Clinical trial results:
Efficacy and Safety of Factor IX (FIX) Contained in AlphaNine® and its Pharmacokinetic Comparison With BENEFIX®, in Patients With Severe Hereditary Haemophilia B

Summary

EudraCT number	2008-002037-67
Trial protocol	BG
Global end of trial date	15 October 2009

Results information

Result version number	v1 (current)
This version publication date	25 December 2022
First version publication date	25 December 2022

Trial information

Trial identification

Sponsor protocol code	IG404/1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Grifols Biologicals Inc.
Sponsor organisation address	5555 Valley Boulevard, Los Angeles, California, United States, 90032
Public contact	Department of Drug Development, Grifols Biologicals Inc, IGregulatory.affairs@grifols.com
Scientific contact	Department of Drug Development, Grifols Biologicals Inc, IGregulatory.affairs@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?	Yes
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	15 October 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 October 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to determine the efficacy and safety of factor IX (FIX) contained in AlphaNine® and its pharmacokinetic comparison with BeneFIX®.

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	16 August 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 16
Country: Number of subjects enrolled	Poland: 9
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	0
Adolescents (12-17 years)	6
Adults (18-64 years)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Bulgaria and Poland from 16 August 2005 to 15 October 2009.

Pre-assignment

Screening details:

25 subjects who had previously participated in FIX Grifols study were enrolled and treated with AlphaNine® and BeneFIX® and their pharmacokinetic profiles were compared according to a single-dose, sequential administration of AlphaNine® and BeneFIX® after a 7 to 15-day washout period.

Period 1

Period 1 title	Pharmacokinetic Period 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	AlphaNine®

Arm description:

Subjects received AlphaNine®, 65-75 international units/kilogram (IU/kg), intravenously (IV) at Week 0 (Pharmacokinetic [PK] 1) and Week 26 (PK2) during the 12 month treatment period.

Arm type	Experimental
Investigational medicinal product name	AlphaNine®
Investigational medicinal product code	
Other name	Plasma-derived coagulation factor IX
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

65-75 IU/kg, IV at Week 0 and Week 26.

Number of subjects in period 1	AlphaNine®
Started	25
Completed	25

Period 2

Period 2 title	Pharmacokinetic Period 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	AlphaNine®

Arm description:

Subjects received AlphaNine®, 65-75 IU/kg, IV at Week 0 (PK 1) and Week 26 (PK2) during the 12 month treatment period.

Arm type	Experimental
Investigational medicinal product name	AlphaNine®
Investigational medicinal product code	
Other name	Plasma-derived coagulation factor IX
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

65-75 IU/kg, IV at Week 0 and Week 26.

Number of subjects in period 2	AlphaNine®
Started	25
Completed	25

Period 3

Period 3 title	Pharmacokinetic Period 3
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	BeneFIX®

Arm description:

Subjects who received AlphaNine® during Pharmacokinetic Periods 1 and 2, also received BeneFIX®, a recombinant FIX that contains nonacog alfa, reconstituted in solvent and administered as a single dose of 65-75 IU/kg (PK3) after a washout period of 7 days (following the second pharmacokinetic study for the Polish subset of subjects and after the 12-month follow-up for the Bulgarian subset).

Arm type	Active comparator

Investigational medicinal product name	BeneFIX®
Investigational medicinal product code	
Other name	Recombinant coagulation factor IX
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

65-75 IU/kg, IV.

Number of subjects in period 3[1]	BeneFIX®
Started	22
Completed	22

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: There were three subjects who did not proceed in BeneFIX® Pharmacokinetic Period 3.

Baseline characteristics

Reporting groups	
Reporting group title	Pharmacokinetic Period 1

Reporting group description: -

Reporting group values	Pharmacokinetic Period 1	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	25.8		
standard deviation	± 8.68	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	25	25	
Race Units: Subjects			
Caucasian	25	25	

End points

End points reporting groups

Reporting group title	AlphaNine®

Reporting group description:

Subjects received AlphaNine®, 65-75 international units/kilogram (IU/kg), intravenously (IV) at Week 0 (Pharmacokinetic [PK] 1) and Week 26 (PK2) during the 12 month treatment period.

Reporting group title	AlphaNine®

Reporting group description:

Subjects received AlphaNine®, 65-75 IU/kg, IV at Week 0 (PK 1) and Week 26 (PK2) during the 12 month treatment period.

Reporting group title	BeneFIX®

Reporting group description:

Subjects who received AlphaNine® during Pharmacokinetic Periods 1 and 2, also received BeneFIX®, a recombinant FIX that contains nonacog alfa, reconstituted in solvent and administered as a single dose of 65-75 IU/kg (PK3) after a washout period of 7 days (following the second pharmacokinetic study for the Polish subset of subjects and after the 12-month follow-up for the Bulgarian subset).

Subject analysis set title	AlphaNine® and BeneFIX®
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received AlphaNine®, 65-75 international units/kilogram (IU/kg), intravenously (IV) at Week 0 (Pharmacokinetic [PK] 1) and Week 26 (PK2) during the 12-month treatment period. After a washout period of 7 days (following the second pharmacokinetic study for the Polish subset of subjects and after the 12-month follow-up for the Bulgarian subset), subjects also received BeneFIX®, a recombinant FIX that contains nonacog alfa, reconstituted in solvent and administered as a single dose of 65-75 IU/kg (PK3). The safety analysis was performed in a combined manner throughout the different periods.

Primary: Number of Subjects Categorised Based on FIX:C Activity Before and at Different Times After Infusion of FIX Concentrate

End point title	Number of Subjects Categorised Based on FIX:C Activity Before and at Different Times After Infusion of FIX Concentrate[1]

End point description:

All subjects treated with AlphaNine® (PK1 and PK2) and BeneFIX® (PK3) were analysed for this endpoint. ‘n’ indicates number analysed are the number of subjects with data available for analysis.

End point type	Primary

End point timeframe:

Weeks 0 and 26, PK-3 (up to approximately 4.2 years)

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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine®	BeneFIX®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	22		
Units: subjects				
FIX Activity<2% at Baseline (n=25,0)	23	0		
FIX Activity ≥2% at Baseline (n=25,0)	2	0		
FIX Activity <2% at Week 0 [PK-1] (n=21,0)	21	0		

FIX Activity ≥2% at Week 0 [PK-1] (n=21,0)	0	0		
FIX Activity <2% at Week 26 [PK-2] (n=25,0)	23	0		
FIX Activity ≥2% at Week 26 [PK-2] (n=25,0)	2	0		
FIX Activity <2% PK-3 (n=0,21)	0	19		
FIX Activity ≥2% at PK-3 (n=0,21)	0	2		

Statistical analyses

No statistical analyses for this end point

Primary: Consumption of FIX Expressed as Total Dose of FIX Infusions in IU/kg per Infusion Used for Prophylaxis and Minor Bleedings

End point title	Consumption of FIX Expressed as Total Dose of FIX Infusions in IU/kg per Infusion Used for Prophylaxis and Minor Bleedings[2]

End point description:

All subjects treated with AlphaNine® (PK1 and PK2) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[2] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine®			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: IU/kg per infusion of AlphaNine	1576890			

Statistical analyses

No statistical analyses for this end point

Primary: Consumption of FIX Expressed as Total Number of FIX Infusions Used for Prophylaxis and Minor Bleedings

End point title	Consumption of FIX Expressed as Total Number of FIX Infusions Used for Prophylaxis and Minor Bleedings[3]

End point description:

All subjects treated with AlphaNine® (PK1 and PK2) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[3] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine®			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: infusions	889			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Bleeding Episodes With Achievement of Haemostasis

End point title	Percentage of Bleeding Episodes With Achievement of Haemostasis[4]

End point description:

Rating of the physician regarding achievement of haemostasis in every major bleeding episode was based on selecting one of the following options: 1.Excellent: accurate haemostasis, bleeding is controlled early; 2.Good: bleeding arrest or slight oozing, haemorrhage duration and severity, loss of blood and FIX concentrate requirements are as expected; 3.Moderate: moderate bleeding persists, greater loss of blood than expected, additional doses of FIX concentrate or other haemostatic products are needed more than expected; 4.None: uncontrolled bleeding, or even worsening, excessive blood loss, much higher doses of blood derivative products than expected are required. All subjects treated with AlphaNine® (PK1 and PK2) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[4] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine®			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: percentage of bleeding episodes				
number (not applicable)				
Excellent	75.9			
Good	16.4			
Moderate	6.0			
None	0.8			
Not Specified	0.2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Requirements of Other Blood Derivative Products

End point title	Number of Subjects With Requirements of Other Blood Derivative Products[5]

End point description:

All subjects treated with AlphaNine® (PK1 and PK2) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[5] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine®			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Major Bleeding Episodes

End point title	Number of Subjects With Major Bleeding Episodes[6]

End point description:

All subjects treated with AlphaNine® (PK1 and PK2) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[6] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine®			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Surgical Interventions for Bleeding

End point title	Number of Subjects With Surgical Interventions for Bleeding[7]

End point description:

All subjects treated with AlphaNine® (PK1 and PK2) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[7] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine®			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Incidences of Inhibitors to FIX

End point title	Number of Incidences of Inhibitors to FIX[8]

End point description:

All subjects treated with AlphaNine® (PK1 and PK2) and BeneFIX® (PK3) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to approximately 4.2 years

Notes:

[8] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine® and BeneFIX®			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: incidences	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Thrombogenic Effects Detected by Relevant Changes in Activation Coagulation Markers

End point title	Number of Subjects With Thrombogenic Effects Detected by Relevant Changes in Activation Coagulation Markers[9]

End point description:

Activation coagulation markers included- D-Dimer, thrombin-antithrombin complex (TAT), and prothrombin fragment 1 and 2 (F1+2). All subjects treated with AlphaNine® (PK1 and PK2) and BeneFIX® (PK3) were analysed for this endpoint. ‘n’ indicates number analysed are the number of subjects with data available for analysis.

End point type	Primary

End point timeframe:

Weeks 0 and 26, PK-3 (up to approximately 4.2 years)

Notes:

[9] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine®	BeneFIX®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	22		
Units: subjects				
D-Dimer: PK-1 (n=25,0)	3	0		
D-Dimer: PK-2 (n=25,0)	2	0		
D-Dimer: PK-3 (n=0,22)	0	0		
TAT: PK-1 (n=25,0)	20	0		
TAT: PK-2 (n=25,0)	5	0		
TAT: PK-3 (n=0,22)	0	14		
F1+2: PK-1 (n=25,0)	13	0		
F1+2: PK-2 (n=25,0)	8	0		
F1+2: PK-3 (n=0,22)	0	6		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Relevant Changes in Vital Signs After the Infusions of the Pharmacokinetic Assessments

End point title	Number of Subjects With Clinically Relevant Changes in Vital Signs After the Infusions of the Pharmacokinetic Assessments[10]

End point description:

All subjects treated with AlphaNine® (PK1 and PK2) and BeneFIX® (PK3) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to approximately 4.2 years

Notes:

[10] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine® and BeneFIX®			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events (AE)

End point title	Number of Subjects With Adverse Events (AE)[11]

End point description:

All subjects treated with AlphaNine® (PK1 and PK2) and BeneFIX® (PK3) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to approximately 4.2 years

Notes:

[11] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine® and BeneFIX®			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: subjects	8			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With New Viral Transmission After Treatment

End point title	Number of Subjects With New Viral Transmission After Treatment[12]

End point description:

Viral transmission was determined for HIV (human immunodeficiency virus) 1-2 Immunoglobulin G (IgG) and hepatitis C virus (HCV) IgG. All subjects treated with AlphaNine® (PK1 and PK2) and BeneFIX® (PK3) were analysed for this endpoint.

End point type	Primary

End point timeframe:

Up to approximately 4.2 years

Notes:

[12] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	AlphaNine® and BeneFIX®			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: subjects				
HIV 1-2 IgG	0			
HCV IgG	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 4.2 years

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	AlphaNine® and BeneFIX®

Reporting group description:

Subjects received AlphaNine®, 65-75 international units/kilogram (IU/kg), intravenously (IV) at Week 0 (Pharmacokinetic [PK] 1) and Week 26 (PK2) during the 12-month treatment period. After a washout period of 7 days (following the second pharmacokinetic study for the Polish subset of subjects and after the 12-month follow-up for the Bulgarian subset), subjects also received BeneFIX®, a recombinant FIX that contains nonacog alfa, reconstituted in solvent and administered as a single dose of 65-75 IU/kg (PK3). The safety analysis was performed in a combined manner throughout the different periods.

Serious adverse events	AlphaNine® and BeneFIX®		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 25 (4.00%)		
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	AlphaNine® and BeneFIX®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 25 (32.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Injury, poisoning and procedural			

complications Limb injury subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Surgical and medical procedures Tooth restoration subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Haemarthrosis subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 5 1 / 25 (4.00%) 1		
Infections and infestations Oral herpes subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1 4 / 25 (16.00%) 5 1 / 25 (4.00%) 1		

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