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

Summary

EudraCT number	2014-005115-16
Trial protocol	Outside EU/EEA
Global end of trial date	11 June 2019

Results information

Result version number	v1 (current)
This version publication date	04 July 2020
First version publication date	04 July 2020

Trial information

Trial identification

Sponsor protocol code	FORMA-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02408484
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, CH-8853
Public contact	SVP Clinical R&D Haematology, Octapharma AG, 0041 554512141, sigurd.knaub@octapharma.com
Scientific contact	SVP Clinical R&D Haematology, Octapharma AG, 0041 554512141, sigurd.knaub@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 ICH- GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki, national regulatory requirements and FDA Code of Federal Regulations.
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 of monitoring of AEs, SAEs, concomitant medication, monitoring of Thromboembolic events (TEEs) and assessments of safety lab parameters.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	15 December 2015
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	Iran, Islamic Republic of: 2
Country: Number of subjects enrolled	India: 4
Country: Number of subjects enrolled	Lebanon: 8
Worldwide total number of subjects	14
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)	1

Children (2-11 years)	13
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:

Patients aged <12 years at the start of treatment 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:

Octafibrin was individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleding or surgery.

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

Dosage and administration details:

Octafibrin is a human plasma-derived fibrinogen concentrate for intravenous use. The product is packed and labelled according to local regulations in vials containing 1 g of lyophilised fibrinogen concentrate powder for reconstitution with 50 mL of water for injection (WFI). It was administered as an intravenous bolus injection at a maximum speed of 5 mL/min. Continuous infusion was not allowed. Octafibrin was individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleeding or surgery (minor or major).

Number of subjects in period 1	Octafibrin
Started	14
Completed	11
Not completed	3
Consent withdrawn by subject	2
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
<6 years	6	6	
6–<12 years	8	8	
Age continuous Units: years			
median	6		
full range (min-max)	1 to 10	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	6	6	

End points

End points reporting groups

Reporting group title	Octafibrin

Reporting group description:

Octafibrin was individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleding or surgery.

Subject analysis set title	Safety Set
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who received at least one infusion of Octafibrin.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) defined according to the intention-to-treat (ITT) principle will include subjects who fulfil all of the following conditions:
• received at least one infusion of the IMP.
• entered the study with a confirmed congenital fibrinogen deficiency

Subject analysis set title	First bleeding analysis set (firstBLEED):
Subject analysis set type	Intention-to-treat

Subject analysis set description:

subjects of the FAS who have at least one episode of acute bleeding treated with Octafibrin.

Subject analysis set title	First bleeding per protocol analysis set (firstBLEED-PP)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients from the firstBLEED analysis set who:
-Provided valid, i.e., non-missing, haemostatic efficacy data for their first BE
-Received ≥90% of the planned total dose of the IMP in the first infusion for the first BE
- Received ≥80% of the calculated dose of the IMP over all further infusions of the first bleeding according to the treatment schedule
- Did not meet specific exclusion criteria as defined per protocol

Subject analysis set title	Investigator
Subject analysis set type	Full analysis

Subject analysis set description:

Ratings performed by the investigator

Subject analysis set title	IDMEAC
Subject analysis set type	Full analysis

Subject analysis set description:

Rating performed by the Independent Data Monitoring & Endpoint Adjudication Committee

Subject analysis set title	Bleeding analysis set (BLEED)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all documented bleeding episodes treated with Octafibrin in subjects of the FAS.

Subject analysis set title	Bleeding per protocol analysis set (BLEED-PP)
Subject analysis set type	Per protocol

Subject analysis set description:

all documented bleeding episodes with no major protocol deviations

Subject analysis set title	Investigator %
Subject analysis set type	Full analysis

Subject analysis set description:

Investigator %

Subject analysis set title	IDMEAC %

Subject analysis set type	Full analysis

Subject analysis set description:

IDMEAC %

Subject analysis set title	Pharmacokinetic analysis set (PK)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients of the FAS who started the PK assessment and have at least one valid post-baseline fibrinogen activity level.

Subject analysis set title	Change in MCF for the firstBLEED Population (p-value 0.0028)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Change in MCF specifically for the first infusions of Octafibrin administered for the treatment of the first bleeding episode of the patients in the firstBLEED population. P-value for the change in MCF from baseline to 1 hour post infusion for the firstBLEED population, were calculated using paired t-test.
Overall Number of Participants Analyzed: 8
Overall Number of Bleeding Episodes Analyzed: 8

p-values were calculated using paired t-test

Subject analysis set title	Change in MCF for the BLEED Population (p-value <0.0002)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Change in MCF for the first infusions of Octafibrin administered for the treatment of all bleeding episodes of patients in the BLEED population.P-value for the change in MCF from baseline to 1 hour post infusion for the firstBLEED population, were calculated using paired t-test.
Overall Number of Participants Analyzed: 8
Overall Number of Bleeding Episodes Analyzed: 10

Subject analysis set title	Change in Fibrinogen Activity for the firstBLEED Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Change in fibrinogen activity specifically for the first infusions of Octafibrin administered for the treatment of the first bleeding episode of the patients in the firstBLEED population.

p-value: <0.0001

Subject analysis set title	Change in Fibrinogen Activity f. BLEED Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Change in fibrinogen activity for the first infusions of Octafibrin administered for the treatment of all bleeding episodes of patients in the BLEED population.
p-value <0.0001

Subject analysis set title	Incremental IVR Response for the firstBLEED Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Incremental IVR response for the first infusions of Octafibrin administered for the treatment of the first bleeding episode of the patients in the firstBLEED population.

Subject analysis set title	Incremental IVR Response for the BLEED Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Incremental IVR response for the first infusions of Octafibrin administered for the treatment of all bleeding episodes of patients in the BLEED population.

Subject analysis set title	Surgeon
Subject analysis set type	Full analysis

Subject analysis set description:

Intra-operative assessment of Octafibrin efficacy in surgical prophylaxis as assessed by the Surgeon.

Subject analysis set title	IDEMEAC.
Subject analysis set type	Full analysis

Subject analysis set description:

Intra-operative assessment of Octafibrin efficacy in surgical prophylaxis as assessed by the IDMEAC.

Subject analysis set title	Prothrombin Fragments (1+2)
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients with elevated values of prothrombin Fragments 1+2 (outside of the reference range of 69 to 229 pmol/L, 3 hours post infusion

Primary: Efficacy Assessment for Treatment of the First Bleeding Episode (4-Point Efficacy Scale)

End point title	Efficacy Assessment for Treatment of the First Bleeding Episode (4-Point Efficacy Scale)[1]

End point description:

Primary Endpoint was the investigators overall clinical assessment of the haemostatic efficacy of Octafibrin in treating the first documented bleeding episode of each patient ((firstBLEED/firstBLEED-PP dataset; n=8)
The investigator's overall clinical assessment of haemostatic efficacy for bleeding was based on a 4-point haemostatic efficacy rating scale (Excellent, Good, Moderate, None) The final efficacy assessment of each patient was adjudicated by the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC). If any intra- or post-operative endpoint data differed between the investigator's assessment and the adjudicated assessment by the IDMEAC, the final endpoint assessment was that based on the adjudicated assessments based on an agreed algorithm.

End point type	Primary

End point timeframe:

First Octafibrin infusion for the treatment of a bleeding episode until 24 hours (i.e., 1 day) after the last infusion or the end of the treatment observation period, whichever comes last.

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 the study data was descriptive and focused on overall clinical assessment of the haemostatic efficacy and safety analyses. The final efficacy assessment of each patient was adjudicated by the IDMEAC.
The statistical analysis of the primary, secondary and safety endpoints were exploratory only and no confirmatory hypothesis testing was carried out.

End point values	Investigator	IDMEAC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	8		
Units: Bleeding Events				
number (not applicable)				
Excellent (N)	5	6		
Excellent (%)	62.5	75.0		
Good (N)	1	2		
Good (%)	12.5	25.0		
Moderate (N)	1	0		
Moderate (%)	12.5	0.0		
None (N)	1	0		
None (%)	12.5	0.0		

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy Assessment for Treatment of the First Bleeding Episode (2-Point Efficacy Scale)

End point title	Efficacy Assessment for Treatment of the First Bleeding Episode

	(2-Point Efficacy Scale)[2]

End point description:

Efficacy rating of excellent or good on the four-point scale indicated success and efficacy rating of moderate or none indicated failure.

End point type	Primary

End point timeframe:

First Octafibrin infusion for the treatment of a bleeding episode until 24 hours (i.e., 1 day) after the last infusion or the end of the treatment observation period, whichever comes last.

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: Analysis of the study data was descriptive and focused on overall clinical assessment of the haemostatic efficacy and safety analyses. The final efficacy assessment of each patient was adjudicated by the IDMEAC.
The statistical analysis of the primary, secondary and safety endpoints were exploratory only and no confirmatory hypothesis testing was carried out.

End point values	Investigator	IDMEAC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	8		
Units: Bleeding Events				
number (not applicable)				
Success Rating (N)	6	8		
Success Rating (%)	75.0	100.0		
95% CI -Pearson Clopper lower	34.91	63.06		
95% CI -Pearson Clopper upper	96.81	100.0		
Failure Rating (N)	2	0		
Failure Rating (%)	25.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Single-dose Pharmacokinetics of Octafibrin: Area Under the Concentration-time Curve Normalised (AUCnorm)

End point title	Single-dose Pharmacokinetics of Octafibrin: Area Under the Concentration-time Curve Normalised (AUCnorm)

End point description:

AUCnorm was assessed after a single intravenous infusion of 70 mg/kg body weight of Octafibrin.

End point type	Secondary

End point timeframe:

Before first infusion, 1 hour, 3 hours, 1 day, 2 days, 4 days, 7 days, 10 days and 14 days post-infusion.

End point values	Pharmacokinetic analysis set (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: h*kg*g/L/mg				
arithmetic mean (standard deviation)	1.419 (± 0.4385)			

Statistical analyses

No statistical analyses for this end point

Secondary: Single-dose Pharmacokinetics of Octafibrin: Response - Incremental in Vivo Recovery (IVR)

End point title	Single-dose Pharmacokinetics of Octafibrin: Response - Incremental in Vivo Recovery (IVR)

End point description:

IVR was assessed after a single intravenous infusion of 70 mg/kg body weight of Octafibrin.

End point type	Secondary

End point timeframe:

Between the pre-infusion and the 3-hour post-infusion.

End point values	Pharmacokinetic analysis set (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: mg/dL/(mg/kg)				
arithmetic mean (standard deviation)	1.592 (± 0.3224)			

Statistical analyses

No statistical analyses for this end point

Secondary: Single-dose Pharmacokinetics of Octafibrin: Terminal Elimination Half-life (t1/2)

End point title	Single-dose Pharmacokinetics of Octafibrin: Terminal Elimination Half-life (t1/2)

End point description:

t1/2 was assessed after a single intravenous infusion of 70 mg/kg body weight of Octafibrin.

End point type	Secondary

End point timeframe:

Before first infusion, 1 hour, 3 hours, 1 day, 2 days, 4 days,7 days, 10 days and 14 days post-infusion.

End point values	Pharmacokinetic analysis set (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hours				
arithmetic mean (standard deviation)	84.356 (± 34.2658)			

Statistical analyses

No statistical analyses for this end point

Secondary: Single-dose Pharmacokinetics of Octafibrin: Maximum Plasma Concentration (Cmax)

End point title	Single-dose Pharmacokinetics of Octafibrin: Maximum Plasma Concentration (Cmax)

End point description:

Cmaxwas assessed after a single intravenous infusion of 70 mg/kg body weight of Octafibrin.

End point type	Secondary

End point timeframe:

Before first infusion, 1 hour, 3 hours, 1 day, 2 days, 4 days,7 days, 10 days and 14 days post-infusion.

End point values	Pharmacokinetic analysis set (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: g/L				
arithmetic mean (standard deviation)	1.559 (± 0.3183)			

Statistical analyses

No statistical analyses for this end point

Secondary: Single-dose Pharmacokinetics of Octafibrin: Time to Reach Maximum Plasma Concentration (Tmax)

End point title	Single-dose Pharmacokinetics of Octafibrin: Time to Reach Maximum Plasma Concentration (Tmax)

End point description:

Tmax was assessed after a single intravenous infusion of 70 mg/kg body weight of Octafibrin

End point type	Secondary

End point timeframe:

Before first infusion, 1 hour, 3 hours, 1 day, 2 days,4 days, 7 days, 10 days and 14 days post-infusion.

End point values	Pharmacokinetic analysis set (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hours				
arithmetic mean (standard deviation)	1.154 (± 0.5547)			

Statistical analyses

No statistical analyses for this end point

Secondary: Single-dose Pharmacokinetics of Octafibrin: Mean Residence Time (MRT)

End point title	Single-dose Pharmacokinetics of Octafibrin: Mean Residence Time (MRT)

End point description:

MRT was assessed after a single intravenous infusion of 70 mg/kg body weight of Octafibrin.

End point type	Secondary

End point timeframe:

Before first infusion, 1 hour, 3 hours, 1 day, 2 days, 4 days,7 days, 10 days and 14 days post-infusion.

End point values	Pharmacokinetic analysis set (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hours				
arithmetic mean (standard deviation)	114.332 (± 37.9732)			

Statistical analyses

No statistical analyses for this end point

Secondary: Single-dose Pharmacokinetics of Octafibrin: Volume of Distribution (Vss)

End point title	Single-dose Pharmacokinetics of Octafibrin: Volume of Distribution (Vss)

End point description:

Vss was assessed after a single intravenous infusion of 70 mg/kg body weight of Octafibrin.

End point type	Secondary

End point timeframe:

Before first infusion, 1 hour, 3 hours, 1 day, 2 days, 4 days,7 days, 10 days and 14 days post-infusion

End point values	Pharmacokinetic analysis set (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: mL/kg				
arithmetic mean (standard deviation)	81.651 (± 15.2735)			

Statistical analyses

No statistical analyses for this end point

Secondary: Single-dose Pharmacokinetics of Octafibrin: Clearance (Cl)

End point title	Single-dose Pharmacokinetics of Octafibrin: Clearance (Cl)

End point description:

Cl was assessed after a single intravenous infusion of 70 mg/kg body weight of Octafibrin.

End point type	Secondary

End point timeframe:

Before first infusion, 1 hour, 3 hours, 1 day, 2 days, 4 days,7 days, 10 days and 14 days post-infusion.

End point values	Pharmacokinetic analysis set (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: mL/h/kg				
arithmetic mean (standard deviation)	0.756 (± 0.1872)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Maximum Clot Firmness (MCF) for the First Bleeding Episode for Each Patients and for All Bleeding Episodes

End point title	Change in Maximum Clot Firmness (MCF) for the First Bleeding Episode for Each Patients and for All Bleeding Episodes

End point description:

MCF was measured using thromboelastometry (ROTEM). ROTEM is a method for the continuous measurement of clot formation and clot firmness. It utilises a mechanical detection system which is based on the ability of the blood or plasma clot to form a mechanical coupling over a distance of 1 mm. ROTEM was used to measure MCF as a surrogate efficacy marker for haemostatic efficacy before and after the first infusion of Octafibrin for treatment of the first bleeding episode and all bleeding episodes. The change in MCF was measured from baseline to 1hour post-infusion of Octafibrin administration.
The analysis was performed in patients in the full-analysis set population that had at least one bleeding episode (BE) treated with Octafibrin (firstBLEED population: n=8), and all patients that had all documented BEs treated with Octafibrin (BLEED population: n=8)

End point type	Secondary

End point timeframe:

Before first infusion and 1 hour post-infusion of Octafibrin.

End point values	Change in MCF for the firstBLEED Population (p-value 0.0028)	Change in MCF for the BLEED Population (p-value <0.0002)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	8		
Units: mm				
arithmetic mean (standard deviation)	3.1 (± 1.96)	3.3 (± 1.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Fibrinogen Activity for All Bleeding Episodes up to 1 Hour-post Infusion for the First Bleeding Episode and All Bleeding Episodes

End point title	Change in the Fibrinogen Activity for All Bleeding Episodes up to 1 Hour-post Infusion for the First Bleeding Episode and All Bleeding Episodes

End point description:

Change in fibrinogen activity was assessed using the Clauss fibrinogen assay for the first bleeding episode and all bleeding episodes. The change in fibrinogen activity was assessed from Day 1 pre-infusion to 1 hour post-infusion of Octafibrin.
The analysis was performed in patients in the full-analysis set population that had at least one bleeding episode (BE) treated with Octafibrin (firstBLEED population: n=8), and all patients that had all documented BEs treated with Octafibrin (BLEED population: n=8)

End point type	Secondary

End point timeframe:

Pre-infusion and 1 hour post-infusion of Octafibrin.

End point values	Change in Fibrinogen Activity for the firstBLEED Population	Change in Fibrinogen Activity f. BLEED Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	8		
Units: mg/dL				
arithmetic mean (standard deviation)	98.9 (± 13.56)	98.1 (± 13.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental in Vivo Recovery Following the First Infusion of Octafibrin Administration for the Treatment of the First Bleeding Episode and of All Bleeding Episodes

End point title	Incremental in Vivo Recovery Following the First Infusion of Octafibrin Administration for the Treatment of the First Bleeding Episode and of All Bleeding Episodes

End point description:

Incremental IVR calculated as the maximum increase in plasma fibrinogen (i.e. Clauss data) between the pre-infusion and the 3-hour post-infusion measurement, (expressed as absolute concentration in plasma [mg/dL]), divided by the exact dose of Octafibrin per body weight (expressed as mg/kg dosed). Incremental (response) IVR data for the firstBLEED and BLEED populations were calculated.
The analysis was performed in patients in the full-analysis set population that had at least one bleeding episode (BE) treated with Octafibrin (firstBLEED population: n=8), and all patients that had all documented BEs treated with Octafibrin (BLEED population: n=8)

End point type	Secondary

End point timeframe:

Pre-infusion and 3 hours post-infusion.

End point values	Incremental IVR Response for the firstBLEED Population	Incremental IVR Response for the BLEED Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	8		
Units: (mg/dL)/(mg/kg)				
arithmetic mean (standard deviation)	1.5 (± 0.29)	1.5 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Octafibrin in All Bleeding Episodes Based on a Four-point Haemostatic Efficacy Scale

End point title	Efficacy of Octafibrin in All Bleeding Episodes Based on a Four-point Haemostatic Efficacy Scale

End point description:

The haemostatic efficacy of Octafibrin in the on-demand treatment of all bleeding episodes was based on a 4-point haemostatic efficacy scale ranging from excellent, good moderate and none. The efficacy assessment of each patients was assessed by the Investigator and the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC).
The analysis was performed in patients in the full-analysis set population that had all documented bleeding episodes treated with Octafibrin (BLEED population: n=8)

End point type	Secondary

End point timeframe:

First Octafibrin infusion for the treatment of a bleeding episode until 24 hours (i.e., 1 day) after the last infusion or the end of the treatment observation period, whichever comes last.

End point values	Investigator	IDMEAC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	8		
Units: Number of bleeding episodes				
number (not applicable)				
Excellent (N)	7	8		
Excellent (%)	70	80		
Good (N)	1	2		
Good (%)	10	20		
Moderate (N)	1	0		
Moderate (%)	10	0		
None (N)	1	0		
None (%)	10	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Octafibrin in All Bleeding Episodes Based on a Two-point Haemostatic Efficacy Scale

End point title	Efficacy of Octafibrin in All Bleeding Episodes Based on a Two-point Haemostatic Efficacy Scale

End point description:

The haemostatic efficacy of Octafibrin in the on-demand treatment of all bleeding episodes was based on a 2-point haemostatic efficacy scale ranging from success to failure. The efficacy assessment of each patients was assessed by the Investigator and the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC).
The analysis was performed in patients in the full-analysis set population that had all documented bleeding episodes treated with Octafibrin (BLEED population: n=8)

End point type	Secondary

End point timeframe:

First Octafibrin infusion for the treatment of a bleeding episode until 24 hours (i.e., 1 day) after the last infusion or the end of the treatment observation period, whichever comes last.

End point values	Investigator	IDMEAC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	8		
Units: bleeding episodes				
number (not applicable)				
Success (N)	8	10		
Success (%)	80	100		
Failure (N)	2	0		
Failure (%)	20	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Octafibrin in Surgical Prophylaxis Based on a Four-point Haemostatic Efficacy Scale

End point title	Efficacy of Octafibrin in Surgical Prophylaxis Based on a Four-point Haemostatic Efficacy Scale

End point description:

The haemostatic efficacy of Octafibrin was assessed during surgery prophylaxis by the surgeon and the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC), on a 4-point scale ranging from excellent, good, moderate and none. Intra-operative blood loss lower or equal to the average expected blood loss was rates as 'Excellent'; intra-operative blood loss higher than average expected blood loss but lower or equal to maximal expected blood loss was rated as 'Good'; intra-operative blood loss was higher than expected blood loss was rated as 'Moderate' and hemostasis that was uncontrolled and necessitated a change in clotting factor replacement regimen was rated as 'None'.
The surgical observation period started lasted from the first dose of Octafibrin to at least 3 post-operative days for minor and 7 post-operative days for major surgeries or until the day of the last post-operative infusion, which ever comes last.

End point type	Secondary

End point timeframe:

First dose of Octafibrin prior to surgery until last day of post-operative infusion.

End point values	Surgeon	IDEMEAC.		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	3		
Units: number of surgeries				
number (not applicable)				
Excellent (N)	3	3		
Excellent (%)	100	100		
Good (N)	0	0		
Good (%)	0	0		
Moderate (N)	0	0		
Moderate (%)	0	0		

None (N)	0	0		
None (%)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Octafibrin in Surgical Prophylaxis Based on a Two-point Haemostatic Efficacy Scale

End point title	Efficacy of Octafibrin in Surgical Prophylaxis Based on a Two-point Haemostatic Efficacy Scale

End point description:

The haemostatic efficacy of Octafibrin was assessed during surgery prophylaxis by the surgeon and the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC), on a 2-point scale ranging from success to failure.
Efficacy rating of excellent or good from the 2-point efficacy scale indicated 'Success', and efficacy rating of moderate or none indicated 'Failure'.
The surgical observation period started lasted from the first dose of Octafibrin to at least 3 post-operative days for minor and 7 post-operative days for major surgeries or until the day of the last post-operative infusion, which ever comes last.
The analysis was performed in patients in the full-analysis set population with documented surgical interventions treated with at least one infusion of Octafibrin (n=3).

End point type	Secondary

End point timeframe:

First dose of Octafibrin prior to surgery until last day of post-operative infusion.

End point values	Surgeon	IDEMEAC.		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	3		
Units: number of surgeries				
number (not applicable)				
Success (N)	3	3		
Success (%)	100	100		
Failure (N)	0	0		
Failure (%)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Assessment to Assess the Safety of Octafibrin in Thromboembolic Complications: Prothrombin F1 + F2 levels

End point title	Safety Assessment to Assess the Safety of Octafibrin in Thromboembolic Complications: Prothrombin F1 + F2 levels

End point description:

Thrombogenicity was assessed by measuring the plasma levels of prothrombin fragment 1 (F1) and prothrombin fragment 2 (F2), before and after each Octafibrin infusion for the treatment of bleeding episodes during the study. This outcome measure examined the number of patients with elevated values of prothrombin F1 + F2 that were outside the reference range of 69 to 229 pmol/L, three hours post-infusion with Octafibrin.
The analysis was performed in all patients in the safety population that met the study inclusion criteria and received at least one infusion of Octafibrin (n=14).

End point type	Secondary

End point timeframe:

3 hours post-infusion of Octafibrin .

End point values	Prothrombin Fragments (1+2)			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: number of patients				
number (not applicable)				
patients (N)	3			
Patients (%)	21.43			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Assessment: Immunogenicity Testing for Anti-fibrinogen Antibodies

End point title	Safety Assessment: Immunogenicity Testing for Anti-fibrinogen Antibodies

End point description:

The number of patients developing anti-fibrinogen antibodies were observed during the observation period using an experimental non-standard ELISA quantitative laboratory test.
Immunogenicity testing for the presence of anti-fibrinogen antibodies before the first infusion of Octafibrin and on Day 30 after the treatment of each bleeding episode.

End point type	Secondary

End point timeframe:

Start of the first Octafibrin infusion to the end of each 30-day observation and follow-up period for on-demand treatment.

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Number of patients				
number (not applicable)				
Patients (N)	2			

Patients (%)	14.29			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-Demand Treatment: Between start of the first Octafibrin infusion and the end of each 30-day observation and follow-up period
Surgical Prophylaxis: between first infusion of IMP before the start of surgery and the Last Post-operative Day

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs): 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
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	Safety Population (TEAEs)

Reporting group 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).

Reporting group title	Safety Population (AEs)

Reporting group description: -

Serious adverse events	Safety Population (TEAEs)	Safety Population (AEs)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety Population (TEAEs)	Safety Population (AEs)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)	4 / 14 (28.57%)	

Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Influenza-like illness			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	
occurrences (all)	3	3	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infections and infestations			
Tonsillitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2015	Amendment#1: • Change in PK time point from Day5 (96 hours) to Day 4 (72 hours as requested by US FDA and after reviewing the results of the FORMA 01 PK study data analysis. • Including the median response in this dose calculation formula as the median incremental in vivo recovery reported for the PK of Octafibrin in the final analysis of study FORMA-01 which was calculated as 1.77 (g/L / mg/kg)
08 July 2016	Amendment#2: was prepared in response to the information request by the Food and Drug Administration (FDA) 1. For the primary analysis of haemostatic efficacy of Octafibrin in the treatment of the first bleeding episode of each patient, the original 90% confidence interval (CI) was replaced with a two-sided 95% CI. 2. For the secondary analysis of haemostatic efficacy of Octafibrin in the treatment of all bleeding episodes, this amendment now clarifies that the 95% CI of success rate estimates will be a two-sided 95% CI 3. The number of patients enrolled for the PK analysis was increased from at least 6 to at least 12 4. Intraoperative efficacy as assessed by the surgeon excluded unexpected blood loss due to surgical complications. The protocol now contains the provision that, in documenting the adjudication process for the assessment of surgical prophylaxis, the IDMEAC explicitly identifies any subjects for whom they considered there to have been 'unexpected blood loss due to surgical complications' and state whether this unexpected blood loss altered the 4-point assessment of surgical prophylaxis. Any such cases shalll be analyzed both including (as a sensitivity analysis) and excluding unexpected blood loss. 5. To facilitate detection of thromboembolic events (TEEs), a 'TEE questionnaire' including symptoms relevant for the diagnosis of deep venous thrombosis has been added to the study.
30 May 2017	Amendment #3 : 1. Addition of a statement regarding a planned interim analysis and when this will be performed. 2. Addition of a statement regarding when the clinical study report will be available for the submission to the competent authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported