Clinical trial results:
Multicenter, randomized, placebo-controlled, double-blind, parallel group, dose-finding Phase 2 study to evaluate efficacy and safety of BAY 2433334 in patients following an acute non-cardioembolic ischemic stroke

Summary

EudraCT number	2019-003431-33
Trial protocol	CZ GB ES PT FI DE NL AT FR HU DK BE BG PL IT
Global end of trial date	18 February 2022

Results information

Result version number	v1 (current)
This version publication date	03 March 2023
First version publication date	03 March 2023

Trial information

Trial identification

Sponsor protocol code	BAY2433334/19766

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04304508
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	20 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the dose-response of 3 different doses of asundexian compared to placebo in reducing the composite of symptomatic ischemic strokes and covert brain infarcts detected by Magnetic resonance imaging (MRI) as well as other cerebro- and cardiovascular endpoints in participants with an acute noncardioembolic ischemic stroke and who are treated with antiplatelet therapy.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Anti-platelet therapy

Evidence for comparator: -

Actual start date of recruitment	15 June 2020
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	Bulgaria: 177
Country: Number of subjects enrolled	Czechia: 68
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Russian Federation: 123
Country: Number of subjects enrolled	Slovakia: 80
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Australia: 116
Country: Number of subjects enrolled	Austria: 40
Country: Number of subjects enrolled	Belgium: 51
Country: Number of subjects enrolled	Switzerland: 64
Country: Number of subjects enrolled	Germany: 73
Country: Number of subjects enrolled	Denmark: 79
Country: Number of subjects enrolled	Spain: 216
Country: Number of subjects enrolled	Finland: 36

Country: Number of subjects enrolled	France: 84
Country: Number of subjects enrolled	United Kingdom: 55
Country: Number of subjects enrolled	Italy: 87
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Portugal: 79
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	China: 81
Country: Number of subjects enrolled	Japan: 173
Worldwide total number of subjects	1808
EEA total number of subjects	1173

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)	709
From 65 to 84 years	1039
85 years and over	60

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 197 centers in 23 countries or regions, between 15-Jun-2020 (first subject first visit) and 18-Feb-2022 (last subject last visit)

Pre-assignment

Screening details:

1880 subjects were screened. 72 subjects were screening failures. 1808 subjects were randomized in a 1:1:1:1 ratio to 4 treatment groups: 455, 450, and 447 subjects to asundexian 10 mg, 20 mg and 50 mg groups, 456 subjects to placebo group. 22 subjects (10, 4, 4 and 4 in the asundexian 10 mg, 20 mg and 50 mg, and placebo groups) never administered.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Asundexian 10 mg

Arm description:

Subjects received Asundexian (BAY2433334) 10 mg for 26 weeks at least and up to 52 weeks

Arm type	Experimental
Investigational medicinal product name	Asundexian
Investigational medicinal product code	BAY2433334
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Asundexian (BAY2433334) 10 mg (5 mg tablets) orally once daily in the morning

Arm title	Asundexian 20 mg

Arm description:

Subjects received Asundexian (BAY2433334) 20 mg for 26 weeks at least and up to 52 weeks

Arm type	Experimental
Investigational medicinal product name	Asundexian
Investigational medicinal product code	BAY2433334
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Asundexian (BAY2433334) 20 mg (5 mg and 15 mg tablets) orally once daily in the morning

Arm title	Asundexian 50 mg

Arm description:

Subjects received Asundexian (BAY2433334) 50 mg for 26 weeks at least and up to 52 weeks

Arm type	Experimental

Investigational medicinal product name	Asundexian
Investigational medicinal product code	BAY2433334
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Asundexian (BAY2433334) 50 mg (25 mg tablets) orally once daily in the morning

Arm title	Placebo

Arm description:

Subjects received Asundexian (BAY2433334) placebo for 26 weeks at least and up to 52 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo orally once daily in the morning.

Number of subjects in period 1	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg
Started	455	450	447
Treated	445	446	443
Completed	335	329	313
Not completed	120	121	134
Physician decision	3	4	9
Physician Decision: COVID-19 Pandemic Related	1	-	-
Consent withdrawn by subject	7	5	11
Subject Decision	29	39	37
Logistical Difficulties	2	2	3
Adverse event, non-fatal	49	50	51
Subject Decision: COVID-19 Pandemic Related	-	1	-
Other	7	6	5
Non-compliance With Study Drug	3	1	2
Death	6	1	8
Missing Information	1	2	1
Study drug never administered	10	4	4
Lost to follow-up	1	5	2
Switching To Other Therapy	1	1	1

Number of subjects in period 1	Placebo
Started	456

Treated	452
Completed	314
Not completed	142
Physician decision	7
Physician Decision: COVID-19 Pandemic Related	-
Consent withdrawn by subject	6
Subject Decision	48
Logistical Difficulties	2
Adverse event, non-fatal	56
Subject Decision: COVID-19 Pandemic Related	2
Other	4
Non-compliance With Study Drug	-
Death	5
Missing Information	3
Study drug never administered	4
Lost to follow-up	3
Switching To Other Therapy	2

Baseline characteristics

Reporting groups	
Reporting group title	Asundexian 10 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 10 mg for 26 weeks at least and up to 52 weeks	
Reporting group title	Asundexian 20 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 20 mg for 26 weeks at least and up to 52 weeks	
Reporting group title	Asundexian 50 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 50 mg for 26 weeks at least and up to 52 weeks	
Reporting group title	Placebo
Reporting group description:	
Subjects received Asundexian (BAY2433334) placebo for 26 weeks at least and up to 52 weeks	

Reporting group values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg
Number of subjects	455	450	447
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)	186	154	174
From 65-84 years	255	279	258
85 years and over	14	17	15
Gender Categorical Units: Subjects			
Female	161	150	154
Male	294	300	293
Race Units: Subjects			
Asian	67	67	68
Black or African American	4	3	8
Native Hawaiian or Other Pacific Islander	0	1	1
Not Reported	3	2	3
White	381	377	367

Reporting group values	Placebo	Total	
Number of subjects	456	1808	
Age Categorical Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	195	709	
From 65-84 years	247	1039	
85 years and over	14	60	
Gender Categorical Units: Subjects			
Female	150	615	
Male	306	1193	
Race Units: Subjects			
Asian	66	268	
Black or African American	3	18	
Native Hawaiian or Other Pacific Islander	1	3	
Not Reported	6	14	
White	380	1505	

Subject analysis sets

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

A subject was included in the FAS if he/she was randomized to a treatment group.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

A subject was included in the SAF if he/she was randomized to study intervention and had taken at least one dose of the study intervention.

Subject analysis set title	Total Asundexian
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subject was included in the Total Asundexian if he/she was randomized to Asundexian 10 mg group or Asundexian 20 mg group or Asundexian 50 mg group and had taken at least one dose of Asundexian.

Reporting group values	Full analysis set (FAS)	Safety analysis set (SAF)	Total Asundexian
Number of subjects	1808	1786	1334
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	709	703	

From 65-84 years	1039	1024	
85 years and over	60	59	

Gender Categorical Units: Subjects			
Female	615	608	
Male	1193	1178	
Race Units: Subjects			
Asian	268	263	
Black or African American	18	18	
Native Hawaiian or Other Pacific Islander	3	3	
Not Reported	14	13	
White	1505	1489	

End points

End points reporting groups

Reporting group title	Asundexian 10 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 10 mg for 26 weeks at least and up to 52 weeks	
Reporting group title	Asundexian 20 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 20 mg for 26 weeks at least and up to 52 weeks	
Reporting group title	Asundexian 50 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 50 mg for 26 weeks at least and up to 52 weeks	
Reporting group title	Placebo
Reporting group description:	
Subjects received Asundexian (BAY2433334) placebo for 26 weeks at least and up to 52 weeks	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
A subject was included in the FAS if he/she was randomized to a treatment group.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
A subject was included in the SAF if he/she was randomized to study intervention and had taken at least one dose of the study intervention.	
Subject analysis set title	Total Asundexian
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
A subject was included in the Total Asundexian if he/she was randomized to Asundexian 10 mg group or Asundexian 20 mg group or Asundexian 50 mg group and had taken at least one dose of Asundexian.	

Primary: Efficacy-Number of subjects with composite of symptomatic ischemic stroke and covert brain infarcts detected by magnetic resonance imaging (MRI)

End point title	Efficacy-Number of subjects with composite of symptomatic ischemic stroke and covert brain infarcts detected by magnetic resonance imaging (MRI)
End point description:	
Ischemic stroke was defined as either of : 1) Rapid onset (or present on awakening) of a new focal neurological deficit with clinical (>24 hours symptoms/signs) or imaging evidence of infarction that was not attributable to a non-ischemic cause; 2) Acute worsening of an existing focal neurological deficit that was judged to be attributable to a new infarction or extension of the previous infarction in the same vascular territory, based on persisting symptoms/signs or imaging evidence of infarction and no evidence of a non-ischemic etiology. If imaging was inconclusive, persistent symptoms/signs must be significant (worsening of NIHSS score of 4 or more) and sustained (duration of ≥24 hours or until death). Covert brain infarcts were defined as incident infarcts detected by serial MRI in the absence of an adjudicated stroke consistent with the location of the infarct. MRI criteria for brain infarction were available in the MRI procedures manual.	
End point type	Primary
End point timeframe:	
From baseline up to 26 weeks	

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	455	450	447	456
Units: Subjects	86	99	90	87

Statistical analyses

Statistical analysis title	Ratio of the incidence proportions
Statistical analysis description:	
Comparison of the Asundexian 10 mg group versus Placebo group	
Comparison groups	Asundexian 10 mg v Placebo
Number of subjects included in analysis	911
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Crude incidence ratio
Point estimate	1.044
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8105
upper limit	1.3478

Statistical analysis title	Dose-response test
Statistical analysis description:	
Dose-response test by using multiple comparison procedures (MCP) Mod method	
Comparison groups	Asundexian 10 mg v Asundexian 20 mg v Asundexian 50 mg v Placebo
Number of subjects included in analysis	1808
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7976
Method	MCP Mod

Statistical analysis title	Ratio of the incidence proportions
Statistical analysis description:	
Comparison of the Asundexian 50 mg group versus Placebo group	
Comparison groups	Placebo v Asundexian 50 mg
Number of subjects included in analysis	903
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Crude incidence ratio
Point estimate	1.0485

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8082
upper limit	1.3619

Statistical analysis title	Ratio of the incidence proportions
Statistical analysis description:	
Comparison of the Asundexian 20 mg group versus Placebo group	
Comparison groups	Placebo v Asundexian 20 mg
Number of subjects included in analysis	906
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Crude incidence ratio
Point estimate	1.1963
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9281
upper limit	1.5428

Primary: Safety-Number of subjects with composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding and clinically relevant non-major (CRNM) bleeding

End point title	Safety-Number of subjects with composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding and clinically relevant non-major (CRNM) bleeding

End point description:

ISTH Major Bleeding criteria: 1. Fatal bleeding, and/or 2. Symptomatic bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or 3. Clinically overt bleeding associated with a recent decrease in the hemoglobin level of ≥ 2 g/dL (20 g/L; 1.24 mmol/L) compared to the most recent hemoglobin value available before the event, and/or 4. Clinically overt bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood. ISTH Clinically Relevant Non-Major Bleeding is considered any sign or symptom of hemorrhage that does not fit the criteria for the ISTH definition of major bleeding, but does meet at least one of the following criteria 1. requiring medical intervention by a healthcare professional. 2. leading to hospitalization or increased level of care. 3. prompting a face to face (i.e. not just a telephone or electronic communication) evaluation.

End point type	Primary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	445	446	443	452
Units: Subjects	19	14	19	11

End point values	Total Asundexian			
Subject group type	Subject analysis set			
Number of subjects analysed	1334			
Units: Subjects	52			

Statistical analyses

Statistical analysis title	Cause specific Hazard ratio (csHR)
Statistical analysis description:	
Comparison of the Asundexian 10 mg group versus Placebo group	
Comparison groups	Asundexian 10 mg v Placebo
Number of subjects included in analysis	897
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.1507
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.724
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.924
upper limit	3.215

Notes:

[1] - Cause specific HRs were only calculated if at least 3 events occurred in 1 of the compared groups and at least 1 event in each of the compared treatment groups.

Statistical analysis title	Cause-specific Hazard Ratio (csHR)
Statistical analysis description:	
Comparison of the Asundexian 50 mg group versus Placebo group	
Comparison groups	Asundexian 50 mg v Placebo
Number of subjects included in analysis	895
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.1401
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.749

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.938
upper limit	3.262

Notes:

[2] - Cause specific HRs were only calculated if at least 3 events occurred in 1 of the compared groups and at least 1 event in each of the compared treatment groups.

Statistical analysis title	Cause specific Hazard ratio (csHR)

Statistical analysis description:

Comparison of the Total Asundexian group versus Placebo group

Comparison groups	Placebo v Total Asundexian
Number of subjects included in analysis	1786
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.1653
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.585
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.918
upper limit	2.736

Notes:

[3] - Cause specific HRs were only calculated if at least 3 events occurred in 1 of the compared groups and at least 1 event in each of the compared treatment groups.

Statistical analysis title	Cause-specific hazard ratio (csHR)

Statistical analysis description:

Comparison of the Asundexian 20 mg group versus Placebo group

Comparison groups	Asundexian 20 mg v Placebo
Number of subjects included in analysis	898
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.5339
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.285
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.662
upper limit	2.494

Notes:

[4] - Cause specific HRs were only calculated if at least 3 events occurred in 1 of the compared groups and at least 1 event in each of the compared treatment groups.

Secondary: Efficacy-Number of subjects with composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI, cardiovascular (CV) death, Myocardial infarction (MI) and systemic embolism.

End point title	Efficacy-Number of subjects with composite of symptomatic

	ischemic stroke and covert brain infarcts detected by MRI, cardiovascular (CV) death, Myocardial infarction (MI) and systemic embolism.

End point description:

CV death included death due to stroke, MI, heart failure or cardiogenic shock, sudden death or any other death due to other cardiovascular causes. Death due to non-traumatic hemorrhage was included. Acute MI was used when there was evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. According to MI Universal Definition from 2018 the diagnosis of MI required the combination of: 1) Presence of acute myocardial injury, and 2) Evidence of acute myocardial ischemia derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging, or in case of post-mortem pathological findings irrespective of biomarker values. Systemic embolism was defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms (this did not include thromboembolism of the pulmonary vasculature or venous thrombosis).

End point type	Secondary

End point timeframe:

From baseline up to 26 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	455	450	447	456
Units: Subjects	80	87	81	79

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy-Number of subjects with symptomatic ischemic stroke

End point title	Efficacy-Number of subjects with symptomatic ischemic stroke

End point description:

Definition of symptomatic ischemic stroke can be referred to first Primary endpoint.

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	455	450	447	456
Units: Subjects	26	26	22	28

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy-Number of subjects with symptomatic ischemic stroke, CV death, MI

End point title	Efficacy-Number of subjects with symptomatic ischemic stroke, CV death, MI

End point description:

Definition of symptomatic ischemic stroke can be referred to first Primary endpoint. Definition of CV death and MI can be referred to first Second endpoint.

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	455	450	447	456
Units: Subjects	33	30	33	35

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy-Number of subjects with covert brain infarcts detected by MRI

End point title	Efficacy-Number of subjects with covert brain infarcts detected by MRI

End point description:

Definition of covert brain infarcts can be referred to first Primary endpoint.

End point type	Secondary

End point timeframe:

From baseline up to 26 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	455	450	447	456
Units: Subjects	62	68	63	60

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy-Number of subjects with symptomatic ischemic and hemorrhagic stroke

End point title	Efficacy-Number of subjects with symptomatic ischemic and hemorrhagic stroke

End point description:

Definition of symptomatic ischemic can be referred to fourth secondary endpoint. Hemorrhagic stroke was defined as an acute, atraumatic extravasation of blood into the brain parenchyma, intraventricular or subarachnoid space with associated neurological symptoms. This did not include microbleeds or hemorrhagic transformation of an ischemic stroke.

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	455	450	447	456
Units: Subjects	26	26	25	30

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy-Number of subjects with Disabling stroke (mRS≥4)

End point title	Efficacy-Number of subjects with Disabling stroke (mRS≥4)

End point description:

Modified ranking score (mRS): 0-No symptoms at all; 1-No significant disability despite symptoms; despite symptoms, able to carry out all usual duties and activities; 2-Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance; 3-Moderate disability; requiring some help, but able to walk without assistance; 4-Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5-Severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6-Death.

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	455	450	447	456
Units: Subjects	5	5	1	3

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy-Number of subjects with All-cause mortality

End point title	Efficacy-Number of subjects with All-cause mortality

End point description:

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	455	450	447	456
Units: Subjects	10	6	17	10

Statistical analyses

No statistical analyses for this end point

Secondary: Safety-Number of subjects with all bleeding

End point title	Safety-Number of subjects with all bleeding

End point description:

All bleeding events occurred from first intake of study intervention until 2 days after the last intake of study intervention.

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	445	446	443	452
Units: Subjects	37	48	48	44

End point values	Total Asundexian			
Subject group type	Subject analysis set			
Number of subjects analysed	1334			
Units: Subjects	133			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety-Number of subjects with ISTH major bleeding

End point title	Safety-Number of subjects with ISTH major bleeding

End point description:

Definition of ISTH major bleeding can be referred to second Primary endpoint.

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	445	446	443	452
Units: Subjects	4	3	7	4

Statistical analyses

No statistical analyses for this end point

Secondary: Safety-Number of subjects with ISTH CRNM bleeding

End point title	Safety-Number of subjects with ISTH CRNM bleeding

End point description:

Definition of ISTH CRNM bleeding can be referred to second Primary endpoint.

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	445	446	443	452
Units: Subjects	15	12	12	7

Statistical analyses

No statistical analyses for this end point

Secondary: Safety-Number of subjects with ISTH minor bleeding

End point title	Safety-Number of subjects with ISTH minor bleeding

End point description:

All other overt bleeding episodes not meeting the above criteria for ISTH major or CRNM bleeding were classified as minor bleeding (e.g. bleeding from a minor wound that does not prompt a face-to-face evaluation for a physical examination or laboratory testing).

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	445	446	443	452
Units: Subjects	21	39	34	34

Statistical analyses

No statistical analyses for this end point

Secondary: Safety-Number of subjects with Intracerebral hemorrhage (non-traumatic)

End point title	Safety-Number of subjects with Intracerebral hemorrhage (non-traumatic)

End point description:

Non-traumatic intracerebral hemorrhage was defined as a hemorrhagic stroke on the “recurrent stroke” CRF page that is in addition classified as a bleeding with bleeding site intracranial (–subarachnoid, –intraparenchymal [excluding microbleeds], or –intraventricular) and spontaneous causality of bleeding, excluding all symptomatic and hemorrhagic transformation (defined by the PT “hemorrhagic transformation”).

End point type	Secondary

End point timeframe:

From baseline up to 52 weeks

End point values	Asundexian 10 mg	Asundexian 20 mg	Asundexian 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	445	446	443	452
Units: Subjects	0	0	3	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
After the first administration of study intervention for up to 52 weeks (but not starting after more than 2 days after the last administration).	
Adverse event reporting additional description:	
Reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact, for up to 54 weeks.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Asundexian 10 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 10 mg for 26 weeks at least and up to 52 weeks	
Reporting group title	Placebo
Reporting group description:	
Subjects received Asundexian (BAY2433334) placebo for 26 weeks at least and up to 52 weeks	
Reporting group title	Asundexian 50 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 50 mg for 26 weeks at least and up to 52 weeks	
Reporting group title	Asundexian 20 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 20 mg for 26 weeks at least and up to 52 weeks	

Serious adverse events	Asundexian 10 mg	Placebo	Asundexian 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 445 (20.22%)	98 / 452 (21.68%)	93 / 443 (20.99%)
number of deaths (all causes)	10	10	17
number of deaths resulting from adverse events	5	7	12
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Glioblastoma multiforme			

subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Metastases to central nervous system			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung neoplasm malignant			
subjects affected / exposed	1 / 445 (0.22%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rectal cancer			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			

subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thymoma malignant			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Colorectal cancer			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Lung neoplasm			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Metastasis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	2 / 443 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic thrombosis			

subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Extremity necrosis			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Thrombophlebitis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Atheroembolism			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Surgical and medical procedures			
Atrial septal defect repair			
subjects affected / exposed	5 / 445 (1.12%)	1 / 452 (0.22%)	3 / 443 (0.68%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac pacemaker insertion			

subjects affected / exposed	2 / 445 (0.45%)	0 / 452 (0.00%)	0 / 443 (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
Carotid endarterectomy			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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 arthroplasty			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Endarterectomy			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
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 bypass			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Cholecystectomy			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Stent placement			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal decompression			

subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Implantable defibrillator insertion			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shoulder arthroplasty			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary angioplasty			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
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 arterial stent insertion			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Aortic bypass			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder polypectomy			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stent insertion			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Bladder neoplasm surgery			

subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transcatheter aortic valve implantation			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord augmentation			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 445 (0.00%)	2 / 452 (0.44%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Chest pain			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Sudden cardiac death			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Inflammation			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Prostatitis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermenstrual bleeding			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 445 (0.22%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	1 / 443 (0.23%)
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 distress			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Sleep apnoea syndrome			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conversion disorder			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Depression			
subjects affected / exposed	2 / 445 (0.45%)	0 / 452 (0.00%)	0 / 443 (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
Investigations			
Angiogram cerebral			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiovascular evaluation			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Sleep study			
subjects affected / exposed	2 / 445 (0.45%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	2 / 445 (0.45%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Magnetic resonance imaging abnormal			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 445 (0.45%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbon monoxide poisoning			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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

Femoral neck fracture			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Foot fracture			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Fibula fracture			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Femur fracture			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Hand fracture			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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	2 / 445 (0.45%)	0 / 452 (0.00%)	0 / 443 (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
Humerus fracture			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Subdural haematoma			

subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Subcutaneous haematoma			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Rib fracture			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
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 haemorrhage			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Traumatic fracture			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Tendon rupture			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Contusion			

subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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 procedural haemorrhage			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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 limb fracture			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body in gastrointestinal tract			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 445 (0.00%)	2 / 452 (0.44%)	2 / 443 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Aortic valve incompetence			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Angina unstable			
subjects affected / exposed	1 / 445 (0.22%)	1 / 452 (0.22%)	0 / 443 (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

Angina pectoris			
subjects affected / exposed	1 / 445 (0.22%)	1 / 452 (0.22%)	0 / 443 (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
Atrial fibrillation			
subjects affected / exposed	3 / 445 (0.67%)	3 / 452 (0.66%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 445 (0.45%)	1 / 452 (0.22%)	2 / 443 (0.45%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Bradycardia			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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 second degree			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 445 (0.22%)	1 / 452 (0.22%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac failure			

subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Cardiac failure acute			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Cardiac failure chronic			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chordae tendinae rupture			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Coronary artery disease			
subjects affected / exposed	1 / 445 (0.22%)	2 / 452 (0.44%)	0 / 443 (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
Myocardial infarction			
subjects affected / exposed	0 / 445 (0.00%)	2 / 452 (0.44%)	3 / 443 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial ischaemia			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			

subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracardiac thrombus			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Sinus node dysfunction			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Brain stem infarction			

subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Carotid artery stenosis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral artery occlusion			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	2 / 443 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 2
Cerebral infarction			
subjects affected / exposed	0 / 445 (0.00%)	3 / 452 (0.66%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	9 / 445 (2.02%)	7 / 452 (1.55%)	9 / 443 (2.03%)
occurrences causally related to treatment / all	0 / 9	0 / 8	0 / 10
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Dizziness			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			

subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive encephalopathy			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Haemorrhagic cerebral infarction			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Facial paralysis			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Myasthenia gravis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Presyncope			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			

subjects affected / exposed	1 / 445 (0.22%)	1 / 452 (0.22%)	0 / 443 (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
Syncope			
subjects affected / exposed	2 / 445 (0.45%)	0 / 452 (0.00%)	0 / 443 (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
Transient ischaemic attack			
subjects affected / exposed	4 / 445 (0.90%)	4 / 452 (0.88%)	2 / 443 (0.45%)
occurrences causally related to treatment / all	0 / 4	0 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Lacunar infarction			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	2 / 443 (0.45%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke in evolution			
subjects affected / exposed	3 / 445 (0.67%)	3 / 452 (0.66%)	2 / 443 (0.45%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Ischaemic stroke			

subjects affected / exposed	9 / 445 (2.02%)	13 / 452 (2.88%)	9 / 443 (2.03%)
occurrences causally related to treatment / all	0 / 9	0 / 14	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Motor dysfunction			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Carotid arteriosclerosis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brachial plexopathy			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral hypoperfusion			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	1 / 445 (0.22%)	2 / 452 (0.44%)	0 / 443 (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
Cerebral amyloid angiopathy			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			

subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral small vessel ischaemic disease			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Cerebellar microhaemorrhage			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar stroke			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemianaesthesia			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood loss anaemia			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Eye disorders			
Macular oedema			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Diabetic retinopathy			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Cataract			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Angle closure glaucoma			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal infarction			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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 disorders			
Abdominal pain			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colitis ischaemic			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Inguinal hernia			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Intussusception			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Umbilical hernia			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Stomach mass			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Paraesthesia oral			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Large intestine polyp			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			

subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Hepatic failure			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Drug-induced liver injury			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Cholelithiasis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Decubitus ulcer			

subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Skin toxicity			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Skin ulcer			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
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 and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Acute kidney injury			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Haematuria			
subjects affected / exposed	1 / 445 (0.22%)	1 / 452 (0.22%)	0 / 443 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	0 / 445 (0.00%)	2 / 452 (0.44%)	0 / 443 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 445 (0.00%)	2 / 452 (0.44%)	0 / 443 (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
Spinal pain			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Tenosynovitis			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Pain in extremity			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Osteoporotic fracture			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	2 / 443 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Diverticulitis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Cellulitis			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 445 (0.67%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 445 (0.22%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Sepsis			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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 tract infection			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Septic shock			

subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Staphylococcal sepsis			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint abscess			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 445 (0.00%)	1 / 452 (0.22%)	0 / 443 (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 bacterial			
subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
COVID-19			
subjects affected / exposed	0 / 445 (0.00%)	4 / 452 (0.88%)	5 / 443 (1.13%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	2 / 443 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	1 / 445 (0.22%)	0 / 452 (0.00%)	0 / 443 (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
Hyponatraemia			
subjects affected / exposed	0 / 445 (0.00%)	0 / 452 (0.00%)	1 / 443 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Asundexian 20 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	83 / 446 (18.61%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Glioblastoma multiforme			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lung cancer metastatic				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal cancer				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal adenocarcinoma				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain neoplasm				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thymoma malignant				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colorectal cancer				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastasis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Invasive ductal breast carcinoma				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive crisis				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic thrombosis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Extremity necrosis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				

subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atheroembolism				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Atrial septal defect repair				
subjects affected / exposed	3 / 446 (0.67%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac pacemaker insertion				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid endarterectomy				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip arthroplasty				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endarterectomy				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery bypass				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystectomy				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Knee arthroplasty				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stent placement				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal decompression				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Implantable defibrillator insertion				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shoulder arthroplasty				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary angioplasty				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary arterial stent insertion				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic bypass				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder polypectomy				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery stent insertion				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder neoplasm surgery				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transcatheter aortic valve implantation				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vocal cord augmentation				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				

Death			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chest pain			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden cardiac death			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inflammation			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostatitis			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Intermenstrual bleeding				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydrothorax				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sleep apnoea syndrome				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Conversion disorder			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Angiogram cerebral			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoglobin decreased			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiovascular evaluation			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sleep study			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver function test increased			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Magnetic resonance imaging abnormal				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SARS-CoV-2 test positive				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carbon monoxide poisoning				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	2 / 446 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Femur fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous haematoma				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foreign body in gastrointestinal tract				

subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic valve incompetence			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	4 / 446 (0.90%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Bradycardia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block second degree				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure chronic				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chordae tendinae rupture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	2 / 446 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intracardiac thrombus				

subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus node dysfunction				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Amnesia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain stem infarction				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral artery occlusion				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	8 / 446 (1.79%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	4 / 446 (0.90%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hypertensive encephalopathy				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic cerebral infarction				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Facial paralysis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myasthenia gravis				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radiculopathy				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	3 / 446 (0.67%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar radiculopathy				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lacunar infarction				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic transformation stroke				
subjects affected / exposed	2 / 446 (0.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Stroke in evolution				
subjects affected / exposed	4 / 446 (0.90%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Ischaemic cerebral infarction				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	7 / 446 (1.57%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Motor dysfunction				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombotic cerebral infarction				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carotid arteriosclerosis				

subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brachial plexopathy				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral hypoperfusion				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral amyloid angiopathy				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neurological decompensation				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral small vessel ischaemic disease				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebellar microhaemorrhage				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lacunar stroke				

subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemianaesthesia			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood loss anaemia			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 446 (0.67%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Macular oedema			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Diabetic retinopathy				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cataract				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angle closure glaucoma				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Retinal infarction				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis ischaemic				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer haemorrhage				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intussusception				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomach mass				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraesthesia oral				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis acute				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis acute				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Decubitus ulcer				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin toxicity				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urticaria				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin ulcer				

subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 446 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal pain			
subjects affected / exposed	0 / 446 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Tenosynovitis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoporotic fracture				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 446 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urosepsis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal abscess				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint abscess				

subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	1 / 446 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19 pneumonia				
subjects affected / exposed	3 / 446 (0.67%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperglycaemia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 446 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Asundexian 10 mg	Placebo	Asundexian 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 445 (28.31%)	136 / 452 (30.09%)	136 / 443 (30.70%)
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 445 (5.17%)	24 / 452 (5.31%)	25 / 443 (5.64%)
occurrences (all)	24	25	25
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	18 / 445 (4.04%)	22 / 452 (4.87%)	16 / 443 (3.61%)
occurrences (all)	18	22	16
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 445 (1.57%)	14 / 452 (3.10%)	17 / 443 (3.84%)
occurrences (all)	7	14	17
Headache			
subjects affected / exposed	19 / 445 (4.27%)	18 / 452 (3.98%)	21 / 443 (4.74%)
occurrences (all)	20	19	31
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	28 / 445 (6.29%)	34 / 452 (7.52%)	28 / 443 (6.32%)
occurrences (all)	29	35	29
Diarrhoea			
subjects affected / exposed	12 / 445 (2.70%)	12 / 452 (2.65%)	15 / 443 (3.39%)
occurrences (all)	12	12	18
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 445 (1.35%)	12 / 452 (2.65%)	11 / 443 (2.48%)
occurrences (all)	6	13	12
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 445 (2.47%)	12 / 452 (2.65%)	16 / 443 (3.61%)
occurrences (all)	11	12	16
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 445 (2.92%)	14 / 452 (3.10%)	13 / 443 (2.93%)
occurrences (all)	15	18	14
COVID-19			

subjects affected / exposed	22 / 445 (4.94%)	12 / 452 (2.65%)	14 / 443 (3.16%)
occurrences (all)	22	12	14

Non-serious adverse events	Asundexian 20 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 446 (28.48%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 446 (4.26%)		
occurrences (all)	19		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	21 / 446 (4.71%)		
occurrences (all)	21		
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 446 (3.59%)		
occurrences (all)	18		
Headache			
subjects affected / exposed	19 / 446 (4.26%)		
occurrences (all)	38		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	18 / 446 (4.04%)		
occurrences (all)	20		
Diarrhoea			
subjects affected / exposed	14 / 446 (3.14%)		
occurrences (all)	15		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 446 (3.59%)		
occurrences (all)	16		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 446 (2.47%)		
occurrences (all)	13		
Infections and infestations			

Urinary tract infection subjects affected / exposed occurrences (all)	11 / 446 (2.47%) 11		
COVID-19 subjects affected / exposed occurrences (all)	14 / 446 (3.14%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36063821