193 (1.04%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood albumin decreased			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			

subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breath sounds abnormal			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 195 (0.51%)	3 / 193 (1.55%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	3 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arterial bypass thrombosis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain herniation			

subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Drug administration error			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 195 (1.03%)	4 / 193 (2.07%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	2 / 195 (1.03%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			

subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia supraventricular			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	10 / 195 (5.13%)	6 / 193 (3.11%)	3 / 194 (1.55%)
occurrences causally related to treatment / all	0 / 10	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	2 / 195 (1.03%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	4 / 195 (2.05%)	3 / 193 (1.55%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac pseudoaneurysm			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale acute			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracardiac thrombus			

subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Carotid artery occlusion			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			

subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	3 / 195 (1.54%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			

subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Epilepsy			
subjects affected / exposed	3 / 195 (1.54%)	1 / 193 (0.52%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 3	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 195 (0.51%)	2 / 193 (1.04%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic transformation stroke			
subjects affected / exposed	1 / 195 (0.51%)	4 / 193 (2.07%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Neurological decompensation			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Partial seizures			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Petit mal epilepsy			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post stroke seizure			

subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke in evolution			
subjects affected / exposed	2 / 195 (1.03%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Subdural hygroma			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	3 / 195 (1.54%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			

subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic erosive gastritis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intestinal pseudo-obstruction			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 195 (1.03%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 195 (1.03%)	3 / 193 (1.55%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nephrolithiasis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 195 (0.51%)	1 / 193 (0.52%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary retention			
subjects affected / exposed	3 / 195 (1.54%)	5 / 193 (2.59%)	4 / 194 (2.06%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acinetobacter bacteraemia			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial prostatitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis intestinal haemorrhagic			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocarditis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis staphylococcal			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 195 (1.54%)	4 / 193 (2.07%)	5 / 194 (2.58%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	2 / 195 (1.03%)	0 / 193 (0.00%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 195 (1.54%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 193 (0.00%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	2 / 195 (1.03%)	2 / 193 (1.04%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 195 (1.54%)	1 / 193 (0.52%)	4 / 194 (2.06%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	2 / 195 (1.03%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 193 (0.52%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			

subjects affected / exposed	0 / 195 (0.00%)	0 / 193 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	S44819 150mg bid	Placebo	S44819 300mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	138 / 195 (70.77%)	140 / 193 (72.54%)	123 / 194 (63.40%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 195 (1.54%)	6 / 193 (3.11%)	3 / 194 (1.55%)
occurrences (all)	3	6	3
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 195 (1.03%)	5 / 193 (2.59%)	1 / 194 (0.52%)
occurrences (all)	2	5	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 195 (2.05%)	6 / 193 (3.11%)	3 / 194 (1.55%)
occurrences (all)	4	6	3
Weight decreased			
subjects affected / exposed	6 / 195 (3.08%)	5 / 193 (2.59%)	3 / 194 (1.55%)
occurrences (all)	6	5	3
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	5 / 195 (2.56%)	4 / 193 (2.07%)	5 / 194 (2.58%)
occurrences (all)	6	5	6
Fall			
subjects affected / exposed	3 / 195 (1.54%)	13 / 193 (6.74%)	13 / 194 (6.70%)
occurrences (all)	3	19	20
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 195 (6.15%)	12 / 193 (6.22%)	15 / 194 (7.73%)
occurrences (all)	12	12	16
Hypotension			

subjects affected / exposed	7 / 195 (3.59%)	5 / 193 (2.59%)	7 / 194 (3.61%)
occurrences (all)	7	5	7
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 195 (4.62%)	9 / 193 (4.66%)	6 / 194 (3.09%)
occurrences (all)	9	10	6
Muscle spasticity			
subjects affected / exposed	5 / 195 (2.56%)	3 / 193 (1.55%)	3 / 194 (1.55%)
occurrences (all)	5	4	3
Neuralgia			
subjects affected / exposed	5 / 195 (2.56%)	5 / 193 (2.59%)	2 / 194 (1.03%)
occurrences (all)	5	5	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 195 (1.03%)	4 / 193 (2.07%)	5 / 194 (2.58%)
occurrences (all)	2	4	5
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	24 / 195 (12.31%)	18 / 193 (9.33%)	13 / 194 (6.70%)
occurrences (all)	24	18	13
Diarrhoea			
subjects affected / exposed	7 / 195 (3.59%)	9 / 193 (4.66%)	10 / 194 (5.15%)
occurrences (all)	8	11	11
Nausea			
subjects affected / exposed	6 / 195 (3.08%)	5 / 193 (2.59%)	11 / 194 (5.67%)
occurrences (all)	6	5	11
Vomiting			
subjects affected / exposed	5 / 195 (2.56%)	10 / 193 (5.18%)	8 / 194 (4.12%)
occurrences (all)	5	12	9
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 195 (1.03%)	5 / 193 (2.59%)	2 / 194 (1.03%)
occurrences (all)	2	5	2
Depressed mood			
subjects affected / exposed	6 / 195 (3.08%)	5 / 193 (2.59%)	4 / 194 (2.06%)
occurrences (all)	6	5	4
Depression			

subjects affected / exposed	10 / 195 (5.13%)	8 / 193 (4.15%)	10 / 194 (5.15%)
occurrences (all)	10	8	10
Insomnia			
subjects affected / exposed	5 / 195 (2.56%)	9 / 193 (4.66%)	6 / 194 (3.09%)
occurrences (all)	5	9	6
Post stroke depression			
subjects affected / exposed	2 / 195 (1.03%)	6 / 193 (3.11%)	2 / 194 (1.03%)
occurrences (all)	2	6	2
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	3 / 195 (1.54%)	5 / 193 (2.59%)	2 / 194 (1.03%)
occurrences (all)	3	6	2
Urinary tract infection			
subjects affected / exposed	14 / 195 (7.18%)	17 / 193 (8.81%)	13 / 194 (6.70%)
occurrences (all)	15	17	15
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 195 (0.51%)	4 / 193 (2.07%)	6 / 194 (3.09%)
occurrences (all)	1	4	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2016	Applicable in all countries. - Implementation of a Data Monitoring Committee of safety in RESTORE Brain study. - Removal of barrier method of contraception from the acceptable list of contraception methods for women of child-bearing potential - Addition of a pregnancy test at DEND and in case of withdrawal (WD). - Clarifications made on exclusion criteria in order to have all results available for inclusion.
24 May 2017	Applicable in all countries. - Contraception: collectively the non-clinical toxicological studies did not indicate a risk to the foetus that would have necessitated the requirement for highly effective methods of contraception in clinical trials. - Update of the list of forbidden treatments in RESTORE Brain study as well as contraceptive methods following complementary results showing that CYP1A2 is the major enzyme involved in S44819 metabolism. - Selection/inclusion and exclusion criteria following major difficulties in recruitment in all countries involved in the study: * Inclusion of patients who underwent only brain CT when MRI was not possible has been possible. * The inclusion of patients with an acute symptomatic ischemic cortical or combined cortical-subcortical lesion responsible for the clinical presentation associated or not with another cerebral ischemic lesions as long as the clinical symptoms, according to the investigator’s judgment, appeared mainly related to the cortical or cortical-subcortical lesion has been possible. * The maximum age increased up to 85 years (inclusive). * Selection and inclusion visits possible until 8 days after stroke onset. * For patients with unknown exact stroke onset time, the time of stroke discovery was considered as time of stroke onset. For these patients, the time interval between last known well and stroke discovery was not to exceed 18 hours.
23 July 2018	Applicable in all countries. - Update of the list of forbidden concomitant treatments based on scientific elements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported