Clinical trial results:
A Study of Immunologic safety for Alphanate in Previously Treated Patients Diagnosed with Severe Hemophilia A

Summary

EudraCT number	2006-002635-24
Trial protocol	PL
Global end of trial date	14 December 2018

Results information

Result version number	v1 (current)
This version publication date	18 April 2022
First version publication date	18 April 2022

Trial information

Trial identification

Sponsor protocol code	GBI04-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00323856
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grifols.Inc
Sponsor organisation address	2410 Lillyvale Avenue, Los Angeles, United States, CA 90032
Public contact	Michael Ken Woodward, Instituto Grifols SA, +34 938008784, michael.woodward@grifols.com
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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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to determine the immunologic and general safety of long-term use of Alphanate in individuals diagnosed with severe hemophilia A.

Protection of trial subjects:

A written informed consent was obtained from the subject after the investigator has provided a full explanation, both verbally and in writing, of the purpose, risks and discomforts involved, and potential benefits of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2003
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	10
Adolescents (12-17 years)	10
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in Poland at 2 centers from January 2003 to July 2020.

Pre-assignment

Screening details:

Male subjects diagnosed with severe hemophilia A who have been previously treated with Factor VIII concentrates, cryoprecipitate, or whole blood for a total of 150 cumulative exposure were enrolled. A total of 51 subjects were enrolled out of which, 50 subjects received the treatment. A total of 45 subjects completed the study.

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	Alphanate

Arm description:

Subjects were treated at home and with in-clinic therapy exclusively with Alphanate as their sole source of Factor VIII (FVIII) concentrate for prophylaxis and treatment of all bleeding episodes and surgical procedures for a period of at least two years and a minimum of 50 exposure days, or, if 50 exposure days were not reached, for a maximum of 30 months. An exposure day was defined as any day on which a subject received one or more infusions of any FVIII containing product. Alphanate was administered intravascularly in accordance with the subject's usual pre-study treatment regimen.

Arm type	Experimental
Investigational medicinal product name	Alphanate
Investigational medicinal product code	
Other name	Antihemophilic Factor (Human)
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Alphanate was administered intravascularly in accordance with the subject’s usual pre-study treatment regimen.

Number of subjects in period 1	Alphanate
Started	50
Completed	45
Not completed	5
Was uncooperative and noncompliant	1
Withdrawal by Subject	1
Reason not specified	1
Missing	2

Baseline characteristics

Reporting groups	
Reporting group title	Alphanate

Reporting group description:

Subjects were treated at home and with in-clinic therapy exclusively with Alphanate as their sole source of Factor VIII (FVIII) concentrate for prophylaxis and treatment of all bleeding episodes and surgical procedures for a period of at least two years and a minimum of 50 exposure days, or, if 50 exposure days were not reached, for a maximum of 30 months. An exposure day was defined as any day on which a subject received one or more infusions of any FVIII containing product. Alphanate was administered intravascularly in accordance with the subject's usual pre-study treatment regimen.

Reporting group values	Alphanate	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 24.8 ± 14.45	 -	
Gender categorical Units: Subjects			
Female	0	0	
Male	50	50	
Race/ Ethnicity Units: Subjects			
Caucasian	30	30	
Hispanic	8	8	
Asian	11	11	
Other	1	1	

End points

End points reporting groups

Reporting group title	Alphanate

Reporting group description:

Subjects were treated at home and with in-clinic therapy exclusively with Alphanate as their sole source of Factor VIII (FVIII) concentrate for prophylaxis and treatment of all bleeding episodes and surgical procedures for a period of at least two years and a minimum of 50 exposure days, or, if 50 exposure days were not reached, for a maximum of 30 months. An exposure day was defined as any day on which a subject received one or more infusions of any FVIII containing product. Alphanate was administered intravascularly in accordance with the subject's usual pre-study treatment regimen.

Primary: Number of Subjects With Factor VIII (FVIII) Inhibitor Development

End point title	Number of Subjects With Factor VIII (FVIII) Inhibitor Development[1]

End point description:

Incidence of FVIII inhibitor development was defined as any result determined positive at a central laboratory (inhibitor titer of greater than 0.6 modified Bethesda Units/milliliters [BU/mL]) using Nijmegen modification of the Bethesda assay. Safety population included all subjects who received at least one infusion of study medication.

End point type	Primary

End point timeframe:

Up to Month 30

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: No subjects developed inhibitors of FVIII during the study.

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AE)

End point title	Number of Subjects With Adverse Events (AE)

End point description:

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product or study treatment, and which did not necessarily have a causal relationship with this administration. Here the end of the study is defined as completion/discontinuation visit. Safety population included all subjects who received at least one infusion of study medication.

End point type	Secondary

End point timeframe:

Up to Month 30

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: subjects	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Alkaline Phosphatase

End point title	Change From Baseline in Alkaline Phosphatase

End point description:

The Baseline value was the last non-missing value before the study drug was taken and the end of study was defined as completion/discontinuation visit. Change from Baseline was calculated by subtracting Baseline value from the post-infusion visit value. Safety population included all subjects who received at least one infusion of study medication. Number analyzed signifies number of subjects evaluable at each specified endpoint.

End point type	Secondary

End point timeframe:

Baseline and Quarterly Visit 1 (Month 3), 2 (Month 6), 3 (Month 9), 4 (Month 12), 5 (Month 15), 6 (Month 18), 7 (Month 21), 8 (Month 24), 9 (Month 27) and 10 (Month 30)

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: microkatal per litre (µkat/L)				
arithmetic mean (standard deviation)				
Baseline (n=44)	2.315 (± 1.3287)			
Change at Quarterly Visit 1 (Month 3) (n=39)	-0.030 (± 0.6136)			
Change at Quarterly Visit 2 (Month 6) (n=39)	-0.146 (± 0.8197)			
Change at Quarterly Visit 3 (Month 9) (n=42)	-0.087 (± 0.8601)			
Change at Quarterly Visit 4 (Month 12) (n=41)	-0.309 (± 0.7635)			
Change at Quarterly Visit 5 (Month 15) (n=40)	-0.127 (± 1.0940)			
Change at Quarterly Visit 6 (Month 18) (n=42)	-0.342 (± 0.9484)			
Change at Quarterly Visit 7 (Month 21) (n=40)	-0.490 (± 1.0561)			
Change at Quarterly Visit 8 (Month 24) (n=42)	-0.299 (± 1.2843)			
Change at Quarterly Visit 9 (Month 27) (n=8)	-1.004 (± 1.2453)			

Change at Quarterly Visit 10 (Month 30) (n=2)	-0.075 (± 0.0827)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Alanine Aminotransferase

End point title	Change From Baseline in Alanine Aminotransferase

End point description:

The Baseline value was the last non-missing value before the study drug was taken and the end of study was defined as completion/discontinuation visit. Change from Baseline was calculated by subtracting Baseline value from the post-infusion visit value. Safety population included all subject who received at least one infusion of study medication. Number analyzed signifies number of subject evaluable at each specified endpoint.

End point type	Secondary

End point timeframe:

Baseline and Quarterly Visit 1 (Month 3), 2 (Month 6), 3 (Month 9), 4 (Month 12), 5 (Month 15), 6 (Month 18), 7 (Month 21), 8 (Month 24), 9 (Month 27) and 10 (Month 30)

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: µkat/L				
arithmetic mean (standard deviation)				
Baseline (n=44)	0.577 (± 0.6770)			
Change at Quarterly Visit 1 (Month 3) (n=39)	-0.005 (± 0.2437)			
Change at Quarterly Visit 2 (Month 6) (n=39)	-0.055 (± 0.2754)			
Change at Quarterly Visit 3 (Month 9) (n=42)	-0.089 (± 0.3625)			
Change at Quarterly Visit 4 (Month 12) (n=43)	-0.114 (± 0.4310)			
Change at Quarterly Visit 5 (Month 15) (n=41)	-0.081 (± 0.3539)			
Change at Quarterly Visit 6 (Month 18) (n=42)	-0.133 (± 0.4109)			
Change at Quarterly Visit 7 (Month 21) (n=41)	-0.117 (± 0.3861)			
Change at Quarterly Visit 8 (Month 24) (n=41)	-0.077 (± 0.3951)			
Change at Quarterly Visit 9 (Month 27) (n=9)	-0.074 (± 0.1730)			
Change at Quarterly Visit 10 (Month 30) (n=3)	-0.150 (± 0.2688)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Aspartate Aminotransferase

End point title	Change From Baseline in Aspartate Aminotransferase

End point description:

The Baseline value was the last non-missing value before the study drug was taken and the end of the study was defined as completion/discontinuation visit. Change from Baseline was calculated by subtracting Baseline value from the post-infusion visit value. Safety population included all subjects who received at least one infusion of study medication. Number analyzed signifies number of subjects evaluable at each specified endpoint.

End point type	Secondary

End point timeframe:

Baseline and Quarterly Visit 1 (Month 3), 2 (Month 6), 3 (Month 9), 4 (Month 12), 5 (Month 15), 6 (Month 18), 7 (Month 21), 8 (Month 24), 9 (Month 27) and 10 (Month 30)

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: µkat/L				
arithmetic mean (standard deviation)				
Baseline (n=44)	0.544 (± 0.6337)			
Change at Quarterly Visit 1 (Month 3) (n=38)	0.023 (± 0.1312)			
Change at Quarterly Visit 2 (Month 6) (n=40)	-0.011 (± 0.2900)			
Change at Quarterly Visit 3 (Month 9) (n=43)	-0.062 (± 0.3885)			
Change at Quarterly Visit 4 (Month 12) (n=43)	-0.092 (± 0.4350)			
Change at Quarterly Visit 5 (Month 15) (n=41)	-0.071 (± 0.3890)			
Change at Quarterly Visit 6 (Month 18) (n=42)	-0.081 (± 0.4083)			
Change at Quarterly Visit 7 (Month 21) (n=40)	-0.074 (± 0.3769)			
Change at Quarterly Visit 8 (Month 24) (n=41)	-0.020 (± 0.3913)			
Change at Quarterly Visit 9 (Month 27) (n=9)	-0.043 (± 0.0963)			
Change at Quarterly Visit 10 (Month 30) (n=3)	-0.039 (± 0.0632)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lactate Dehydrogenase

End point title	Change From Baseline in Lactate Dehydrogenase

End point description:

The Baseline value was the last non-missing value before study drug was taken and the end of study was defined as completion/discontinuation visit. Change from Baseline was calculated by subtracting Baseline value from the post-infusion visit value. Safety population included all subjects who received at least one infusion of study medication. Number analyzed signifies number of subjects evaluable at each specified endpoint.

End point type	Secondary

End point timeframe:

Baseline and Quarterly Visit 1 (Month 3), 2 (Month 6), 3 (Month 9), 4 (Month 12), 5 (Month 15), 6 (Month 18), 7 (Month 21), 8 (Month 24), 9 (Month 27) and 10 (Month 30)

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: µkat/L				
arithmetic mean (standard deviation)				
Baseline (n=43)	5.64 (± 2.089)			
Change at Quarterly Visit 1 (Month 3) (n=40)	-0.07 (± 0.926)			
Change at Quarterly Visit 2 (Month 6) (n=37)	-0.04 (± 1.703)			
Change at Quarterly Visit 3 (Month 9) (n=41)	-0.01 (± 1.595)			
Change at Quarterly Visit 4 (Month 12) (n=40)	-0.31 (± 2.231)			
Change at Quarterly Visit 5 (Month 15) (n=39)	-0.47 (± 1.388)			
Change at Quarterly Visit 6 (Month 18) (n=42)	-0.52 (± 1.814)			
Change at Quarterly Visit 7 (Month 21) (n=40)	-0.65 (± 1.560)			
Change at Quarterly Visit 8 (Month 24) (n=39)	-0.21 (± 2.413)			
Change at Quarterly Visit 9 (Month 27) (n=9)	-0.21 (± 1.497)			
Change at Quarterly Visit 10 (Month 30) (n=3)	0.22 (± 0.972)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bilirubin

End point title	Change From Baseline in Bilirubin

End point description:

The Baseline value was the last non-missing value before the study drug was taken and the end of study was defined as completion/discontinuation visit. Change from Baseline was calculated by subtracting Baseline value from the post-infusion visit value. Safety population included all subjects who received at least one infusion of study medication. Number analyzed signifies number of subjects evaluable at each specified endpoint.

End point type	Secondary

End point timeframe:

Baseline and Quarterly Visit 1 (Month 3), 2 (Month 6), 3 (Month 9), 4 (Month 12), 5 (Month 15), 6 (Month 18), 7 (Month 21), 8 (Month 24), 9 (Month 27) and 10 (Month 30)

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: micromole per litre (µmol/L)				
arithmetic mean (standard deviation)				
Baseline (n=44)	12.346 (± 6.2515)			
Change at Quarterly Visit 1 (Month 3) (n=40)	41.387 (± 255.8005)			
Change at Quarterly Visit 2 (Month 6) (n=40)	-0.815 (± 5.0952)			
Change at Quarterly Visit 3 (Month 9) (n=42)	40.485 (± 253.2611)			
Change at Quarterly Visit 4 (Month 12) (n=43)	1.461 (± 7.2030)			
Change at Quarterly Visit 5 (Month 15) (n=41)	-0.031 (± 4.0146)			
Change at Quarterly Visit 6 (Month 18) (n=41)	0.759 (± 4.0038)			
Change at Quarterly Visit 7 (Month 21) (n=40)	0.498 (± 5.3277)			
Change at Quarterly Visit 8 (Month 24) (n=42)	0.060 (± 4.4453)			
Change at Quarterly Visit 9 (Month 27) (n=8)	0.760 (± 2.9257)			
Change at Quarterly Visit 10 (Month 30) (n=3)	-1.539 (± 3.8664)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Blood Urea Nitrogen

End point title	Change From Baseline in Blood Urea Nitrogen

End point description:

The Baseline value was the last non-missing value before the study drug was taken and the end of study was defined as completion/discontinuation visit. Change from Baseline was calculated by subtracting Baseline value from the post-infusion visit value. Safety population included all subjects who received at least one infusion of study medication. Number analyzed signifies number of subjects evaluable at each specified endpoint.

End point type	Secondary

End point timeframe:

Baseline and Quarterly Visit 1 (Month 3), 2 (Month 6), 3 (Month 9), 4 (Month 12), 5 (Month 15), 6 (Month 18), 7 (Month 21), 8 (Month 24), 9 (Month 27) and 10 (Month 30)

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: millimole per litre (mmol/L)				
arithmetic mean (standard deviation)				
Baseline (n=44)	5.330 (± 2.8786)			
Change at Quarterly Visit 1 (Month 3) (n=41)	0.140 (± 1.8371)			
Change at Quarterly Visit 2 (Month 6) (n=40)	0.177 (± 1.8985)			
Change at Quarterly Visit 3 (Month 9) (n=43)	0.489 (± 2.1387)			
Change at Quarterly Visit 4 (Month 12) (n=43)	1.356 (± 5.6452)			
Change at Quarterly Visit 5 (Month 15) (n=41)	13.476 (± 79.9256)			
Change at Quarterly Visit 6 (Month 18) (n=42)	1.331 (± 3.6889)			
Change at Quarterly Visit 7 (Month 21) (n=41)	0.766 (± 2.2935)			
Change at Quarterly Visit 8 (Month 24) (n=41)	0.907 (± 2.7810)			
Change at Quarterly Visit 9 (Month 27) (n=9)	0.728 (± 1.4505)			
Change at Quarterly Visit 10 (Month 30) (n=3)	0.119 (± 2.0300)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Creatinine

End point title	Change From Baseline in Creatinine

End point description:

The Baseline value was the last non-missing value before the study drug was taken and the end of study was defined as completion/discontinuation visit. Change from Baseline was calculated by subtracting Baseline value from the post-infusion visit value. Safety population included all subjects who received at least one infusion of study medication. Number analyzed signifies number of subjects evaluable at each specified endpoint.

End point type	Secondary

End point timeframe:

Baseline and Quarterly Visit 1 (Month 3), 2 (Month 6), 3 (Month 9), 4 (Month 12), 5 (Month 15), 6 (Month 18), 7 (Month 21), 8 (Month 24), 9 (Month 27) and 10 (Month 30)

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline (n=44)	61.30 (± 15.067)			
Change at Quarterly Visit 1 (Month 3) (n=41)	3.47 (± 21.125)			
Change at Quarterly Visit 2 (Month 6) (n=40)	-1.76 (± 12.956)			
Change at Quarterly Visit 3 (Month 9) (n=43)	4.18 (± 13.627)			
Change at Quarterly Visit 4 (Month 12) (n=43)	18.56 (± 111.453)			
Change at Quarterly Visit 5 (Month 15) (n=41)	5.80 (± 18.984)			
Change at Quarterly Visit 6 (Month 18) (n=42)	5.44 (± 15.480)			
Change at Quarterly Visit 7 (Month 21) (n=41)	5.55 (± 15.475)			
Change at Quarterly Visit 8 (Month 24) (n=42)	6.11 (± 18.426)			
Change at Quarterly Visit 9 (Month 27) (n=9)	4.93 (± 12.605)			
Change at Quarterly Visit 10 (Month 30) (n=3)	7.37 (± 11.367)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Human Immunodeficiency Virus Type 1 and 2 (HIV-1/HIV-2), Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or Parvovirus B19 -Negative at Baseline Who Are Seropositive for Any of These Viruses

End point title	Number of Subjects With Human Immunodeficiency Virus Type 1 and 2 (HIV-1/HIV-2), Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or Parvovirus B19 - Negative at Baseline Who Are Seropositive for Any of These Viruses

End point description:

Seroconversion based on Enzyme-linked Immunosorbent Assay (ELISA). Seronegative defined as non-reactive in an ELISA test for antibody to the virus in question. Seropositive defined as reactive in an ELISA test for antibody to the virus in question. Safety population included all subjects who received at least one infusion of study medication.

Note: Results will be added once available.

End point type	Secondary

End point timeframe:
Up to Month 30

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Month 30

Adverse event reporting additional description:

Safety population included all subjects who received at least one infusion of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Alphanate

Reporting group description:

Subjects were treated at home and with in-clinic therapy exclusively with Alphanate as their sole source of Factor VIII (FVIII) concentrate for prophylaxis and treatment of all bleeding episodes and surgical procedures for a period of at least two years and a minimum of 50 exposure days, or, if 50 exposure days were not reached, for a maximum of 30 months. An exposure day was defined as any day on which a subject received one or more infusions of any FVIII containing product. Alphanate was administered intravascularly in accordance with the subject's usual pre-study treatment regimen.

Serious adverse events	Alphanate		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Post Procedural Discharge			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device Malfunction			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal Haemorrhage			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Joint Swelling			
subjects affected / exposed	1 / 50 (2.00%)		
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	Alphanate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 50 (44.00%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Joint Injury			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	4		
Ligament Sprain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Limb Injury			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	7		
Skin Abrasion			

subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Vascular disorders Haemorrhage subjects affected / exposed occurrences (all)	 3 / 50 (6.00%) 6		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 4 / 50 (8.00%) 7		
General disorders and administration site conditions Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 4 / 50 (8.00%) 7 4 / 50 (8.00%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal Pain subjects affected / exposed occurrences (all) Nasal Congestion subjects affected / exposed occurrences (all)	 8 / 50 (16.00%) 13 5 / 50 (10.00%) 8 4 / 50 (8.00%) 6		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 3 / 50 (6.00%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back Pain	 4 / 50 (8.00%) 6		

subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Infections and infestations Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all)	 5 / 50 (10.00%) 8 3 / 50 (6.00%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2002	The overall reason for this amendment was to update the study title, to change the age group, to change the minimum potency of Alphanate to be used, to change endpoints terminology, to update schedules of laboratory testing, to specify the amount of serum samples, to change collection criteria of plasma samples, to change the anti-HIV testing criteria, to specify inhibitor assay for subjects who develop inhibitors, to revise visits, to add a section on home treatment, to add the physician assessment in 'in-hospital and in-clinic treatments' and to modify dosing guidelines.
14 October 2002	The overall reason for this amendment was to update the study design, to update inclusion criteria, to update screening details, to update factor VIII:C inhibitor test, to update serum sample saving and freezing criteria, to update the subject assignment number criteria, to change the viral serological tests criteria, to change the unscheduled visit criteria and to update product usage and subject diaries criteria, to update concurrent medication criteria.
17 April 2003	The overall reason for this amendment was to update inclusion criteria, to update study procedures and schedule of events, to update visit criteria for subjects who tests positive for the presence of factor VIII inhibitors, to update informed consent form, to update institutional review board section, to update the details of documents required before a study is initiated, to update investigator's agreement and to update schedule of events.
16 December 2003	The overall reason for this amendment was to change the name of the sponsor, to update screening, enrollment, quarterly clinic/office visits details and to update schedule of events.
01 May 2006	The overall reason for this amendment was to update quarterly testing criteria, to update the criteria for unscheduled visits, to update the visit and testing criteria for subjects who develop inhibitors, to update sample size and to update primary endpoint details.
10 January 2007	The overall reason for this amendment was to update the study design, exclusion criteria, study procedures and serious adverse event section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported