# Clinical trial results:
# A Multicenter Phase 2 Open-Label, Single-Arm, Prospective, Interventional Study of Plasma-Derived Factor VIII/VWF (Alphanate®) in Immune Tolerance Induction Therapy in Subjects with Congenital Hemophilia A

## Summary

| | |
|---|---|
| EudraCT number | 2015-005524-26 |
| Trial protocol | ES IT |
| Global end of trial date | 18 September 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 02 October 2021 |
| First version publication date | 02 October 2021 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | GBI1406 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03095287 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND/CTA Number: 016703 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Grifols Biologicals LLC |
| Sponsor organisation address | 5555 Valley Boulevard, Los Angeles, United States, CA 90032 |
| Public contact | Rhonda Griffin, Grifols Therapeutics LLC, +1 919 316 6693, Rhonda.griffin@grifols.com |
| Scientific contact | Rhonda Griffin, Grifols Therapeutics LLC, +1 919 316 6693, Rhonda.griffin@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? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 18 September 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 18 September 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of the study is to assess the percentage of subjects who achieve complete immune tolerance within 33 months of initiating Alphanate for immune tolerance induction (ITI) and to assess the safety of Alphanate treatment for ITI.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 January 2018 |
| 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 | India: 2 |
| Worldwide total number of subjects | 2 |
| EEA total number of subjects | 0 |

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) | 2 |
| 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:

Subjects took part in the study at two sites in India from 03 January 2018 (first subject enrolled to receive the study drug) to 18 September 2020 (last subject completed).

### Pre-assignment

Screening details:

Male subjects with diagnosis of Congenital Hemophilia A were enrolled in a single arm to receive alphanate. The study was to be conducted in 2 phases: Immune Tolerance Induction Phase followed by Prophylactic Phase. However, due to the limited enrollment, the study was terminated prior to the start of Prophylactic Phase.

### 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 entered the immune tolerance induction (ITI) phase and received alphanate IV at a starting dose of 100 IU/kg/day. Dose could be uptitrated to 200 IU/kg/day based on investigator's discretion. The maximum duration of treatment was 32 months and 2 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Alphanate |
| Investigational medicinal product code | |
| Other name | Plasma Derived Factor VIII/von Willebrand Factor |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received Alphanate IV daily until complete immune tolerance was achieved or for 33 months if complete immune tolerance was not achieved. Alphanate was administered 100 International units (IU)/kg/day for at least 90 days during ITI phase. After the first 90 days, dose could be increased to 200 IU/kg/day if there was <20% decrease in inhibitor titer or an increase in the rate of bleeding events relative to the rate of bleeding events experienced during the first 90 days of treatment, or if the inhibitor increased to >500 Bethesda Units (BU), after initiation of Alphanate ITI treatment.

| **Number of subjects in period 1** | Alphanate |
|---|---|
| Started | 2 |
| Completed | 0 |
| Not completed | 2 |
| Adverse Event | 1 |
| Treatment Failure | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Alphanate |
| Reporting group description: | |
| Subjects entered the immune tolerance induction (ITI) phase and received alphanate IV at a starting dose of 100 IU/kg/day. Dose could be uptitrated to 200 IU/kg/day based on investigator's discretion. The maximum duration of treatment was 32 months and 2 weeks. | |

| Reporting group values | Alphanate | Total | |
|---|---|---|---|
| Number of subjects | 2 | 2 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 2 | 2 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Due to low number of participants enrolled in the study 0 participants are reported to maintain participant confidentiality. | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 2 | 2 | |

## End points

### End points reporting groups

| Reporting group title | Alphanate |
|---|---|

Reporting group description:

Subjects entered the immune tolerance induction (ITI) phase and received alphanate IV at a starting dose of 100 IU/kg/day. Dose could be uptitrated to 200 IU/kg/day based on investigator's discretion. The maximum duration of treatment was 32 months and 2 weeks.

### Primary: Percentage of Subjects who Achieved Complete Immune Tolerance Within 33 Months of Initiation of Immune Tolerance Induction (ITI) Treatment Phase

| End point title | Percentage of Subjects who Achieved Complete Immune Tolerance Within 33 Months of Initiation of Immune Tolerance Induction (ITI) Treatment Phase[1] |
|---|---|

End point description:

Complete immune tolerance was defined as the participants achieving 2 consecutive undetectable inhibitor titers (<0.6 BU) performed within 2 weeks of each other, Factor VIII activity (FVIII:C) in vivo plasma recovery ≥66% of the predicted normal value and FVIII:C half-life ≥6 hours after a 72-hour FVIII treatment-free period.

| End point type | Primary |
|---|---|

End point timeframe:

Up to 32.5 months

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: Data for this outcome measure was not collected and analysed, as the study was terminated early by the sponsor due to limited enrollment (non-safety related decision).

| End point values | Alphanate | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0[2] | | | |
| Units: number | | | | |
| number (not applicable) | | | | |

Notes:

[2] - The data was not analysed as the study was terminated by sponsor due to limited enrollment.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects who Achieved Either Complete or Partial Immune Tolerance Within 33 Months of Initiation of ITI Treatment Phase

| End point title | Percentage of Subjects who Achieved Either Complete or Partial Immune Tolerance Within 33 Months of Initiation of ITI Treatment Phase |
|---|---|

End point description:

Complete immune tolerance was defined as the participants achieving 2 consecutive undetectable inhibitor titers (<0.6 BU) performed within 2 weeks of each other, Factor VIII activity (FVIII:C) in vivo plasma recovery ≥66% of the predicted normal value and FVIII:C half-life ≥6 hours after a 72-hour FVIII treatment-free period. Partial immune tolerance was defined as participants achieving reduction of inhibitor titer to <5 BU confirmed at 2 consecutive assessments within 2 weeks of each other, FVIII:C in vivo plasma recovery of <66% of the predicted normal value or FVIII:C half-life of <6 hours after a 72-hour FVIII treatment-free period and clinical response to FVIII therapy. Data for this outcome measure

was not collected and analysed, as the study was terminated early by the sponsor due to limited enrollment (non-safety related decision).

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 32.5 months

| **End point values** | Alphanate | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0[3] | | | |
| Units: number | | | | |
| number (not applicable) | | | | |

Notes:

[3] - The data was not analysed as the study was terminated by sponsor due to limited enrollment.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects who Achieved Complete or Partial Immune Tolerance Without Relapse During the Prophylactic Phase

| End point title | Percentage of Subjects who Achieved Complete or Partial Immune Tolerance Without Relapse During the Prophylactic Phase |
|---|---|

End point description:

Relapse during the prophylactic phase for participants who have achieved complete immune tolerance was defined as a return of FVIII inhibitor titer to detectable levels (≥0.6 BU) or FVIII:C recovery <66% of the predicted normal value or FVIII:C half-life <6 hours, confirmed by repeat assessment within approximately 2 weeks. Relapse for participants who have achieved partial immune tolerance was defined as an increase of FVIII inhibitor titer to ≥5 BU, confirmed by repeat assessment within approximately 2 weeks. Data for this outcome measure was not collected and analysed, as the study was terminated early by the sponsor due to limited enrollment (non-safety related decision).

| End point type | Secondary |
|---|---|

End point timeframe:

12 months during prophylactic phase

| **End point values** | Alphanate | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0[4] | | | |
| Units: number | | | | |
| number (not applicable) | | | | |

Notes:

[4] - The data was not analysed as the study was terminated by sponsor due to limited enrollment.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Bleeding Events During ITI Treatment Phase and Prophylactic Phase

| End point title | Number of Bleeding Events During ITI Treatment Phase and Prophylactic Phase |
|---|---|

End point description:

This study was terminated, and the data is not reported for this outcome measure to main participant's confidentiality.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 32.5 months

| **End point values** | Alphanate | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0[5] | | | |
| Units: number | | | | |
| number (not applicable) | | | | |

Notes:

[5] - Study was terminated, the data is not reported for this endpoint to maintain subject confidentiality

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Up to 32.5 months | |
| Adverse event reporting additional description: | |
| Safety population included all subjects who received any amount of Alphanate. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Alphanate |
| Reporting group description: | |
| Subjects entered the immune tolerance induction (ITI) phase and received alphanate IV at a starting dose of 100 IU/kg/day. Dose could be uptitrated to 200 IU/kg/day based on investigator's discretion. The maximum duration of treatment was 32 months and 2 weeks. | |

| Serious adverse events | Alphanate | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Hepatitis C Antibody positive | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Subdural hemorrhage | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Alphanate | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | | |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences (all) | 2 | | |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences (all) | 2 | | |
| Vascular disorders | | | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | | |
| occurrences (all) | 8 | | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|---|---|---|
| disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 2 (50.00%)<br>1 | | |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Ligament sprain<br>subjects affected / exposed<br>occurrences (all)<br><br>Varicella<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 2 (50.00%)<br>1<br><br>1 / 2 (50.00%)<br>2<br><br>1 / 2 (50.00%)<br>1<br><br>1 / 2 (50.00%)<br>1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 February 2016 | The purpose of the amendment was to add synopsis, visits were changed from every month to Weeks 2, 4, 6, and 8 and monthly thereafter, inclusion criterion was changed to restrict range of inhibitor titer levels to > 0.6 BU and < 10 BU at Screening, exclusion criteria was changed to allow for previous use of treatments prohibited during the study (i.e., immunosuppressive drugs azathioprine, cyclophosphamide, high-dose immunoglobulin, interferon, or protein A column or plasmapheresis) prior to study enrolment, requirement to discontinue subjects who experience an interruption of ITI treatments for > 2 weeks, who receive < 80% of prescribed ITI treatment over a continuous 8-week period, or who experience a relapse during the Prophylactic Phase of the study was removed, assessment was added of FVIII:C in vivo recovery and if FVIII:C in vivo recovery is ≥ 66%, that separate visits will be needed to perform the FVIII:C half-life assessment. |
| 20 December 2016 | The purpose of the amendment was to add 2-hour time window at the 12-hour timepoint when sampling for FVIII:C<br>half-life, immunosuppressive treatment initiated after inhibitor diagnosis will be collected under baseline characteristics was added. |
| 21 March 2019 | The purpose of the amendment was to increase participating sites from 20 to 30, emicizumab was added as a permitted concomitant medication. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 18 September 2020 | The study was terminated by the sponsor in September 2020 due to limited enrolment (non-safety-related decision). | - |

Notes:

## Limitations and caveats

None reported