Clinical trial results:
Prospective, open-label, uncontrolled, Phase III study to assess the efficacy and safety of Octafibrin for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in subjects with congenital fibrinogen deficiency.

Summary

EudraCT number	2011-002419-27
Trial protocol	GB BG
Global end of trial date	14 February 2018

Results information

Result version number	v1 (current)
This version publication date	16 February 2019
First version publication date	16 February 2019

Trial information

Trial identification

Sponsor protocol code	FORMA-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02267226
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, 8853
Public contact	Bruce SCHWARTZ. PhD, Octapharma AG, bruce.schwartz@octapharma.com
Scientific contact	Bruce SCHWARTZ. PhD, Octapharma AG, bruce.schwartz@octapharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001208-PIP01-11
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	13 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study aims to demonstrate the efficacy of Octafibrin for on-demand treatment of acute bleeding episodes (spontaneous or after trauma).

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.
Throughout the study safety was assessed, such as occurrence of AEs, safety labs and vital signs.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	13 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	India: 5
Country: Number of subjects enrolled	Iran, Islamic Republic of: 3
Worldwide total number of subjects	25
EEA total number of subjects	5

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: -

Pre-assignment

Screening details:

Patients with documented diagnosis of congenital fibrinogen deficiency, expected to require on-demand treatment for bleeding or surgical prophylaxis were screened according to predefined in- and exclusion criteria.

Period 1

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

Arms

Arm title	Octafibrin

Arm description: -

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

Dosage and administration details:

It was administered as an intravenous bolus injection at a maximum speed of 5 mL/min. Continuous infusion was not allowed. Octafibrin was recommended to be individually dosed to achieve a target fibrinogen
plasma level dependent on the bleeding type (minor or major) or type of surgery (minor or major) as defined per protocol.

Number of subjects in period 1	Octafibrin
Started	25
Completed	18
Not completed	7
Physician decision	1
PI decided to close the site	2
Sponsor Request	4

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	25	25	
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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	6	6	
Adults (18-64 years)	19	19	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
geometric mean	29.04		
full range (min-max)	12 to 54	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	14	14	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who fulfilled all the inclusion criteria and met none of the exclusion criteria for the study and who received at least one infusion of Octafibrin

Subject analysis set title	Full analysis set (FAS)-Bleeding population
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS defined according to the intention-to-treat (ITT) principle included patients in the Safety population who presented with an episode of acute bleeding and received at least one infusion of Octafibrin for treatment of a Bleeding Episode (BE)

Subject analysis set title	Surgical Prophylaxis population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the Safety population who underwent a surgical procedure with a need for at least one infusion of Octafibrin.

Subject analysis set title	Investigator Assessment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Efficacy as assessed by the investigator

Subject analysis set title	IDMEAC Assessment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Efficacy as assessed by the IDMEAC

Reporting group values	Safety Population	Full analysis set (FAS)-Bleeding population	Surgical Prophylaxis population
Number of subjects	25	24	9
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)	6	6	1
Adults (18-64 years)	19	18	8
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
geometric mean	29.04	28.5	31
full range (min-max)	12 to 54	12 to 54	12 to 49
Gender categorical			
Units: Subjects			
Female	11	11	2
Male	14	13	7

Reporting group values	Investigator Assessment	IDMEAC Assessment	
Number of subjects	24	24	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)	6	6	
Adults (18-64 years)	18	18	
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
geometric mean	28.5	28.5	
full range (min-max)	12 to 54	12 to 54	

Gender categorical Units: Subjects			
Female	11	11	
Male	13	13	

End points

End points reporting groups

Reporting group title	Octafibrin
Reporting group description: -	
Subject analysis set title	Safety Population
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who fulfilled all the inclusion criteria and met none of the exclusion criteria for the study and who received at least one infusion of Octafibrin	
Subject analysis set title	Full analysis set (FAS)-Bleeding population
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS defined according to the intention-to-treat (ITT) principle included patients in the Safety population who presented with an episode of acute bleeding and received at least one infusion of Octafibrin for treatment of a Bleeding Episode (BE)	
Subject analysis set title	Surgical Prophylaxis population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients in the Safety population who underwent a surgical procedure with a need for at least one infusion of Octafibrin.	
Subject analysis set title	Investigator Assessment
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Efficacy as assessed by the investigator	
Subject analysis set title	IDMEAC Assessment
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Efficacy as assessed by the IDMEAC	

Primary: Haemostatic Efficacy in On-Demand Treatment of the First Bleeding Episode

End point title	Haemostatic Efficacy in On-Demand Treatment of the First Bleeding Episode[1]
End point description:	
The investigator's overall clinical assessment of haemostatic efficacy for bleeding was based on a 4 point haemostatic efficacy scale. The final efficacy assessment of each patient was adjudicated by the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC). The success rate was calculated as the proportion of patients with treatment success. The 90% CI for the success rate was calculated according to Blyth–Still–Casella interval for the proportion of patients with successful haemostatic efficacy with the predefined threshold of 0.7; values were manually rounded.	
End point type	Primary
End point timeframe:	
The first bleeding episode covers the time period from the first Octafibrin infusion until 24 hours (i.e., 1 day) after the last infusion.	

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: Analysis of data was descriptive. Continuous variables were summarized using descriptive statistics (arithm. mean, standard deviation (SD), median, min/max, number of observations and missing observations). Categorical variables were summarized with counts and percentages. 90% CI for success rate was calculated according to Blyth–Still–Casella interval for the proportion of patients with successful haemostatic efficacy with a predefined threshold of 0.7. Values were manually rounded.

End point values	Investigator Assessment	IDMEAC Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	24		
Units: Number of patients				
number (not applicable)				
Excellent	19	23		
Good	5	1		
Moderate	0	0		
None	0	0		
Success rate (%)	100	100		
Success rate (90% confidence interval [CI]) lower	0.885	0.885		
Success rate (90% confidence interval [CI]) upper	1.000	1.000		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start of the first Octafibrin infusion until the end of each 30-day observation and follow-up period for on-demand treatment or until the Last Post-Operative Day in surgeries.

Adverse event reporting additional description:

AEs occurring between the start of the first Octafibrin infusion and the end of each 30-day observation and follow-up period and during the surgical follow-up were recorded as treatment-emergent adverse events (TEAEs). Non-TEAEs were all AEs not falling into the follow-up periods.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Octafibrin

Reporting group description: -

Serious adverse events	Octafibrin		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Patella fracture			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ligament sprain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transfusion reaction			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Hepatitis C			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dengue fever			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypocalcaemia			
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: 5 %

Non-serious adverse events	Octafibrin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 25 (28.00%)		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Gingival bleeding			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	8		
Vomiting			

subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 4		
Skin and subcutaneous tissue disorders Ecchymosis subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 4		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 3 / 25 (12.00%) 4 2 / 25 (8.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2014	Amendment 2: -More clearly definition of 'subject observation and follow-up period,' 'treatment observation period,' and 'surgical observation period has been added. -Specification that the documentation of a bleeding episode extends across the entire 'treatment observation period has been added. - Details for the time periods during which adverse events (AEs) and relevant concomitant medications are recorded have been added. - Details for the period of observation during which SAEs and relevant concomitant medications are documented have been added. - Further detail to the formula used to calculate the Octafibrin dose to be administered has been added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported