Clinical trial results:
SFX-01 AFTER SUBARACHNOID HAEMORRHAGE - SAS

Summary

EudraCT number	2014-003284-38
Trial protocol	GB
Global end of trial date	06 September 2019

Results information

Result version number	v1 (current)
This version publication date	02 June 2021
First version publication date	02 June 2021

Trial information

Trial identification

Sponsor protocol code	EVG001SAH

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02614742
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Evgen Pharma plc
Sponsor organisation address	Suite 24G13, Alderley Park, Alderley Edge, United Kingdom, SK10 4TG
Public contact	Clinical Trials Information, Evgen Pharma plc, 44 1625466591, randd@evgen.com
Scientific contact	Clinical Trials Information, Evgen Pharma plc, 44 1625466591, randd@evgen.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	31 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of up to 28 days of SFX-01 dosed at up to 600mg (92mg sulforaphane [SFN]) per day vs placebo, following spontaneous aneurysmal subarachnoid haemorrhage (SAH) and given in addition to Nimodipine as standard of care.

To determine if a minimum of 7 days treatment with SFX-01 vs placebo reduces Middle Cerebral Artery (MCA) peak flow velocity following SAH, in addition to Nimodipine as standard of care.

To determine the levels of SFN and principal metabolites in Cerebrospinal Fluid (CSF) after treatment with SFX-01 vs placebo following SAH.

Protection of trial subjects:

All patients admitted to study sites with a diagnosis of spontaneous SAH were assessed by the hospital study team against the protocol inclusion and exclusion criteria. Identified subjects who fulfilled the criteria were subsequently approached by a member of the research team, who would seek to obtain consent from the subject, or in the case of adults lacking capacity, the Personal Legal Representative, if available or if not, a Professional Legal representative.
The Patient Information was given to the subject, Personal Legal Representative or Professional Legal representative and they were given sufficient time to review and discuss material in order to make a decision to participate in the study or not.
Patients and/or Personal Legal Representative had the right to discontinue trial medication at any time and for any reason. The Investigator also had the right to discontinue trial medication if they felt that treatment was no longer appropriate, if in their opinion the patient’s clinical condition was worsening or for safety (adverse events).

Background therapy:

The aims of the study were to assess the safety and tolerability of SFX-01 vs placebo, and if the addition of SFX-01 to nimodipine as standard of care could improve outcomes and reduce the long-term complications of spontaneous aneurysmal SAH, such as Delayed Cerebral Ischaemia (DCI), as reflected by Trans-Cranial Doppler (TCD) readings, other neurological and quality of life rating scales.

Evidence for comparator:

The only effective approved treatment to reduce morbidity from SAH is nimodipine. However, its effects are small and despite its use, poor outcomes remain a significant problem as evidenced by contemporary outcome data since its introduction. Moreover, even in survivors conventionally considered to have made a good recovery, neurocognitive deficits are common leading to extensive problems with social reintegration and functioning in the workplace. In this study, SFX-01/placebo was used in conjunction with nimodipine as per routine clinical care along with other standard supportive measures as required. The placebo arm therefore represents standard care alone. The study was randomised in order to prevent bias in the allocation of treatment and to ensure the comparability of baseline characteristics between the treatment groups. In order to prevent bias in the conduct of the clinical assessments, the study was double blind, so that neither the investigators nor the patients knew whether the patient was receiving active treatment or placebo.

Actual start date of recruitment	14 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 105
Worldwide total number of subjects	105
EEA total number of subjects	105

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)	90
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients admitted to study sites with a diagnosis of spontaneous SAH were assessed by the hospital study team against the protocol inclusion and exclusion criteria. Identified subjects who fulfilled the criteria were subsequently approached by a member of the research team, who would seek to obtain consent for subject to participate.

Pre-assignment

Screening details:

Subjects providing consent to participate underwent a screening assessment within 48h of ictus and prior to first dosing with SFX-01/placebo.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	SFX-01

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SFX-01 300mg capsules
Investigational medicinal product code	SFX-01
Other name	Sulforadex 300mg capsules
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

SFX-01 (300 mg) or matching placebo were taken orally as capsules or as a suspension via a nasogastric tube (NG) twice-daily (morning and evening) for up to 28 days.
Patients were randomised within 48 hours of ictus to one of the IMP treatment groups by allocation of the appropriate, numbered, treatment pack. The treatment packs were pre-numbered according to a block balanced randomisation code. Patients were not discharged with the investigational medicine until 20 patients had completed dosing up to day 7 post ictus and the DSMB had issued their positive decision regarding dosing after discharge from tertiary care. After 35 patients had been treated in the study, the DSMB mandated a stratified randomisation schedule for further enrolment, with the strata defined by site and by baseline severity defined by WFNS score of 1- 3 or 4 & 5.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo to match SFX-01 300mg capsules
Investigational medicinal product code	Placebo for SFX-01
Other name	Placebo 300mg capsules
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

SFX-01 (300 mg) or matching placebo were taken orally as capsules or as a suspension via a nasogastric tube (NG) twice-daily (morning and evening) for up to 28 days.
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Number of subjects in period 1	SFX-01	Placebo
Started	54	51
Completed	47	42
Not completed	7	9
Adverse event, serious fatal	4	4
Consent withdrawn by subject	2	-
Treatment was no longer appropriate	-	1
Not specified	-	1
Lost to follow-up	1	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period

Reporting group description: -

Reporting group values	Treatment Period	Total	
Number of subjects	105	105	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age at study entry			
Units: years			
arithmetic mean	56		
standard deviation	± 12	-	
Gender categorical Units: Subjects			
Female	78	78	
Male	27	27	
Baseline weight (Kg)			
Weight (Kg) at baseline			
Units: Kg			
arithmetic mean	76		
standard deviation	± 19.1	-	

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who had taken at least one dose of study medication. This population was applied to all safety endpoints and pharmacokinetic data recorded in all patients.

Subject analysis set title	Intent-To-Treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who received at least one dose of study medication. Analyses of the TCD, mRS and GOSE endpoints were performed in both the PP and ITT populations with the PP population considered as primary. Other endpoints were initially analysed in the PP population and were to be analysed in the ITT population only if there was a meaningful discrepancy in the results of endpoints analysed in both populations (which there was not).

Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population consisted of all patients who received at least 10 doses of randomised treatment within the first 7 days of the first dose of study medication. However, there were 9 patients who were either known to have had (n=2), potentially had (n=3), or were associated with patients who had (n=4), a discrepancy in dispensing of randomised therapy and were therefore were excluded from the PP population. Analyses of the TCD, mRS and GOSE endpoints were performed in both the PP and ITT populations with the PP population considered as primary. Other endpoints were initially analysed in the PP population and were to be analysed in the ITT population only if there was a meaningful discrepancy in the results of endpoints analysed in both populations (which there was not).

Reporting group values	Safety population	Intent-To-Treat (ITT) population	Per Protocol (PP) population
Number of subjects	105	105	90
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age at study entry			
Units: years			
arithmetic mean	56	56	55.2
standard deviation	± 12	± 12	± 11.3
Gender categorical Units: Subjects			
Female	78	78	66
Male	27	27	24
Baseline weight (Kg)			
Weight (Kg) at baseline			
Units: Kg			
arithmetic mean	76	76	76.3
standard deviation	± 19.1	± 19.1	± 19.3

End points

End points reporting groups

Reporting group title	SFX-01
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who had taken at least one dose of study medication. This population was applied to all safety endpoints and pharmacokinetic data recorded in all patients.

Subject analysis set title	Intent-To-Treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who received at least one dose of study medication. Analyses of the TCD, mRS and GOSE endpoints were performed in both the PP and ITT populations with the PP population considered as primary. Other endpoints were initially analysed in the PP population and were to be analysed in the ITT population only if there was a meaningful discrepancy in the results of endpoints analysed in both populations (which there was not).

Subject analysis set title	Per Protocol (PP) population
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Primary: Per-protocol (PP) Maximum post-dose TCD middle cerebral artery (MCA) mean flow velocity (MFV)

End point title	Per-protocol (PP) Maximum post-dose TCD middle cerebral artery (MCA) mean flow velocity (MFV)

End point description:

Per Protocol population - primary endpoint analysis.
TCDs were performed by an experienced member of the medical physics or neuro-intensive care team, or other appropriately trained personnel who had otherwise carried out the same procedure on the same group of patients.

End point type	Primary

End point timeframe:

An initial TCD reading was to be taken within 48h of ictus. TCD readings were then to be taken 3 times a week on alternate days (according to standard care procedures) until at least until Day 7 post ictus and then until no longer clinically indicated.

End point values	SFX-01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	44		
Units: cm/s				
arithmetic mean (standard deviation)	131.9 (± 66.9)	121.8 (± 45.8)		

Statistical analyses

Statistical analysis title	ANOVA for the maximum post-dose TCD MCA-MFV - PP
Comparison groups	SFX-01 v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5448
Method	ANOVA
Parameter estimate	Ratio of GLS means
Point estimate	1.0458
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9032
upper limit	1.2108

Secondary: Per-protocol (PP) - Modified Rankin Scale score (mRS) - Day 90

End point title	Per-protocol (PP) - Modified Rankin Scale score (mRS) - Day 90

End point description:

The mRS is widely used as a functional outcome measure in stroke. The purpose of the Rankin Focused Assessment (RFA) is to assign patients to mRS grades in a systematic way. The assessment consists of sections corresponding to levels of disability among stroke survivors on the mRS.

End point type	Secondary

End point timeframe:

The Modified Rankin Scale (mRS) was recorded at Day 7, 28, 90 and 180 post-ictus, as well as at discharge.

End point values	SFX-01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	44		
Units: mRS score				
0 - No symptom at all	4	0		
1 - No significant disability	11	3		
2 - Slight Disability	12	26		
3 - Moderate disabilty	10	6		
4 - Moderately severe disability	2	3		
5 - Severe disability	1	1		

6 - Dead	3	1		

Statistical analyses

Statistical analysis title	PP - mRS Day 90 proportional odds analysis
Comparison groups	Placebo v SFX-01
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2675
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.598
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.699
upper limit	3.704

Secondary: Per-protocol (PP) - Glasgow Outcome Score Extended (GOSE) - Day 90

End point title	Per-protocol (PP) - Glasgow Outcome Score Extended (GOSE) - Day 90

End point description:

End point type	Secondary

End point timeframe:

The Glasgow Outcome Scale Extended (GOSE) was recorded at Day 28, 90 and 180 post-ictus.

End point values	SFX-01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	44		
Units: GOSE scale score				
8 - Upper good recovery	6	4		
7 - Lower good recovery	5	12		
6 - Upper moderate disability	11	8		
5 - Lower moderate disability	6	5		
4 - Upper severe disability	4	6		
3 - Lower severe disability	4	3		
2 - Vegetative state	0	1		
1 - Death	3	1		

Statistical analyses

Statistical analysis title	PP - GOSE Day 90 proportional odds analysis
Comparison groups	SFX-01 v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8341
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.917
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.406
upper limit	2.068

Secondary: Per-protocol (PP) - Subarachnoid haemorrhage outcomes tool (SAHOT) - Day 90

End point title	Per-protocol (PP) - Subarachnoid haemorrhage outcomes tool (SAHOT) - Day 90

End point description:

End point type	Secondary

End point timeframe:

The Subarachnoid Haemorrhage Outcomes Tool (SAHOT) was recorded at Day 28, 90 and 180 post-ictus.

End point values	SFX-01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	44		
Units: SAHOT (Category) raw score				
1 - Raw score 0-7	4	1		
2 - Raw score 8-17	6	8		
3 - Raw score 18-29	8	7		
4 - Raw score 30-42	5	8		
5 - Raw score 43-56	6	4		
6 - Raw score 57-73	5	3		
7 - Raw score 74-89	1	2		
8 - Raw score 90-112	1	0		

9 - Death	3	1		

Statistical analyses

Statistical analysis title	PP - SAHOT Day 90 proportional odds analysis
Comparison groups	SFX-01 v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.626
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.811
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.348
upper limit	1.882

Secondary: Per-protocol (PP) - Incidence of Delayed Cerebral Ischaemia (DCI)

End point title	Per-protocol (PP) - Incidence of Delayed Cerebral Ischaemia (DCI)

End point description:

End point type	Secondary

End point timeframe:

Delayed Cerebral Ischaemia (DCI) was defined as a new focal deficit or reduction in Glasgow Coma Scale ≥2 if not explained by other causes during the study (i.e. re-bleed, hydrocephalus, seizure, meningitis, sepsis or hyponatremia).

End point values	SFX-01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	44		
Units: Number of patients				
Yes	9	6		
No	37	38		

Statistical analyses

Statistical analysis title	PP - incidence of DCI proportional odds analysis
Comparison groups	SFX-01 v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3895
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.728
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	6.463

Secondary: Per-protocol (PP) - Length of acute hospital stay

End point title	Per-protocol (PP) - Length of acute hospital stay
End point description:	
End point type	Secondary
End point timeframe:	
Length of acute hospital stay was the time from ictus to discharge	

End point values	SFX-01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	44		
Units: Days				
arithmetic mean (full range (min-max))	21.8 (8 to 77)	21.1 (9 to 88)		

Statistical analyses

Statistical analysis title	PP-acute hospital stay proportional odds analysis
Comparison groups	SFX-01 v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6448
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.574
upper limit	1.411

Other pre-specified: Intent-to-treat (ITT) - Maximum post-dose TCD middle cerebral artery (MCA) mean flow velocity (MFV)

End point title	Intent-to-treat (ITT) - Maximum post-dose TCD middle cerebral artery (MCA) mean flow velocity (MFV)

End point description:

Intent to treat population - primary endpoint analysis.
TCDs were performed by an experienced member of the medical physics or neuro-intensive care team, or other appropriately trained personnel who had otherwise carried out the same procedure on the same group of patients.

End point type	Other pre-specified

End point timeframe:

An initial TCD reading was to be taken within 48 hours of ictus. Subsequent TCD readings were then taken three times a week on alternate days (according to standard care procedures). They were performed at least until Day 7 post ictus (± 1d) and then un

End point values	SFX-01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: cm/s				
arithmetic mean (standard deviation)	135.9 (± 67.9)	117.6 (± 45.5)		

Statistical analyses

Statistical analysis title	ANOVA for the maximum post-dose TCD MCA-MFV - ITT
Comparison groups	Placebo v SFX-01
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2738
Method	ANOVA
Parameter estimate	Ratio of GLS means
Point estimate	1.0803
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9398
upper limit	1.2417

Other pre-specified: Per-protocol (PP) Mean of 3 largest post-dose TCD middle cerebral artery (MCA) mean flow velocity (MFV)

End point title	Per-protocol (PP) Mean of 3 largest post-dose TCD middle cerebral artery (MCA) mean flow velocity (MFV)

End point description:

Per Protocol population - supplementary TCD endpoint analysis.
TCDs were performed by an experienced member of the medical physics or neuro-intensive care team, or other appropriately trained personnel who had otherwise carried out the same procedure on the same group of patients.

End point type	Other pre-specified

End point timeframe:

An initial TCD reading was to be taken within 48h of ictus. TCD readings were then to be taken 3 times a week on alternate days (according to standard care procedures) until at least until Day 7 post ictus and then until no longer clinically indicated.

End point values	SFX-01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	46		
Units: cm/s				
arithmetic mean (standard deviation)	116.8 (± 61.3)	108.7 (± 42.1)		

Statistical analyses

Statistical analysis title	ANOVA mean of 3 largest post-dose TCD MCA-MFV - PP
Comparison groups	SFX-01 v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7077
Method	ANOVA
Parameter estimate	Ratio of GLS means
Point estimate	1.0282
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8874
upper limit	1.1915

Other pre-specified: Per protocol (PP) - Maximum post-dose TCD Lindergaard ratio

End point title	Per protocol (PP) - Maximum post-dose TCD Lindergaard ratio

End point description:

Per Protocol population - supplementary TCD endpoint analysis.
TCDs were performed by an experienced member of the medical physics or neuro-intensive care team, or other appropriately trained personnel who had otherwise carried out the same procedure on the same group of patients.

End point type	Other pre-specified

End point timeframe:

An initial TCD reading was to be taken within 48h of ictus. TCD readings were then to be taken 3 times a week on alternate days (according to standard care procedures) until at least until Day 7 post ictus and then until no longer clinically indicated.

End point values	SFX-01	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	44		
Units: ratio				
arithmetic mean (standard deviation)	3.3 (± 1.5)	3.1 (± 1.2)		

Statistical analyses

Statistical analysis title	ANOVA Maximum post-dose Lindergaard Ratio - PP
Comparison groups	SFX-01 v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4609
Method	ANOVA
Parameter estimate	Ratio of GLS means
Point estimate	1.0606
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9053
upper limit	1.2425

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs/SAEs were to be reported from the time a signed patient informed consent form was obtained and pre-first dose study treatment assessments performed until the end of study/early termination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Safety population

Reporting group description:

All randomised patients who had taken at least one dose of study medication (SFX-01 or placebo).

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 105 (40.95%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	6		
Vascular disorders			
Cerebral ischaemia			
subjects affected / exposed	7 / 105 (6.67%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Vasospasm			
subjects affected / exposed	9 / 105 (8.57%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Delayed ischaemic neurological deficit			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Subdural haemorrhage				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aneurysm				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cerebral ischaemia				
subjects affected / exposed	7 / 105 (6.67%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 3			
Atrial fibrillation				
subjects affected / exposed	3 / 105 (2.86%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Headache				
subjects affected / exposed	2 / 105 (1.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	2 / 105 (1.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cerebral infarction				
subjects affected / exposed	2 / 105 (1.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			

Cerebral ventricle dilatation				
subjects affected / exposed	2 / 105 (1.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Brain abscess				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
IIIrd nerve paralysis				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
IVth nerve paralysis				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General disorders and administration site conditions				
Device related infection				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection			
subjects affected / exposed	9 / 105 (8.57%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 1		
Pulmonary oedema			
subjects affected / exposed	4 / 105 (3.81%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
CNS ventriculitis			
subjects affected / exposed	4 / 105 (3.81%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 105 (3.81%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Lower respiratory tract infection			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device malfunction			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 105 (96.19%)		
Investigations			
Blood triglycerides increased			
subjects affected / exposed	5 / 105 (4.76%)		
occurrences (all)	5		
Vascular disorders			
Vasospasm			
subjects affected / exposed	20 / 105 (19.05%)		
occurrences (all)	20		
Cerebral ischaemia			
subjects affected / exposed	8 / 105 (7.62%)		
occurrences (all)	8		
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	15 / 105 (14.29%)		
occurrences (all)	15		
Headache			
subjects affected / exposed	6 / 105 (5.71%)		
occurrences (all)	6		
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	8 / 105 (7.62%)		
occurrences (all)	8		

Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 10 / 105 (9.52%) 10 7 / 105 (6.67%) 7		
Respiratory, thoracic and mediastinal disorders Lower respiratory tract infection subjects affected / exposed occurrences (all) Pulmonary oedema subjects affected / exposed occurrences (all)	 22 / 105 (20.95%) 22 4 / 105 (3.81%) 4		
Infections and infestations CNS ventriculitis subjects affected / exposed occurrences (all)	 6 / 105 (5.71%) 6		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) Hypocholesterolaemia subjects affected / exposed occurrences (all) Hypernatraemia subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all)	 28 / 105 (26.67%) 28 29 / 105 (27.62%) 29 14 / 105 (13.33%) 14 7 / 105 (6.67%) 7 6 / 105 (5.71%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2016	Various protocol clarifications and administrative updates.
23 August 2016	Temporary halt to patient recruitment was required because of a short term interruption in the SFX-01/placebo IMP supply to the study site.
10 February 2017	Additional of new study site/investigator and various protocol clarifications regarding alternate day timing of TCD and other assessments post-dose, removal of requirement for fasting safety bloods (as not practical), removal of urine dipstick testing and clarification of use of routine safety test results for the study.
17 March 2017	A temporary halt of trial was put in place to allow permanent corrective and preventive actions to be implemented at site before restart, following investigation into potential SFX-01/placebo dispensing errors for 9 patients, who were either known to have had (n=2), potentially had (n=3), or were associated with patients who had (n=4), a discrepancy in dispensing of randomised therapy; these patients were excluded from the PP analysis population.
27 June 2017	Update to SFX-01/placebo study drug kits/bottle labelling and submission of IMPD v8.
10 August 2017	Restart of study after temporary halt.
25 September 2017	Submission of SFX-01 Investigator's Brochure v7.
04 January 2018	Submission of study Protocol v6 and revised SFX-01/placebo study drug labels.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This summary provides an overview of the key study results.

Notes: