



## Clinical trial results:

### A Phase 3, Prospective, Open-label, Randomized Study to Evaluate Safety and Efficacy of Recombinant Activated FVII BI (rFVIIa BI) in the Treatment of Acute Bleeding Episodes per an On-demand Regimen in Patients with Hemophilia A or B with Inhibitors.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

## Summary

EudraCT number	2011-006294-26
Trial protocol	ES BE PL
Global end of trial date	11 November 2014

## Results information

Result version number	v1 (current)
This version publication date	13 February 2016
First version publication date	13 February 2016

## Trial information

### Trial identification

Sponsor protocol code	021101
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01757405
WHO universal trial number (UTN)	-

Notes:

## Sponsors

Sponsor organisation name	Baxalta Innovations GmbH
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, A-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, CA, 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)	Yes
EMA paediatric investigation plan number(s)	EMA-001382-PIP01-12

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	17 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2014
Global end of trial reached?	Yes
Global end of trial date	11 November 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of rFVIIa BI in the treatment of acute bleeding episodes per an on demand regimen in hemophilia A or B patients with inhibitors

Protection of trial subjects:

This study was conducted in accordance with the clinical protocol, the International Conference on Harmonisation 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	20 February 2013
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	Romania: 2
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Japan: 2
Worldwide total number of subjects	38
EEA total number of subjects	9

Notes:

<b>Subjects enrolled per age group</b>	
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)	7
Adults (18-64 years)	31
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled (signed informed consent) from 16 sites in 9 countries.

### Pre-assignment

Screening details:

A total of 40 subjects provided informed consent and were screened for study participation, of which there was 1 screen failure. 39 subjects (in pre-assignment period) were randomized where 1 subject withdrew after randomization prior to treatment, therefore 38 subjects were enrolled and treated with rFVIIa BI.

### Pre-assignment period milestones

Number of subjects started	39 <sup>[1]</sup>
Number of subjects completed	38

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	subject w/d after randomization prior to treatment: 1
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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 40 subjects provided informed consent and were screened for study participation, of which there was 1 screen failure. 39 subjects (in pre-assignment period) were randomized where 1 subject withdrew after randomization prior to treatment, therefore 38 subjects were enrolled and treated with rFVIIa BI.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Arm 1: up to 3 x 90 µg/kg rFVIIa BI
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Arm description:

Bleeding episodes treated with up to 3 doses of 90 µg/kg of recombinant activated factor VII BI (rFVIIa BI) every 3 hours as on-demand intravenous bolus infusions.

Arm type	Experimental
Investigational medicinal product name	rFVIIa BI
Investigational medicinal product code	BAX817
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

either up to 3 x 90 µg/kg rFVIIa BI (ARM 1) OR 1 x 270 µg/kg rFVIIa BI (ARM 2)

<b>Arm title</b>	Arm 2: 1 x 270 µg/kg rFVIIa BI
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Arm description:

Bleeding episodes treated with 1 dose of 270 µg/kg of recombinant activated factor VII BI (rFVIIa BI) as on-demand intravenous bolus infusion.

Arm type	Experimental
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Investigational medicinal product name	rFVIIa BI
Investigational medicinal product code	BAX817
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

either up to 3 x 90 µg/kg rFVIIa BI (ARM 1) OR 1 x 270 µg/kg rFVIIa BI (ARM 2)

<b>Number of subjects in period 1</b>	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI
Started	18	20
Completed	17	18
Not completed	1	2
Consent withdrawn by subject	-	1
Lost to follow-up	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Arm 1: up to 3 x 90 µg/kg rFVIIa BI
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Reporting group description:

Bleeding episodes treated with up to 3 doses of 90 µg/kg of recombinant activated factor VII BI (rFVIIa BI) every 3 hours as on-demand intravenous bolus infusions.

Reporting group title	Arm 2: 1 x 270 µg/kg rFVIIa BI
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Reporting group description:

Bleeding episodes treated with 1 dose of 270 µg/kg of recombinant activated factor VII BI (rFVIIa BI) as on-demand intravenous bolus infusion.

Reporting group values	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI	Total
Number of subjects	18	20	38
Age categorical			
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)	3	4	7
Adults (18-64 years)	15	16	31
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	28	28	
full range (min-max)	12 to 53	12 to 54	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	18	20	38

## End points

### End points reporting groups

Reporting group title	Arm 1: up to 3 x 90 µg/kg rFVIIa BI
Reporting group description: Bleeding episodes treated with up to 3 doses of 90 µg/kg of recombinant activated factor VII BI (rFVIIa BI) every 3 hours as on-demand intravenous bolus infusions.	
Reporting group title	Arm 2: 1 x 270 µg/kg rFVIIa BI
Reporting group description: Bleeding episodes treated with 1 dose of 270 µg/kg of recombinant activated factor VII BI (rFVIIa BI) as on-demand intravenous bolus infusion.	

### Primary: Percentage of bleeding episodes with "Treatment Success".

End point title	Percentage of bleeding episodes with "Treatment Success".
End point description: "Treatment Success" defined as no additional haemostatic product required within 12 hours of the first dose of rFVIIa BI per bleeding episode, other than the prescribed dosing regimen (either up to 3 x 90 µg/kg doses of rFVIIa B [Arm 1] OR - 1 x 270 µg/kg dose rFVIIa BI [Arm 2]). There were a total of 289 bleeding episodes in Arm 1 and 256 bleeding episodes in Arm 2. The analysis was conducted on subjects in the Full Analysis Dataset.	
End point type	Primary
End point timeframe: From first exposure to rFVIIa BI until the end of the study, up to 6 months (day 180) per subject.	

End point values	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Percent of bleeding episodes				
number (confidence interval 95%)	96.19 (93.31 to 97.86)	79.3 (73.92 to 83.81)		

### Statistical analyses

Statistical analysis title	Equivalence test of successfully treated BEs
Statistical analysis description: Equivalence test of successfully treated bleeding episodes (BEs) between or within treatment arms. Denoting the success rates in the two treatment groups by p1 and p2 , the null hypotheses of H01 : $p1/p2 < 0.83$ and H02 : $p1/p2 > 1.20$ was implicitly tested against the one-sided alternatives Ha1: $0.83 \leq p1/p2$ and Ha2 : $p1/p2 \leq 1.20$ , by comparing the 90% two-sided confidence interval (CI) of the ratio of success proportions to the equivalence region defined as [0.83, 1.20].	
Comparison groups	Arm 2: 1 x 270 µg/kg rFVIIa BI v Arm 1: up to 3 x 90 µg/kg rFVIIa BI

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[1]</sup>
Parameter estimate	Ratio of success proportion
Point estimate	1.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.15
upper limit	1.28

Notes:

[1] - Equivalence of treatment success proportions in all bleeding episodes for the two treatment groups was determined by comparing the 90% two-sided CI of the ratio of success proportions to the equivalence region defined as [0.83, 1.20].

### Secondary: Treatment Response based on a four-point scale.

End point title	Treatment Response based on a four-point scale.
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End point description:

Subject or investigator used a four point rating scale:-

EXCELLENT - full relief of pain and cessation of objective signs of bleeding (swelling, tenderness, decrease in range of motion [for muscle bleeds]) within 9 hours of treatment initiation. No additional infusion required to control bleeding, other than prescribed dosing regimen.

GOOD - Substantial relief of pain and/or cessation of objective signs of bleeding within 9 hours of treatment initiation. No additional infusion required to control bleeding, other than prescribed dosing regimen.

MODERATE - slight relief of pain and slight improvement of signs of bleeding within 9 hours of treatment initiation. Requires additional infusion beyond treatment regimen.

NONE - No improvement or condition worsens.

SUCCESSFUL = EXCELLENT or GOOD.

There were 289 bleeding episodes in Arm 1 ( up to 3 x 90 µg/kg rFVIIa BI) and 256 bleeding episodes in Arm 2 (1 x 270 µg/kg rFVIIa BI).

Analysis conducted on subjects in Full Analysis Dataset.

End point type	Secondary
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End point timeframe:

From first exposure to rFVIIa BI until the end of the study, up to 6 months (day 180) per subject.

End point values	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Percent of bleeding episodes				
number (confidence interval 95%)				
Successful	87.89 (83.62 to 91.16)	79.3 (73.92 to 83.31)		
Excellent	34.6 (29.35 to 40.26)	36.72 (31.05 to 42.78)		
Good	53.29 (47.53 to 58.96)	42.58 (36.67 to 48.7)		
Moderate	9.69 (6.79 to 13.65)	18.36 (14.1 to 23.56)		
No Assessment Available	0 (0 to 0)	0.39 (0.07 to 2.18)		
None	2.42 (1.18 to 4.91)	1.95 (0.84 to 4.49)		



## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of clinical responders for all acute bleeding episodes at 24 hours after rFVIIa BI infusion

End point title	Percentage of clinical responders for all acute bleeding episodes at 24 hours after rFVIIa BI infusion
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End point description:

Clinical responders defined as sustained bleeding control, (no additional hemostatic medication including rFVIIa BI required between 12 and 24 hours after first infusion of the successfully treated bleeding episode).

There were a total of 289 bleeding episodes in Arm 1 (up to 3 x 3 x 90 µg/kg rFVIIa BI) and 256 bleeding episodes in Arm 2 (1 x 270 µg/kg rFVIIa BI).

The analysis was conducted on subjects in the Full Analysis Dataset.

End point type	Secondary
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End point timeframe:

From first exposure to rFVIIa BI until the end of the study, up to 6 months (day 180) per subject.

End point values	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Percent of bleeding episodes				
number (confidence interval 95%)	93.43 (89.96 to 95.75)	76.17 (70.59 to 80.98)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Safety and Tolerability of Treatment Regimens by Clinical Assessment of Adverse Events (AEs) per Subject

End point title	Safety and Tolerability of Treatment Regimens by Clinical Assessment of Adverse Events (AEs) per Subject
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End point description:

Safety was determined by the number of AEs (both serious AEs [SAEs] and non-serious AEs [nsAE]). Tolerability was determined by the number of AEs related to rFVIIa BI (both SAEs and nsAEs) as determined by causality assessment of the AEs by the investigator. An AE was deemed Related if the investigator judged the AE to be "possibly related" or "probably related" to rFVIIa BI.

The percentage of subjects with AEs were presented by seriousness (SAE, nsAE), severity (Mild, Moderate or Severe) and causality (Related or Not Related to rFVIIa BI).

The analysis was conducted on subjects in the Safety Analysis Dataset.

End point type	Secondary
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End point timeframe:

From first exposure to rFVIIa BI until the end of the study, up to 6 months (day 180) per subject.

End point values	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Percent of subjects with AEs				
number (not applicable)				
SAE-Moderate-Unrelated	5.6	5		
SAE-Severe-Unrelated	11.1	0		
SAE-Severe-Related	0	5		
nsAE-Mild-Unrelated	22.2	30		
nsAE-Moderate-Unrelated	0	15		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety and Tolerability of Treatment Regimens by Clinical Assessment of Adverse Events (AEs)

End point title	Safety and Tolerability of Treatment Regimens by Clinical Assessment of Adverse Events (AEs)
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End point description:

Safety was determined by the number of AEs (both serious AEs [SAEs] and non-serious AEs [nsAE]). Tolerability was determined by the number of AEs related to rFVIIa BI (both SAEs and nsAEs) as determined by causality assessment of the AEs by the investigator. An AE was deemed Related if the investigator judges the AE to be "possibly related" or "probably related" to rFVIIa BI. The percentage of AEs were presented by seriousness (SAE, nsAE), severity (Mild, Moderate or Severe) and causality (Related or Not Related [to rFVIIa BI]). The analysis was conducted on subjects in the Safety Analysis Dataset.

End point type	Secondary
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End point timeframe:

From first exposure to rFVIIa BI until the end of the study, up to 6 months (day 180) per subject.

End point values	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Percent of AEs				
number (not applicable)				
SAE-Moderate-Unrelated	6.7	6.3		
SAE-Severe-Unrelated	20	0		
SAE-Severe-Related	0	12.5		
nsAE-Mild-Unrelated	73.3	62.5		

nsAE-Moderate-Unrelated	0	18.8		
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Inhibitor Development to FVII

End point title	Percentage of Subjects with Inhibitor Development to FVII
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End point description:

Development of rFVII inhibitors or FVIIa binding antibodies during the study.  
The analysis was conducted on subjects in the Safety Analysis Dataset.

End point type	Secondary
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End point timeframe:

From first exposure to rFVIIa BI until the end of the study, up to 6 months (day 180) per subject.

End point values	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Percent of subjects				
number (not applicable)	0	0		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first exposure of rFVIIa BI until the end of the study, up to 6 months (day 180) per subject.

Adverse event reporting additional description:

The population consisted of subjects who received at least one dose of rFVIIa BI during the study.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Arm 1: up to 3 x 90 µg/kg rFVIIa BI
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Reporting group description:

Subjects who received at least 1 dose of 90 µg/kg of rFVIIa BI as on-demand intravenous bolus infusion during the study.

Reporting group title	Arm 2: 1 x 270 µg/kg rFVIIa BI
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Reporting group description:

Subjects who received at least 1 dose of 270 µg/kg of rFVIIa BI as on-demand intravenous bolus infusion during the study.

Serious adverse events	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Limb injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug ineffective			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Arm 1: up to 3 x 90 µg/kg rFVIIa BI	Arm 2: 1 x 270 µg/kg rFVIIa BI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 18 (22.22%)	2 / 20 (10.00%)	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Sinus headache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 20 (0.00%) 0	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 20 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Nasal congestion subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1  1 / 18 (5.56%) 2	0 / 20 (0.00%) 0  0 / 20 (0.00%) 0	
Infections and infestations Influenza subjects affected / exposed occurrences (all)  Nasopharyngitis subjects affected / exposed occurrences (all)  Tinea versicolour subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0  1 / 18 (5.56%) 1  1 / 18 (5.56%) 1	2 / 20 (10.00%) 2  0 / 20 (0.00%) 0  0 / 20 (0.00%) 0	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported