Clinical trial results:
Phase I/IIa study of intratumoral/intracerebral or intravenous/intracerebral administration of Parvovirus H-1 (ParvOryx) in patients with progressive primary or recurrent glioblastoma multiforme

Summary

EudraCT number	2011-000572-33
Trial protocol	DE
Global end of trial date	08 May 2015

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	CTR synopsis (20160412_ParvOryx01_Synopsis_sign.pdf)

Trial information

Trial identification

Sponsor protocol code	ParvOryx01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01301430
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oryx GmbH & Co. KG
Sponsor organisation address	Marktplatz 1, Baldham, Germany, 85598
Public contact	Dr. Bernard Huber (CEO), Oryx GmbH & Co. KG, +49 8106213110, info@oryx-medicine.com
Scientific contact	Dr. Ottheinz Krebs (COO), Oryx GmbH & Co. KG, +49 8106213110, info@oryx-medicine.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	15 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2015
Global end of trial reached?	Yes
Global end of trial date	08 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Local and systemic safety and tolerability of the IMP,
- Maximum tolerated dose (MTD) of the IMP,
- Viremia following administration of the IMP,
- Virus shedding/persistence following administration of the IMP.

Protection of trial subjects:

Sequential enrolment
Sequential dose escalation
Monitoring of safety data by Data Safety Monitoring Board (DSMB)
Hospitalisation during and after administration of the IMP

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 October 2011
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	Germany: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	13
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients were recruited in Germany; Recruitment period: overall first subject enrolled: 24.10.2011, overall last subject enrolled: 23.01.15, overall last visit of the last subject: 08.05.15.

Pre-assignment

Screening details:

Screening was performed within 14 days before the first dose of IMP. Main eligibility criteria: confirmation of disease, safety parameters (physical examination, vital signs, ECG, laboratory evaluations). All screened subjects enrolled the trial (no screening failures).

Period 1

Period 1 title	Screening
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 Level 1

Arm description:

Administration of IMP at the total dose of 1E06. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use, Intracerebral use

Dosage and administration details:

Total dose of 1E06 pfu: 5E05 pfu on Day 1 intratumorally (via intratumoral catheter) over 15 minutes, 5E05 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Arm title	Group 1 Level 2

Arm description:

Administration of IMP at the total dose of 5E07. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use, Intracerebral use

Dosage and administration details:

Total dose of 5E07 pfu: 2.5E07 pfu on Day 1 intratumorally (via intratumoral catheter) over 15 minutes, 2.5E07 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes.

Arm title	Group 1 Level 3

Arm description:

Administration of IMP at the total dose of 1E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use, Intracerebral use

Dosage and administration details:

Total dose of 1E09 pfu: 5E08 pfu on Day 1 intratumorally (via intratumoral catheter) over 15 minutes, 5E08 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Arm title	Group 2 Level 2

Arm description:

Administration of IMP at the total dose of 5E07. Day 1-5: 10% of the total dose intravenously, Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Intracerebral use

Dosage and administration details:

Total dose of 5E07 pfu: Daily 5E06 pfu on Days 1 to 5 intravenously over 2 hours, 2.5E07 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Arm title	Group 2 Level 3

Arm description:

Administration of IMP at the total dose of 1E09. Day 1-5: 10% of the total dose intravenously, Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Intracerebral use

Dosage and administration details:

Total dose of 1E09 pfu: Daily 1E08 pfu on Days 1 to 5 intravenously over 2 hours, 5E08 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Arm title	Group 3 Level 4

Arm description:

Administration of IMP at the total dose of 5E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental

Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use, Intracerebral use

Dosage and administration details:

Total dose of 5E09 pfu: 2.5E09 pfu on Day 1 intratumorally (via intratumoral catheter) over 15 minutes, 2.5E09 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Number of subjects in period 1	Group 1 Level 1	Group 1 Level 2	Group 1 Level 3
Started	3	3	3
Completed	3	3	3

Number of subjects in period 1	Group 2 Level 2	Group 2 Level 3	Group 3 Level 4
Started	3	3	3
Completed	3	3	3

Period 2

Period 2 title	Treatment & Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 Level 1

Arm description:

Administration of IMP at the total dose of 1E06. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use, Intracerebral use

Dosage and administration details:

Total dose of 1E06 pfu: 5E05 pfu on Day 1 intratumorally (via intratumoral catheter) over 15 minutes, 5E05 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Arm title	Group 1 Level 2

Arm description:

Administration of IMP at the total dose of 5E07. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use, Intracerebral use

Dosage and administration details:

Total dose of 5E07 pfu: 2.5E07 pfu on Day 1 intratumorally (via intratumoral catheter) over 15 minutes, 2.5E07 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes.

Arm title	Group 1 Level 3

Arm description:

Administration of IMP at the total dose of 1E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use, Intracerebral use

Dosage and administration details:

Total dose of 1E09 pfu: 5E08 pfu on Day 1 intratumorally (via intratumoral catheter) over 15 minutes, 5E08 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Arm title	Group 2 Level 2

Arm description:

Administration of IMP at the total dose of 5E07. Day 1-5: 10% of the total dose intravenously, Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Intracerebral use

Dosage and administration details:

Total dose of 5E07 pfu: Daily 5E06 pfu on Days 1 to 5 intravenously over 2 hours, 2.5E07 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Arm title	Group 2 Level 3

Arm description:

Administration of IMP at the total dose of 1E09. Day 1-5: 10% of the total dose intravenously, Day 10:

50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Intracerebral use

Dosage and administration details:

Total dose of 1E09 pfu: Daily 1E08 pfu on Days 1 to 5 intravenously over 2 hours, 5E08 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Arm title	Group 3 Level 4

Arm description:

Administration of IMP at the total dose of 5E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Arm type	Experimental
Investigational medicinal product name	ParvOryx
Investigational medicinal product code	ParvOryx
Other name	Parvovirus H-1 in visipaque/ringer solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use, Intracerebral use

Dosage and administration details:

Total dose of 5E09 pfu: 2.5E09 pfu on Day 1 intratumorally (via intratumoral catheter) over 15 minutes, 2.5E09 pfu on Day 10 intratumorally (direct injection at several locations of the resection wall) over 15-30 minutes

Number of subjects in period 2	Group 1 Level 1	Group 1 Level 2	Group 1 Level 3
Started	3	3	3
Completed	3	3	3

Number of subjects in period 2	Group 2 Level 2	Group 2 Level 3	Group 3 Level 4
Started	3	3	3
Completed	3	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Group 1 Level 1
Reporting group description:	
Administration of IMP at the total dose of 1E06. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 1 Level 2
Reporting group description:	
Administration of IMP at the total dose of 5E07. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 1 Level 3
Reporting group description:	
Administration of IMP at the total dose of 1E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 2 Level 2
Reporting group description:	
Administration of IMP at the total dose of 5E07. Day 1-5: 10% of the total dose intravenously, Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 2 Level 3
Reporting group description:	
Administration of IMP at the total dose of 1E09. Day 1-5: 10% of the total dose intravenously, Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 3 Level 4
Reporting group description:	
Administration of IMP at the total dose of 5E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	

Reporting group values	Group 1 Level 1	Group 1 Level 2	Group 1 Level 3
Number of subjects	3	3	3
Age categorical			
Age categorical per group			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	2	3
From 65-84 years	0	1	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	51.6	62.2	45.6
standard deviation	± 10.1	± 8.5	± 1.8

Gender categorical			
Gender characteristics per group			
Units: Subjects			
Female	0	1	1
Male	3	2	2

Reporting group values	Group 2 Level 2	Group 2 Level 3	Group 3 Level 4
Number of subjects	3	3	3
Age categorical			
Age categorical per group			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	2	1
From 65-84 years	1	1	2
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	60.3	57.8	69.7
standard deviation	± 11.4	± 7.6	± 7.2
Gender categorical			
Gender characteristics per group			
Units: Subjects			
Female	0	1	1
Male	3	2	2

Reporting group values	Total		
Number of subjects	18		
Age categorical			
Age categorical per group			
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)	13		
From 65-84 years	5		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical			
Gender characteristics per group			
Units: Subjects			
Female	4		
Male	14		

Subject analysis sets

Subject analysis set title	All groups, all dose levels
Subject analysis set type	Full analysis

Subject analysis set description:

Result pooled for all groups and all dose levels

Reporting group values	All groups, all dose levels		
Number of subjects	18		
Age categorical			
Age categorical per group			
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)	13		
From 65-84 years	5		
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Gender characteristics per group			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Group 1 Level 1
Reporting group description:	
Administration of IMP at the total dose of 1E06. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 1 Level 2
Reporting group description:	
Administration of IMP at the total dose of 5E07. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 1 Level 3
Reporting group description:	
Administration of IMP at the total dose of 1E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 2 Level 2
Reporting group description:	
Administration of IMP at the total dose of 5E07. Day 1-5: 10% of the total dose intravenously, Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 2 Level 3
Reporting group description:	
Administration of IMP at the total dose of 1E09. Day 1-5: 10% of the total dose intravenously, Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 3 Level 4
Reporting group description:	
Administration of IMP at the total dose of 5E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 1 Level 1
Reporting group description:	
Administration of IMP at the total dose of 1E06. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 1 Level 2
Reporting group description:	
Administration of IMP at the total dose of 5E07. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 1 Level 3
Reporting group description:	
Administration of IMP at the total dose of 1E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 2 Level 2
Reporting group description:	
Administration of IMP at the total dose of 5E07. Day 1-5: 10% of the total dose intravenously, Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 2 Level 3
Reporting group description:	
Administration of IMP at the total dose of 1E09. Day 1-5: 10% of the total dose intravenously, Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).	
Reporting group title	Group 3 Level 4

Reporting group description:

Administration of IMP at the total dose of 5E09. Day 1: 50% of the total dose intratumorally (via catheter), Day 10: 50% of the total dose intracerebrally (direct injection at several locations in resection wall).

Subject analysis set title	All groups, all dose levels
Subject analysis set type	Full analysis

Subject analysis set description:

Result pooled for all groups and all dose levels

Primary: Number of adverse events

End point title	Number of adverse events[1]

End point description:

End point type	Primary

End point timeframe:

Between first administration of the IMP and the last study visit (at month 6)

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: Only descriptive statistical methods were employed in this trial (no confirmatory statistics)

End point values	Group 1 Level 1	Group 1 Level 2	Group 1 Level 3	Group 2 Level 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: unit	19	32	25	28

End point values	Group 2 Level 3	Group 3 Level 4	All groups, all dose levels	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	18	
Units: unit	23	58	185	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival at 6 months (6-m-PFS)

End point title	Progression-free survival at 6 months (6-m-PFS)

End point description:

End point type	Secondary

End point timeframe:

Between surgery and last study visit (at 6 months)

End point values	Group 1 Level 1	Group 1 Level 2	Group 1 Level 3	Group 2 Level 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: percent				
number (not applicable)	66.6	33.3	0.0	33.3

End point values	Group 2 Level 3	Group 3 Level 4	All groups, all dose levels	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	18	
Units: percent				
number (not applicable)	0	33.3	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival at 6 months (6-m-OS)

End point title	Overall survival at 6 months (6-m-OS)

End point description:

End point type	Secondary

End point timeframe:

Between surgery and the last study visit (at month 6)

End point values	Group 1 Level 1	Group 1 Level 2	Group 1 Level 3	Group 2 Level 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: percent				
number (not applicable)	100	66.6	100	66.6

End point values	Group 2 Level 3	Group 3 Level 4	All groups, all dose levels	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	18	
Units: percent				
number (not applicable)	100	0.0	72	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were documented between 1st administration of the IMP and the last follow-up visit (approx. 6 months after 1st administration of the IMP)	
Adverse event reporting additional description:	
Adverse events were asked for at each contact with trial participants	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Group 1 Level 1
Reporting group description:	
Group 1 Level 1	
Reporting group title	Group 1 Level 2
Reporting group description:	
Group 1 Level 2	
Reporting group title	Group 1 Level 3
Reporting group description:	
Group 1 Level 3	
Reporting group title	Group 2 Level 2
Reporting group description:	
Group 2 Level 2	
Reporting group title	Group 2 Level 3
Reporting group description:	
Group 2 Level 3	
Reporting group title	Group 3 Level 4
Reporting group description:	
Group 3 Level 4	

Serious adverse events	Group 1 Level 1	Group 1 Level 2	Group 1 Level 3
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	1 / 3 (33.33%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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			
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Cerebrospinal fistula			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural hygroma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Hydrocephalus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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			
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cystitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urosepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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	Group 2 Level 2	Group 2 Level 3	Group 3 Level 4
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 3 (66.67%)
number of deaths (all causes)	2	0	2

number of deaths resulting from adverse events	1	0	2
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Upper limb fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Fall			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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			
Cerebrospinal fistula			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Subdural hygroma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Depressed level of consciousness			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Hydrocephalus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Epilepsy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Urosepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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

Product issues			
Device occlusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2

Frequency threshold for reporting non-serious adverse events: 2.5 %

Non-serious adverse events	Group 1 Level 1	Group 1 Level 2	Group 1 Level 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
occurrences (all)	0	3	2
Procedural complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	2	2
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 3 (66.67%)	3 / 3 (100.00%)	0 / 3 (0.00%)
occurrences (all)	2	4	0
Epilepsy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	8
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	2 / 3 (66.67%)
occurrences (all)	2	2	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Group 2 Level 2	Group 2 Level 3	Group 3 Level 4
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Procedural complication			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 3 (33.33%)	3 / 3 (100.00%)	2 / 3 (66.67%)
occurrences (all)	2	5	2
Epilepsy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	1 / 3 (33.33%)
occurrences (all)	1	2	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2012	This amendment (approved by the PEI on 22nd February 2012 and by the EC on 7th February 2012) concerned the timing of the determinations of viral shedding and antibody determinations, and also regulated the exact timing of the Day 28 visit such as to avoid difficulties arising through week-ends etc.
13 September 2012	This amendment (approved by the PEI on 13th September 2012 and by the EC on 27th September 2012) concerned the up-dating of the IB only.
13 May 2013	This amendment (approved by the PEI on 2nd May 2013 and by the EC on 10th April 2013) was planned before the start of the trial and was aimed at informing the higher federal authority (PEI) and the responsible EC on the safety-related findings obtained from Group I. On the basis of these findings the sponsor additionally proposed the following protocol changes: (i) a reduction in the intervals between inclusions of individual subjects in a given dose group; these intervals were no longer considered necessary, as there had been no safety issues; (ii) an increase of the highest dose (introduction of Group III); and (iii) an increase in the number of blood samples required for viral genome analysis. However, only changes (ii) and (iii) were approved. These were implemented; change (i) was not.
15 July 2013	This amendment (approved by the PEI on 15th July 2013 and by the EC on 19th July 2013) introduced parallel, rather than serial, treatment of patients in Groups II and III , again as there had been no relevant safety issues.
04 October 2013	This amendment (approved by the PEI on 4th October 2013 and by the EC on 16 September 2013) concerned the up-dating of the IB and IMPD.
14 November 2013	This amendment (approved by the PEI on 14th November 2013 and by the EC on 28th October 2013) allowed flexibility in respect of the minimum intervals between inclusions of the subjects of the 3rd dose level in Group II on the basis of pharmacokinetic data.
14 March 2014	This amendment (confirmed by the PEI on 25th March 2014; EC approval was not required) instituted a temporary halt to recruitment because of a SUSAR.
29 June 2014	This amendment (approved by the PEI on 29th June 2014 and by the EC on 22nd June 2014) ended the temporary halt to recruitment instituted by Amendment no. 7.
30 September 2014	This amendment (approved by the PEI on 30th September 2014 and by the EC on the same day) concerned the up-dating of the IB only.
18 December 2014	This amendment (approved by the PEI on 18th December 2014; EC approval was not necessary) concerned the up-dating of the IMPD only.
08 May 2015	This amendment (approved by the PEI on 8th May 2015; EC approval was not necessary) concerned the up-dating of the IMPD only.
08 May 2015	This amendment (approved by the PEI on 1st July 2015; EC approval was not necessary) concerned the up-dating of the IMPD only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 February 2014	The trial was interrupted due to a SUSAR (main diagnoses: hydrocephalus and decreased consciousness). Since the causality between the event and the IMP could not be excluded the case was reported to the competent authority and the leading ethics committee. After an intense discussion between involved parties, the sponsor decided to temporary stop patients' recruitment until clarification of the case. Based a thorough evaluation of different aspects of the event, performed by the sponsor in cooperation with the competent authority, no change in the positive risk-benefit-assessment of the trial and of the IMP was concluded. Hence, the trial recruitment was resumed. No similar adverse events were ever since observed.	29 July 2014

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22436661

http://www.ncbi.nlm.nih.gov/pubmed/28967558