



Clinical trial results:

Multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel group, dose-finding Phase 2 study to compare the safety of the oral FXIa inhibitor BAY 2433334 to apixaban in patients with atrial fibrillation

Summary

EudraCT number	2019-002365-35
Trial protocol	CZ SE NL FR GB HU BE LV AT ES IT
Global end of trial date	08 October 2021

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	BAY2433334/19765
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04218266
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	05 November 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate that the oral FXIIa inhibitor BAY 2433334 (asundexian) when compared to apixaban leads to a lower incidence of bleeding in participants with atrial fibrillation

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: -

Evidence for comparator: -

Actual start date of recruitment	30 January 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	Japan: 119
Country: Number of subjects enrolled	Czechia: 64
Country: Number of subjects enrolled	Hungary: 105
Country: Number of subjects enrolled	Latvia: 95
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Austria: 52
Country: Number of subjects enrolled	Belgium: 41
Country: Number of subjects enrolled	Switzerland: 20
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	United Kingdom: 37
Country: Number of subjects enrolled	Italy: 47
Country: Number of subjects enrolled	Netherlands: 49
Country: Number of subjects enrolled	Sweden: 24
Worldwide total number of subjects	755
EEA total number of subjects	558

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)	110
From 65 to 84 years	582
85 years and over	63

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 94 centers in 14 countries or regions, between 30-Jan-2020 (first subject first visit) and 08-Oct-2021 (last subject last visit)

Pre-assignment

Screening details:

862 subjects were enrolled. 107 subjects were screening failures. 755 subjects were randomized in a 1:1:1 ratio to 3 treatment groups: 251 subjects to the asundexian 20 mg group, 254 subjects to the asundexian 50 mg group and 250 subjects to the apixaban group. 2 subjects of asundexian 20 mg group never administered drug.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Asundexian 20 mg

Arm description:

Subjects received Asundexian (BAY2433334) 20 mg and Apixaban placebo for 12 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, and Apixaban placebo capsule orally twice daily for 12 weeks

Arm title	Asundexian 50 mg
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Arm description:

Subjects received Asundexian (BAY2433334) 50 mg and Apixaban placebo for 12 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 (two 25 mg tablets) orally once daily in the morning, and Apixaban placebo capsule orally twice daily for 12 weeks

Arm title	Apixaban
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Arm description:

Subjects received Asundexian (BAY2433334) placebo and Apixaban for 12 weeks

Arm type	Active comparator
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Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received Asundexian (BAY2433334) placebo tablet orally once daily in the morning, and Apixaban 2.5 mg or 5 mg capsule orally twice daily for 12 weeks

Number of subjects in period 1^[1]	Asundexian 20 mg	Asundexian 50 mg	Apixaban
Started	249	254	250
Completed	226	227	218
Not completed	23	27	32
Consent withdrawn by subject	1	3	1
Physician decision	1	3	2
Adverse event, non-fatal	13	14	11
Death	1	2	3
Non-compliance with study drug	-	-	1
Unspecified	7	5	14

Notes:

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

Justification: The worldwide number of subjects enrolled was 755, however, the baseline data is presented for the 753 subjects treated.

Baseline characteristics

Reporting groups

Reporting group title	Asundexian 20 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 20 mg and Apixaban placebo for 12 weeks	
Reporting group title	Asundexian 50 mg
Reporting group description:	
Subjects received Asundexian (BAY2433334) 50 mg and Apixaban placebo for 12 weeks	
Reporting group title	Apixaban
Reporting group description:	
Subjects received Asundexian (BAY2433334) placebo and Apixaban for 12 weeks	

Reporting group values	Asundexian 20 mg	Asundexian 50 mg	Apixaban
Number of subjects	249	254	250
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)	33	43	34
From 65-84 years	198	191	191
85 years and over	18	20	25
Gender Categorical			
Units: Subjects			
Female	102	97	109
Male	147	157	141
Race			
Units: Subjects			
Asian	39	40	40
Black or African American	1	1	1
White	209	212	209
Not reported	0	1	0

Reporting group values	Total		
Number of subjects	753		
Age Categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	110		
From 65-84 years	580		
85 years and over	63		
Gender Categorical			
Units: Subjects			
Female	308		
Male	445		
Race			
Units: Subjects			
Asian	119		
Black or African American	3		
White	630		
Not reported	1		

End points

End points reporting groups

Reporting group title	Asundexian 20 mg
Reporting group description:	Subjects received Asundexian (BAY2433334) 20 mg and Apixaban placebo for 12 weeks
Reporting group title	Asundexian 50 mg
Reporting group description:	Subjects received Asundexian (BAY2433334) 50 mg and Apixaban placebo for 12 weeks
Reporting group title	Apixaban
Reporting group description:	Subjects received Asundexian (BAY2433334) placebo and Apixaban for 12 weeks
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 a treatment group and had taken at least one unit of the study medication.
Subject analysis set title	Asundexian pooled
Subject analysis set type	Sub-group analysis
Subject analysis set description:	Asundexian 20 mg group and Asundexian 50 mg group

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

End point title	Number of subjects with composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding or 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:	After the first administration of study intervention with an average administration of 12 weeks (but not starting after more than 2 days after the last administration)

End point values	Asundexian 20 mg	Asundexian 50 mg	Apixaban	Asundexian pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	249	254	250	503
Units: Subjects				
ISTH major bleeding or CRNM bleeding	3	1	6	4

Statistical analyses

Statistical analysis title	Pooled ratio of the incidence proportions
Statistical analysis description: Comparison of the Asundexian pooled group versus Apixaban group in ISTH major bleeding or CRNM bleeding	
Comparison groups	Apixaban v Asundexian pooled
Number of subjects included in analysis	753
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Crude incidence ratio
Point estimate	0.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.09
upper limit	0.97

Secondary: Number of subjects with all bleeding

End point title	Number of subjects with all bleeding
End point description: Adjudication of all bleeding events was performed by members of the Clinical events committee (CEC) who reviewed events in a blinded fashion and adjudicated and classified the following events in a consistent and unbiased manner according to the following classifications: ISTH (major, clinically relevant non-major and minor); Thrombolysis in myocardial infarction (TIMI major, minor, requiring medical attention, minimal); Bleeding Academic Research Consortium (BARC type 1, 2, 3, 5).	
End point type	Secondary
End point timeframe: After the first administration of study intervention with an average administration of 12 weeks (but not starting after more than 2 days after the last administration)	

End point values	Asundexian 20 mg	Asundexian 50 mg	Apixaban	Asundexian pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	249	254	250	503
Units: Subjects	12	10	26	22

Statistical analyses

Statistical analysis title	Pooled ratio of the incidence proportions
Statistical analysis description:	
Comparison of the Asundexian pooled group versus Apixaban group in all bleeding	
Comparison groups	Apixaban v Asundexian pooled
Number of subjects included in analysis	753
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Crude incidence ratio
Point estimate	0.42
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.26
upper limit	0.67

Secondary: Number of subjects with ISTH major bleeding

End point title	Number of subjects with ISTH major 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.	
End point type	Secondary
End point timeframe:	
After the first administration of study intervention with an average administration of 12 weeks (but not starting after more than 2 days after the last administration)	

End point values	Asundexian 20 mg	Asundexian 50 mg	Apixaban	Asundexian pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	249	254	250	503
Units: Subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects of ISTH clinically relevant non-major (CRNM) bleeding

End point title	Number of subjects of ISTH clinically relevant non-major (CRNM) bleeding
End point description:	
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	Secondary
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End point timeframe:

After the first administration of study intervention with an average administration of 12 weeks (but not starting after more than 2 days after the last administration)

End point values	Asundexian 20 mg	Asundexian 50 mg	Apixaban	Asundexian pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	249	254	250	503
Units: Subjects	3	1	6	4

Statistical analyses

Statistical analysis title	Pooled ratio of the incidence proportions
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Statistical analysis description:

Comparison of the Asundexian pooled group versus Apixaban group in ISTH CRNM bleeding

Comparison groups	Apixaban v Asundexian pooled
Number of subjects included in analysis	753
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Crude incidence ratio
Point estimate	0.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.09
upper limit	0.97

Secondary: Number of subjects with ISTH minor bleeding

End point title	Number of subjects with ISTH minor bleeding
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End point description:

All other overt bleeding episodes not meeting ISTH Major Bleeding criteria or clinically relevant non major bleeding were classified as minor bleeding.

End point type	Secondary
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End point timeframe:

After the first administration of study intervention with an average administration of 12 weeks (but not starting after more than 2 days after the last administration)

End point values	Asundexian 20 mg	Asundexian 50 mg	Apixaban	Asundexian pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	249	254	250	503
Units: Subjects	10	9	20	19

Statistical analyses

Statistical analysis title	Pooled ratio of the incidence proportions
Statistical analysis description:	
Comparison of the Asundexian pooled group versus Apixaban group in ISTH minor bleeding	
Comparison groups	Apixaban v Asundexian pooled
Number of subjects included in analysis	753
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Crude incidence ratio
Point estimate	0.47
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.28
upper limit	0.83

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first administration of study intervention with an average administration of 12 weeks (but not starting after more than 2 days after the last administration).

Adverse event reporting additional description:

Adverse event reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact, with an average of 14 weeks.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Asundexian 50 mg
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Reporting group description:

Subjects received Asundexian (BAY2433334) 50 mg and Apixaban placebo for 12 weeks

Reporting group title	Asundexian 20 mg
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Reporting group description:

Subjects received Asundexian (BAY2433334) 20 mg and Apixaban placebo for 12 weeks

Reporting group title	Apixaban
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Reporting group description:

Subjects received Asundexian (BAY2433334) placebo and Apixaban for 12 weeks

Serious adverse events	Asundexian 50 mg	Asundexian 20 mg	Apixaban
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 254 (7.87%)	22 / 249 (8.84%)	20 / 250 (8.00%)
number of deaths (all causes)	4	2	5
number of deaths resulting from adverse events	3	1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
Colon neoplasm			

subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cardiac ablation			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
Percutaneous coronary intervention			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 254 (0.39%)	1 / 249 (0.40%)	0 / 250 (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
Bronchial haemorrhage			

subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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
Completed suicide			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
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 disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 254 (1.18%)	3 / 249 (1.20%)	2 / 250 (0.80%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	4 / 254 (1.57%)	3 / 249 (1.20%)	3 / 250 (1.20%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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 chronic			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
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 disease			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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
Myocardial infarction			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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
Palpitations			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
Sinus arrest			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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
Atrial thrombosis			

subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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
Tachyarrhythmia			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
Sinus node dysfunction			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 254 (0.39%)	2 / 249 (0.80%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Presyncope			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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 sensorimotor neuropathy			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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			

Colitis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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
Inguinal hernia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
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 impairment			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (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 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
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			
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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
Erysipelas			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (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

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

Non-serious adverse events	Asundexian 50 mg	Asundexian 20 mg	Apixaban
Total subjects affected by non-serious adverse events			
subjects affected / exposed	116 / 254 (45.67%)	110 / 249 (44.18%)	113 / 250 (45.20%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Prostate cancer			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Haematoma			

subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	3 / 250 (1.20%) 3
Hypertension subjects affected / exposed occurrences (all)	5 / 254 (1.97%) 6	6 / 249 (2.41%) 6	7 / 250 (2.80%) 7
Hypotension subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	2 / 249 (0.80%) 2	3 / 250 (1.20%) 3
Orthostatic hypotension subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Peripheral coldness subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	2 / 249 (0.80%) 2	0 / 250 (0.00%) 0
Phlebitis superficial subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Subclavian artery thrombosis subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Hypertensive urgency subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Hot flush subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Surgical and medical procedures			
Cardiac pacemaker insertion subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Cardioversion subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Tooth extraction subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0

Cataract operation subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	3 / 249 (1.20%) 3	4 / 250 (1.60%) 4
Chest discomfort subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Discomfort subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Chest pain subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2	3 / 249 (1.20%) 3	0 / 250 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	10 / 254 (3.94%) 10	5 / 249 (2.01%) 5	2 / 250 (0.80%) 2
Feeling abnormal subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Feeling cold subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
Feeling hot subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Oedema subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Oedema peripheral			

subjects affected / exposed	3 / 254 (1.18%)	2 / 249 (0.80%)	3 / 250 (1.20%)
occurrences (all)	3	2	3
Pyrexia			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	2 / 254 (0.79%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	2	0	0
Thirst			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	1 / 250 (0.40%)
occurrences (all)	0	1	1
Hernia pain			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
General physical health deterioration			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Inflammation			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Adverse drug reaction			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Medical device site inflammation			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			

Amyloidosis subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Reproductive system and breast disorders Prostatitis subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	2 / 249 (0.80%) 2	0 / 250 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	5 / 254 (1.97%) 6	3 / 249 (1.20%) 3	3 / 250 (1.20%) 3
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Emphysema subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	5 / 254 (1.97%) 8	3 / 249 (1.20%) 3	11 / 250 (4.40%) 12
Hiccups subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Productive cough subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 2	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Pulmonary embolism subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0

Pulmonary haemorrhage subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Sleep apnoea syndrome subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Sputum discoloured subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Hydrothorax subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Pharyngeal paraesthesia subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Pharyngeal swelling subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Confusional state subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Delirium subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Depression			

subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Insomnia subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 3	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
Nightmare subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Investigations			
Amylase increased subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Blood glucose increased subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Blood potassium increased subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Blood pressure increased subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Blood thyroid stimulating hormone decreased subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Blood urea increased			

subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	3 / 250 (1.20%)
occurrences (all)	0	1	3
Haemoglobin decreased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Heart rate decreased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	2
Neutrophil count increased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	2
Reticulocyte count decreased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 254 (0.00%)	2 / 249 (0.80%)	1 / 250 (0.40%)
occurrences (all)	0	2	1
Urinary occult blood positive			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	2 / 250 (0.80%)
occurrences (all)	0	0	2
Angiocardiogram			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0

SARS-CoV-2 test positive subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Injury, poisoning and procedural complications			
Accident subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Facial bones fracture subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Haematuria traumatic subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Ligament sprain subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Humerus fracture subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 2
Sunburn subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Wrist fracture subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Lumbar vertebral fracture subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	1 / 249 (0.40%) 1	3 / 250 (1.20%) 3
Inflammation of wound subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Lip injury			

subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Joint injury subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Tooth fracture subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Skin abrasion subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Post-traumatic pain subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Craniocerebral injury subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Skin wound subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Congenital, familial and genetic disorders			
Accessory spleen subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Cardiac disorders			
Angina pectoris subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2	2 / 249 (0.80%) 2	1 / 250 (0.40%) 1
Aortic valve stenosis subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Arrhythmia supraventricular subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Atrial fibrillation			

subjects affected / exposed	8 / 254 (3.15%)	7 / 249 (2.81%)	7 / 250 (2.80%)
occurrences (all)	9	7	7
Atrial flutter			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	1 / 250 (0.40%)
occurrences (all)	0	1	2
Atrial tachycardia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Atrioventricular block first degree			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Bradycardia			
subjects affected / exposed	1 / 254 (0.39%)	1 / 249 (0.40%)	2 / 250 (0.80%)
occurrences (all)	1	1	2
Cardiac failure			
subjects affected / exposed	0 / 254 (0.00%)	2 / 249 (0.80%)	5 / 250 (2.00%)
occurrences (all)	0	2	5
Cardiac failure acute			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Cardiac failure chronic			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	2 / 250 (0.80%)
occurrences (all)	0	1	2
Cardiomegaly			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Coronary artery disease			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Coronary artery stenosis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	2
Myocardial ischaemia			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Palpitations			

subjects affected / exposed occurrences (all)	4 / 254 (1.57%) 4	3 / 249 (1.20%) 3	1 / 250 (0.40%) 2
Sinus bradycardia subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2	0 / 249 (0.00%) 0	2 / 250 (0.80%) 2
Ventricular tachycardia subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Nervous system disorders			
Ageusia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Dizziness subjects affected / exposed occurrences (all)	8 / 254 (3.15%) 8	9 / 249 (3.61%) 9	7 / 250 (2.80%) 10
Dysgeusia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
Essential tremor subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Head discomfort subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	7 / 254 (2.76%) 7	4 / 249 (1.61%) 4	5 / 250 (2.00%) 5
Hypertonia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0

Hypoaesthesia			
subjects affected / exposed	0 / 254 (0.00%)	2 / 249 (0.80%)	0 / 250 (0.00%)
occurrences (all)	0	2	0
Neuritis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	1 / 254 (0.39%)	3 / 249 (1.20%)	0 / 250 (0.00%)
occurrences (all)	1	3	0
Parkinsonism			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	2 / 254 (0.79%)	2 / 249 (0.80%)	0 / 250 (0.00%)
occurrences (all)	2	2	0
Orthostatic intolerance			
subjects affected / exposed	0 / 254 (0.00%)	2 / 249 (0.80%)	0 / 250 (0.00%)
occurrences (all)	0	2	0
Tremor			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 254 (0.39%)	2 / 249 (0.80%)	0 / 250 (0.00%)
occurrences (all)	1	2	0
Polycythaemia			

subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Spontaneous haematoma subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	4 / 254 (1.57%) 4	2 / 249 (0.80%) 2	3 / 250 (1.20%) 3
Vertigo labyrinthine subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Eye disorders			
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	2 / 249 (0.80%) 2	2 / 250 (0.80%) 2
Dry eye subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Myopia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Eye irritation subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Photophobia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Swelling of eyelid subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Vision blurred			

subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	2 / 250 (0.80%) 2
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	2 / 249 (0.80%) 2	0 / 250 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3	2 / 249 (0.80%) 2	6 / 250 (2.40%) 6
Change of bowel habit subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Constipation subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Dental caries subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Dry mouth subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3	3 / 249 (1.20%) 3	1 / 250 (0.40%) 1
Diarrhoea subjects affected / exposed occurrences (all)	11 / 254 (4.33%) 11	4 / 249 (1.61%) 5	5 / 250 (2.00%) 5
Dyspepsia subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1

Eructation			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Food poisoning			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 254 (0.39%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Gingival bleeding			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	1	0	1
Haematochezia			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	8 / 254 (3.15%)	6 / 249 (2.41%)	9 / 250 (3.60%)
occurrences (all)	8	7	10
Melaena			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Oesophagitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Oral discomfort			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0

Saliva altered			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	1 / 254 (0.39%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	2 / 254 (0.79%)	2 / 249 (0.80%)	1 / 250 (0.40%)
occurrences (all)	2	2	1
Large intestinal haemorrhage			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 254 (0.39%)	1 / 249 (0.40%)	1 / 250 (0.40%)
occurrences (all)	1	1	1
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Abdominal symptom			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Cholestasis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Hepatic fibrosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Hepatomegaly			

subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	2 / 249 (0.80%) 2	1 / 250 (0.40%) 1
Blister			
subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Dermatitis			
subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Dermatitis contact			
subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Hyperhidrosis			
subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
Intertrigo			
subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Papule			
subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Pruritus			
subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3	5 / 249 (2.01%) 5	3 / 250 (1.20%) 3
Rash			
subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Rash papular			
subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Rash pruritic			
subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 2	0 / 250 (0.00%) 0

Skin disorder			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Skin fissures			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Skin ulcer			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Skin reaction			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Skin haemorrhage			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	1 / 250 (0.40%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	1	0	1
Haematuria			
subjects affected / exposed	0 / 254 (0.00%)	2 / 249 (0.80%)	6 / 250 (2.40%)
occurrences (all)	0	2	6
Hydronephrosis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Nocturia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 254 (0.00%)	2 / 249 (0.80%)	0 / 250 (0.00%)
occurrences (all)	0	2	0
Renal colic			

subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Renal cyst subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Renal failure subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Urinary retention subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Renal impairment subjects affected / exposed occurrences (all)	3 / 254 (1.18%) 3	2 / 249 (0.80%) 2	0 / 250 (0.00%) 0
Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	2 / 250 (0.80%) 2
Acute kidney injury subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Endocrine disorders			
Hyperthyroidism subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Hypothyroidism subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	2 / 250 (0.80%) 2
Autoimmune thyroiditis subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 254 (1.57%) 4	0 / 249 (0.00%) 0	2 / 250 (0.80%) 2
Back pain			

subjects affected / exposed	1 / 254 (0.39%)	4 / 249 (1.61%)	1 / 250 (0.40%)
occurrences (all)	1	5	1
Bursitis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	1 / 254 (0.39%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	1	1	0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 254 (0.39%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	1	1	0
Muscle spasms			
subjects affected / exposed	2 / 254 (0.79%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	2	1	0
Muscular weakness			
subjects affected / exposed	0 / 254 (0.00%)	2 / 249 (0.80%)	0 / 250 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal pain			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	1	0	1
Pain in extremity			
subjects affected / exposed	2 / 254 (0.79%)	2 / 249 (0.80%)	0 / 250 (0.00%)
occurrences (all)	2	2	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Intervertebral disc protrusion			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			

subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Musculoskeletal discomfort subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Limb discomfort subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Spinal stenosis subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Cystitis subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
Erysipelas subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Gingivitis subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Herpes zoster subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	3 / 249 (1.20%) 3	0 / 250 (0.00%) 0

Localised infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	3 / 254 (1.18%)	1 / 249 (0.40%)	2 / 250 (0.80%)
occurrences (all)	3	1	3
Pharyngitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Periodontitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	2 / 254 (0.79%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	2	0	0
Pulpitis dental			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Tinea cruris			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 254 (0.00%)	2 / 249 (0.80%)	3 / 250 (1.20%)
occurrences (all)	0	2	3
Viral infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0

Gingival abscess			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 254 (0.39%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	1	0	0
Oral fungal infection			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 254 (0.00%)	1 / 249 (0.40%)	0 / 250 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	2 / 254 (0.79%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Diabetes mellitus			
subjects affected / exposed	2 / 254 (0.79%)	0 / 249 (0.00%)	0 / 250 (0.00%)
occurrences (all)	2	0	0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Fluid overload			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Gout			
subjects affected / exposed	1 / 254 (0.39%)	4 / 249 (1.61%)	1 / 250 (0.40%)
occurrences (all)	1	4	1
Folate deficiency			
subjects affected / exposed	0 / 254 (0.00%)	0 / 249 (0.00%)	1 / 250 (0.40%)
occurrences (all)	0	0	1
Hypercholesterolaemia			

subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	1 / 249 (0.40%) 1	2 / 250 (0.80%) 2
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
Hyperuricaemia subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	1 / 250 (0.40%) 1
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	1 / 249 (0.40%) 1	0 / 250 (0.00%) 0
Decreased appetite subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0	0 / 249 (0.00%) 0	1 / 250 (0.40%) 1
Hyperlipidaemia subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1	0 / 249 (0.00%) 0	0 / 250 (0.00%) 0

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