Clinical trial results:
Phase 3B Recombinant Antihemophilic Factor Manufactured and Formulated without Added Human or Animal Proteins (rAHF-PFM): Evaluation of Immunogenicity, Efficacy, and Safety in Previously Untreated Patients with Hemophilia A

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	2004-001623-38
Trial protocol	AT
Global end of trial date	11 September 2009

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	060103

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Baxter Innovations GmbH
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, A-1221
Public contact	Clinical Trial Registries and Results Disclosure, Baxter Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxter Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Sponsor organisation name	Baxter Healthcare Corporation
Sponsor organisation address	One Baxter Way, Westlake Village, United States, CA 91362-3811
Public contact	Clinical Trial Registries and Results Disclosure, Baxter Healthcare Corporation, ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxter Healthcare Corporation, 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	Yes

1901/2006 apply to this trial?	
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	11 September 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2009
Global end of trial reached?	Yes
Global end of trial date	11 September 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of study 060103 were: To assess the immunogenicity of rAHF-PFM by determining the risk of FVIII inhibitor development; To assess in vivo incremental recovery of rAHF-PFM at the first study visit, at every other interval study visit, and at the study termination visit; To evaluate the hemostatic efficacy of rAHF-PFM in the management and prevention of acute bleeding events; To evaluate the hemostatic efficacy of rAHF-PFM during perioperative management, if surgery was required; To assess the safety of rAHF-PFM; To assess the incidence of the development of antibodies to CHO protein, murine IgG, and human VWF.

Protection of trial subjects:

This study was conducted in accordance with this protocol, the ICH Guideline for Good Clinical Practice, Title 21 of the U.S. Code of Federal Regulations, the European Directive, and the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2004
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	Italy: 2
Country: Number of subjects enrolled	United States: 35
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	55
EEA total number of subjects	17

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	8
Infants and toddlers (28 days-23 months)	47
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was conducted in the U.S., Canada, and Europe at 24 study sites.

Pre-assignment

Screening details:

Participants screened for maximum 21 days. Study was not randomized; it was an open-label evaluation. Prior to initial infusion, a minimum washout period of 3 days was required. 11 participants who enrolled did not receive any rAHF-PFM infusions (3 withdrew consent, 6 screen failures, 1 non-compliance with screening, 1 pre-existing low hemoglobin)

Period 1

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

Arms

Arm title	PUPs

Arm description:

All treated subjects

Arm type	Experimental
Investigational medicinal product name	rAHF-PFM
Investigational medicinal product code	ADVATE
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

rAHF-PFM was to be dosed according to a therapeutic regimen which was determined by the investigator (ie: standard regimen [25 to 50 IU/kg body weight, 3 to 4 times per week]; a modified prophylactic regimen [dose and frequency selected by investigator] or on–demand treatment [dose selected by investigator]). The dosing regimen used to treat BEs was at the discretion of the investigator and in accordance with the institution’s standard of care for the type of BE diagnosed.

Number of subjects in period 1	PUPs
Started	55
Completed	44
Not completed	11
Physician decision	1
Consent withdrawn by subject	6
Enrolled in another study	1
Lost to follow-up	1
Met exclusion criteria	1
Inclusion not met- baseline FVIII value	1

Baseline characteristics

Reporting groups	
Reporting group title	PUPs
Reporting group description:	
All treated subjects	

Reporting group values	PUPs	Total	
Number of subjects	55	55	
Age categorical			
Age categorical description			
Units: participants			
<6 months	21	21	
6-12 months	26	26	
≥13 months	8	8	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	
Male	55	55	

End points

End points reporting groups

Reporting group title	PUPs
Reporting group description:	
All treated subjects	
Subject analysis set title	Did not Develop Factor VIII Inhibitor
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects in Immunogenicity Analysis Set who did not develop Factor VIII Inhibitor	
Subject analysis set title	Developed Factor VIII Inhibitor
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects in Immunogenicity Analysis Set who developed Factor VIII Inhibitor	

Primary: Factor VIII Inhibitor Development

End point title	Factor VIII Inhibitor Development[1]
End point description:	
Percentage of treated participants who developed factor VIII inhibitors	
End point type	Primary
End point timeframe:	
Assessed during study period which was to be at least 75 exposure days or 3 years (whichever came first)	
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	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: percentage				
number (confidence interval 95%)	29.1 (17.1 to 41.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Episodes Treated With 1 to ≥4 Infusions

End point title	Bleeding Episodes Treated With 1 to ≥4 Infusions
End point description:	
The number of bleeding episodes treated with 1, 2, 3, or ≥4 infusions of rAHF-PFM to achieve adequate hemostasis	
End point type	Secondary
End point timeframe:	
Reported during study period which was to be at least 75 exposure days or 3 years (whichever came first)	

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Bleeding episodes				
1 infusion	356			
2 infusions	107			
3 infusions	35			
4 or more infusions	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Hemostasis for Treatment of Bleeding Episodes

End point title	Assessment of Hemostasis for Treatment of Bleeding Episodes

End point description:

Number of rAHF-PFM-treated bleeding episodes with treater assessment of hemostasis (4-point ordinal scale): Excellent: Full pain relief & bleeding cessation within ~8 hrs of 1 infusion. Additional infusions may have been given to maintain hemostasis; Good: Definite pain relief and/or improvement in bleeding within ~8 hrs after infusion. Possibly requires >1 infusion for complete resolution; Fair: Probable or slight relief of pain & slight improvement in bleeding within ~8 hrs after infusion. Requires >1 infusion for complete resolution; or None: No improvement or condition worsens.

End point type	Secondary

End point timeframe:

Reported during study period which was to be at least 75 exposure days or 3 years (whichever came first)

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: bleeding episodes				
Excellent	258			
Good	177			
Fair	30			
None	1			
Unknown/not assessed	51			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Bleeding Episodes

End point title	Annualized Rate of Bleeding Episodes

End point description:

Number of bleeding episodes per subject annualized over 1 year for all etiologies

End point type	Secondary

End point timeframe:

Reported during study period which was to be at least 75 exposure days or 3 years (whichever came first)

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: bleeding episodes per subject per year				
median (full range (min-max))	4.95 (1.01 to 32.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly rAHF-PFM Utilization

End point title	Weekly rAHF-PFM Utilization

End point description:

Weight-Adjusted Weekly Dose for Prophylaxis, On-Demand Treatment, and Perioperative Management. rAHF-PFM dose determined by the investigator (ie: standard regimen [25-50 IU/kg body weight, 3-4 times per week]; modified prophylactic regimen [dose and frequency selected by investigator] or on–demand treatment [dose selected by investigator]). Dosing to treat BEs was at investigator's discretion and in accordance with institution’s standard of care. rAHF-PFM was administered I.V. via bolus infusion, except for perioperative management when it was given either by continuous or bolus

End point type	Secondary

End point timeframe:

Reported during study period which was to be at least 75 exposure days or 3 years (whichever came first)

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: IU/kg				
median (full range (min-max))				
During Prophylaxis (n=36)	87.1 (6.5 to 352.3)			
During On-Demand Treatment (n=47)	12.5 (2.4 to 176.8)			
During Perioperative Management (n=25)	606.4 (256.5 to 1951)			

Statistical analyses

No statistical analyses for this end point

Secondary: In Vivo Incremental Recovery

End point title	In Vivo Incremental Recovery

End point description:

Change in factor VIII concentration from pre- to post-infusion at initial and termination study visits.

End point type	Secondary

End point timeframe:

30 minutes pre-infusion to 30 minutes post-infusion

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: IU/dL per IU/kg				
median (full range (min-max))				
Initial Visit (n=4) Termination Visit (n=12)	1.81 (0.74 to 1.92) 1.71 (1.32 to 2.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Intra-operative Hemostasis

End point title	Assessment of Intra-operative Hemostasis

End point description:

Number of surgical procedures managed with rAHF-PFM and with surgeon's assessment of hemostasis based on a 4-point ordinal scale: Excellent: ≤ average predicted blood loss for matched procedures in healthy individuals Good: > average predicted blood loss, but ≤ maximal predicted blood loss for matched procedures in healthy individuals Fair: > maximal predicted blood loss for matched procedures in healthy individuals, and hemostasis was achieved None: uncontrolled hemostasis with proper dosing, necessitating a change in treatment regimen

End point type	Secondary

End point timeframe:

Assessed at the time of discharge from recovery room

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Procedures				
Excellent	18			
Good	4			
Not Applicable	0			
Not Done	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Postoperative Hemostasis

End point title	Assessment of Postoperative Hemostasis

End point description:

Number of surgical procedures managed with rAHF-PFM and with investigator's assessment of hemostasis based on a 4-point ordinal scale: Excellent: hemostasis was as good as or better than other licensed factor VIII products for matched procedure Good: hemostasis was probably as good as other licensed factor VIII products for matched procedure Fair: hemostasis was clearly < optimal for matched procedure, without need to change regimen None: bleeding from inadequate response with proper dosing, necessitating a change in regimen

End point type	Secondary

End point timeframe:

Assessed at the time of discharge from hospital or clinic

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Procedures				
Excellent	23			
Good	2			
Not Applicable	1			
Not Done	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Blood Loss During Surgical Procedures

End point title	Assessment of Blood Loss During Surgical Procedures

End point description:

Percentage of actual intraoperative blood loss compared to preoperatively predicted average and maximal blood loss in hemostatically normal matched individuals (from institutional blood bank records)

End point type	Secondary

End point timeframe:

Predicted volumes preoperatively estimated and actual volumes intraoperatively recorded

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Percentage Blood Loss				
median (full range (min-max))				
Blood loss as percentage of predicted average	50 (0 to 250)			
Blood loss as percentage of predicted maximal	20 (0 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events Deemed Related to Treatment

End point title	Adverse Events Deemed Related to Treatment

End point description:

Number of participants who reported AEs deemed related to treatment with rAHF-PFM

End point type	Secondary

End point timeframe:

Reported during the study period which was to be at least 75 exposure days or 3 years (whichever came first)

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Percentage of Participants	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Development of Antibodies to Heterologous Proteins

End point title	Development of Antibodies to Heterologous Proteins

End point description:

Number of treated participants who developed antibodies to heterologous proteins (ie, Chinese Hamster Ovary Cell Protein, Murine IgG, or Recombinant Human VWF)

End point type	Secondary

End point timeframe:

Assessed at baseline, throughout the duration of the study, which was to be at least 75 exposure days or 3 years (whichever came first), and at the termination visit.

End point values	PUPs			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Percentage of Participants				
Antibodies to Chinese Hamster Ovary Cell Protein	0			
Antibodies to Murine IgG	0			
Antibodies to Recombinant Human VWF (n=54)	0			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Factor VIII Inhibitor Risk Factor: Genetic Risk Factor- Family History of Inhibitors

End point title	Factor VIII Inhibitor Risk Factor: Genetic Risk Factor- Family History of Inhibitors

End point description:

Number of treated participants who developed an inhibitor

End point type	Post-hoc

End point timeframe:

Duration of study which was to be at least 75 exposure days or 3 years (whichever came first)

End point values	Did not Develop Factor VIII Inhibitor	Developed Factor VIII Inhibitor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	16		
Units: Participants				
Has Family History of Inhibitors	6	8		
Unknown Family History of Inhibitors	2	1		
No Family History of Inhibitors	26	7		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Did not Develop Factor VIII Inhibitor v Developed Factor VIII Inhibitor

Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	4.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	19.06

Post-hoc: Factor VIII Inhibitor Risk Factor: Race

End point title	Factor VIII Inhibitor Risk Factor: Race
End point description:	
Number of treated participants who developed an inhibitor	
End point type	Post-hoc
End point timeframe:	
Duration of study which was to be at least 75 exposure days or 3 years (whichever came first)	

End point values	Did not Develop Factor VIII Inhibitor	Developed Factor VIII Inhibitor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	16		
Units: Participants				
Non-Caucasian	8	9		
Caucasian	26	7		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Did not Develop Factor VIII Inhibitor v Developed Factor VIII Inhibitor
Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	4.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	14.82

Post-hoc: Factor VIII Inhibitor Risk Factor: Number of Participants with Intensive Treatment and High Dose (≤20 Exposure Days (EDs))

End point title	Factor VIII Inhibitor Risk Factor: Number of Participants with Intensive Treatment and High Dose (≤20 Exposure Days (EDs))

End point description:

Immunogenicity Analysis Set- Participants with 5 consecutive study days of a mean infusion dose of FVIII >50 IU/kg within ≤20 EDs who developed an inhibitor

End point type	Post-hoc

End point timeframe:

Duration of study which was to be at least 75 exposure days or 3 years (whichever came first)

End point values	Did not Develop Factor VIII Inhibitor	Developed Factor VIII Inhibitor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	16		
Units: Participants				
Received intensive treatment & high dose	4	6		
No intensive treatment & high dose	30	10		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Did not Develop Factor VIII Inhibitor v Developed Factor VIII Inhibitor
Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	19.25

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Study period was to be at least 75 exposure days or 3 years (whichever came first)	
Adverse event reporting additional description:	
Median days on study was 498 (range: 82 to 1360) days. Median days of rAHF-PFM exposure was 76 (range: 1 to 414) exposure days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups	
Reporting group title	PUPs
Reporting group description:	
Reporting group 1 description	

Serious adverse events	PUPs		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 55 (50.91%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Mouth injury			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin laceration			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue injury			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Factor VIII inhibition			
subjects affected / exposed	16 / 55 (29.09%)		
occurrences causally related to treatment / all	16 / 16		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Catheter site haematoma			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			

subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Wheezing				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Haemarthrosis				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacteraemia				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter bacteraemia				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter related infection				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Pneumonia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PUPs		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 55 (94.55%)		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	11		
Arthropod bite			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		
Mouth injury			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Skin laceration			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	39 / 55 (70.91%) 137 4 / 55 (7.27%) 6		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Iron deficiency anaemia subjects affected / exposed occurrences (all)	 10 / 55 (18.18%) 13 5 / 55 (9.09%) 8		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 3 / 55 (5.45%) 3		
Eye disorders Conjuctivitis subjects affected / exposed occurrences (all)	 9 / 55 (16.36%) 12		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	 20 / 55 (36.36%) 31 17 / 55 (30.91%) 29 3 / 55 (5.45%) 5		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Rhinorrhoea	 23 / 55 (41.82%) 65 		

subjects affected / exposed	22 / 55 (40.00%)		
occurrences (all)	54		
Nasal congestion			
subjects affected / exposed	15 / 55 (27.27%)		
occurrences (all)	48		
Wheezing			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	10		
Oropharyngeal pain			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	13 / 55 (23.64%)		
occurrences (all)	18		
Dermatitis diaper			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	8		
Urticaria			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	28 / 55 (50.91%)		
occurrences (all)	80		
Ear infection			
subjects affected / exposed	20 / 55 (36.36%)		
occurrences (all)	44		
Upper respiratory tract infection			
subjects affected / exposed	16 / 55 (29.09%)		
occurrences (all)	35		
Otitis media			

subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	13		
Hand-foot-and-mouth disease			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Bronchitis			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	10		
Influenza			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	8		
Pharyngitis			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Varicella			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	14		
Croup infectious			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Gasteroenteritis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	5		

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