Clinical trial results:
Start or STop Anticoagulants Randomised Trial (SoSTART) after spontaneous intracranial haemorrhage

Summary

EudraCT number	2016-004121-16
Trial protocol	GB
Global end of trial date	31 March 2021

Results information

Result version number	v1 (current)
This version publication date	01 October 2021
First version publication date	01 October 2021
Summary attachment (see zip file)	Published results of SoSTART (PIIS1474442221002647.pdf)

Trial information

Trial identification

Sponsor protocol code	AC16141

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03153150
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov Identifier: NCT03153150

Notes:

Sponsors

Sponsor organisation name	Academic and Clinical Central Office for Research and Development (ACCORD)
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Professor Rustam Al-Shahi Salman, University of Edinburgh, +44 0131 242 7014, rustam.al-shahi@ed.ac.uk
Scientific contact	Head of Research Governance, Academic and Clinical Central Office for Research and Development (ACCORD), +44 0131 242 3330, enquiries@accord.scot

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	16 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2021
Global end of trial reached?	Yes
Global end of trial date	31 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

SoSTART aims to study at least 190 people aged ≥18 years, >24 hours after onset of spontaneous symptomatic intracranial haemorrhage, with AF and CHA2DS2VASc score ≥2 to determine the safety of starting full treatment dose OAC compared to not starting OAC for the prevention of the primary outcome of recurrent symptomatic intracranial haemorrhage over ≥1 year after randomisation.

Protection of trial subjects:

SoSTART was conducted in accordance with all relevant data protection, ethical and regulatory requirements to ensure the privacy and security of patient information and to ensure the rights, safety and well-being of the patients and the quality of the research data.

We sought support and advice from members of the patient reference group for the Research to Understand Stroke due to Haemorrhage (RUSH) programme for ongoing review of our study materials and on trial progress. We also included a member of this group as part of our Trial Steering Committee.

We sought to minimise risk and the burden to the patient without compromising the scientific rigour of the trial. Annual follow-up questionnaires were kept to a minumum to avoid burden and a central helpline was available to support participants, families, GPs and research staff.

Background therapy:

Any background therapy in standard clinical practice for this patient population (e.g. antihypertensive drugs) was determined for participants by the clinical teams at each of our 67 hospital sites.

Evidence for comparator:

Standard clinical practice for patients with atrial fibrillation after intracranial haemorrhage, who do not start oral anticoagulation, is either complete avoidance of antithrombotic drugs or the use of an antiplatelet drug (used either for secondary prevention following vaso-occlusive comorbidites, or for reduction of systemic embolism in AF based on existing data [Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67]).

Actual start date of recruitment	28 March 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 203
Worldwide total number of subjects	203
EEA total number of subjects	0

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)	7
From 65 to 84 years	147
85 years and over	49

Subject disposition

Recruitment

Recruitment details:

Between March 28, 2018 and February 27, 2020, consent was obtained at 61 sites for 218 people to participate, of whom 203 (93%) were randomised a median of 115 days (IQR 49–265) after intracranial haemorrhage onset. 15 were not enrolled; 5 were ineligible, 2 had deterioration of health condition, and 8 were uncertain about oral anticoagulation.

Pre-assignment

Screening details:

During the feasibility phase only, sites were required to provide screening log data on all potentially eligible patients at each site, which patients were recruited, and reasons why the others were not. These data helped confirm the suitability of the eligibility criteria, understand recruitment, and inform the feasibility of a definitive trial.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Start

Arm description:

Start long-term (≥1y) full treatment dose open-label oral anticoagulation.

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

Dosage and administration details:

As prescribed by randomising clinician.

Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As prescribed by randomising clinician.

Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As prescribed by randomising clinician.

Investigational medicinal product name	Dabigatran etexilate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details: As prescribed by randomising clinician.	
Investigational medicinal product name	Warfarin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Concentrate for oral suspension
Routes of administration	Oral use
Dosage and administration details: As prescribed by randomising clinician.	
Investigational medicinal product name	Acenocoumarol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: As prescribed by randomising clinician.	
Investigational medicinal product name	Phenindione
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: As prescribed by randomising clinician.	
Arm title	Avoid
Arm description: Avoid long-term (≥1y) full treatment dose open-label oral anticoagulation.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Start	Avoid
Started	101	102
Completed	101	102

Baseline characteristics

Reporting groups	
Reporting group title	Start
Reporting group description:	
Start long-term (≥1y) full treatment dose open-label oral anticoagulation.	
Reporting group title	Avoid
Reporting group description:	
Avoid long-term (≥1y) full treatment dose open-label oral anticoagulation.	

Reporting group values	Start	Avoid	Total
Number of subjects	101	102	203
Age categorical Units: Subjects			
Age continuous			
At randomisation, participants in the two treatment groups were on average 79 years old.			
Units: years			
median	79	79	
inter-quartile range (Q1-Q3)	74 to 85	74 to 84	-
Gender categorical Units: Subjects			
Female	39	37	76
Male	62	65	127
Ethnicity Units: Subjects			
White	92	96	188
Asian	7	4	11
Black	1	1	2
Mixed	0	1	1
Other	1	0	1
Type of qualifying spontaneous intracranial haemorrhage Units: Subjects			
Lobar intracerebral haemorrhage	35	38	73
Non-lobar intracerebral haemorrhage	58	56	114
Other	8	8	16
Time since qualifying intracranial haemorrhage symptom onset Units: Subjects			
<10 weeks	37	38	75
>=10 weeks	64	64	128
Probability of good 6-month outcome Units: Subjects			
<0·15	21	22	43
≥0·15	80	80	160
Type of atrial arrhythmia Units: Subjects			

Persistent atrial fibrillation	28	24	52
Permanent atrial fibrillation	51	51	102
Paroxysmal atrial fibrillation	22	26	48
Atrial flutter	0	1	1
Detection of atrial arrhythmia Units: Subjects			
Before intracranial haemorrhage	92	95	187
After intracranial haemorrhage	9	7	16
CHA2DS2-VASc score			
The CHA2DS2-VASc score to predict the risk of ischaemic stroke or systemic embolism for patients with atrial fibrillation ranges from 0-9 and is based on the sum of individual scores for: congestive heart failure or left ventricular dysfunction (1); systemic arterial hypertension (1); age ≥75 years (2); diabetes mellitus (1); stroke or transient ischaemic attack or other thromboembolism (2); vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque) (1); age 65-74 years (1); female sex (1).			
Units: Subjects			
Two	14	18	32
Three	22	20	42
Four	32	26	58
Five	21	15	36
Six	9	17	26
Seven	3	6	9
Use of oral anticoagulation before qualifying intracranial haemorrhage Units: Subjects			
Yes	84	86	170
No	17	16	33
HAS-BLED score			
The HAS-BLED score to predict the risk of major bleeding for patients with atrial fibrillation ranges from 0-9 and is based on the sum of the individual scores for: hypertension (1); abnormal renal and liver function (1 point each); stroke (1); bleeding history or disposition (1), labile international normalised ratio (1); elderly i.e. age >65 years (1); drugs or alcohol concomitantly (1 point each).			
Units: Subjects			
Zero	3	0	3
One	48	46	94
Two	34	31	65
Three	12	20	32
Four	4	5	9
Intended type of oral anticoagulation (if allocated to start) Units: Subjects			
Direct oral anticoagulant	97	101	198
Other	4	1	5
Intended comparator (if allocated to avoid) Units: Subjects			
No antithrombotic agents	77	70	147
Antiplatelet agent	24	32	56
Time since qualifying intracranial haemorrhage symptom onset Units: day			
median	104	115	
inter-quartile range (Q1-Q3)	44 to 244	51 to 288	-

End points

End points reporting groups

Reporting group title	Start
Reporting group description:	
Start long-term (≥1y) full treatment dose open-label oral anticoagulation.	
Reporting group title	Avoid
Reporting group description:	
Avoid long-term (≥1y) full treatment dose open-label oral anticoagulation.	

Primary: Recurrent symptomatic spontaneous intracranial haemorrhage

End point title	Recurrent symptomatic spontaneous intracranial haemorrhage
End point description:	
End point type	Primary
End point timeframe:	
First event after randomisation and before death or most recent follow up.	

End point values	Start	Avoid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	102		
Units: Events				
Recurrent symptomatic spontaneous intracranial hae	8	4		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards analysis
Statistical analysis description:	
Cox proportional hazards models were adjusted for two of the six minimisation variables: time since intracranial haemorrhage symptom onset (<10 weeks [reference] vs ≥10 weeks) and type of qualifying intracranial haemorrhage (lobar intracerebral haemorrhage vs non-lobar intracerebral haemorrhage and lobar intracerebral haemorrhage vs other); model non-convergence due to the low number of events prevented the inclusion of any more minimisation variables.	
Comparison groups	Start v Avoid
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.152 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	8.09

Notes:

[1] - Our prespecified margin for declaring non-inferiority was not met.

Secondary: Composite secondary outcome - Any symptomatic major vascular event

End point title	Composite secondary outcome - Any symptomatic major vascular event

End point description:

Myocardial infarction; symptomatic spontaneous intracerebral, subarachnoid, intraventricular or subdural haemorrhage; ischaemic stroke; death within 30 days of recurrent symptomatic spontaneous intracranial haemorrhage, ischaemic stroke, myocardial infarction, or symptomatic deep vein thrombosis; sudden cardiac death; death from another vascular cause (i.e. not within 30 days of an outcome event); death of an unknown cause.

End point type	Secondary

End point timeframe:

First event after randomisation and before death or most recent follow up.

End point values	Start	Avoid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	102		
Units: Events				
Any symptomatic major vascular event	12	24		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards analysis

Statistical analysis description:

Cox proportional hazards models were adjusted for two of the six minimisation variables time since intracranial haemorrhage symptom onset (<10 weeks [reference] vs ≥10 weeks) and type of qualifying intracranial haemorrhage (lobar intracerebral haemorrhage vs non-lobar intracerebral haemorrhage and lobar intracerebral haemorrhage vs other); model non-convergence due to the low number of events prevented the inclusion of any more minimisation variables.

Comparison groups	Start v Avoid
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.03

Secondary: Composite secondary outcome - Any stroke

End point title	Composite secondary outcome - Any stroke

End point description:

End point type	Secondary

End point timeframe:

First event after randomisation and before death or most recent follow up.

End point values	Start	Avoid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	102		
Units: Events				
Any stroke	11	22		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards analysis

Statistical analysis description:

Cox proportional hazards models were adjusted for two of the six minimisation variables time since intracranial haemorrhage symptom onset (<10 weeks [reference] vs ≥10 weeks) and type of qualifying intracranial haemorrhage (lobar intracerebral haemorrhage vs non-lobar intracerebral haemorrhage and lobar intracerebral haemorrhage vs other); model non-convergence due to the low number of events prevented the inclusion of any more minimisation variables.

Comparison groups	Avoid v Start
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.084
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	1.09

Secondary: Composite secondary outcomes - Any stroke or vascular death

End point title	Composite secondary outcomes - Any stroke or vascular death

End point description:

End point type	Secondary

End point timeframe:

First event after randomisation and before death or most recent follow up.

End point values	Start	Avoid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	102		
Units: Events				
Any stroke or vascular death	12	23		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards analysis

Statistical analysis description:

Cox proportional hazards models were adjusted for two of the six minimisation variables time since intracranial haemorrhage symptom onset (<10 weeks [reference] vs ≥10 weeks) and type of qualifying intracranial haemorrhage (lobar intracerebral haemorrhage vs non-lobar intracerebral haemorrhage and lobar intracerebral haemorrhage vs other); model non-convergence due to the low number of events prevented the inclusion of any more minimisation variables.

Comparison groups	Avoid v Start
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.1

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious adverse events in the SoSTART trial were collected for all participants from the period between randomisation and the end of the trial (unless they withdrew).

Adverse event reporting additional description:

Only serious adverse events were required to be reported by the protocol.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Start

Reporting group description:

Start long-term (≥1y) full treatment dose open-label oral anticoagulation.

Reporting group title	Avoid

Reporting group description:

Avoid long-term (≥1y) full treatment dose open-label oral anticoagulation.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Section 16.6 of the protocol states, "safety assessments in SoSTART are focussed on detecting: primary and secondary outcomes (all of which relate to the safety of antithrombotic drugs in this patient group) and any SAEs and SUSARs that may occur after randomisation."

Serious adverse events	Start	Avoid	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 101 (24.75%)	25 / 102 (24.51%)	
number of deaths (all causes)	15	11	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	3 / 101 (2.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bladder neoplasm surgery			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral endovascular aneurysm repair			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 101 (0.99%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	2 / 101 (1.98%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 101 (1.98%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Splenic infarction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 101 (0.99%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystectomy			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 101 (0.99%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 101 (0.99%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 101 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			

subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Start	Avoid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 101 (0.00%)	0 / 102 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2018	An update to the Reference Safety Information (RSI)
29 August 2018	- Addition of 30 sites - Change of PI
06 September 2018	- Inclusion of a safety phase in the study between the pilot and main phases of the study; - Addition of spontaneous haemorrhage as a primary outcome in the protocol; - Inclusion of the EQ-5D-5L to the annual questionnaire which contributes to the secondary objectives of the main phase
29 November 2018	- Addition of 9 sites - 2 Change of PIs
08 January 2019	Change of PI
05 February 2019	2 Change of PIs
25 April 2019	Change of PI
28 June 2019	2 Change of PIs
14 August 2019	Change of PI
07 October 2019	Change of PI
04 November 2019	- Protocol: outcome definition clarification - GP annual questionnaire: outcome wording changed as per new version of the protocol - GP letter changes to include a Professional Summary from a new version of the protocol - Change of PI
12 December 2019	2 Change of PIs
12 February 2020	- Protocol: main phase removal - Change of PI
29 April 2020	SmPC update
29 July 2020	2 Change of PIs

Notes:

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/33598560