Clinical trial results:
A Phase IIa: single ascending dose safety, tolerability and pharmacokinetic study of NicaPlant® in aneurysmal subarachnoid haemorrhage patients undergoing aneurysm clipping

Summary

EudraCT number	2016-004521-17
Trial protocol	AT
Global end of trial date	09 January 2019

Results information

Result version number	v1 (current)
This version publication date	01 March 2020
First version publication date	01 March 2020

Trial information

Trial identification

Sponsor protocol code	BIT-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	BIT Pharma GmbH
Sponsor organisation address	Leonhardstrasse 109, Graz, Austria, 8010
Public contact	Dr. Tiziana Adage, BIT Pharma GmbH, tiziana.adage@bit-pharma.com
Scientific contact	Dr. Tiziana Adage, BIT Pharma GmbH, tiziana.adage@bit-pharma.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	01 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2019
Global end of trial reached?	Yes
Global end of trial date	09 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety and tolerability of single ascending doses (as number of implants/patient) of local nicardipine application via polymers (NicaPlant®).

Protection of trial subjects:

A Data Safety Monitoring Board (DSMB) was set-up to monitor safety throughout the trial period.
The DSMB performed dose escalation reviews between cohorts and prepared written reports advising the steering committee to progress to the next higher dose, to implement modifications or to terminate the study.
The DSMB also performed interim meetings in case of the occurance of a SUSAR during the trial.

Background therapy: -

Evidence for comparator:

The comparator used in the clinical trial was nimodipine, of which 60 mg were administered every 4 hours. This treatment is the standard of care for patients suffering from an aneurysmal subarachnoid haemorrhage for prevention of ischemic neurological deficit following cerebral vasospasm.

Actual start date of recruitment	25 April 2018
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	Austria: 11
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	12
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period of cohort 1: 12APR2018 - 28APR2018 (Austria)
Recruitment period of cohort 2: 25MAY2018 - 27JUN2018 (Austria)
Recruitment period of cohort 3: 19JUL2018 - 24SEP2018 (Austria and Germany)
Recruitment period of cohort 4: 22OCT2018 - 20DEC2018 (Austria and Germany)

Pre-assignment

Screening details:

The screening period was between 0 and 48 hours after aneurysm rupture.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Control patients received 60 mg of orally administered nimodipine every 4 hours for 21 days. They did not receive the NicaPlant® implants.

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

Dosage and administration details:

60 mg every 4 hours for 21 days

Arm title	3 Implants

Arm description:

3 Implants patients received 3 NicaPlant® implants at aneurysm clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.

Arm type	Experimental
Investigational medicinal product name	NicaPlant®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Implantation

Dosage and administration details:

3 NicaPlant® implants with 4 mg nicardipine load each.
NicaPlant® is a biodegradable, rod shaped modified release formulation in implant form.

Investigational medicinal product name	Placebo-Nimodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Enteral use

Dosage and administration details:

60 mg every 4 hours for 21 days

Arm title	6 Implants

Arm description:

6 Implants patients received 6 NicaPlant® implants at aneurysm clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.

Arm type	Experimental
Investigational medicinal product name	NicaPlant®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Implantation

Dosage and administration details:

6 NicaPlant® implants with 4 mg nicardipine load each.
NicaPlant® is a biodegradable, rod shaped modified release formulation in implant form.

Investigational medicinal product name	Placebo-Nimodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Enteral use

Dosage and administration details:

60 mg every 4 hours for 21 days

Arm title	10 Implants

Arm description:

10 Implants patients received 10 NicaPlant® implants at aneurysm clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.

Arm type	Experimental
Investigational medicinal product name	NicaPlant®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Implantation

Dosage and administration details:

10 NicaPlant® implants with 4 mg nicardipine load each.
NicaPlant® is a biodegradable, rod shaped modified release formulation in implant form.

Investigational medicinal product name	Placebo-Nimodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Enteral use

Dosage and administration details:

60 mg every 4 hours for 21 days

Arm title	13 Implants

Arm description:

13 Implants patients received 13 NicaPlant® implants at aneurysm clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.

Arm type	Experimental

Investigational medicinal product name	NicaPlant®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Implantation

Dosage and administration details:

13 NicaPlant® implants with 4 mg nicardipine load each.
NicaPlant® is a biodegradable, rod shaped modified release formulation in implant form.

Investigational medicinal product name	Placebo-Nimodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Enteral use

Dosage and administration details:

60 mg every 4 hours for 21 days

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: No placebo implants were implanted due to ethical reasons. It was for this reason not possible to blind the surgeon/investigator of the trial. The trial was conducted as a single blinded trial, i. e. the subject was blinded.
However, the trial was conducted maintaining the blinding as much as possible. Therefore, besides the subjects, also the monitor, data analyst, carers and assessor of DSA and CT were blinded.

Number of subjects in period 1	Control	3 Implants	6 Implants
Started	4	2	2
Completed	4	2	2

Number of subjects in period 1	10 Implants	13 Implants
Started	3	3
Completed	3	3

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
Adults (18-64 years)	12	12	
From 65-84 years	2	2	
Gender categorical Units: Subjects			
Female	10	10	
Male	4	4	

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Control patients received 60 mg of orally administered nimodipine every 4 hours for 21 days. They did not receive the NicaPlant® implants.	
Reporting group title	3 Implants
Reporting group description:	
3 Implants patients received 3 NicaPlant® implants at aneurysm clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.	
Reporting group title	6 Implants
Reporting group description:	
6 Implants patients received 6 NicaPlant® implants at aneurysm clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.	
Reporting group title	10 Implants
Reporting group description:	
10 Implants patients received 10 NicaPlant® implants at aneurysm clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.	
Reporting group title	13 Implants
Reporting group description:	
13 Implants patients received 13 NicaPlant® implants at aneurysm clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.	

Primary: Safety and tolerability of single ascending doses of NicaPlant® by drug related adverse event reporting

End point title	Safety and tolerability of single ascending doses of NicaPlant® by drug related adverse event reporting[1]
End point description:	
End point type	Primary
End point timeframe:	
continuouse over 21 days post-aneurysm rupture	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the small number of patients in each treatment arm, the results were only descriptively summerized and no formal statistical analysis was done.

End point values	Control	3 Implants	6 Implants	10 Implants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	2	3
Units: drug related adverse events				
Drug related adverse events	2	0	0	1
Drug related serious adverse events	0	0	0	3

End point values	13 Implants			

Subject group type	Reporting group			
Number of subjects analysed	3			
Units: drug related adverse events				
Drug related adverse events	1			
Drug related serious adverse events	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter nicardipine in plasma

End point title	Pharmacokinetic parameter nicardipine in plasma[2]

End point description:

End point type	Secondary

End point timeframe:

21 days post implantation of NicaPlant®

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Pharmacokinetic samples were only analysed in the treatment arms. The control arm did not receive NicaPlant® of which the pharmacokinetic profile was analysed.

End point values	3 Implants	6 Implants	10 Implants	13 Implants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[3]	0[4]	3	3
Units: Cmax (ng/mL)				
arithmetic mean (standard deviation)	()	()	1.903 (± 0.51)	2.366 (± 1.372)

Notes:

[3] - Subject number too small.

[4] - Subject number too small.

Attachments (see zip file)	Plasma Nicardipine/PK Plasma Graph.pdf Plasma Nicardipine/PK Plasma Table.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter nicardipine in cerebrospinal fluid

End point title	Pharmacokinetic parameter nicardipine in cerebrospinal fluid[5]

End point description:

Cmax of the individual participant of the arm with the highest Cmax

End point type	Secondary

End point timeframe:

21 days post implantation of NicaPlant®

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic samples were only analysed in the treatment arms. The control arm did not receive NicaPlant® of which the pharmacokinetic profile was analysed.

End point values	3 Implants	6 Implants	10 Implants	13 Implants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[6]	1[7]	1[8]	0[9]
Units: Cmax (ng/ml)				
number (not applicable)	23.5	207	147	

Notes:

[6] - Tmax = day 10
The concentration of the second participant in the arm was below the detection limit.
[7] - Tmax = day 14
The Cmax of the second participant of the arm was 117 ng/mL (Tmax = day 6).
[8] - Tmax = day 0
Only one participant in the arm had an EVD.
[9] - 1 patient with samples. Values below det. limit probably due to loss of drug in op 1 day after admin

Attachments (see zip file)	CSF Nicardipine/PK CSF Graph.pdf

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of moderate or severe cerebral angiographic vasospasm at 8±1 days after aneurysm rupture

End point title	Incidence of moderate or severe cerebral angiographic vasospasm at 8±1 days after aneurysm rupture

End point description:

Incidence of moderate or severe cerebral angiographic vasospasm assessed by digital subtraction angiography (DSA) or CT angiography (CTA) at 8±1 days after aneurysm rupture, at the discretion of the physician and according to the institutional protocol. DSA or CTA were only performed if medically indicated, where angiographic vasospasm was defined as a ≥33% reduction in diameter in at least one vessel segment by comparison to preoperative (pre NicaPlant® implantation) angiography. If the patient develops clinical or sonographic changes suggestive of vasospasm prior to day 8, an angiogram was performed to confirm the vasospasm and the angiographic measurement replaced the one scheduled at day 8±1.

End point type	Other pre-specified

End point timeframe:

8±1 days after aneurysm rupture or earlier if the patient develops clinical or sonographic changes suggestive of vasospasm.

End point values	Control	3 Implants	6 Implants	10 Implants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	1[10]	2	3
Units: moderate or severe vasospasm				
≥33% to ≤66% lumen reduction	0	0	0	0
>66% lumen reduction	2	1	0	0

Notes:
[10] - One patient was not assessable because only a DSA of the left carotis interna (LCI) was available.

End point values	13 Implants			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: moderate or severe vasospasm				
≥33% to ≤66% lumen reduction	1			
>66% lumen reduction	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of vasospasm-related morbidity/mortality within 21 days post-aneurysm rupture

End point title	Incidence of vasospasm-related morbidity/mortality within 21 days post-aneurysm rupture

End point description:

End point type	Other pre-specified

End point timeframe:
within 21 days post-aneurysm rupture

End point values	Control	3 Implants	6 Implants	10 Implants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	2	3
Units: Vasospasm-related morbidity/mortality				
morbidity	0	1	0	1
mortality	0	0	0	0

End point values	13 Implants			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Vasospasm-related morbidity/mortality				
morbidity	1			
mortality	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Need for anti-vasospasm rescue therapy within 21 days post-aneurysm rupture

End point title	Need for anti-vasospasm rescue therapy within 21 days post-aneurysm rupture

End point description:

End point type	Other pre-specified

End point timeframe:

within 21 days post-aneurysm rupture

End point values	Control	3 Implants	6 Implants	10 Implants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	2	3
Units: anti-vasospasm therapy	2	1	0	1

End point values	13 Implants			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: anti-vasospasm therapy	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of new cerebral infarcts at day 14±1 post-aneurysm rupture

End point title	Incidence of new cerebral infarcts at day 14±1 post-aneurysm rupture

End point description:

Incidence of new cerebral infarcts on CT scan performed at day 14±1 post-aneurysm rupture versus post-treatment (i.e. post clip ligation and NicaPlant Implantation) CT scan.

End point type	Other pre-specified

End point timeframe:

at day 14±1 post-aneurysm rupture

End point values	Control	3 Implants	6 Implants	10 Implants
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	2	3
Units: New cerebral infarcts	1	0	1	0

End point values	13 Implants			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: New cerebral infarcts	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 25APR2018 - 08FEB2019	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Control
Reporting group description: Control patients received 60 mg of orally administered nimodipine every 4 hours for 21 days. They did not receive the NicaPlant implants.	
Reporting group title	3 Implants
Reporting group description: 3 Implants patients received 3 NicaPlant implants at clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.	
Reporting group title	6 Implants
Reporting group description: 6 Implants patients received 6 NicaPlant implants at clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.	
Reporting group title	10 Implants
Reporting group description: 10 Implants patients received 10 NicaPlant implants at clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.	
Reporting group title	13 Implants
Reporting group description: 13 Implants patients received 13 NicaPlant implants at clipping. They also received 60 mg of placebo-nimodipine every 4 hours for 21 days.	

Serious adverse events	Control	3 Implants	6 Implants
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
CSF culture positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Cerebral artery occlusion			

subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral vasoconstriction			
subjects affected / exposed	2 / 4 (50.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	10 Implants	13 Implants	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
CSF culture positive			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Cerebral artery occlusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral vasoconstriction			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control	3 Implants	6 Implants
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	2 / 2 (100.00%)	2 / 2 (100.00%)
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Postoperative wound complication			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	1 / 4 (25.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Tracheostomy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Ventricular drainage			

subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Diplopia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 4 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Hydrocephalus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Intracranial pressure increased			
subjects affected / exposed	2 / 4 (50.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Cerebral vasoconstriction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Thrombocytosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Respiratory, thoracic and mediastinal disorders			
Hiccups			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Upper respiratory fungal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Fungal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vaginal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
CNS ventriculitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 2 (100.00%)	1 / 2 (50.00%)
occurrences (all)	0	2	1
Product issues			
Device failure			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	10 Implants	13 Implants	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	3 / 3 (100.00%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Hepatic enzyme increased			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Postoperative wound complication			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Tracheostomy			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Ventricular drainage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Diplopia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Hydrocephalus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Intracranial pressure increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Cerebral vasoconstriction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Thrombocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Hiccups			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Upper respiratory fungal infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	

Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Fungal infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Vaginal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
CNS ventriculitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Product issues			
Device failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	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

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

Due to the small number of patients in each treatment arm, the results were only descriptively summerized and no formal statistical analysis was done.
CSF analysis was further limited because CSF samples were only taken of patients who had an EVD.

Notes: