Clinical trial results:
INCIDENCE OF INHIBITORS IN PREVIOUSLY UNTREATED PATIENTS WITH SEVERE HEAMOPHILIA A TREATED WITH OCTANATE

Summary

EudraCT number	2005-004435-22
Trial protocol	CZ FR
Global end of trial date	29 December 2015

Results information

Result version number	v1 (current)
This version publication date	19 August 2017
First version publication date	19 August 2017

Trial information

Trial identification

Sponsor protocol code	AVI-403

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, CH-8853
Public contact	Clinical Research and Development, Octapharma Pharmazeutika Produktionsgesellschaft mbH, 0043 1610320, clinical.department@octapharma.com
Scientific contact	Clinical Research and Develpoment, Octapharma Pharmazeutika Produktionsgesellschaft mbH, 0043 1610320, clinical.department@octapharma.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	17 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess immunogenicity of Octanate® in PUPs by monitoring the levels of inhibitor against FVIII (Bethesda assay) every 3-4 exposure days until the 20th exposure day and every 10th exposure day until exposure day 100 or every 3 months, whichever comes first.

Protection of trial subjects:

This trial was conducted in accordance to the principles of GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki. Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and risk factors associated with the investigational medicinal product. Safety was assessed throughout the study, such as occurrence of AEs, testing of virology and testing of immunogenicity .

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	16 February 2000
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	Russian Federation: 4
Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Czech Republic: 5
Worldwide total number of subjects	51
EEA total number of subjects	47

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	2
Infants and toddlers (28 days-23 months)	47
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: -

Pre-assignment

Screening details:

- Previously untreated patients with severe (FVIII:C [factor VIII coagulant activity] <2%) haemophilia A
- Patients registered for regular treatment at the study site
- Patients without any inhibitor activity prior to admission (cut-off: 0.6 BU).

Period 1

Period 1 title	Overall Trail (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Octanate

Arm description:

Octanate, a stable, highly purified, freeze-dried concentrate of human coagulation FVIII stabilised with Von Willebrand factor (VWF), and virus inactivated by a Solvent/Detergent method and terminal dry-heat treatment.

Arm type	Experimental
Investigational medicinal product name	Octanate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Determined according to the clinical needs of the subject and the opinion of the treating physician.

Number of subjects in period 1	Octanate
Started	51
Completed	51

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trail

Reporting group description: -

Reporting group values	Overall Trail	Total	
Number of subjects	51	51	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	0.81		
full range (min-max)	0.01 to 5.61	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	51	51	

End points

End points reporting groups

Reporting group title	Octanate

Reporting group description:

Octanate, a stable, highly purified, freeze-dried concentrate of human coagulation FVIII stabilised with Von Willebrand factor (VWF), and virus inactivated by a Solvent/Detergent method and terminal dry-heat treatment.

Primary: development of FVIII-inhibitor

End point title	development of FVIII-inhibitor[1]

End point description:

The primary endpoint is the absence or occurence of inhibitor activity after treatment start with Octanate® determined by Bethesda assay (Nijmegen method, cut-off point: 0.6 B.U.)

End point type	Primary

End point timeframe:

-Study Entry (pre-treatment)
-Exposure day 1 - 20 every 3-4 exposure days,
-Exposure day 21 - 100 every 10 exposure days

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: Descriptive statistical methods (frequency distributions, descriptive statistics and figures) were used to analyse the data.

End point values	Octanate			
Subject group type	Reporting group			
Number of subjects analysed	5[2]			
Units: Patients				
number (not applicable)				
clinically relevant and high responders	3			

Notes:

[2] - Of 5 subjects with inhibitors,2 underwent ITI treatment, 1 with successful tolerisation, 1 without

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded throughout the study.

Adverse event reporting additional description:

For subjects on home-treatment, any AEs were reported on a treatment form provided. If subjects experienced any confirmed seroconversion during the study, the event was considered serious and handled in the same way as serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Octanate

Reporting group description:

Octanate, a stable, highly purified, freeze-dried concentrate of human coagulation FVIII stabilised with Von Willebrand factor (VWF), and virus inactivated by a Solvent/Detergent method and terminal dry-heat treatment.

Serious adverse events	Octanate		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 51 (66.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal			

disorders			
Epistaxis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Parvovirus B19 test positive			
subjects affected / exposed	16 / 51 (31.37%)		
occurrences causally related to treatment / all	16 / 16		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Traumatic haematoma			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			

subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Factor F VIII inhibition				
subjects affected / exposed	5 / 51 (9.80%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Enterocolitis				
subjects affected / exposed	2 / 51 (3.92%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mouth haemorrhage				
subjects affected / exposed	2 / 51 (3.92%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gingival bleeding				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				

Skin haemorrhage				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Haemarthrosis				
subjects affected / exposed	4 / 51 (7.84%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	2 / 51 (3.92%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	2 / 51 (3.92%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	2 / 51 (3.92%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Acute tonsillitis				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteristis				

subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gatroenteritis rotavirus			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Streptococcal sepsis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gingivitis			
subjects affected / exposed	1 / 51 (1.96%)		
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	Octanate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 51 (70.59%)		
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	5		
Vomiting			

subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	16		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 51 (27.45%)		
occurrences (all)	21		
Nasopharyngitis			
subjects affected / exposed	12 / 51 (23.53%)		
occurrences (all)	31		
Pharyngitis			
subjects affected / exposed	12 / 51 (23.53%)		
occurrences (all)	30		
Respiratory tract infection			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	6		
Laryngitis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 1999	Amendment I : - Following an update of the Sponsor's Safety SOPs, relevant changes were implemented into clinical studies not yet clinically started. Unlikely has been added to the causality assessment scheme -Insurance details corrected - Update of Patient Information and Informed Consent as requested by the Polish regulatory authorities
08 February 2002	Amendment II : - Octapharma AG moved to new facilities - Contracting a new insurance company
17 July 2006	Amendment IV: - due ro recruitment of additional centres . To get more clinically significant data it was decided to increase the number of patients to be enrolled from 25 to 35 - Due to the fact that the study was ongoing since more than 6 years, an interim analyses on the safety and efficacy data has been added
24 October 2007	Amendment VII: - The total number of patients planned to be enrolled is increased from 35 to 50 - Second interim analyses added - New Facility of central lab
17 November 2011	Amendment VIII: -Change of laboratories addresses -The duration of the study was prolonged until December 2013 -Addition of a new centre in Russia -The conditions for storage of IMP were updated in accordance with Instruction for Octanate -The AE and SAE sections were amended in accordance with current requirements

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported