



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 |
| Scientific contact | Michael Ken Woodward, Instituto Grifols SA, +34 938008784, michael.woodward@grifols.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? | 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: $\mu\text{kat/L}$ | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=44) | 0.544 (\pm 0.6337) | | | |
| Change at Quarterly Visit 1 (Month 3) (n=38) | 0.023 (\pm 0.1312) | | | |
| Change at Quarterly Visit 2 (Month 6) (n=40) | -0.011 (\pm 0.2900) | | | |
| Change at Quarterly Visit 3 (Month 9) (n=43) | -0.062 (\pm 0.3885) | | | |
| Change at Quarterly Visit 4 (Month 12) (n=43) | -0.092 (\pm 0.4350) | | | |
| Change at Quarterly Visit 5 (Month 15) (n=41) | -0.071 (\pm 0.3890) | | | |
| Change at Quarterly Visit 6 (Month 18) (n=42) | -0.081 (\pm 0.4083) | | | |
| Change at Quarterly Visit 7 (Month 21) (n=40) | -0.074 (\pm 0.3769) | | | |
| Change at Quarterly Visit 8 (Month 24) (n=41) | -0.020 (\pm 0.3913) | | | |
| Change at Quarterly Visit 9 (Month 27) (n=9) | -0.043 (\pm 0.0963) | | | |
| Change at Quarterly Visit 10 (Month 30) (n=3) | -0.039 (\pm 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: $\mu\text{kat/L}$ | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=43) | 5.64 (\pm 2.089) | | | |
| Change at Quarterly Visit 1 (Month 3) (n=40) | -0.07 (\pm 0.926) | | | |
| Change at Quarterly Visit 2 (Month 6) (n=37) | -0.04 (\pm 1.703) | | | |
| Change at Quarterly Visit 3 (Month 9) (n=41) | -0.01 (\pm 1.595) | | | |
| Change at Quarterly Visit 4 (Month 12) (n=40) | -0.31 (\pm 2.231) | | | |
| Change at Quarterly Visit 5 (Month 15) (n=39) | -0.47 (\pm 1.388) | | | |
| Change at Quarterly Visit 6 (Month 18) (n=42) | -0.52 (\pm 1.814) | | | |
| Change at Quarterly Visit 7 (Month 21) (n=40) | -0.65 (\pm 1.560) | | | |
| Change at Quarterly Visit 8 (Month 24) (n=39) | -0.21 (\pm 2.413) | | | |
| Change at Quarterly Visit 9 (Month 27) (n=9) | -0.21 (\pm 1.497) | | | |
| Change at Quarterly Visit 10 (Month 30) (n=3) | 0.22 (\pm 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

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|-----------------|---|
| 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: $\mu\text{mol/L}$ | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=44) | 61.30 (\pm 15.067) | | | |
| Change at Quarterly Visit 1 (Month 3) (n=41) | 3.47 (\pm 21.125) | | | |
| Change at Quarterly Visit 2 (Month 6) (n=40) | -1.76 (\pm 12.956) | | | |
| Change at Quarterly Visit 3 (Month 9) (n=43) | 4.18 (\pm 13.627) | | | |
| Change at Quarterly Visit 4 (Month 12) (n=43) | 18.56 (\pm 111.453) | | | |
| Change at Quarterly Visit 5 (Month 15) (n=41) | 5.80 (\pm 18.984) | | | |
| Change at Quarterly Visit 6 (Month 18) (n=42) | 5.44 (\pm 15.480) | | | |
| Change at Quarterly Visit 7 (Month 21) (n=41) | 5.55 (\pm 15.475) | | | |
| Change at Quarterly Visit 8 (Month 24) (n=42) | 6.11 (\pm 18.426) | | | |
| Change at Quarterly Visit 9 (Month 27) (n=9) | 4.93 (\pm 12.605) | | | |
| Change at Quarterly Visit 10 (Month 30) (n=3) | 7.37 (\pm 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 | 5 / 50 (10.00%) | | |
| occurrences (all) | 8 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | | |
| occurrences (all) | 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