



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) | EMA-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) Adults (18-64 years) From 65-84 years 85 years and over | 6 19 | 6 18 | 1 8 |
| Age continuous Units: years geometric mean full range (min-max) | 29.04 12 to 54 | 28.5 12 to 54 | 31 12 to 49 |
| Gender categorical Units: Subjects | | | |
| Female Male | 11 14 | 11 13 | 2 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) Adults (18-64 years) From 65-84 years 85 years and over | 6 18 | 6 18 | |
| Age continuous Units: years geometric mean full range (min-max) | 28.5 12 to 54 | 28.5 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