Clinical trial results:
A Multicentre, Interventional, Non-randomized, Open-label, Single-group Phase III Study to Evaluate Plasma-Derived Antihaemophilic Factor/von Willebrand Factor Concentrate (Biostate®) for Immune Tolerance Induction in Male Paediatric Subjects With Haemophilia A (</=2%) Who Have Developed High-titre Antibodies to Factor VIII (Factor VIII Inhibitors)

Summary

EudraCT number	2010-020113-85
Trial protocol	DE FR AT GR IT
Global end of trial date	10 December 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	CSLCT-BIO-10-67

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01445197
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring-Str. 76, Marburg, Germany, 35041
Public contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.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	16 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the proportion of subjects who achieve a complete response (success) following immune tolerance induction (ITI) treatment with Biostate.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and standard operating procedures for clinical research and development at CSL Behring (CSLB). The study protocol and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating centers. Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

The investigator may cease study treatment and withdraw the subject, or the subject may withdraw himself from participation in the study at any time. If a subject is withdrawn from the study or further participation is declined, the subject will continue to have access to medical care and will be treated according to routine medical practice, but will no longer receive the investigational medicinal product (IMP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2012
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	Germany: 1
Worldwide total number of subjects	1
EEA total number of subjects	1

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)	1
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a Screening period of up to 28 days (plus an optional waiting period of up to 11 months). If the waiting period of up to 11 months was added at the discretion of the investigator to allow the subject's inhibitor titre to decrease prior to the start of ITI treatment, the screening period duration was up to 12 months in total.

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	Biostate

Arm description:

During ITI treatment, Biostate was administered intravenously at a daily dose of approximately 200 international units (IU)/kg body weight (b.w.), preferably split into 2 doses of 100 IU/kg b.w. per day.

Arm type	Experimental
Investigational medicinal product name	Human coagulation Factor VIII / von Willebrand Factor
Investigational medicinal product code	
Other name	Biostate®, Voncento®
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doses were administered as bolus intravenous injections at a rate not exceeding 6 mL/min.

Number of subjects in period 1	Biostate
Started	1
Completed Treatment Period	1
Completed	1

Baseline characteristics

Reporting groups	
Reporting group title	Biostate

Reporting group description:

During ITI treatment, Biostate was administered intravenously at a daily dose of approximately 200 international units (IU)/kg body weight (b.w.), preferably split into 2 doses of 100 IU/kg b.w. per day.

Reporting group values	Biostate	Total	
Number of subjects	1	1	
Age categorical 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)	1	1	
Children (2-11 years)	0	0	
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 Units: Subjects			
Female	0	0	
Male	1	1	

End points

End points reporting groups

Reporting group title	Biostate

Reporting group description:

During ITI treatment, Biostate was administered intravenously at a daily dose of approximately 200 international units (IU)/kg body weight (b.w.), preferably split into 2 doses of 100 IU/kg b.w. per day.

Primary: Number of Subjects Who Achieve Complete, Partial, and No Response (ITI Failure) to Treatment

End point title	Number of Subjects Who Achieve Complete, Partial, and No Response (ITI Failure) to Treatment[1]

End point description:

Complete Response = The following criteria were met in the given order: 1. An undetectable inhibitor titre (<0.6 BU/mL) at 2 consecutive assessments, tested at intervals of 2 weeks (±3 days); 2. After the subject was placed on prophylaxis and after a 48-hour wash-out period, FVIII plasma recovery of ≥66% of predicted and FVIII half-life of ≥6 hours based on blood samples taken prior to and at 10 min, 30 min, 2, 8, 12 (optional), and 24 hrs after administration of 50 IU/kg b.w. Biostate. ITI Failure = One of the following 2 conditions was fulfilled: 1. For a non-overlapping 6-month period, a reduction in the inhibitor titre of ≥20% based on 2 measurements taken 2 weeks (±3 days) apart was not achieved; 2. after 30 months of ITI treatment, the inhibitor titre was >5.0 BU/mL. Partial Response = If subject at the end of ITI treatment met neither the criteria for complete response nor those for ITI failure, the outcome for that subject was to be regarded as partial response.

End point type	Primary

End point timeframe:

Up to approximately 9 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: Because the study was terminated and only 1 subject was enrolled into the study, the primary objective could not be assessed with any further statistical analysis.

End point values	Biostate			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects				
Complete Response	0			
Partial Response	0			
No Response (ITI Failure)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Overall Treatment-Emergent Adverse Events (AEs) and Serious AEs

End point title	Summary of Overall Treatment-Emergent Adverse Events (AEs) and Serious AEs

End point description:

An AE was defined as any untoward medical occurrence in a subject administered an IMP (whether it is the study or any reference product[s]), which does not necessarily have a causal relationship with the IMP. An SAE was defined as any untoward medical occurrence that at any dose: results in death; is life-threatening; requires in-patient hospitalisation or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is medically significant. Treatment-emergent events were defined as those occurring after the first dose of IMP.

End point type	Secondary

End point timeframe:

From first IMP dose through Final Visit (3 months [±2 weeks]) after complete response or the final dose of IMP (total study duration was up to approximately 9 months). AE/SAEs considered related to a study procedure were recorded from informed consent.

End point values	Biostate			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: subjects				
Overall TESAEs	5			
Overall Unrelated TESAEs	2			
Overall Possibly Related TESAEs	3			
Overall Related TESAEs	0			
Overall Non-serious TEAEs	5			
Overall Unrelated Non-serious TEAEs	5			
Overall Possibly Related Non-serious TEAEs	0			
Overall Related Non-serious TEAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Markers of Activation of Coagulation

End point title	Number of Subjects With Clinically Significant Markers of Activation of Coagulation

End point description:

Thrombogenic risk was assessed by reporting the number of subjects with clinical symptoms or increased markers of activation of coagulation (eg, fibrin fragments, thrombin-antithrombin complex [TAT]).

End point type	Secondary

End point timeframe:

Up to approximately 9 months

End point values	Biostate			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: subjects	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Bleeding Events

End point title	Summary of Bleeding Events

End point description:

The frequency, nature and location of bleeding events were recorded in the subject's e-diary and/or the electronic case report form (eCRF). A major bleeding event was classified as one for which a subject was required to visit the Hemophilia Treatment Center to seek treatment recommendations from the treating physician. Major bleeding events may include: cerebral bleeding, severe bleeding into muscle or mucosal bleeding of the gastrointestinal tract (excluding nasal or oral bleeding) and bleeding events in target joints or those associated with swelling, pain, a decreased range of motion and an intensified treatment (use of bypassing agents for > 3 days). All other bleeding events were classified as minor unless the Investigator assessment noted otherwise.

End point type	Secondary

End point timeframe:

Up to approximately 9 months

End point values	Biostate			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: bleeding events				
Overall	10			
Major	0			
Minor	9			
Unspecified	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Catheter-related Complications

End point title	Number of Catheter-related Complications

End point description:

Occurrence of catheter-related complications (eg, line infections) were recorded in the subject's e-diary.

End point type	Secondary

End point timeframe:

up to approximately 9 months

End point values	Biostate			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: complications	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Response (Success)

End point title	Time to Complete Response (Success)

End point description:

The time point for complete response (success) was defined as the time when recovery is ≥ 66% of predicted, FVIII half-life is ≥ 6 hours, and a titre of < 0.6 BU/mL is confirmed, after the subject had been placed in prophylaxis.

End point type	Secondary

End point timeframe:

Up to approximately 38 months (30-month treatment period plus approximately 8 months for establishing complete response)

End point values	Biostate			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: days				

Notes:

[2] - The subject in this study did not achieve a complete response.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Inhibitor Titre <0.6 BU/mL for the First Time

End point title	Time to Inhibitor Titre <0.6 BU/mL for the First Time

End point description:

Time to the first instance of an inhibitor titre of <0.6 BU/mL, as assessed by the central laboratory.

End point type	Secondary

End point timeframe:

30 months

End point values	Biostate			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: days				

Notes:

[3] - The subject in this study did not reach an inhibitor titre of <0.6 BU/mL.

Statistical analyses

No statistical analyses for this end point

Secondary: FVIII Inhibition Titres

End point title	FVIII Inhibition Titres

End point description:

End point type	Secondary

End point timeframe:

Screening through End-of-study (EOS; total study duration was up to approximately 9 months)

End point values	Biostate			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Bethesda units (BU)/mL				
number (not applicable)				
Screening	128			
Day 1	101			
Day 3	66			
Day 7	83			
Day 14	44			
Month 1	32.96			
Month 2	26.88			
Month 3	32.96			
Month 4	64			
Month 5	103.7			
Unscheduled visit (between Months 5 and 6)	135.7			
Month 6	111.36			
Month 7	118			
Month 8	66			
Unscheduled visit (between Month 8 and EOS) 1	169			
Unscheduled visit (between Month 8 and EOS) 2	159			
EOS	143			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first IMP dose through Final Visit (3 months [±2 weeks]) after complete response or the final dose of IMP (total study duration was up to approximately 9 months). AE/SAEs considered related to a study procedure were recorded from informed consent.

Adverse event reporting additional description:

All events presented were treatment-emergent (defined as those occurring after the first dose of IMP).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Biostate

Reporting group description:

During ITI treatment, Biostate was administered intravenously at a daily dose of approximately 200 international units (IU)/kg body weight (b.w.), preferably split into 2 doses of 100 IU/kg b.w. per day.

Serious adverse events	Biostate		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery stenosis			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Mouth haemorrhage			

subjects affected / exposed	1 / 1 (100.00%)		
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 / 1 (100.00%)		
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	Biostate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2011	Following discussion with External Expert and comments from competent authorities: - Recalculation of sample size - Dosing range introduced - Day 14 Visit introduced - Dose reduction scheme clarified - Definition major bleedings added - Orthopedic score (Gilbert Score) added - Editorial changes: consistent use of terms, consistent use of American English vs British English - Change of study team members

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Because the study was terminated due to lack of enrolment and overall feasibility, and only 1 subject was enrolled into the study, the primary objective could not be assessed and no conclusions about the efficacy of Biostate in ITI can be drawn.

Notes: