



Clinical trial results:

Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (OBI-1) in the Treatment of Acquired Hemophilia A Due to Autoimmune Anti-Factor VIII Inhibitory Antibodies

Summary

EudraCT number	2011-000181-34
Trial protocol	GB SE DE HU IT
Global end of trial date	09 October 2013

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	OBI-1-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01178294
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxalta Innovations GmbH
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, 1221
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Sponsor organisation name	Baxalta US Inc.
Sponsor organisation address	One Baxter Way, Westlake Village, United States, 91362
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.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	27 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2013
Global end of trial reached?	Yes
Global end of trial date	09 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Studies OBI-1-301 and extended protocol OBI-1-301a were to evaluate the efficacy of OBI-1 for the treatment of serious bleeding events in subjects with acquired hemophilia with autoimmune inhibitory antibodies to human factor VIII. The primary efficacy outcome was the proportion of serious bleeding events responsive to OBI-1 therapy at 24 hours after the initiation of treatment determined using a well-defined, ordinal scale (effective - partially effective - poorly effective - not effective).

Protection of trial subjects:

This study was conducted in accordance with the clinical protocol, the International Conference on Harmonization Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2010
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	Canada: 5
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	India: 4
Worldwide total number of subjects	29
EEA total number of subjects	4

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	10
From 65 to 84 years	16
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Enrollment was conducted at 12 clinical sites in 4 countries (USA, Canada, UK, India). Eight sites enrolled subjects under Protocol OBI-1-301 only. Two US sites enrolled subjects under the expanded access protocol OBI-1-301a and subsequently under protocol OBI-1-301. Another 2 US sites enrolled subjects under OBI-1-301a only.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	29
Number of subjects completed	29

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment of serious bleeding episodes
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Arm description:

Initial treatment with OBI-1 at dose of 200 U/kg, additional doses at the discretion of the investigator based on FVIII activity level and clinical assessment of response to treatment (upper limit: 400 U/kg every 2 hours)

Arm type	Experimental
Investigational medicinal product name	OBI-1
Investigational medicinal product code	
Other name	Obizur
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Initial dose: 200 U/kg - additional doses at the discretion of the investigator based on FVIII activity level and clinical assessment of response to treatment (upper limit: 400 U/kg every 2 hours)

Number of subjects in period 1	Treatment of serious bleeding episodes
Started	29
Completed	18
Not completed	11
Adverse event, serious fatal	1
Adverse event, non-fatal	3
Lost to follow-up	3
Death, OBI-1 inhibitors, subject terminal	3

Lack of efficacy	1
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Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description:	
Overall trial	

Reporting group values	Overall trial	Total	
Number of subjects	29	29	
Age categorical			
Units: Subjects			
85 years and over	3	3	
From 65-84 years	16	16	
Adults (18-64 years)	10	10	
Adolescents (12-17 years)	0	0	
Children (2-11 years)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Newborns (0-27 days)	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
In utero	0	0	
Age continuous			
Units: years			
arithmetic mean	69.8		
standard deviation	± 13.28	-	
Gender categorical			
Units:			
Female	10	10	
Male	19	19	

Subject analysis sets

Subject analysis set title	Intent to Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Comprises subjects with initial serious bleeding episodes who were dosed and for whom any post-screening data are available.	
Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Consists of all subjects in the ITT population with available PK data	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Comprises all subjects who received one or more doses of investigational product.	

Reporting group values	Intent to Treat Population	Pharmacokinetic Population	Safety Population
Number of subjects	29	5	29
Age categorical Units: Subjects			
85 years and over	3	1	3
From 65-84 years	16	1	16
Adults (18-64 years)	10	3	10
Adolescents (12-17 years)	0	0	0
Children (2-11 years)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Newborns (0-27 days)	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
In utero	0	0	0
Age continuous Units: years			
arithmetic mean	69.8	68.8	69.8
standard deviation	± 13.28	±	± 13.28
Gender categorical Units:			
Female	10	1	10
Male	19	4	19

End points

End points reporting groups

Reporting group title	Treatment of serious bleeding episodes
Reporting group description: Initial treatment with OBI-1 at dose of 200 U/kg, additional doses at the discretion of the investigator based on FVIII activity level and clinical assessment of response to treatment (upper limit: 400 U/kg every 2 hours)	
Subject analysis set title	Intent to Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: Comprises subjects with initial serious bleeding episodes who were dosed and for whom any post-screening data are available.	
Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Consists of all subjects in the ITT population with available PK data	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Comprises all subjects who received one or more doses of investigational product.	

Primary: Percentage of Serious Bleeding Episodes Responsive to OBI-1

End point title	Percentage of Serious Bleeding Episodes Responsive to OBI-1
End point description: The initial serious ("qualifying") bleeding episode for each subject was analyzed for the primary efficacy outcome measure. A 'positive response' is defined as 'effective' (bleeding stopped with clinical control and FVIII levels of 50% or higher) or 'partially effective' (bleeding reduced with clinical stabilization and FVIII levels of 20% or higher) control of bleeding, as determined by the investigator using a 4-point rating scale (effective - partially effective - poorly effective - not effective). 'Poorly effective' is defined as 'bleeding slightly reduced or unchanged and FVIII levels of less than 50%'. 'Not effective' is defined as 'bleeding worsening and FVIII levels of less than 50%'. 	
End point type	Primary
End point timeframe: 24 hours after initiation of treatment	

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	29	29		
Units: Percentage of serious bleeding episodes				
arithmetic mean (confidence interval 100%)	100 (88.1 to 100)	100 (88.1 to 100)		

Statistical analyses

Statistical analysis title	Statistical significance
Statistical analysis description: Summary statistics for the percentage of participants with serious bleeding episodes responsive at 24 hours after the initiation of treatment are presented, along with the 95% confidence interval (two-sided 95% Clopper-Pearson confidence interval).	
Comparison groups	Treatment of serious bleeding episodes v Intent to Treat Population
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 ^[1]
Method	one-sided binomial exact test

Notes:

[1] - The p-value was determined from an exact approach because of the relatively small sample size.

Secondary: Overall Percentage of Serious Bleeding Episodes Successfully Controlled With OBI-1 Therapy, as Assessed by the Investigator

End point title	Overall Percentage of Serious Bleeding Episodes Successfully Controlled With OBI-1 Therapy, as Assessed by the Investigator
End point description: Treatment success was defined as control of qualifying bleeding episode at the time of final treatment dosing. A serious bleeding episode was considered 'successfully controlled' if the investigator had checked 'completed OBI-1 therapy as treatment success' on the eCRF.	
End point type	Secondary
End point timeframe: At the time of final treatment dosing (varied from participant to participant depending on bleeding episodes)	

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	29	29		
Units: Percentage of serious bleeding episodes				
number (confidence interval 86.2%)	86.2 (68.3 to 96.1)	86.2 (68.3 to 96.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Serious Bleeding Episodes Responsive to OBI-1 Therapy at 8 Hours After the Initiation of Therapy, as Assessed by the Investigator

End point title	Percentage of Serious Bleeding Episodes Responsive to OBI-1 Therapy at 8 Hours After the Initiation of Therapy, as Assessed by the Investigator
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End point description:

A 'positive response' is defined as 'effective' (bleeding stopped with clinical control and FVIII levels of 50% or higher) or 'partially effective' (bleeding reduced with clinical stabilization and FVIII levels of 20% or higher) control of bleeding, as determined by the investigator using a 4-point rating scale (effective - partially effective - poorly effective - not effective). 'Poorly effective' is defined as 'bleeding slightly reduced or unchanged and FVIII levels of less than 50%'. 'Not effective' is defined as 'bleeding worsening and FVIII levels of less than 50%'. Please note that 21 subjects of the ITT population (n=29) had responses available at 8 hours after initial infusion of OBI-1.

End point type	Secondary
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End point timeframe:

8 hours after initiation of therapy

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: Percentage				
number (confidence interval 95.2%)	95.2 (76.2 to 99.9)	95.2 (76.2 to 99.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Serious Bleeding Episodes Responsive to OBI-1 Therapy at 16 Hours After the Initiation of Therapy, as Assessed by the Investigator

End point title	Percentage of Serious Bleeding Episodes Responsive to OBI-1 Therapy at 16 Hours After the Initiation of Therapy, as Assessed by the Investigator
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End point description:

A 'positive response' is defined as 'effective' (bleeding stopped with clinical control and FVIII levels of 50% or higher) or 'partially effective' (bleeding reduced with clinical stabilization and FVIII levels of 20% or higher) control of bleeding, as determined by the investigator using a 4-point rating scale (effective - partially effective - poorly effective - not effective). 'Poorly effective' is defined as 'bleeding slightly reduced or unchanged and FVIII levels of less than 50%'. 'Not effective' is defined as 'bleeding worsening and FVIII levels of less than 50%'. Please note that 19 subjects of the ITT population (n=29) had responses available at 16 hours after initial infusion of OBI-1.

End point type	Secondary
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End point timeframe:

16 hours after initiation of therapy

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	19		
Units: Percentage of serious bleeding episodes				
number (confidence interval 100%)	100 (82.4 to 100)	100 (82.4 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Infusions of OBI-1 Required to Successfully Control Qualifying Bleeding Episodes

End point title	Frequency of Infusions of OBI-1 Required to Successfully Control Qualifying Bleeding Episodes
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End point description:

'Frequency of infusions' was calculated as the 'average number of infusions per day'. 'Qualifying bleeding episode' was defined as the 'initial, serious bleeding episode'. The analysis was performed in 25 of 29 participants in the ITT population whose 'qualifying' bleeding episode was controlled successfully.

End point type	Secondary
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End point timeframe:

Time of successful control of qualifying bleeding episode (varied from subject to subject)

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	25		
Units: Infusions per day				
arithmetic mean (standard deviation)	2.1 ($\pm$ 1.109)	2.1 ($\pm$ 1.109)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose of OBI-1 Required to Successfully Control 'Qualifying' Bleeding Episodes

End point title	Total Dose of OBI-1 Required to Successfully Control 'Qualifying' Bleeding Episodes
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End point description:

'Qualifying bleeding episode' was defined as the 'initial, serious bleeding episode'.

End point type	Secondary
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End point timeframe:

Time of successful control of qualifying bleeding episode (varied from subject to subject)

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	25		
Units: U/kg				
arithmetic mean (standard deviation)	2683.2 (± 2928.61)	2683.2 (± 2928.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Infusions of OBI-1 Required to Successfully Control 'Qualifying' Bleeding Episodes

End point title	Total Number of Infusions of OBI-1 Required to Successfully Control 'Qualifying' Bleeding Episodes
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End point description:

'Qualifying bleeding episode' was defined as the 'initial, serious bleeding episode'. A serious bleeding episode was considered 'successfully controlled' if the investigator had checked 'completed OBI-1 therapy as treatment success' on the eCRF.

End point type	Secondary
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End point timeframe:

Time of successful control of qualifying bleeding episode (varied from subject to subject)

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	25		
Units: Infusions per subject				
arithmetic mean (standard deviation)	15.4 (± 12.64)	15.4 (± 12.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Response to OBI-1 Therapy at 8 Hours and Eventual Control of Serious Bleeding Episodes

End point title	Correlation Between Response to OBI-1 Therapy at 8 Hours and Eventual Control of Serious Bleeding Episodes
End point description:	
It was assessed how many of the subjects who had a positive response at 8 hours after initial infusion of OBI-1 had their qualifying bleeding event eventually controlled. Of 21 subjects in the ITT population (n=29) with responses available at 8 hours after initial infusion of OBI-1, 20 had a positive response.	
End point type	Secondary
End point timeframe:	
Time of successful control of qualifying bleeding episode (varied from subject to subject)	

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: subjects with eventual bleed control				
Response at 8 hours (n=21)	17	17		
Positive response at 8 hours (n=20)	17	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Response to OBI-1 Therapy at 16 Hours and Eventual Control of Serious Bleeding Episodes

End point title	Correlation Between Response to OBI-1 Therapy at 16 Hours and Eventual Control of Serious Bleeding Episodes
End point description:	
It was assessed how many of the subjects who had a positive response at 16 hours after initial infusion of OBI-1 had their qualifying bleeding event eventually controlled. All 19 subjects in the ITT population (n=29) with responses available at 16 hours after initial infusion of OBI-1 had a positive response.	
End point type	Secondary
End point timeframe:	
Time of successful control of qualifying bleeding episode (varied from subject to subject)	

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	19		
Units: subjects with eventual bleed control				
Response at 16 hours (n=19)	17	17		
Positive response at 16 hours (n=19)	17	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Response to OBI-1 Therapy at 24 Hours and Eventual Control of Serious Bleeding Episodes

End point title	Correlation Between Response to OBI-1 Therapy at 24 Hours and Eventual Control of Serious Bleeding Episodes
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End point description:

It was assessed how many of the subjects who had a positive response at 24 hours after initial infusion of OBI-1 had their qualifying bleeding event eventually controlled. Of 29 subjects in the ITT population (n=29) with responses available at 24 hours after initial infusion of OBI-1, 25 had a positive response.

End point type	Secondary
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End point timeframe:

Time of successful control of qualifying bleeding episode (varied from subject to subject)

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	29	29		
Units: subjects				
Response at 24 hours (n=29)	25	25		
Positive response at 24 hours (n=25)	25	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Analysis: Plasma clearance

End point title	Pharmacokinetic (PK) Analysis: Plasma clearance
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End point description:

Participation in the PK sampling was optional. PK parameters obtained from the non-bleeding state were summarized with descriptive statistics.

End point type	Secondary
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End point timeframe:

Pre-infusion: 15-20 minutes, Post-infusion: 1, 3, 6, 12, 18, 24 hours

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: U/(percent activity*hours)				
arithmetic mean (standard deviation)				
Chromogenic FVIII activity assay	11.8 (± 13.44)			
One-stage FVIII activity assay	18.07 (± 21.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Analysis: Volume of distribution at steady state

End point title	PK Analysis: Volume of distribution at steady state
End point description: Participation in the PK sampling was optional. PK parameters obtained from the non-bleeding state were summarized with descriptive statistics.	
End point type	Secondary
End point timeframe: Pre-infusion: 15-20 minutes, Post-infusion: 1, 3, 6, 12, 18, 24 hours	

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: U/percent activity				
arithmetic mean (standard deviation)				
Chromogenic FVIII activity assay	53.8 (± 52.9)			
One-stage FVIII activity assay	65.1 (± 45.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Analysis: Area Under the concentration-time curve (AUC) from time 0 to the last measurable concentration

End point title	PK Analysis: Area Under the concentration-time curve (AUC) from time 0 to the last measurable concentration
End point description: Participation in the PK sampling was optional. PK parameters obtained from the non-bleeding state were summarized with descriptive statistics. AUC was calculated as area under the percent activity-time curve.	
End point type	Secondary

End point timeframe:

Pre-infusion: 15-20 minutes, Post-infusion: 1, 3, 6, 12, 18, 24 hours

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: percent activity*hours				
arithmetic mean (standard deviation)				
Chromogenic FVIII activity assay	599 (± 459)			
One-stage FVIII activity assay	423 (± 340)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Analysis: Terminal half-life

End point title	PK Analysis: Terminal half-life
End point description: Participation in the PK sampling was optional. PK parameters obtained from the non-bleeding state were summarized with descriptive statistics. Half-life was calculated as the time it took to reduce percent activity by half.	
End point type	Secondary
End point timeframe: Pre-infusion: 15-20 minutes, Post-infusion: 1, 3, 6, 12, 18, 24 hours	

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: hours				
arithmetic mean (standard deviation)				
Chromogenic FVIII activity assay	3.3 (± 0.4)			
One-stage FVIII activity assay	3.5 (± 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who developed de novo anti-OBI-1 antibody titers

End point title	Number of subjects who developed de novo anti-OBI-1 antibody titers
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End point description:

Of 28 eligible subjects with acquired hemophilia A and autoimmune inhibitors to hFVIII in the ITT population (n=29), 18 had no detectable anti-porcine FVIII inhibitor titers at baseline (<0.6 BU) and 10 had detectable anti-porcine FVIII antibody titers at baseline (≥ 0.6 BU).

End point type	Secondary
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End point timeframe:

Through 90 days $\pm$ 7 days following final OBI-1 dose

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: subjects	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who developed an anti-host cell protein baby hamster kidney (BHK) antibody titer

End point title	Number of subjects who developed an anti-host cell protein baby hamster kidney (BHK) antibody titer
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End point description:

21 subjects in the ITT population (n=29) had baseline and follow-up test results available.

End point type	Secondary
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End point timeframe:

Through 90 days $\pm$ 7 days following final OBI-1 dose

End point values	Treatment of serious bleeding episodes	Intent to Treat Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through 90 days $\pm$ 7 days following final OBI-1 dose

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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Reporting groups

Reporting group title	Safety Analysis Population
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Reporting group description:

Comprises all subjects who received one or more doses of investigational product (OBI-1).

Serious adverse events	Safety Analysis Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 29 (44.83%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Tracheostomy malfunction			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hematoma			

subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain edema			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischemic attack			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial hemorrhage			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Immune system disorders Anaphylactic reaction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0		
Gastrointestinal disorders Esophagitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0		
Intestinal hemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 1		
Gastrointestinal hemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0		
Hepatobiliary disorders Cholangitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 1		
Respiratory, thoracic and mediastinal disorders Respiratory failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 1		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hemarthrosis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint swelling			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Systemic mycosis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		

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

Non-serious adverse events	Safety Analysis Population		
Total subjects affected by non-serious adverse events subjects affected / exposed	27 / 29 (93.10%)		
Investigations			
Antibody test positive subjects affected / exposed occurrences (all)	Additional description: Positive OBI-1 (anti-porcine FVIII) inhibitor test result 2 / 29 (6.90%) 2		
Troponin I increased subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 4		
Hypotension subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Cardiac disorders			
Cardiac failure congestive subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Blood and lymphatic system disorders			
Anemia subjects affected / exposed occurrences (all)	6 / 29 (20.69%) 6		
General disorders and administration site conditions			
Chest pain subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Fatigue subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Peripheral edema subjects affected / exposed occurrences (all)	6 / 29 (20.69%) 7		
Pyrexia			

subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	12 / 29 (41.38%)		
occurrences (all)	12		
Diarrhea			
subjects affected / exposed	7 / 29 (24.14%)		
occurrences (all)	7		
Mouth ulceration			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Wheezing			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Insomnia subjects affected / exposed occurrences (all)	4 / 29 (13.79%) 6		
Musculoskeletal and connective tissue disorders Muscle hemorrhage subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Infections and infestations Bacteriuria subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Bacteremia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Candidiasis subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Oral candidiasis subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Sepsis subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		

Hypoglycemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Hypokalemia			
subjects affected / exposed	7 / 29 (24.14%)		
occurrences (all)	11		
Hypomagnesemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Hypophosphatemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2010	- PK analyses modified to indicate that PK would be performed in both the non-bleeding and bleeding states (However, PK in bleeding state eventually not performed due to lack of acceptable data) - Clarification made why serious subsequent bleeds would not be considered new qualifying bleeds - Subjects who have received bypassing agents (eg, rFVIIa) or blood products would not be automatically excluded - New maximum target blood level of FVIII for OBI-1 provided - Inclusion and exclusion criteria were modified to clarify the required life expectancy before the qualifying bleeding event, the limit for prothrombin time (PT), and the required wash-out period for previous bypass therapy
25 January 2011	- Schedule of assessments was modified beyond the 24-hour primary efficacy assessment to be less demanding for subjects who do not require frequent dosing, without changing the primary endpoint - In response to an IRB request, language was added to specify that investigators are not required to collect information from pregnant subjects after study end but are required to provide counseling regarding risks to all pregnant subjects
12 February 2012	The following changes were made based on comments received from health authorities in the United Kingdom, India and from the Voluntary Harmonized Procedure countries (France, Germany, Italy, Hungary and Sweden) during their assessment of the clinical trial application: - Changes were made to indicate that no subject could be included in the primary endpoint analysis for more than one bleeding event and that all subsequent bleeding events after the initial qualifying bleed would only be included in the safety analysis. - Inclusion criteria were added to indicate that subjects of reproductive age must use acceptable methods of contraception and if female, undergo pregnancy testing as part of the screening process. - The scale used for the primary endpoint was changed from a three-point to a four-point ordinal scale with the inclusion of the assessment of "poorly controlled" bleeding. - The minimum number of subjects to be included in the study was changed from 20 to 28. The following additional change was made in response to a request from the DSMB: - Assessment of complete blood count (CBC) with platelets was added to the schedule of assessments.
13 May 2012	The wording of one inclusion criterion and two exclusion criteria was changed slightly in response to comments received from the French central ethics committee.
03 July 2012	Wording of one inclusion criterion changed to allow for inclusion of a subject if consent is given by the subject, a trusted person or a person who is legally authorized to sign on behalf of the subject
17 April 2013	The sponsor was changed from Inspiration Biopharmaceuticals, Inc. to Baxter.

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.

Due to the low number of subjects available for evaluation, statistical tests could only be performed for the primary outcome measure. The results of all other outcome measures are descriptive.

Notes: