

**Clinical trial results:****IMMUNINE – Purified Factor IX Concentrate Virus-Inactivated: A Phase IV,****Prospective, Open-label Multicenter Study to Prospectively Document the Exposure****of IMMUNINE and to Monitor FIX Inhibitors in Previously Treated Patients with****Severe (FIX level < 1%) or Moderately Severe (FIX level 2%) Hemophilia B Who****are Planned to Enter BAX 326 Study 250901 to investigate a New Recombinant FIX****Concentrate****Summary**

EudraCT number	2009-016719-39
Trial protocol	CZ BG PL
Global end of trial date	28 August 2012

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	05 August 2015

Trial information**Trial identification**

Sponsor protocol code	050901
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, Baxter Innovations GmbH, 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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2012
Global end of trial reached?	Yes
Global end of trial date	28 August 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to prospectively document the exposure to IMMUNINE and to monitor FIX inhibitors over a period of approximately 20 – 50 EDs while receiving prophylactic treatment in up to 50 PTPs aged 12 – 64 years and approximately 20 pediatric PTPs up to 11 years of age with severe (FIX level < 1%) or moderately severe (FIX level ≤ 2%) hemophilia B who were planned to enter BAX 326 pivotal study 250901 or BAX 326 pediatric study 251101, provided all eligibility criteria had been met.

Protection of trial subjects:

The study was conducted in accordance with the principles set forth in Title 21 of the US Code of Federal Regulations (CFR), parts 50, 54, 56, 312 and 314, International Committee on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), and applicable local and national regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 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	Bulgaria: 4
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Colombia: 4
Worldwide total number of subjects	49
EEA total number of subjects	25

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)	2
Children (2-11 years)	10
Adolescents (12-17 years)	1
Adults (18-64 years)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled (signed informed consent) from 18 sites in 9 countries.

Pre-assignment

Screening details:

A total of 57 subjects were enrolled in the study. Of these, 49 (86.0%) subjects were exposed to IMMUNINE, the investigational product.

Pre-assignment period milestones

Number of subjects started	57 ^[1]
Number of subjects completed	49

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Screen Failure-5; Eligibility criteria changes-1: 6

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 57 subjects were enrolled in the study. Of these, 49 subjects were exposed to IMMUNINE, the investigational product.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Pediatric subjects (<= 11 years)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	IMMUNINE (pediatric)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

once or twice weekly 20 - 40 IU/kg, or more according to the bleeding pattern

Arm title	Adolescent/adult subjects (>= 12 years)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	IMMUNINE (adolescent/adult)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

20–40 IU/kg twice weekly

Number of subjects in period 1	Pediatric subjects (≤ 11 years)	Adolescent/adult subjects (≥ 12 years)
Started	12	37
Completed	12	35
Not completed	0	2
Adverse event, serious fatal	-	1
Eligibility criteria changed	-	1

Baseline characteristics

Reporting groups

Reporting group title	Pediatric subjects (≤ 11 years)
Reporting group description: -	
Reporting group title	Adolescent/adult subjects (≥ 12 years)
Reporting group description: -	

Reporting group values	Pediatric subjects (≤ 11 years)	Adolescent/adult subjects (≥ 12 years)	Total
Number of subjects	12	37	49
Age categorical			
Units: Subjects			
Adults (18-64 years)	0	36	36
Adolescents (12-17 years)	0	1	1
Children (2-11 years)	10	0	10
Infants and toddlers (28 days-23 months)	2	0	2
Age continuous			
Units: years			
arithmetic mean	6.6	32.9	-
standard deviation	± 3.73	± 11.24	
Gender categorical			
Units:			
Female	0	0	0
Male	12	37	49

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Comprised all subjects who met inclusion and exclusion criteria and received at least one infusion of IP	

Reporting group values	Full Analysis Set		
Number of subjects	49		
Age categorical			
Units: Subjects			
Adults (18-64 years)	36		
Adolescents (12-17 years)	1		
Children (2-11 years)	10		
Infants and toddlers (28 days-23 months)	2		
Age continuous			
Units: years			
arithmetic mean	26.5		
standard deviation	± 15.13		

Gender categorical			
Units:			
Female	0		
Male	49		

End points

End points reporting groups

Reporting group title	Pediatric subjects (<= 11 years)
Reporting group description: -	
Reporting group title	Adolescent/adult subjects (>= 12 years)
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	Comprised all subjects who met inclusion and exclusion criteria and received at least one infusion of IP

Primary: Number of IMMUNINE infusions administered for each bleeding episode

End point title	Number of IMMUNINE infusions administered for each bleeding episode ^[1]
End point description:	
End point type	Primary
End point timeframe:	From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	37	49	
Units: Number of bleeding episodes				
1 infusion	8	32	40	
2 infusions	4	13	17	
3 and more infusions	0	4	4	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects who developed inhibitory and total binding antibodies to Factor IX (FIX), severe allergic reaction, thrombotic event

End point title	Number of subjects who developed inhibitory and total binding antibodies to Factor IX (FIX), severe allergic reaction, thrombotic event ^[2]
End point description:	
End point type	Primary
End point timeframe:	From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

Notes:

[2] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	37	49	
Units: Number of subjects				
Inhibitory antibody to FIX	0	0	0	
Total binding antibody to FIX	2	0	2	
Treatment related total binding antibody to FIX	0	0	0	
Severe allergic reaction	0	0	0	
Thrombotic event	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Hemostatic efficacy rating of IMMUNINE at resolution of bleeding

End point title	Hemostatic efficacy rating of IMMUNINE at resolution of bleeding
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End point description:

Excellent: Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis

would not affect this scoring.

Good: Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.

Fair: Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.

None: No improvement or condition worsens.

End point type	Secondary
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End point timeframe:

From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	37	49	
Units: Number of treated bleeding episodes				
Excellent	4	20	24	
Good	7	27	34	
Fair	0	2	2	
None	0	0	0	

Not Done	1	0	1	
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Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate

End point title	Annualized Bleeding Rate
End point description:	Annualized Bleeding Rate (ABR) in Subjects with 3+ Months of Prophylaxis
End point type	Secondary
End point timeframe:	From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	29	35	
Units: Annualized Bleeding Rate				
arithmetic mean (standard deviation)	5.7 (± 7.33)	3.9 (± 7.33)	4.2 (± 7.25)	

Statistical analyses

No statistical analyses for this end point

Secondary: IMMUNINE exposure days

End point title	IMMUNINE exposure days
End point description:	
End point type	Secondary
End point timeframe:	From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	37	49	
Units: Number of exposure days				
arithmetic mean (standard deviation)	31 (± 11.92)	40 (± 13.84)	37.8 (± 13.84)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total weight-adjusted consumption of IMMUNINE

End point title	Total weight-adjusted consumption of IMMUNINE
End point description:	
End point type	Secondary
End point timeframe:	
From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.	

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	37	49	
Units: IU/kg				
arithmetic mean (standard deviation)	1200.7 (± 532.37)	1369.9 (± 458.59)	1328.5 (± 477.58)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of infusions for prophylaxis per month and year

End point title	Number of infusions for prophylaxis per month and year
End point description:	
End point type	Secondary
End point timeframe:	
From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.	

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	37	49	
Units: Number of infusions				
arithmetic mean (standard deviation)				
Per Month	5.5 (± 1.16)	5.6 (± 1.18)	5.6 (± 1.16)	
Per Year	65.6 (± 13.87)	67 (± 14.12)	66.7 (± 13.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of infusions for bleeding episode treatment per month and year

End point title	Number of infusions for bleeding episode treatment per month and year
End point description:	
End point type	Secondary
End point timeframe:	From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	21	25	
Units: Number of infusions				
arithmetic mean (standard deviation)				
Per Month	0.8 (± 0.67)	0.7 (± 0.6)	0.7 (± 0.6)	
Per Year	9.2 (± 8.07)	8.2 (± 7.26)	8.3 (± 7.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: IMMUNINE weight-adjusted consumption for prophylaxis per month and year

End point title	IMMUNINE weight-adjusted consumption for prophylaxis per month and year
End point description:	
End point type	Secondary
End point timeframe:	From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	37	49	
Units: IU/kg				
arithmetic mean (standard deviation)				
Per Month	205.1 (± 49.72)	173.9 (± 51.32)	181.5 (± 52.2)	
Per Year	2460.7 (± 596.6)	2086.7 (± 615.81)	2178.3 (± 626.41)	

Statistical analyses

No statistical analyses for this end point

Secondary: IMMUNINE weight-adjusted consumption for bleeding episode treatment per month and year

End point title	IMMUNINE weight-adjusted consumption for bleeding episode treatment per month and year
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End point description:

End point type	Secondary
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End point timeframe:

From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	21	25	
Units: IU/kg				
arithmetic mean (standard deviation)				
Per Month	30.6 (± 24.04)	24.7 (± 20.67)	25.6 (± 20.82)	
Per Year	367.3 (± 288.54)	296 (± 248.09)	307.4 (± 249.82)	

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery over time

End point title	Incremental recovery over time
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End point description:

Incremental recovery (IR) was measured at Week 4, Week 12, Week 26, and Termination. Time points for blood sampling for IR were 0-30 minutes prior to infusion and 30 minutes \pm 5 minutes post-infusion. Pediatric subjects (\leq 11 years) were 4 (Week 4); 2 (Week 12 and Week 26); 0 at Termination. '9999999999' was entered as result for termination since the results cannot be left blank. Adolescent/adult subjects (\geq 12 years) were 27 (Week 4); 20 (Week 12); 7 (Week 26); 18 (Termination). Subjects in Full Analysis Set were 31 (Week 4); 22 (Week 12); 9 (Week 26); 18 (Termination).

End point type	Secondary
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End point timeframe:

From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

End point values	Pediatric subjects (\leq 11 years)	Adolescent/adult subjects (\geq 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	27	31	
Units: Number				
arithmetic mean (standard deviation)				
Week 4	0.9 (\pm 0.12)	1.1 (\pm 0.27)	1.1 (\pm 0.26)	
Week 12	0.9 (\pm 0.21)	1.1 (\pm 0.26)	1.1 (\pm 0.25)	
Week 26	0.8 (\pm 0.16)	1.2 (\pm 0.22)	1.1 (\pm 0.26)	
Termination	9999999999 (\pm 9999999999)	1.1 (\pm 0.22)	1.1 (\pm 0.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life: Annualized Rate of Health Resource Use

End point title	Quality of Life: Annualized Rate of Health Resource Use
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End point description:

Subjects were:

For days lost from work or school: 11 pediatric subjects, 36 adolescent/adult subjects; 47 subjects in Full Analysis Set.

For all other categories: 12 pediatric subjects, 37 adolescent/adult subjects; 49 subjects in Full Analysis Set .

Arithmetic mean value for Emergency room visits (for Full Analysis Set and for adolescent/adult subjects) and for Hospitalizations (for Full Analysis Set) was ' <0.1 '. Since this value could not be entered into the system, '0.1' was entered instead.

End point type	Secondary
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End point timeframe:

From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	37	49	
Units: Number				
arithmetic mean (standard deviation)				
Days lost from work or school	1 (± 3.38)	1.7 (± 5.04)	1.6 (± 4.68)	
Unscheduled visits to a practitioner	1.1 (± 1.64)	0.5 (± 1.29)	0.7 (± 1.39)	
Emergency room visits	0 (± 0)	0.1 (± 0.38)	0.1 (± 0.33)	
Hospitalizations	0 (± 0)	0.1 (± 0.44)	0.1 (± 0.39)	
Length of hospital stay	0 (± 0)	0.2 (± 0.91)	0.2 (± 0.79)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events (AEs) related to investigational product

End point title | Adverse events (AEs) related to investigational product

End point description:

Serious and non-serious AEs included.

End point type | Secondary

End point timeframe:

From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

End point values	Pediatric subjects (<= 11 years)	Adolescent/adult subjects (>= 12 years)	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	37	49	
Units: Number of related AEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first exposure to IMMUNINE until the end of the study, approximately 3-8 months per subject.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Adolescent/adult subjects (equal or greater than 12 years)
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Reporting group description:

Reporting group 2 description

Reporting group title	Pediatric subjects (equal or lower than 11 years)
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Reporting group description:

Reporting group 1 description

Serious adverse events	Adolescent/adult subjects (equal or greater than 12 years)	Pediatric subjects (equal or lower than 11 years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 37 (13.51%)	0 / 12 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Investigations			
Hepatitis b surface antibody positive subjects affected / exposed	1 / 37 (2.70%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 37 (2.70%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 37 (2.70%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Haemorrhage intracranial subjects affected / exposed	1 / 37 (2.70%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed	1 / 37 (2.70%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic subjects affected / exposed	1 / 37 (2.70%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis subjects affected / exposed	1 / 37 (2.70%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis subjects affected / exposed	1 / 37 (2.70%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Adolescent/adult subjects (equal or greater than 12 years)	Pediatric subjects (equal or lower than 11 years)	
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 37 (13.51%)	2 / 12 (16.67%)	
Nervous system disorders			
Headache subjects affected / exposed	4 / 37 (10.81%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 6	2 / 12 (16.67%) 2	
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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

None reported