octapharma

CLINICAL STUDY PROTOCOL
FORMA-04

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 deficiency

Investigational Product:	*Octafibrin*
Indication:	Congenital fibrinogen deficiency
Study Design:	Multinational, multi-centre, prospective, open-label, uncontrolled
Sponsor:	Octapharma AG
Study Number:	FORMA-04
EudraCT Number:	2014-005115-16
Development Phase:	Phase III
Planned Clinical Start:	3rd quarter 2015
Planned Clinical End:	3rd quarter 2020
Date of Protocol:	30-May-2017
Version:	4.0, includes Protocol Amendment #3, 30-May-2017 Protocol Amendment #2, 08-Jul-2016 (CSP V3.0) Protocol Amendment #1, 15-Sep-2015 (CSP V2.0)
Co-ordinating Investigator:	[redacted]

STUDY OUTLINE

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Title of Study:

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-fi-ciency

Indication: Congenital fibrinogen deficiency

Number of Study Centres: Approximately 5 study centres worldwide.

Study Duration: 3rd quarter 2015 to 3rd quarter 2020	**Development Phase:** III

Objectives:

Primary:

- To demonstrate the efficacy of *Octafibrin* for on-demand treatment of acute bleeding episodes (spontaneous or after trauma)

Secondary:

- To determine the single-dose pharmacokinetics of *Octafibrin* in paediatric subjects with congenital fibrinogen deficiency
- To investigate an association between the overall clinical assessment of haemostatic efficacy and the surrogate endpoint ‘clot strength’ or ‘clot firmness’ (referred to as ‘maximum clot firmness’ [MCF] in this protocol) via thromboelastometry (ROTEM). Therefore, MCF as surrogate efficacy parameter will be determined before and after the first infusion of IMP for treatment of a bleeding episode
- To achieve a peak target plasma fibrinogen level of 100 mg/dL in minor bleeds and 150 mg/dL for major bleeds 1 hour post-infusion
- To determine the response to *Octafibrin* based on incremental in vivo recovery (IVR)
- To demonstrate the efficacy of *Octafibrin* in preventing bleeding during and after sur-gery
- To assess the safety of *Octafibrin* in subjects with congenital fibrinogen deficiency, including immunogenicity, thromboembolic complications, and early signs of allergic or hypersensitivity reactions

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Study Design:

Multinational, multi-centre, prospective, open-label, uncontrolled, Phase III study.

Number of Subjects:

At least 12 male or female paediatric subjects with congenital fibrinogen deficiency will be enrolled into the study and undergo PK assessment. Of these 12 subjects, at least 6 subjects will undergo on-demand treatment of 6 first bleeding episodes. Of these 6 subjects, at least 3 should be aged between 0 and <6 years and 3 should be aged between 6 and <12 years. In addition, at least 2 surgical procedures will be assessed.

Subject Selection Criteria:

Inclusion criteria:

1. Aged <12 years (at the start of treatment)
2. Documented diagnosis of congenital fibrinogen deficiency, expected to require on-demand treatment for bleeding or surgical prophylaxis:
   - Fibrinogen deficiency manifested as afibrinogenaemia or severe hypofibrinogenaemia
   - Historical plasma fibrinogen activity of <50 mg/dL or levels below the limit of detection of the local assay method.
3. Expected to have an acute bleeding episode (spontaneous or after trauma) or planning to undergo elective surgery
4. Informed consent signed by the subject's legal guardian

Exclusion criteria:

1. Life expectancy <6 months
2. Bleeding disorder other than congenital fibrinogen deficiency, including dysfibrinogenaemia
3. Prophylactic treatment with a fibrinogen concentrate
4. Treatment with:
   - Any fibrinogen concentrate or other fibrinogen-containing blood product within 2 weeks prior to start of treatment for the PK phase, a bleeding episode, or surgery
   - Any coagulation-active drug (i.e., non-steroidal anti-inflammatory drugs, warfarin, coumarin derivatives, platelet aggregation inhibitors) within 1 week prior to start of the PK phase or treatment for the bleeding episode or surgery, or as a planned or expected medication during the time period from Day 1 until 24 hours (i.e., 1 day) after the last *Octafibrin* infusion

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

5. Presence or history of:
   - Hypersensitivity to study medication
   - Deep vein thrombosis or pulmonary embolism within 1 year prior to start of treatment for the bleeding episode or surgery
   - Arterial thrombosis within 1 year prior to start of treatment for the bleeding episode or surgery
   - Hypersensitivity to human plasma proteins
   - Oesophageal varicose bleeding
   - End-stage liver disease (i.e., Child-Pugh score B or C)
6. Known positive HIV infection with a viral load >200 particles/µL or >400,000 copies/mL
7. Polytrauma 1 year prior to start of treatment for the bleeding episode or surgery
8. Diagnosis or suspicion of a neutralizing anti-fibrinogen inhibitor currently or at any time in the past
9. Acute or chronic medical condition which may, in the opinion of investigator, affect the conduct of the study, including subjects receiving immune-modulating drugs (other than anti-retroviral chemotherapy), such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs, at study start
10. Treatment with IMP in another interventional clinical study currently or during the past 4 weeks

Test Product, Dose, Mode of Administration, and Batch Number(s):

In this study, *Octafibrin* will be administered as intravenous (i.v.) bolus injection. Continuous infusion is not allowed.

PK Dose Schedule and Mode of Administration

For PK assessments, subjects will receive a single intravenous infusion of 70 mg/kg body weight of *Octafibrin*.

Octafibrin Treatment Dose Calculation

Octafibrin will be individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleeding or surgery (minor or major). The dose will be calculated individually as follows:

$$\text{Fibrinogen dose (mg/kg body weight)} = \frac{\text{[Target peak plasma level (mg/dL) – measured level (mg/dL)**]}}{\text{Median response* (mg/dL per mg/kg body weight)}}$$

* The median response in this dose calculation formula is 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.
**The measured level for the first infusion will be the historical level for that patient after a washout or, if below the limit of detection of the local assay, zero (0) will be used.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Dosing for On-Demand Treatment of Bleeding

For each bleeding episode that is treated as part of the study, each subject will receive at least 1 infusion of *Octafibrin* for the treatment of a major or minor acute bleeding episode on Day 1.

Octafibrin will be individually dosed to achieve a recommended target fibrinogen plasma level dependent on the bleeding type (minor or major).

- **Minor bleeding** will be treated to achieve a recommended target fibrinogen plasma level of 100 mg/dL and an accepted lower limit of 80 mg/dL.
- **Major bleeding** will be treated to achieve a recommended target fibrinogen plasma level of 150 mg/dL and an accepted lower limit of 130 mg/dL.

On subsequent study days, fibrinogen plasma levels will be measured daily to determine whether additional infusions of *Octafibrin* are needed:

- **Minor bleeding** will be observed for at least 3 days.
- **Major bleeding** will be observed for at least 7 days.

Additional Octafibrin infusions, as required

- Additional infusions of *Octafibrin* **should** be administered if the actual fibrinogen plasma level measured on subsequent study days is below the accepted lower limit of the target level (80 mg/dL for minor bleeding, 130 mg/dL for major bleeding).
- If the actual fibrinogen plasma level is above the accepted lower limit of the target level, *Octafibrin* **should not** be administered.

Definition of minor and major bleeding

- **Minor bleeding** events are defined as mild haemarthrosis or superficial muscle, soft tissue, and oral bleeding.
- **Major bleeding** events are defined as symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial bleeding, or intramuscular bleeding with compartment syndrome, or bleeding causing a decrease in haemoglobin level by 20 g/L (1.24 mmol/L) or more.

Characterisation of any other bleeding events not within these categories will be discussed individually with the investigator.

Dosing for Surgery

For each surgery that is treated as part of the study, within 3 hours prior to surgery, each subject will receive a loading infusion of *Octafibrin.*

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Octafibrin will be individually dosed to achieve a recommended target fibrinogen plasma level dependent on the surgery type (minor or major).

- Patients undergoing **minor surgery** will be treated to achieve a recommended target fibrinogen plasma level of 100 mg/dL and an accepted lower limit of 80 mg/dL.
- Patients undergoing **major surgery** will be treated to achieve a recommended target fibrinogen plasma level of 150 mg/dL and an accepted lower limit of 130 mg/dL.

On each post-operative day, fibrinogen plasma levels will be measured daily to determine whether maintenance infusions of *Octafibrin* are needed:

- **Minor surgery** will be observed for at least 3 post-operative days.
- **Major surgery** will be observed for at least 7 post-operative days.

Maintenance infusions, as required:

- Additional infusions of *Octafibrin* **should** be administered if the actual fibrinogen plasma level measured on subsequent study days is below the accepted lower limit of the target level (80 mg/dL for minor surgery, 130 mg/dL for major surgery).
- If the actual fibrinogen plasma level is above the accepted lower limit of the target level, *Octafibrin* **should not** be administered.

Definition of minor and major surgery

Surgeries are defined as **major**, if any of the following criteria are met:

- Requiring general or spinal anaesthesia.
- Requiring opening into the great body cavities.
- In the course of which hazards of severe haemorrhage is possible.
- Requiring haemostatic therapy for at least 6 days.
- Orthopaedic interventions involving joints (ankle, knee, hip, wrist, elbow, shoulder).
- Surgeries/conditions in which the subject's life is at stake.

Characterisation of any other surgery not within these categories and considered major by the investigator will be discussed individually with the investigator.

All other surgeries are classified as minor. The classification is made prospectively.

Duration of Treatment:

Planned duration over the entire study: The planned study duration is up to 5 years. The study will be considered completed when a minimum of 12 subjects have undergone PK assessments, 6 subjects (i.e., at least 3 subjects aged between 0 and <6 years and 3 subjects aged between 6 and <12 years) have at least one documented bleeding episode, and a minimum of 2 surgical procedures have been performed.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Planned duration for an individual subject:

All patients (at least 12) will undergo a PK study after screening. This will have a duration of 14 days, after which a patient can be treated for a bleeding episode or planned surgical procedure when they occur.

For subjects receiving on-demand treatment,

- The individual **subject observation and follow-up period** for each documented episode starts with the first dose of *Octafibrin* administered for on-demand treatment of an acute bleeding episode (Day 1) and will be followed up to at least Day 30.
- Each subject's **treatment observation period** is defined according to the severity of the event and will last at least 3 days for minor and 7 days for major bleeding episodes.

For subjects undergoing surgical prophylaxis,

- the **surgical observation period** starts with the first dose of *Octafibrin* administered prior to elective surgery (Day 1) and, depending on the severity of the event, will last 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, whichever comes last.

During the study observation period, enrolled patients will be treated for any bleeding episodes or planned surgeries that can be managed under the protocol. Patients may remain in the study until the 6th patient (at least 3 patients each in the specified age groups) has at least one documented bleeding episode and there are at least 2 surgical procedures documented.

As many bleeding episodes or surgeries as possible occurring throughout the study observation period will be documented. Only the first bleeding episodes will be used for the analysis of the primary endpoint. All bleeding episodes documented in the study will be assessed as a secondary endpoint.

Patients who were screened for the study but did not receive any IMP will be considered 'no treatment' patients and reported separately.

All patients completing the PK phase will also be analyzed separately, regardless of whether they received any IMP for the treatment of a bleeding episode or surgery.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):
Not applicable.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary endpoint

The primary endpoint is the **overall clinical assessment of the haemostatic efficacy of *Octafibrin*** in treating the first documented bleeding episode of each patient. The first bleeding episode covers the time period from the 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.

The investigator's overall clinical assessment of haemostatic efficacy for bleeding will be based on a 4-point haemostatic efficacy scale (see table below). The final efficacy assessment of each patient will be adjudicated by the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC). The number of subjects per outcome category will be assessed in the final analysis.

4-point haemostatic efficacy scale

Category	Definition
Excellent	Immediate and complete cessation of bleeding in the absence of other haemostatic intervention as clinically assessed by the treating physician; and/or <10% drop in haemoglobin compared to pre-infusion.
Good	Eventual complete cessation of bleeding in the absence of other haemostatic intervention as clinically assessed by the treating physician; and/or <20% drop in haemoglobin compared to pre-infusion.
Moderate	Incomplete cessation of bleeding and additional haemostatic intervention required, as clinically assessed by the treating physician; and/or between 20 and 25% drop in haemoglobin compared to pre- infusion.
None	No cessation of bleeding and alternative haemostatic intervention required, as clinically assessed by the treating physician; and/or >25% drop in haemoglobin compared to pre-infusion.

Secondary endpoints

PK endpoints:

- Area under the concentration-time curve (AUC)
- Response: Incremental In Vivo Recovery (IVR)
- Classical IVR
- Terminal elimination half-life ($t_{1/2}$)
- Maximum plasma concentration (C_{max})
- Time to reach maximum plasma concentration (T_{max})
- Mean residence time (MRT)

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

- Volume of distribution (Vss)
- Clearance (Cl)

Secondary efficacy endpoints:

- MCF assessment before first infusion and 1 hour after end of first infusion of each documented bleeding episode.
- Fibrinogen plasma level before and 1 hour after the end of each infusion as well as at the time of the overall clinical assessment of haemostatic efficacy (i.e., 24 hours after the last infusion or end of the observation period of each documented bleeding episode).
- Response after the first infusion of each bleeding episode as indicated by incremental IVR, calculated as the maximum increase in plasma fibrinogen (Clauss data) between the pre-infusion and the 3-hour post-infusion measurement, divided by the exact dose of *Octafibrin* (expressed as mg/kg dosed).
- Efficacy of *Octafibrin* in all bleeding episodes collected in the study using the investigator's overall clinical assessment of haemostatic efficacy for bleeding based on a 4-point haemostatic efficacy scale.
- Efficacy of *Octafibrin* in surgical prophylaxis will be assessed at the end of surgery by the surgeon and post-operatively by the haematologist using the following scales:

Category	**Definition**
Intra-operative efficacy as assessed by surgeon (at the end of the surgery=after last suture)	
Excellent	Intra-operative blood loss* was lower than or equal to the average expected blood loss for the type of procedure performed in a subject with normal haemostasis and of the same sex, age, and stature.
Good	Intra-operative blood loss* was higher than average expected blood loss but lower or equal to the maximal expected blood loss for the type of procedure in a subject with normal haemostasis.
Moderate	Intra-operative blood loss* was higher than maximal expected blood loss for the type of procedure performed in a subject with normal haemostasis, but haemostasis was controlled.
None	Haemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.

*Excludes unexpected blood loss due to surgical complications, i.e.,
–Direct injury of a vessel (artery or vein)
–Vessel injury not adequately responding to routine surgical procedures achieving haemostasis
–Accidental injury of parenchymatous tissue (e.g., liver, lung)

Post-operative efficacy as assessed by haematologist

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Excellent	No post-operative bleeding or oozing that was not due to complications of surgery. All post-operative bleeding (due to complications of surgery) was controlled with *Octafibrin* as anticipated for the type of procedure.
Good	No post-operative bleeding or oozing that was not due to complications of surgery. Control of post-operative bleeding due to complications of surgery required increased dosing with *Octafibrin* or additional infusions, not originally anticipated for the type of procedure.
Moderate	Some post-operative bleeding and oozing that was not due to complications of surgery; control of post-operative bleeding required increased dosing with *Octafibrin* or additional infusions, not originally anticipated for the type of procedure.
None	Extensive uncontrolled post-operative bleeding and oozing. Control of post-operative bleeding required use of an alternate fibrinogen concentrate.

An overall efficacy assessment taking both the intra- and post-operative assessment into account will be adjudicated by the IDMEAC. The final endpoint determination will be based on the adjudicated assessments using an agreed algorithm.

The **surgical observation period** starts with the first dose of *Octafibrin* administered prior to elective surgery (Day 1) and, depending on the severity of the event, will last 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, whichever comes last.

In addition, the location, severity and type of surgery will be documented. Expected and actual duration of surgical procedure and details of administered dose(s) of *Octafibrin* (pre-, intra- and/or post-operatively) will be recorded. Fibrinogen plasma levels (pre-, intra-, and post-operatively) will be measured. Details of concomitantly administered products (except standard anaesthesia) along with a brief narrative describing the outcome of the intervention will be recorded.

Safety endpoints:

- Vital signs
- Physical examination
- Thromboembolic event (TEE) questionnaire
- Routine clinical laboratory assessment, including coagulation parameters
- Adverse events (AEs), including thromboembolic complications and early signs of allergic or hypersensitivity reactions
- Thrombogenicity testing before and after each IMP infusion for the treatment of bleeding, except on the Day of Last Infusion
- Immunogenicity testing before the first infusion of IMP and on Day 30 after the treatment of each bleeding episode

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Summary of Study Procedures:

SCREENING ASSESSMENTS

Patients identified by the study sites as potential study participants will undergo the following screening assessments:

- Inclusion and exclusion criteria, including written informed consent by the subject's legal guardian for participation in the study
- Demography, medical history (including details concerning allergic tendencies), review of previous therapy, and prior/concomitant medication

PHARMACOKINETICS ASSESSMENTS

Within 2 weeks after the screening process, subjects will receive a single infusion of 70 mg/kg *Octafibrin* on Day 1 of PK testing (PK-Day 1). Before the start of the PK phase, there must be an at least 2-week wash-out period of any fibrinogen containing product.

Before first injection vital signs and blood draws for baseline fibrinogen levels will be assessed. Retention serum samples for potential retesting will be collected within 30 minutes before the PK infusion. At 1 and 3 hours post-infusion, vital signs and fibrinogen for PK will be assessed, and AEs will be recorded. Subjects will be further followed on:

- **PK-Days 2, 4, 7, and 10**
  - Fibrinogen for PK
  - Recording of AEs, including potential thromboembolic events
- **PK-Day 14**
  - Fibrinogen for PK
  - Vital signs
  - Physical examination including any signs or symptoms of potential thromboembolic events
  - Recording of AEs, including potential thromboembolic events

ASSESSMENTS IN SUBJECTS UNDERGOING ON-DEMAND TREATMENT OF BLEEDING

Subjects presenting to the study site for an acute bleeding episode will undergo a 30-day observation and follow-up period as outlined below. Throughout the study, subjects may undergo more than one 30-day observation and follow-up period for additional bleeding episodes as required until the close of the study. At the end of their study participation, patients will be asked to return for a final Study Completion Visit.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

NOTE: All adverse events (AEs), including thromboembolic events and early signs of allergic or hypersensitivity reactions, occurring between the start of the first *Octafibrin* infusion and the end of each 30-day observation and follow-up period will be recorded. The detection of thromboembolic events will be supported by completing a TEE questionnaire at each study visit for the treatment of bleeding episodes and for surgeries. Concomitant medications will also be recorded throughout each 30-day observation and follow-up period. Administered doses of *Octafibrin* will be recorded for every infusion, including dates, times, and batch numbers.

All SAEs occurring after the first IMP infusion will be documented and reported for a patient throughout the duration of the patient's participation in the study or as required to meet local regulations. Also, any concomitant medications used to treat an SAE will be recorded.

Day 1 (first day of treatment)

On Day 1, subjects will visit their site for treatment of an acute bleeding episode.

Pre-infusion assessments

The following assessments will be performed before the first infusion of *Octafibrin* for each bleeding episode:

- Medical history (including details of any non-study bleeding episodes and therapy), and prior/concomitant medication
- Characterisation of bleeding episode
- Vital signs
- Physical examination
- TEE questionnaire
- Height and weight
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity; within 30 minutes before infusion)
  - MCF (within 30 minutes before infusion)
  - safety lab (local–haematology and clinical chemistry)
  - thrombogenicity
  - immunogenicity

NOTE: If the period between screening and treatment is more than 3 months, informed consent will be re-reviewed and confirmed prior to treatment, and details of the review process will be recorded in the patient chart and indicated in the CRF by the investigator. Also, inclusion/exclusion criteria will be confirmed prior to treatment.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

First infusion of Octafibrin

After the pre-infusion assessments, subjects will receive the first infusion of *Octafibrin* for treatment of bleeding.

Post-infusion assessments

On Day 1, the following post-infusion assessments will be performed:

1 hour (±15 minutes) after the end of infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)
  - MCF

3 hours (±15 minutes) after the end of infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (central lab–antigen and activity)
  - thrombogenicity
- AEs and concomitant medications

NOTE: If, in the investigator's judgement, the infusion of *Octafibrin* administered on Day 1 is deemed the only infusion needed for treatment of the subject's bleeding event, the subject will need to reach the end of the treatment observation period, where the "24 hours (i.e., 1 day) after the last infusion" assessments should be performed.

All study days after Day 1 (treatment observation period)

Each subject's **treatment observation period** is defined according to the severity of the event and will last at least **3 days for minor and 7 days for major bleeding episodes**.

If the patient requires multiple infusions, the actual treatment duration will be determined by the investigator based on his/her judgement of the subject's condition.

On subsequent study days (at least 3 days for minor bleeding or 7 days for major bleeding), fibrinogen plasma levels will be measured daily to determine whether additional infusions of *Octafibrin* are needed.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Daily assessments (for at least 3 days for minor bleeding or 7 days for major bleeding)

- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity): Based on local lab results, the investigator will determine whether additional infusions of *Octafibrin* are needed.
  - safety lab (local–haematology)
- AEs and concomitant medications

Octafibrin infusion, as required

After these daily assessments, additional IMP dosing should occur as required depending on the actual and target plasma level and based on the following criteria:

- If the actual fibrinogen plasma level is below the accepted lower limit of the target fibrinogen plasma level (80 mg/dL for minor bleeding, 130 mg/dL for major bleeding), the subject **should** receive another infusion of *Octafibrin*.
- If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, *Octafibrin* **should not** be administered on that day.

Pre- and post-infusion assessments

If the subject receives an additional infusion of *Octafibrin*, the following pre- and post-infusion assessments will be done.

Pre-infusion assessments:

- TEE questionnaire
- Blood draw for (within 30 minutes before infusion):
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)
  - thrombogenicity

1 hour (±15 minutes) after the end of each infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)
  - thrombogenicity

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

NOTE: If, in the investigator's judgement, there are no additional infusions of *Octafibrin* needed to treat the bleeding event, the subject will need to reach the end of the treatment observation period, where the "24 hours (i.e., 1 day) after the last infusion" assessments should be performed.

Last Infusion or End of the Treatment Observation Period (whichever comes last)

On the Day of Last Infusion for a patient requiring multiple infusions for a bleeding event as defined by the investigator based on his/her judgement of the subject's condition or if the subject comes to the end of the treatment observation period (whichever comes last), the following assessments will be performed:

Pre-infusion assessments

The following assessments will be performed prior to the last infusion of *Octafibrin* if multiple infusions are needed:

- TEE questionnaire
- Blood draw for (within 30 minutes before infusion):
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)

Last infusion of Octafibrin

Following the pre-infusion assessments, subjects will receive their last infusion of *Octafibrin* depending on the actual and target plasma levels.

Post-infusion assessments

On the Day of Last Infusion, post-infusion assessments will be as follows:

1 hour (±15 minutes) after the end of last infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)

24 hours (i.e., 1 day) after the last infusion or at the end of the treatment observation period (whichever comes last):

- Vital signs
- Physical examination
- TEE questionnaire

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

- Blood draw for:
  - fibrinogen plasma level (central lab–antigen and activity)
- Final assessment of haemostatic efficacy by the investigator with respect to the adequacy of stopping an acute bleed. The assessment is to include the entire period from the start of the first infusion until 24 hours (i.e., 1 day) after the last infusion and includes the clinical condition of the subject, laboratory values such as haematocrit and haemoglobin, and any additional haemostatic treatments.

Day 30 (29 days after the first infusion)—Final Examination

On Day 30 (± 1 week), the following assessments will be performed:

- Physical examination
- TEE questionnaire
- Blood draw for:
  - immunogenicity
  - retention serum sample for potential retesting
- AEs and concomitant medications

The Day 30 assessment concludes the series of observations for a bleeding episode. No further study-related assessments for this episode will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up. Subjects returning to the study site for another acute bleeding episode within the study observation period will again undergo the same series of Day 1 to Day 30 assessments as outlined above. At the end of the study duration, all subjects having received any IMP will be asked to return for a Study Completion Visit.

If the patient experiences another bleeding event before Day 30, this will be treated as a new bleeding event, provided that it is not directly related to the prior event. In this case, Day 30 evaluations will be postponed until 30 days after the start of the new bleeding episode.

ASSESSMENTS IN SUBJECTS UNDERGOING SURGICAL PROPHYLAXIS

In the case of a surgical procedure, *Octafibrin* will be given prior to surgery as well as during and after surgery based on the physician's judgement, the patient's history, and the severity of the procedure. Subjects enrolled for elective surgery will be treated (as required) and assessed throughout the surgical observation period.

The **surgical observation period** starts with the first dose of *Octafibrin* administered prior to elective surgery (Day 1) and, depending on the severity of the event, will last 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, whichever comes last.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

NOTE: All adverse events (AEs), including thromboembolic events and early signs of allergic or hypersensitivity reactions, occurring between first infusion of IMP before the start of surgery and the Last Post-operative Day will be recorded.

All SAEs occurring after the first IMP infusion will be documented and reported for a patient throughout the duration of the patient's participation in the study or as required to meet local regulations. Also, any concomitant medications used to treat an SAE will be recorded.

Day 1

For subjects enrolled for surgical prevention, Day 1 is the day they undergo surgery and receive their first dose of *Octafibrin* in this study. The following surgery-related data will be recorded:

Pre-operative assessments

The following data will be recorded before surgery:

- Medical history
- Vital signs
- Physical examination
- TEE questionnaire
- Body weight (kg)
- Blood draw for:
  - fibrinogen plasma levels (local lab–activity; central lab–antigen and activity)
  - safety lab (local–haematology and clinical chemistry).
- Location and type of surgery
- Severity of surgery (minor/major)
- Expected duration of surgical procedure (start and end times, i.e., skin to skin)
- Expected blood loss for the procedure
- Estimate of any blood/blood product transfusions needed during the surgery
- Any planned ancillary therapy to be used during the surgery (e.g., antifibrinolytics, pre-panned blood transfusions, etc.)

First infusion of Octafibrin

Following the pre-operative assessments and within 3 hours before the start of surgery, the subject may receive the first infusion of *Octafibrin*.

NOTE: If, in the investigator's judgement, there are no additional infusions of *Octafibrin* needed to prevent bleedings post surgery, the post-infusion assessments as detailed in the schedule for the **Last Post-Operative Day** should be performed instead.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Intra-operative assessments

The following data will be recorded during and at the end of surgery:

- Blood draw for:
  - intra-operative fibrinogen plasma levels (local lab–activity; central lab–antigen and activity)
- AEs and concomitant medications

Assessments at the end of surgery

- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma levels (local lab–activity; central lab–antigen and activity)
- Actual duration of surgical procedure (start and end times, i.e., skin to skin)
- Details of surgery
- Actual blood loss
- Details on concomitantly administered products including any blood/blood product transfusions but excluding drugs given for routine anaesthesia
- Intra-operative efficacy assessment at the end of surgical procedure by the surgeon.
- AEs and concomitant medications

Any post-operative day before the Last Post-Operative Day

On any post-operative day before the Last Post-Operative Day, the following assessments will be performed:

Daily post-operative assessments

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma levels (local lab–activity; central lab–antigen and activity)
  - safety lab (local–haematology and clinical chemistry)
- Wound haematomas and oozing (noting whether surgical evacuation is required and severity and volume of oozing)
- AEs and concomitant medications

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Octafibrin infusion, as required

Additional dosing should occur as required depending on the actual and target plasma level and based on the following criteria:

- If the actual fibrinogen plasma level is below the accepted lower limit of the target fibrinogen plasma level (80 mg/dL for minor surgery, 130 mg/dL for major surgery), the subject **should** receive another infusion of *Octafibrin*.
- If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, *Octafibrin* **should not** be administered on that day.

Pre- and post-infusion assessments

If the subject receives an infusion of *Octafibrin*, the following pre- and post-infusion assessments will be performed:

Pre-infusion assessments:

- TEE questionnaire
- Blood draw for (within 30 minutes before infusion):
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)
- AEs and concomitant medications

1 hour (±15 minutes) after the end of each infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)
  - safety lab (local–haematology and clinical chemistry)
- AEs and concomitant medications

Last Post-Operative Day

The Last Post-Operative Day is either at least post-operative day 3 for minor and post-operative day 7 for major surgery or the day of the last post-operative infusion, whichever comes last.

The assessments performed on the Last Post-Operative Day are identical to those performed on any other post-operative day (see 'Any post-operative day before the Last Post-Operative Day' as described on page xvii).

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

In addition, the following assessments will be performed on the Last Post-Operative Day:

- post-operative efficacy assessment by the haematologist
- brief narrative describing the details of hospitalisation (start and end date, details of the procedure), follow-up, outcome, and efficacy of the intervention

The assessments performed on the Last Post-Operative Day conclude the surgical observation period. No further study-related assessments will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up.

Patients may remain in the study until at least 12 patients have undergone PK assessment, the 6th patient (at least 3 patients each in the specified age groups) has at least one documented bleeding episode, and at least 2 surgical procedures have been documented. When the study is closed, all subjects having received any IMP will be asked to return for a Study Completion Visit.

Study Completion Visit

At the end of the study duration, all subjects having received any IMP will be asked to return for a Study Completion Visit, during which the following assessments will be performed:

- Medical history since the last study visit
- Physical examination
- TEE questionnaire

After the Study Completion Visit, the clinical study is considered completed for the subject.

Patients who were screened for the study but did not receive any IMP throughout the study duration will be notified of the end of the study. No further assessments will need to be performed. These patients will be considered ‘no treatment’ patients and reported separately.

Statistical analysis:

Continuous variables will be summarised using descriptive statistics (including arithmetic mean, standard deviation (SD), median, minimum and maximum, and number of observations and missing observations). Categorical variables will be summarised with counts and percentages. Additionally, for PK data and efficacy parameters, two-sided 95% confidence intervals will be calculated where appropriate.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

Primary endpoint

The primary endpoint is the overall clinical assessment of the haemostatic efficacy of *Octafibrin* in treating the first documented bleeding episode of each patient. The first bleeding episode covers the time period from the 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.

For the analysis, the assessment made by the investigator on the 4-point rating scale will be transformed to a dichotomous endpoint with success defined as a rating of excellent or good. The final efficacy assessment of each patient will be adjudicated by an Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC). Bleeding efficacy data will be summarised using descriptive statistics and displayed graphically, differentiating between the first bleeding episode per patient (primary endpoint) and all bleeding episodes (secondary endpoint).

Secondary endpoints

PK endpoints:

The PK endpoints (i.e., area under the concentration-time curve (AUC), incremental IVR, classical IVR, terminal elimination half-life ($t_{1/2}$), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), mean residence time (MRT), volume of distribution (Vss), and clearance (Cl)) will be assessed after a single intravenous infusion of 70 mg/kg body weight of *Octafibrin*.

PK analysis on fibrinogen activity and antigen levels will be performed per patient with a non-compartmental model using standard PK software (Phoenix); this includes graphical displays of individual elimination curves. The resulting PK parameters will be summarized and presented as described for continuous variables.

Secondary efficacy endpoints:

Clot strength (MCF)

Fibrinogen levels 1 hour after infusion of the investigational medicinal product (IMP), MCF at pre-infusion and at 1 hour after the first infusion as well as changes of MCF from pre-infusion will be summarised using descriptive statistics and displayed graphically.

Octafibrin use

The dose of the IMP used per day and in total will be summarised using descriptive statistics for minor and major bleeding events. Frequency of infusions and duration of treatment will also be summarised.

Name of Sponsor/Company: **Octapharma AG**	
Name of Investigational Product: *Octafibrin*	**Protocol Identification Code:** FORMA-04
Name of Active Ingredient: Fibrinogen	**Date of Final Protocol:** 30-May-2017

In-vivo recovery (IVR)

IVR will be calculated for the first infusion of each bleeding episode. Descriptive tables will show the distributions of the IVR, separated by minor and major bleeding events.

Haemostatic efficacy in the treatment of all bleeding episodes

In addition to the 'first BE per patient approach' (primary endpoint), success rates will be presented with two-sided 95% confidence intervals for all documented bleeding episodes, both considering each bleeding episode as an independent case within each subject and considering outcomes of assessments as repeated measurements within the same patient, if applicable (e.g., by general estimation equations with intra-subject correlation structure).

Surgical prophylaxis

Efficacy of *Octafibrin* in surgical prophylaxis will be assessed intra-operatively (at the end of surgery = after last suture) by the surgeon and post-operatively by the haematologist using two 4-point efficacy scales. The overall surgical efficacy will be adjudicated by the IDMEAC and summarised using descriptive statistics.

Safety analysis:

Safety parameters will be descriptively summarised.

Interim analysis

An administrative interim analysis will be performed after at least 12 patients have undergone PK assessment within the study. The interim analysis will focus on the PK data only.

FLOW CHART OF ASSESSMENTS FOR ON-DEMAND TREATMENT OF ACUTE BLEEDING

	Screening	14-day PK Phase within 14 days after screening [j]	On Demand Bleeding - OBSERVATION AND FOLLOW-UP PERIOD											Study Completion Visit
			Day 1			All study days after Day 1 TREATMENT OBSERVATION PERIOD (at least 3 days for minor bleeding, 7 days for major bleeding)			Day of Last Infusion		24 hours (i.e., 1 day) after last infusion or end of the observation period	Day 30 (± 1 week)	
			Pre-infusion	Post-infusion 1 h (± 15 min)	Post-infusion 3 h (± 15 min)	Daily	Pre-infusion [a]	1 h post-infusion [a] (± 15 min)	Pre-infusion	1 h post-infusion (± 15 min)			
Eligibility and informed consent	x		#											
Demography	x													
Medical history, review of previous therapy	x		x											
Physical examination			x								x	x	x	
Vital signs			x	x	x			x		x	x			
TEE questionnaire			x	x	x	x	x	x	x	x	x	x	x	
Height and weight			x											
Characterisation of bleeding episode			x											
Blood draw for:														
Fibrinogen activity			x **[b,c,d]**	x **[c,d]**	x **[d]**	x **[c,d]**	x **[b,c,d]**	x **[c,d]**	x **[b,c,d]**	x **[c,d]**	x **[d]**			
Fibrinogen antigen			x **[b,d]**	x **[d]**	x **[d]**	x **[d]**	x **[b,d]**	x **[d]**	x **[b,d]**	x **[d]**	x **[d]**			
MCF **[d]**			x **[b]**	x										
Thrombogenicity **[d]**			x		x		x	x						
Immunogenicity **[d]**			x									x		
Safety lab (haematology and clinical chemistry) **[c]**			x			x **[i]**								
Retention serum samples **[e]**												x		
Infusion of *Octafibrin*			x **[f]**				x **[f,g]**		x					
Final haemostatic efficacy assessment											x			
AEs [h]			>	>	>	>	>	>	>	>	>	>		
Concomitant medications			>	>	>	>	>	>	>	>	>	>		
Medical history since last study visit														x

TEE = thromboembolic event; AE = adverse event; MCF = Maximum clot firmness (clot strength).

To be re-reviewed if period between screening and treatment is more than 3 months.

[a] If, based on the daily assessment, the investigator considers an additional infusion of *Octafibrin* necessary (see footnote f).

[b] Within 30 minutes before infusion.

[c] Measured in local laboratories.

[d] Measured in the central laboratory.

[e] Serum retention sample for potential viral testing.

[f] If the *Octafibrin* infusion administered on this day is deemed the only infusion needed for treatment of the subject's bleeding event, the post-infusion assessments as detailed in the more comprehensive schedule for the Day of Last Infusion must be performed.

[g] If the actual fibrinogen plasma level is below the accepted lower limit of the target fibrinogen plasma level, the subject **should** receive another infusion of *Octafibrin.* If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, *Octafibrin* **should not** be administered.

[h] Including thromboembolic events or hypersensitivity reactions.

[i] Haematology only.

[j] Retention serum sample taken before PK infusion; PK infusion of 70 mg/kg of *Octafibrin;* subsequent blood sampling (see separate PK flow chart) (if not previously performed prior to a surgical procedure).

FLOW CHART OF ASSESSMENTS FOR SURGICAL PROPHYLAXIS

	Screening	14-day PK Phase within 14 days after screening [i]	SURGICAL OBSERVATION PERIOD											Study Completion Visit
			Before surgery		Day 1 Surgery			Any POP day (i.e., up to and excluding either Day 4 for minor and Day 8 for major surgery or the day of the last post-operative infusion, whichever comes later)			Last POP Day (i.e., either Day 4 for minor and Day 8 for major surgery or the day of the last post-operative infusion, whichever comes later)			
			Within 12 h before start	Within 3 h before start	Start	Intra-operative	End	Daily [i]	Pre-infusion	1 h post-infusion (± 15 min)	Daily [i]	Pre-infusion	1 h post-infusion (± 15 min)	
Eligibility and informed consent	x		#											
Demography	x													
Medical history, review of previous therapy	x		x											
Details of surgery (location, type, severity)			x											
Estimated blood loss, duration of surgery, transfusion requirements			x											
Any planned ancillary therapy during the surgery (e.g., antifibrinolytics)			x											
Actual duration of surgery							x							
Details of hospitalisation and follow-up (narrative)							x							
Actual blood loss and transfusion requirements							x							
Physical examination			x											x
Vital signs			x					x		x	x		x	
TEE questionnaire			x				x	x	x	x	x	x	x	x
Body weight			x											
Blood draw for:														
Fibrinogen activity				x **[a,b,c]**		x **[a,b,c]**	x **[b,c]**	x **[b,c]**	x* **[b,c]**	x **[b,c]**	x **[b,c]**	x* **[b,c]**	x **[b,c]**	
Fibrinogen antigen				x **[a,c]**		x **[a,c]**	x **[c]**	x **[c]**	x **[c]**	x **[c]**	x **[c]**	x **[c]**	x **[c]**	
Safety lab (haematology and clinical chemistry) **[b]**				x				x			x			
Infusion of *Octafibrin*				x		x**			x **[e]**			x **[e]**		
Haemostatic efficacy assessments (intra- and postoperative)							x **[f]**						x **[g]**	
Wound haematomas and oozing								x			x			
Narrative of outcome													x	
AEs [h]				>	>	>	>	>	>	>	>	>	>	
Concomitant medications			>	>	>	>	>	>	>	>	>	>	>	
Medical history since last study visit														x

TEE = thromboembolic event; AE = adverse event; POP = postoperative.

* ≤ 30 minutes before each infusion of *Octafibrin.*

** If considered necessary.

To be re-reviewed if period between screening and treatment is more than 3 months.

[a] ≤30 minutes before and after each infusion of *Octafibrin* .

[b] Measured in local laboratories.

[c] Measured in central laboratory.

[d] Plasma retain sample for potential retesting; serum retain sample for potential viral testing.

[e] If the actual fibrinogen plasma level is below the accepted lower limit of the target fibrinogen plasma level, the subject **should** receive another infusion of *Octafibrin.*
If the fibrinogen level is greater than or equal to the accepted lower limit of the the target fibrinogen level, *Octafibrin* **should not** be administered.

[f] Intraoperative efficacy assessment by surgeon.

[g] Postoperative efficacy assessment by haematologist.

[h] Including thromboembolic events and hypersensitivity reactions.

[i] Only if no infusions given.

[j] Retention serum sample taken before PK infusion; PK infusion of 70 mg/kg of *Octafibrin;* subsequent blood sampling (see separate PK flow chart) (if not previously performed prior to a bleeding episode).

FLOW CHART OF ASSESSMENTS FOR PK PHASE

PK days		Vital signs	Fibrinogen (Clauss and Fib:Ag) [1]	Retention serum sample	Physical and clinical examination	Recording of AEs [2]
PK-Day 1*	Before first infusion	x	x **[3]**	x **[4]**		
	Single-dose infusion at a **dose of 70 mg/kg**					
	1 hour**	x	x			x
	3 hours**	x	x			x
PK-Day 2	24 hours**		x			x
PK-Day 4	72 hours**		x			x
PK-Day 7	144 hours**		x			x
PK-Day 10	216 hours**		x			x
PK-Day 14	312 hours**	x	x		x	x

[1] Measured in the central laboratory

[2] Including potential thromboembolic events and early signs of allergic or hypersensitivity reactions

[3] Baseline fibrinogen for PK analysis (Clauss assay and ELISA) to be collected immediately prior to infusion of IMP

[4] Collected within 30 min before infusion

* Before the start of the PK phase, there must be an at least 2-week wash-out period of any fibrinogen containing product.

** Time relative to end of infusion

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements.

Signature of the Sponsor's Representative

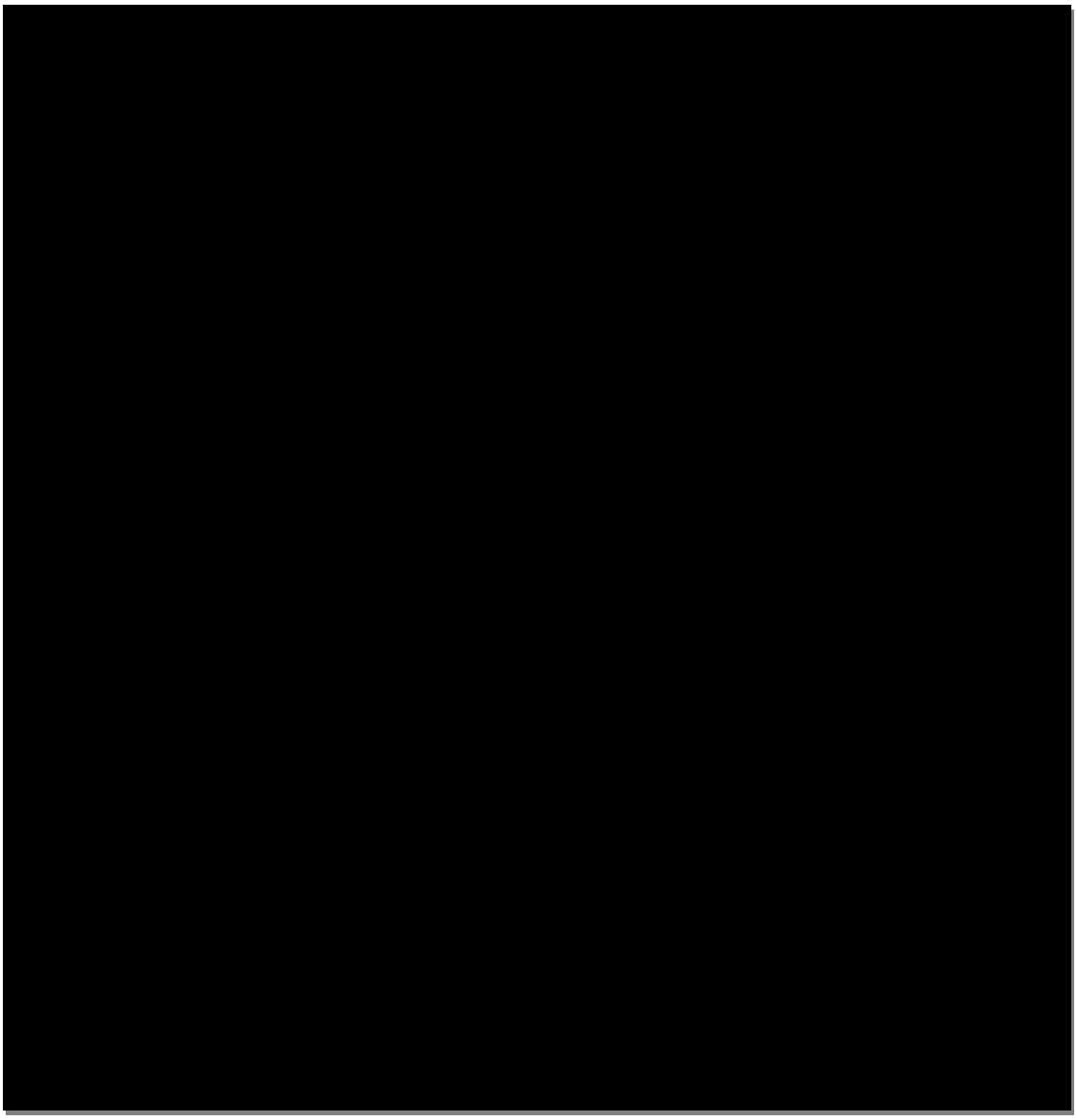

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse event
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BLEED	Analysis population of all treated bleeding episodes
b.w.	Body weight
CI	Confidence interval
Cl	Clearance
Cmax	Maximum concentration
CRF	Case report form
CRO	Contract research organisation
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
FirstBLEED	Analysis population of subjects with at least one treated bleeding episode
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDMEAC	Independent Data Monitoring & Endpoint Adjudication Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intention-to-treat
IVR	In vivo recovery
MCF	Maximum clot firmness (‘clot strength’)
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PP	Per protocol
SAE	Serious adverse events
SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
SURG	Analysis population of all surgeries with IMP prophylaxis/treatment
$t_{1/2}$	Half-life

TEE	Thromboembolic event
TEM	Thromboelastometry
T_{max}	Time of maximum concentration
US	United States
V_{ss}	Volume of distribution at steady state
WFI	Water for injection
WNV	West Nile virus

1 INTRODUCTION

1.1 Background

Human fibrinogen is a plasma glycoprotein synthesised in the liver, and it circulates in the plasma at a concentration of 2.9–4.5 g/L. In healthy human adults, about 2–5 g of fibrinogen is synthesised daily, and the same amount is catabolised [1, 2]. Fibrinogen is essential for haemostasis, wound healing, fibrinolysis, inflammation, angiogenesis, cellular and matrix interactions, and neoplasia. These processes involve the conversion of fibrinogen into fibrin, and often the interaction of fibrinogen with various proteins and cells. The plasma half-life of fibrinogen, under normal physiological conditions, has been estimated to be 3–5 days [3, 4].

The plasma level of clottable fibrinogen may be markedly decreased or even undetectable in various congenital or acquired conditions [5, 6]. Conditions of congenital fibrinogen deficiency include:

- Afibrinogenaemia: Complete absence or extremely low levels of plasma fibrinogen
- Hypofibrinogenaemia: Reduced concentration of plasma fibrinogen
- Dysfibrinogenaemia: Presence of abnormal or dysfunctional fibrinogen molecules

Congenital afibrinogenaemia is a rare inherited autosomal recessive disorder occurring in homozygotic patients with an estimated incidence of 1 in 10^6 in the European population [7]. The disease is characterised by a complete lack of coagulable and/or immunologically determinable fibrinogen in the plasma. Patients present with frequent severe bleeding episodes since birth or early childhood [8, 9]. Bleeding may occur after a minor trauma or a small surgical intervention, into the skin, mucosa, muscles, gastrointestinal tract, or the brain.

Congenital hypofibrinogenaemia is more common than afibrinogenaemia and is characterised by low but measurable fibrinogen plasma levels. Clinical symptoms of hypofibrinogenaemia are usually milder compared to afibrinogenaemia, and the condition is frequently combined with a dysfibrinogenaemia that is characterised by an abnormal fibrinogen variant. Several missense mutations in the 3 fibrinogen genes have been identified as the cause of dysfibrinogenaemia and hypofibrinogenaemia that lead to abnormal gene expression resulting in the decreased fibrinogen concentration or dysfunctional fibrinogen molecules.

Therapeutic substitution with human fibrinogen concentrate can correct the haemostatic defect and arrest bleeding in patients with these fibrinogen deficiencies [5, 7, 9, 10, 11].

1.2 Octafibrin

Octafibrin is a highly purified, lyophilised, human plasma fibrinogen concentrate, without added albumins. *Octafibrin* is double virus inactivated using 2 dedicated virus inactivation/removal steps, i.e., solvent/detergent treatment and nanofiltration.

Solvent/detergent treatment mode of action causes enveloped viruses to be irreversibly destroyed. These include the most transfusion-relevant viruses, such as human immunodeficiency virus types l and 2 (human immunodeficiency virus [HIV]-1, HIV-2), hepatitis B virus (HBV) and hepatitis C virus (HCV), but also many other adventitious agents, e.g., newly emerging viruses that are enveloped, such as West Nile virus (WNV).The Planova 20N filter wasspecif-

ically developed by Asahi Kasei Pharma Corp. to remove infectious agents from protein solutions on the basis of their size. Thus, this nanofiltration step is in principle effective for removing even very small enveloped and non-enveloped viruses. Nanofiltration may be the only method to date permitting efficient removal of enveloped and non-enveloped viruses under conditions where 90-95% of protein activity is recovered [12].

1.3 Rationale for Conducting the Study

It is estimated that there are 500 to 1000 patients with congenital fibrinogen deficiency in the European Union (EU). Historically, the principal source for the treatment of congenital fibrinogen deficiency has been cryoprecipitate [7]. Plasma-derived and viral-inactivated fibrinogen concentrates are proven to be safer and more specific in the treatment of congenital fibrinogen deficiency compared to cryoprecipitate [13].

The introduction of *Octafibrin* will present an additional and safe option, providing more choices of supply for the benefit of the medical community and patients affected by congenital fibrinogen deficiency.

This phase III study is designed as a multinational, multi-centre, prospective, open-label, uncontrolled study to assess the efficacy, safety, and pharmacokinetics of *Octafibrin* for on-demand treatment of acute bleeding in paediatric subjects with congenital fibrinogen de-ficiency.

As there are currently no guidelines concerning fibrinogen concentrates in either the United States (US) or the EU, this pivotal study was designed following the European Medicines Agency (EMA) Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor IX Products (CHMP/BPWP/144552/2009) [14] and discussions with the Paul Ehrlich Institute and the Paediatric Committee (PDCO) of the EMA.

1.4 Dose Rationale

The dose rationale is based on published data from an assessment survey based upon the data obtained in 100 a- or hypofibrinogenaemic patients [15]. Based on this representative sample (53 males and 47 females with median fibrinogen plasma level of 6 mg dL^{-1}), the peak fibrinogen plasma level most often recommended for on-demand treatment of minor bleeding was approximately 100 mg/dL, but the target level for major episodes, such as central nervous system bleeding, was higher (150 mg/dL). Minor episodes, like epistaxis, gum bleeding, menorrhagia, were usually treated with target peaks of 50 to 70 mg/dL. Duration of treatment ranged from 1 to 2 weeks for major events, from 1 to 7 days for minor events. Minor surgeries were treated for up to 7 days with a target fibrinogen plasma level of 100 mg/dL. Major surgeries were treated for 4 to 14 days with a target fibrinogen plasma level of 150 mg/dL.

1.5 Benefit-Risk Statement

Effective management of congenital fibrinogen deficiencies in bleeding situations is necessary for the prevention of potentially life-threatening bleeding episodes.

Studies consistently showed that fibrinogen substitution was able to successfully control bleeding, increase fibrinogen plasma levels, and reduce the amount of transfusions needed with allogeneic blood products. In addition, it was shown to be well tolerated and to have a very good overall safety profile.

Provided that the pharmacokinetic (PK) values are in the same range as for the already licensed fibrinogen concentrate, *Octafibrin* is expected to be efficacious in the treatment of congenital fibrinogen deficiency.

As known for other fibrinogen plasma-derived concentrates, the following adverse reactions may occur with the use of *Octafibrin*:

1. **Hypersensitivity or allergic reactions**
   Observed symptoms may include hives, generalised urticaria, tightness of the chest, wheezing, and hypotension. These reactions may progress to severe anaphylaxis, including shock.
2. **Thromboembolic events**
   Such events have been reported in patients treated with plasma-derived fibrinogen concentrates. Thus, patients receiving *Octafibrin* should be monitored for signs and symptoms of thrombosis.
3. **Infections caused by medicinal products prepared from human blood or plasma** Standard measures to prevent these infections include the selection of donors, screening of individual donations and plasma pools for specific markers of infection, and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses, such as HIV, HBV, and HCV, and for the non-enveloped hepatitis A virus (HAV). The measures taken may be of limited value against non-enveloped viruses, such as parvovirus B19.

In conclusion, there is no reason to believe that participation in this study presents the subjects with any greater risk of viral transmission or thrombosis than treatment with currently marketed products. The manufacturing process of *Octafibrin*, which includes 2 viral inactivation steps with different chemical/physical action principles, represents a high standard for plasma-derived concentrates in terms of viral safety.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate the efficacy of *Octafibrin* for on-demand treatment of acute bleeding episodes (spontaneous or after trauma).

2.2 Secondary Objectives

The secondary objectives are:

- To determine the single-dose pharmacokinetics of *Octafibrin* in paediatric subjects with congenital fibrinogen deficiency
- To investigate an association between the overall clinical assessment of haemostatic efficacy and the surrogate endpoint 'clot strength' or 'clot firmness' (referred to as 'maximum clot firmness' [MCF] in this protocol) that was used as a surrogate endpoint for haemostatic efficacy and determined via thromboelastometry (ROTEM) in the pivotal PK study FORMA-01. Therefore, MCF as surrogate efficacy parameter will be determined before and after the first infusion of IMP for treatment of a bleeding episode.
- To achieve a peak target plasma fibrinogen level of 100 mg/dL in minor bleeds and 150 mg/dL for major bleeds 1 hour post-infusion
- To determine the response to *Octafibrin* based on incremental in vivo recovery (IVR)
- To demonstrate the efficacy of *Octafibrin* in preventing bleeding during and after surgery
- To assess the safety of *Octafibrin* in subjects with congenital fibrinogen deficiency, including immunogenicity, thromboembolic complications, and early signs of allergic or hypersensitivity reactions

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary endpoint is the **overall clinical assessment of the haemostatic efficacy of *Octafibrin*** in treating the first documented bleeding episode of each patient.

The first bleeding episode covers the time period from the 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.

The investigator's overall clinical assessment of haemostatic efficacy for bleeding will be based on a 4-point haemostatic efficacy scale as described in Section 7.2.1. The final efficacy assessment of each patient will be adjudicated by the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC).

In the final analysis, the number of subjects per outcome category will be assessed.

3.1.2 Secondary Endpoints

3.1.2.1 Secondary PK Endpoints

The following PK parameters will be assessed as secondary endpoints:

- Area under the concentration-time curve (AUC)
- Response: Incremental In Vivo Recovery (IVR)
- Classical IVR
- Terminal elimination half-life ($t_{1/2}$)
- Maximum plasma concentration (C_{max})
- Time to reach maximum plasma concentration (T_{max})
- Mean residence time (MRT)
- Volume of distribution (Vss)
- Clearance (Cl)

3.1.2.2 Secondary Efficacy Endpoints

The following efficacy parameters will be calculated as secondary endpoints:

- MCF assessment before first infusion and 1 hour after end of first infusion of each documented bleeding episode (see Section 7.2.2.2)
- Fibrinogen plasma level before and 1 hour after the end of each subsequent infusion as well as at the time of the overall clinical assessment of haemostatic efficacy (i.e., 24 hours after the last infusion or end of the observation period of each documented bleeding episode)

- Response after the first infusion of each bleeding episode as indicated by incremental IVR, calculated as the maximum increase in plasma fibrinogen (Clauss data) between the pre-infusion and the 3-hour post-infusion measurement, divided by the exact dose of *Octafibrin* (expressed as mg/kg dosed) (see Section 7.2.2.3)
- Efficacy of *Octafibrin* in all bleeding episodes collected in the study using the investigator's overall clinical assessment of haemostatic efficacy for bleeding based on a 4-point haemostatic efficacy scale
- Efficacy of *Octafibrin* in preventing bleeding during and after surgery as assessed at the end of surgery by the surgeon and post-operatively by the haematologist using two 4-point haemostatic efficacy scales (see Section 7.2.2.4). An overall efficacy assessment taking both the intra- and post-operative assessment into account will be adjudicated by the IDMEAC. The surgical observation period starts with the first dose of *Octafibrin* administered prior to elective surgery (Day 1) and, depending on the severity of the event, will last 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, whichever comes last. The number of subjects per outcome category will be assessed and will include at least 4 surgeries.

3.1.2.3 Safety Endpoints

The following safety parameters will be calculated as secondary safety endpoints:

- Vital signs
- Physical examination
- Thromboembolic event (TEE) questionnaire
- Routine clinical laboratory assessment, including coagulation parameters
- Adverse events (AEs), including thromboembolic complications and early signs of allergic or hypersensitivity reactions
- Thrombogenicity testing before and after each IMP infusion for the treatment of bleeding, except on the Day of Last Infusion
- Immunogenicity testing before the first infusion of IMP and on Day 30 after the treatment of each bleeding episode

3.2 Overall Study Design and Plan

This is a multinational, multi-centre, prospective, open-label, uncontrolled, Phase III study to assess the efficacy, safety, and pharmacokinetics of *Octafibrin* for on-demand treatment of acute bleeding and surgical prophylaxis in paediatric subjects with congenital fibrinogen deficiency.

At least 12 male or female paediatric subjects with congenital fibrinogen deficiency will be enrolled into the study and undergo PK assessment. Of these 12 subjects, at least 6 subjects will undergo on-demand treatment of 6 first bleeding episodes. Of these 6 subjects, at least 3 should be aged between 0 and <6 years and 3 should be aged between 6 and <12 years. In addition, at least 2 surgical procedures will be assessed. The study will be conducted in approximately 5 study centres worldwide.

During the study observation period, enrolled patients will participate in a 14-day PK phase with administration of a single dose of *Octafibrin* and will subsequently be treated for any bleeding episodes or planned surgeries that can be managed under the protocol. Patients may remain in the study until at least 12 patients have undergone PK assessment, the 6th patient (at least 3 patients each in the specified age groups) has at least one documented bleeding episode, and a minimum of 2 surgical procedures have been performed.

The study will be considered completed when a minimum of 12 subjects have undergone PK assessment, 6 subjects (at least 3 subjects aged between 0 and <6 years and 3 subjects aged between 6 and <12 years) have at least one documented bleeding episode, and at least 2 surgical procedures have been documented. The study as a whole should be completed within 5 years.

As many bleeding episodes or surgeries as possible occurring throughout the study observation period will be documented. Only the first bleeding episodes will be used for the analysis of the primary endpoint. All bleeding episodes documented in the study will be assessed as a secondary endpoint.

The investigator will inform the monitor of any recruitment difficulty or delay of the anticipated completion date.

Patients should be treated with the investigational medicinal product (IMP) whenever possible. If, in the opinion of the investigator, a bleeding episode is not effectively stopped or surgical prophylaxis is not adequate after the recommended dose of *Octafibrin* has been administered, the subject may receive a different licensed fibrinogen concentrate (e.g., Haemocomplettan P®/RiaSTAP™) or whatever the investigator considers standard of care. The use of another licensed fibrinogen concentrate is also permitted in emergency situations, e.g., if the IMP is not available for the patient in time.

3.2.1 Pharmacokinetics Assessment

Within 2 weeks after screening, subjects will receive a single infusion of 70 mg/kg *Octafibrin*. Before the start of the PK phase, there must be an at least 2-week wash-out period of any fibrinogen containing product.

Before first injection vital signs and blood draws for baseline fibrinogen levels will be assessed. Retention serum samples for potential retesting will be collected within 30 minutes before the PK infusion. At 1 and 3 hours post-infusion, vital signs and fibrinogen for PK will be assessed. Subjects will be further followed on days 2, 4, 7, 10, and 14 and undergo study assessments as specified.

All adverse events (AEs), including thromboembolic events and early signs of allergic or hypersensitivity reactions, occurring between the start of the first *Octafibrin* infusion and the end of the PK phase will be recorded.

All SAEs occurring after the first IMP infusion will be documented and reported for a patient throughout the duration of the patient's participation in the study or as required to meet local regulations.

At the end of the study (i.e., when at least 12 patients have completed the PK assessment, 3 patients in each of the specified age groups have had at least one treated bleeding episode, and a minimum of 2 surgical procedures have been performed), all patients having received any IMP will be asked to return for a Study Completion Visit.

3.2.2 On-demand Treatment of Acute Bleeding

Subjects presenting to the study site for on-demand treatment of an acute bleeding episode who are eligible for enrolment and whose legal guardians have provided written informed consent will be included into the study.

Each subject will receive at least 1 infusion of *Octafibrin* for the treatment of acute bleeding on Day 1. The individual **subject observation and follow-up period** for each documented episode starts with the first dose of *Octafibrin* administered for on-demand treatment of an acute bleeding episode (Day 1) and will be followed up to at least Day 30.

Each subject's **treatment observation period** is defined according to the severity of the event and will last at least 3 days for minor and 7 days for major bleeding episodes.

On each day of the treatment observation period (i.e., 3 days for minor and 7 days for major bleeding), fibrinogen plasma levels will be measured daily to determine whether additional infusions of *Octafibrin* are needed:

- Additional infusions of *Octafibrin* **should** be administered if the actual fibrinogen plasma level measured on these days is below the accepted lower limit of the target level (80 mg/dL for minor bleeding, 130 mg/dL for major bleeding).
- If the actual fibrinogen plasma level is above the accepted lower limit of the target level, *Octafibrin* **should not** be administered.

The actual treatment duration will be determined by the investigator based on his/her judgement of the subject's condition.

All adverse events (AEs), including thromboembolic events and early signs of allergic or hypersensitivity reactions, occurring between the start of the first *Octafibrin* infusion and the end of each 30-day observation and follow-up period will be recorded. The detection of thromboembolic events (TEEs) will be supported by completing a TEE questionnaire at each study visit for the treatment of bleeding episodes and for surgeries. Concomitant medications will also be recorded throughout each 30-day observation and follow-up period.

All SAEs occurring after the first IMP infusion will be documented and reported for a patient throughout the duration of the patient's participation in the study or as required to meet local regulations. Also, any concomitant medications used to treat an SAE will be recorded.

At the end of the study (i.e., when at least 3 patients in each of the specified age groups have had at least one treated bleeding episode and when a minimum of 2 surgical procedures have been performed) all patients having received any IMP will be asked to return for a Study Completion Visit.

3.2.3 Surgical Prophylaxis

Subjects planning to undergo elective surgery may also be enrolled in the study.

Within 3 hours prior to surgery, each patient will receive a loading infusion of *Octafibrin* to achieve a recommended fibrinogen plasma level of 100 mg/dL for minor surgeries and 150 mg/dL for major surgeries.

Each subject's **surgical observation period** starts with the first dose of *Octafibrin* administered prior to elective surgery (Day 1) and, depending on the severity of the event, will last 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, whichever comes last.

On each post-operative day, fibrinogen plasma levels will be measured daily (i.e., at least 3 post-operative days for minor and 7 post-operative days for major surgeries) to determine whether additional infusions of *Octafibrin* are needed.

- Additional infusions of *Octafibrin* **should** be administered if the actual fibrinogen plasma level measured on subsequent days is below the accepted lower limit of the target level (80 mg/dL for minor surgeries, 130 mg/dL for major surgery).
- If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, *Octafibrin* **should not** be administered.

The actual treatment duration will be determined by the investigator based on his/her judgement of the subject's condition.

All AEs, including thromboembolic events and early signs of allergic or hypersensitivity reactions, occurring between first infusion of IMP before the start of surgery and the Last Post-Operative Day will be recorded. The detection of thromboembolic events (TEEs) will be supported by completing a TEE questionnaire at each study visit for the treatment of bleeding episodes and for surgeries.

All SAEs occurring after the first IMP infusion will be documented and reported for a patient throughout the duration of the patient's participation in the study or as required to meet local regulations. Also, any concomitant medications used to treat an SAE will be recorded.

At the end of the study (i.e., when at least 3 patients in each of the specified age groups have had at least one treated bleeding episode and when a minimum of 2 surgical procedures have been performed. All patients having received any IMP will be asked to return for a Study Completion Visit.

3.3 Discussion of Study Design and Choice of Control Group(s)

As there are currently no guidelines concerning fibrinogen concentrates in either the US or the EU, the study was designed following established programs for Factor IX concentrates.

Typically, the clinical evaluation of a new concentrate initially examines the IVR and the PK properties of the principal active factor. Prior to initiating the present study, comparative PK data in adults were obtained in study FORMA-01. A study similar to the one described in this protocol, i.e., FORMA-04, is currently ongoing in adults patients (FORMA-02), the main difference being the additional examination of PK properties in paediatric patients in FORMA-04.

The open-label uncontrolled design and choice of study objectives are motivated by regulatory requirements for Factor IX [14] and discussions with the regulatory bodies.

The median response value used in the fibrinogen dosage calculation is the median incremental in vivo recovery reported in the final analysis of study FORMA-01.

Although all bleeding episodes occurring throughout the study observation period will be documented, only the first bleeding episode per patient will be used for the analysis of the primary endpoint (see Section 3.1.1). This is because the study will end once at least 12 patients have undergone PK assessment and the 6th patient (i.e., at least 3 patients in each of the specified age groups) has at least one documented bleeding episode, potentially resulting in a large diversity in the number of bleeding episodes between patients; also, the haemostatic outcomes in different bleeding episodes within one patient cannot be regarded as independent/uncorrelated. The entirety of bleeding episodes documented in the study will be assessed as a secondary endpoint (see Section 3.1.2).

4 STUDY POPULATION

4.1 Population Base

At least 12 paediatric subjects with clinically diagnosed congenital fibrinogen deficiency (i.e., afibrinogenaemia or severe hypofibrinogenaemia) will be enrolled into the study and undergo PK assessment. Of these 12 subjects, at least 6 subjects will undergo on-demand treatment of 6 first bleeding episodes. Of these 6 subjects, at least 3 should be aged between 0 and <6 years and 3 should be aged between 6 and <12 years.

4.2 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for the study:

1. Aged <12 years (at the start of treatment)
2. Documented diagnosis of congenital fibrinogen deficiency, expected to require on-demand treatment for bleeding or surgical prophylaxis:
   - Fibrinogen deficiency manifested as afibrinogenaemia or severe hypofibrinogenaemia
   - Historical plasma fibrinogen activity of<50 mg/dL or levels below the limit of detection of the local assay method
3. Expected to have an acute bleeding episode (spontaneous or after trauma) or planning to undergo elective surgery.
4. Informed consent signed by the subject's legal guardian

4.3 Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for the study:

1. Life expectancy <6 months
2. Bleeding disorder other than congenital fibrinogen deficiency, including dysfibrinogenaemia
3. Prophylactic treatment with a fibrinogen concentrate
4. Treatment with:
   - Any fibrinogen concentrate or other fibrinogen-containing blood product within 2 weeks prior to start of treatment for the PK phase, a bleeding episode, or surgery
   - Any coagulation-active drug (i.e., non-steroidal anti-inflammatory drugs, warfarin, coumarin derivatives, platelet aggregation inhibitors) within 1 week prior to start of the PK phase or treatment for the bleeding episode or surgery, or as a planned or expected medication during the time period from Day 1 until 24 hours (i.e., 1 day) after the last *Octafibrin* infusion

5. Presence or history of:
   - Hypersensitivity to study medication
   - Deep vein thrombosis or pulmonary embolism within 1 year prior to start of treatment for the bleeding episode or surgery
   - Arterial thrombosis within 1 year prior to start of treatment for the bleeding episode or surgery
   - Hypersensitivity to human plasma proteins
   - Oesophageal varicose bleeding
   - End-stage liver disease (i.e., Child-Pugh score B or C)
6. Known positive HIV infection with a viral load >200 particles/µL or >400,000 copies/mL
7. Polytrauma 1 year prior to start of treatment for the bleeding episode or surgery
8. Diagnosis or suspicion of a neutralising anti-fibrinogen inhibitor currently or at any time in the past
9. Acute or chronic medical condition which may, in the opinion of investigator, affect the conduct of the study, including subjects receiving immune-modulating drugs (other than anti-retroviral chemotherapy), such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs, at study start
10. Treatment with IMP in another interventional clinical study currently or during the past 4 weeks

NOTE: If the period between screening and treatment or between treatments is more than 3 months, informed consent will be re-reviewed and confirmed prior to treatment, and details of the review process will be recorded in the patient chart and indicated in the CRF by the investigator. Also, inclusion/exclusion criteria will be confirmed prior to treatment.

4.4 Prior and Concomitant Therapy

4.4.1 Permitted Concomitant Therapy

Concomitant administration of therapies not interfering with the primary objective of the study is permitted. Details of any concomitant therapies, including other fibrinogen concentrates, must be recorded in the case report forms (CRFs).

Concomitant medications will be recorded only for each patient's 30-day observation and follow-up period (for on-demand treatments) and during their surgical observation period (for treatment during surgeries).

In addition, concomitant medications used to treat SAEs will be reported throughout the duration of the patient's participation in the study or as required to meet local regulations for SAE reporting.

Patients should be treated with IMP whenever possible. If, in the opinion of the investigator, a bleeding episode is not effectively stopped or surgical prophylaxis is not adequate after the recommended dose of *Octafibrin* has been administered, the subject may receive a different licensed fibrinogen concentrate (e.g., Haemocomplettan P®/RiaSTAP™) or whatever the investigator considers standard of care. The use of another licensed fibrinogen concentrate is also permitted in emergency situations, e.g., if the IMP is not available for the patient in time.

4.4.2 Forbidden Concomitant Therapy

Subjects may not receive any coagulation-active drug (i.e., non-steroidal anti-inflammatory drugs, warfarin, coumarin derivatives, platelet aggregation inhibitors) within 1 week prior to start of treatment for the bleeding episode or surgery, or as a planned or expected medication during the time period from Day 1 until 24 hours after the last *Octafibrin* infusion.

4.5 Withdrawal and Replacement of Subjects

4.5.1 Premature Subject Withdrawal

The subjects' legal guardians have the right to withdraw the subject from the study at any time for any reason, without the need to justify their decision. The investigator also has the right to withdraw subjects in case of AEs, protocol violations, or other reasons. Since an excessive rate of withdrawal can render the study non-interpretable, the unnecessary withdrawal of subjects must be avoided.

For any discontinuation after study entry, the investigator will obtain all the required details and document the reason(s) for discontinuation in the CRF. If the reason for withdrawal of a subject is an AE, the main specific event or laboratory test will be recorded in the CRF, and the investigator will make thorough efforts to clearly document the outcome.

If possible, the Study Completion Visit should be performed.

4.5.2 Subject Replacement Policy

The study will recruit patients until a minimum of 12 subjects have undergone PK assessment, 6 subjects (at least 3 subjects aged between 0 and <6 years and 3 subjects aged between 6 and <12 years) have at least one documented bleeding episode, and a minimum of 2 surgical procedures have been documented. Patients with no documented bleeding episode, e.g., those only receiving PK treatment or those withdrawn for safety reasons before the first bleeding, will be replaced.

4.6 Assignment of Subjects to Treatment Groups

Not applicable.

4.7 Relevant Protocol Deviations

In the case of any major protocol deviation or violation, the investigator and Octapharma will decide on the further participation of the subject in this study, after having discussed all relevant aspects.

4.8 Subsequent Therapy

In case the bleeding is not effectively stopped or surgical prophylaxis is deemed not to be adequate after the recommended *Octafibrin* dosing as judged by the investigator (see Section 5.4), the subject may receive a different licensed fibrinogen concentrate (e.g., Haemocomplettan P®/RiaSTAP™) or whatever the investigator considers standard of care.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Characterisation of Investigational Product

Octafibrin is a human plasma-derived fibrinogen concentrate for intravenous use. Its ingredients are listed in Table 1.

Table 1: Composition of *Octafibrin*

Ingredients	Quantity per mL reconstituted solution, mean values	Standard
Active ingredient		
Fibrinogen as clottable protein	20 mg	Ph. Eur.
Excipients		
Sodium chloride	6 mg	Ph. Eur.
Sodium citrate dehydrate	1.5 mg	Ph. Eur.
Glycine	10 mg	Ph. Eur.
L-arginine hydrochloride	10 mg	Ph. Eur.

Ph. Eur. = Pharmacopoea Europaea.

Octafibrin is a powder for solution for injection supplied in labelled 100 mL vials to be reconstituted with 50 mL sterile Water for Injection (WFI).

Several batches of the product will be used in the study. The batch numbers will be reported in the final study report.

The final product will be released by the responsible Octapharma Quality Control Department, according to a defined final product specification.

5.2 Packaging and Labelling

The open-label study design does not necessitate the blinding of study participants or study site personnel to treatment information.

The IMP will be labelled according to GMP Annex 13. Final labelling and packaging will comply with the national requirements of each country where the study is to be conducted.

5.3 Conditions for Storage and Use

The IMP has to be stored at 2°C to 8°C and protected from light. The product must not be frozen. The investigator/authorised personnel at the site will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

In this study, *Octafibrin* will be administered as **intravenous (i.v.) bolus injection**. Continuous infusion is not allowed.

5.4.1 PK Dose Schedule and Mode of Administration

For PK assessments, subjects will receive a single intravenous infusion of 70 mg/kg body weight of *Octafibrin.*

5.4.2 Octafibrin Treatment Dose Calculation

Octafibrin will be individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleeding or surgery (minor or major). The dose will be calculated individually as follows:

$$\text{Fibrinogen dose (mg/kg body weight)} = \frac{\text{[Target peak plasma level (mg/dL) – measured level (mg/dL)**]}}{\text{Median response* (mg/dL per mg/kg body weight)}}$$

*The median response in this dose calculation formula is 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).
**The measured level for the first infusion will be the historical level for that patient after a washout or, if below the limit of detection of the local assay, zero (0) will be used.

5.4.3 Dosing for On-demand Treatment of Bleeding

For each bleeding episode that is treated as part of the study, each subject will receive at least 1 infusion of *Octafibrin* for the treatment of a major or minor acute bleeding episode on Day 1.

Octafibrin will be individually dosed to achieve a recommended target fibrinogen plasma level dependent on the bleeding type (minor or major).

- **Minor bleeding** will be treated to achieve a recommended target fibrinogen plasma level of 100 mg/dL and an accepted lower limit of 80 mg/dL.
- **Major bleeding** will be treated to achieve a recommended target fibrinogen plasma level of 150 mg/dL and an accepted lower limit of 130 mg/dL.

On subsequent study days, fibrinogen plasma levels will be measured daily to determine whether additional infusions of *Octafibrin* are needed:

- **Minor bleeding** will be observed for at least 3 days.
- **Major bleeding** will be observed for at least 7 days.

Additional Octafibrin infusions, as required

- Additional infusions of *Octafibrin* **should** be administered if the actual fibrinogen plasma level measured on subsequent study days is below the accepted lower limit of the target level (80 mg/dL for minor bleeding, 130 mg/dL for major bleeding).
- If the actual fibrinogen plasma level is above the accepted lower limit of the target level, *Octafibrin* **should not** be administered.

Definition of minor and major bleeding

- **Minor bleeding** events are defined as mild haemarthrosis or superficial muscle, soft tissue, and oral bleeding.
- **Major bleeding** events are defined as symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial bleeding, or intramuscular bleeding with compartment syndrome, or bleeding causing a decrease in haemoglobin level by 20 g/L (1.24 mmol/L) or more.

Characterisation of any other bleeding events not within these categories will be discussed individually with the investigator.

5.4.4 Dosing for Surgery

For each surgery that is treated as part of the study, within 3 hours prior to surgery, subjects will receive a loading infusion of *Octafibrin*.

Octafibrin will be individually dosed to achieve a recommended target fibrinogen plasma level dependent on the surgery type (minor or major).

- Patients undergoing **minor surgery** will be treated to achieve a recommended target fibrinogen plasma level of 100 mg/dL and an accepted lower limit of 80 mg/dL.
- Patients undergoing **major surgery** will be treated to achieve a recommended target fibrinogen plasma level of 150 mg/dL and an accepted lower limit of 130 mg/dL.

On each post-operative day, fibrinogen plasma levels will be measured daily to determine whether maintenance infusions of *Octafibrin* are needed.

- **Minor surgery** will be observed for at least 3 post-operative days.
- **Major surgery** will be observed for at least 7 post-operative days.

Maintenance infusions, as required:

- Additional infusions of *Octafibrin* **should** be administered if the actual fibrinogen plasma level measured on subsequent study days is below the accepted lower limit of the target level (80 mg/dL for minor surgery, 130 mg/dL for major bleeding).
- If the actual fibrinogen plasma level is above the accepted lower limit of the target level, *Octafibrin* **should not** be administered.

Definition of minor and major surgery

Surgeries are defined as **major**, if any of the following criteria are met:

- Requiring general or spinal anaesthesia
- Requiring opening into the great body cavities
- In the course of which hazards of severe haemorrhage is possible
- Requiring haemostatic therapy for at least 6 days
- Orthopaedic interventions involving joints (ankle, knee, hip, wrist, elbow, shoulder)
- Surgeries/conditions in which the subject's life is at stake

Characterisation of any other surgery not within these categories and considered major by the investigator will be discussed individually with the investigator.

All other surgeries are classified as **minor**.

The classification is made prospectively.

5.5 Preparation and Method of Administration

5.5.1 Preparation

Each vial of *Octafibrin* will be reconstituted with 50 mL WFI. The solvent (i.e., WFI) and the concentrate in the closed vials must be warmed up to room temperature. Room temperature must be maintained during reconstitution. *Octafibrin* dissolves at room temperature to an almost colourless and slightly opalescent solution within 30 minutes. If the solution is cloudy or contains particulates, it should not be used. The solution should not be frozen.

Octafibrin should be administered immediately after reconstitution at a rate not exceeding 5 mL per minute. *Octafibrin* should not be mixed with other medicinal products or intravenous solutions.

5.5.2 Method of Administration

Octafibrin will be administered as intravenous (i.v.) bolus injection not exceeding an injection rate of 5 mL per minute.

NOTE: In this study, **only bolus injections** of *Octafibrin* are permitted. Continuous infusion is not allowed.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

Not applicable.

5.7 Drug Dispensing and Accountability

A drug dispensing log and the inventory will be kept current by the investigator, detailing the dates and quantities of IMP received at the site/pharmacy, and dispensed to each subject. The inventory will be available to the monitor to verify drug accountability during the study. Any unused or partially used IMP, including empty containers (if possible), will be accounted for.

Unused IMP may be destroyed at the study site, however, only after drug accountability has been verified and fully re-conciliated and written approval from the Sponsor has been obtained. Unused IMP can be returned to the Sponsor for destruction when drug accountability has been verified and fully re-conciliated and written approval from the Sponsor has been received.

5.8 Assessment of Treatment Compliance

Treatment compliance will be measured in terms of the subject receiving an infusion of *Octafibrin* from the study personnel. Administered doses of *Octafibrin* will be recorded for every infusion, including dates, times, and batch numbers; the batch numbers will be reported in the final study report.

6 STUDY CONDUCT

6.1 Observations Performed Throughout the Study

Patients identified by the study sites as potential study participants will be screened for inclusion into the study. The screening assessments will be performed as summarised in Section 6.1.1.

The PK assessments are summarised in Section 6.1.2. The assessments for patients enrolled and then having on-demand treatment of an active bleeding episode are summarised in Section 6.1.3. The assessments for patients planning to undergo elective surgery are summarised see Section 6.1.4.

All treated patients will undergo a Study Completion Visit as summarised in Section 6.1.5.

6.1.1 Screening Assessments

Patients identified by the study sites as potential study participants will undergo the following screening assessments:

- Inclusion and exclusion criteria, including written informed consent for participation in the study by the subject's legal guardian
- Demography, medical history (including details concerning allergic tendencies), review of previous therapy

NOTE: If the period between screening and first treatment of acute bleeding or surgical prophylaxis is more than 3 months, informed consent will be re-reviewed and confirmed prior to treatment, and details of the review process will be recorded in the patient chart and indicated in the CRF by the investigator. Also, inclusion/exclusion criteria will be confirmed prior to treatment.

6.1.2 Assessments During the PK Phase

Within 2 weeks after the screening process, subjects will receive a single infusion of 70 mg/kg *Octafibrin* on Day 1 of PK testing (PK-Day 1). Before the start of the PK phase, there must be an at least 2-week wash-out period of any fibrinogen containing product.

Before first injection vital signs and blood draws for baseline fibrinogen levels will be assessed. Retention serum samples for potential retesting will be collected within 30 minutes before infusion. At 1 and 3 hours post-infusion, vital signs and fibrinogen for PK will be assessed, and AEs will be recorded. Subjects will be further followed on:

PK-Days 2 (24 hrs), 4 (72 hrs), 7 (144 hrs), and 10 (216 hrs)

- Fibrinogen for PK
- Recording of AEs, including potential thromboembolic events

PK-Day 14 (312 hrs)

- Fibrinogen for PK
- Vital signs
- Physical examination, including any signs or symptoms of potential thromboembolic events
- Recording of AEs, including potential thromboembolic events

The flow chart of assessments for the PK phase is provided on page xxiv.

NOTE: All adverse events (AEs, see Section 7.4), including thromboembolic events and early signs of allergic or hypersensitivity reactions, occurring between the start of the first *Octafibrin* infusion and the end of the PK phase will be recorded.

All SAEs occurring after the first IMP infusion will be documented and reported for a patient throughout the duration of the patient's participation in the study or as required to meet local regulations.

6.1.3 Assessments in Subjects Undergoing On-demand Treatment of Bleeding

Subjects presenting to the study site for an acute bleeding episode will undergo a 30-day observation and follow-up period as outlined below. Throughout the study, subjects may undergo more than one 30-day observation and follow-up periods for treatment of additional bleeding episodes as required until the close of the study. At the end of their study participation, patients will be asked to return for a final Study Completion Visit.

For information on the dose calculation and a definition of minor and major bleeding, see Section 5.4.3. The flow chart of assessments for on-demand treatment is provided on page xxii.

NOTE: All adverse events (AEs, see Section 7.4), including thromboembolic events and early signs of allergic or hypersensitivity reactions, occurring between the start of the first *Octafibrin* infusion and the end of each 30-day observation and follow-up period will be recorded. The detection of thromboembolic events will be supported by completing a TEE questionnaire at each study visit for the treatment of bleeding episodes and for surgeries. Concomitant medications will also be recorded throughout each 30-day observation and follow-up period. Administered doses of *Octafibrin* will be recorded for every infusion, including dates, times, and batch numbers.

All SAEs occurring after the first IMP infusion will be documented and reported for a patient throughout the duration of the patient's participation in the study or as required to meet local regulations. Also, any concomitant medications used to treat an SAE will be recorded.

6.1.3.1 Day 1 (first day of treatment)

For subjects requiring on-demand treatment, Day 1 is the day they present for treatment of an acute bleeding episode.

Pre-infusion assessments

The following assessments will be performed before the first infusion of *Octafibrin* for each bleeding episode:

- Medical history (including details of any non-study bleeding episodes and therapy), and prior/concomitant medication
- Characterisation of bleeding episode
- Vital signs
- Physical examination
- TEE questionnaire
- Height and weight
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity; within 30 minutes before infusion)
  - MCF (within 30 minutes before infusion)
  - safety lab (local–haematology and clinical chemistry)
  - thrombogenicity
  - immunogenicity

NOTE: If the period between screening and first treatment of acute bleeding is more than 3 months, informed consent will be re-reviewed and confirmed prior to treatment, and details of the review process will be recorded in the patient chart and indicated in the CRF by the investigator. Also, inclusion/exclusion criteria will be confirmed prior to treatment.

First infusion of Octafibrin

After the pre-infusion assessments, subjects will receive the first infusion of *Octafibrin* for treatment of bleeding (see Section 5.4).

Post-infusion assessments

On Day 1, the following post-infusion assessments will be performed:

1 hour (±15 minutes) after the end of infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)
  - MCF
- AEs and concomitant medications

3 hours (±15 minutes) after the end of infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (central lab–antigen and activity)
  - thrombogenicity
- AEs and concomitant medications

NOTE: If, in the investigator's judgement, the infusion of *Octafibrin* administered on Day 1 is deemed the only infusion needed for treatment of the subject's bleeding event, the subject will need to reach the end of the treatment observation period, where the "24 hours (i.e., 1 day) after the last infusion" assessments should be performed.

6.1.3.2 All Study Days after Day 1 (Treatment Observation Period)

Each subject's **treatment observation period** is defined according to the severity of the event and will last at least **3 days for minor and 7 days for major bleeding episodes**. If the patient requires multiple infusions, the actual treatment duration will be determined by the investigator based on his/her judgement of the subject's condition, and the treatment observation period will last until 24 hours after the last infusion.

Daily assessments (for at least 3 days for minor bleeding or 7 days for major bleeding)

- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity): Based on local lab results, the investigator will determine whether additional infusions of *Octafibrin* are needed.
  - safety lab (local–haematology)
- AEs and concomitant medications

Octafibrin infusion, as required

After these daily assessments, additional IMP dosing should occur as required depending on the actual and target plasma levels based on the following criteria:

- If the actual fibrinogen plasma level is below the accepted lower limit of the target fibrinogen plasma level (80 mg/dL for minor bleeding, 130 mg/dL for major bleeding; see Section 5.4), the subject should receive another infusion of *Octafibrin*.
- If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, *Octafibrin* **should not** be administered on that day.

Pre- and post-infusion assessments

If the subject receives an additional infusion of *Octafibrin*, the following pre- and post-infusion assessments will be performed:

Pre-infusion assessments:

- TEE questionnaire
- Blood draw for (within 30 minutes before infusion):
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)
  - thrombogenicity

1 hour (±15 minutes) after the end of each infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)
  - thrombogenicity

NOTE: If, in the investigator's judgement, there are no additional infusions of *Octafibrin* needed to treat the bleeding event, the subject will need to reach the end of the treatment observation period, where the "24 hours (i.e., 1 day) after the last infusion" assessments should be performed.

6.1.3.3 Last Infusion or End of the Observation Period (whichever comes last)

If a patient requires multiple infusions for a bleeding event as defined by the investigator based on his/her judgement of the subject's condition, or the subject comes to the end of the observation period (whichever comes last), the following assessments will be performed:

Pre-infusion assessments

The following assessments will be performed prior to the last infusion of *Octafibrin* if multiple infusions are needed:

- TEE questionnaire
- Blood draw for (within 30 minutes before infusion):
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)

Last infusion of Octafibrin

Following the pre-infusion assessments, subjects will receive their last infusion of *Octafibrin* depending on the actual and target plasma levels (see Section 5.4).

Post-infusion assessments

On the Day of Last Infusion, post-infusion assessments will be as follows:

1 hour (±15 minutes) after the end of last infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)

24 hours (i.e., 1 day) after the last infusion or at the end of the treatment observation period (whichever comes last)

- Vital signs
- Physical examination
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma levels (central lab–antigen and activity)
- Final assessment of haemostatic efficacy by the investigator with respect to the adequacy of stopping an acute bleed. The assessment is to include the entire period from the start of the first infusion until 24 hours (i.e., 1 day) after the last infusion and includes the clinical condition of the subject, laboratory values such as haematocrit and haemoglobin, and any additional haemostatic treatments (see Section 7.2.1).
- AEs and concomitant medications

6.1.3.4 Day 30 (29 Days after the First Infusion)—Final Examination

On Day 30 (± 1 week), the following assessments will be performed:

- Physical examination
- TEE questionnaire
- Blood draw for:
  - immunogenicity
  - retention serum sample for potential retesting
- AEs and concomitant medications

The Day 30 assessment concludes the series of observations by bleeding episode. No further study-related assessments will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up.

If the patient experiences another bleeding event before Day 30, this will be treated as a new bleeding event, provided that it is not directly related to the prior event. In this case, Day 30 evaluations will be postponed until 30 days after the start of the new bleeding episode.

Subjects returning to the study site for another acute bleeding episode within the study will again undergo the same Day 1 to Day 30 assessments as outlined in Section 6.1.3.1 through Section 6.1.3.4. At the end of the study duration, all subjects having received any IMP will be asked to return for a Study Completion Visit as summarised in Section 6.1.5.

6.1.4 Assessments in Subjects Undergoing Surgical Prophylaxis

Subjects enrolled for elective surgery will undergo a treatment and assessment cycle as outlined in Section 6.1.4.1 through Section 6.1.4.3. *Octafibrin* will be given prior to surgery as well as during and after surgery based on the physician's judgement, the patient's history, and the severity of the procedure. Subjects enrolled for elective surgery will be treated (as required) and assessed from Day 1 (i.e., the day of surgery) to the Last Post-Operative Day. The Last Post-Operative Day is either at least post-operative day 3 for minor and post-operative day 7 for major surgery or the day of the last post-operative infusion, whichever comes last.

For information on the dose calculation and a definition of minor and major surgery, see Section 5.4.

The flow chart of assessments for surgical prophylaxis is provided on page xxiii.

Definitions of Pre-, Intra-, and Post-operative

- **Pre-operative** refers to the time period covering the last 12 hours before the start of surgery.
- **Intra-operative** is defined as the time from the start of surgery to the end of surgery, i.e., the time of completion of the last suture.
- **Post-operative** refers to the time from the end of surgery to the Last Post-Operative Day.

Determination of Fibrinogen Plasma Levels in Surgical Prophylaxis

Fibrinogen plasma levels will be documented immediately (≤30 minutes) before and after each pre-, intra-, or post-operative injection of *Octafibrin*.

Estimation of Blood Loss

Prior to surgery, the surgeon will provide written estimates of the following:

- Volume (mL) of **average expected blood loss** for the planned surgical procedure, as it would be expected for the same procedure in a subject with normal haemostasis, of the same sex, age, and stature.
- Volume (mL) of **maximal expected blood loss** for the planned surgical procedure as it would be expected for the same procedure in a subject with normal haemostasis, of the same sex, age, and stature.

Following surgery, the **actual blood loss** will be estimated by the surgeon.

NOTE: All adverse events (AEs), including thromboembolic events and early signs of allergic or hypersensitivity reactions, occurring between first infusion of IMP before the start of surgery and the Last Post-operative Day will be recorded. The detection of thromboembolic events will be supported by completing a TEE questionnaire at each study visit for the treatment of bleeding episodes and for surgeries. All SAEs occurring after the first IMP infusion will be documented and reported for a patient throughout the duration of the patient's participation in the study or as required to meet local regulations. Also, any concomitant medications used to treat an SAE will be recorded.

6.1.4.1 Day 1

For subjects enrolled for surgical prevention, Day 1 is the day they undergo surgery and receive their first dose of *Octafibrin*.

The following surgery-related data will be recorded:

Pre-operative assessments

The following pre-operative assessments will be performed:

- Medical history
- Vital signs
- Physical examination
- TEE questionnaire
- Body weight (kg)
- Blood draw for:
  - fibrinogen plasma levels (local lab–activity; central lab–antigen and activity)
  - safety lab (local—haematology and clinical chemistry)
- Location and type of surgery
- Severity of surgery (minor/major)
- Expected duration of surgical procedure (start and end times, i.e., skin to skin)
- Expected blood loss for the procedure
- Estimate of any blood/blood product transfusions needed during the surgery
- Any planned ancillary therapy to be used during the surgery (e.g., antifibrinolytics, pre-panned blood transfusions, etc.)

First infusion of Octafibrin

Following the pre-operative assessments and within 3 hours before the start of surgery, the subject may receive the first infusion of *Octafibrin* (see Section 5.4).

NOTE: If, in the investigator's judgement, there are no additional infusions of *Octafibrin* needed to prevent bleedings post surgery, the post-infusion assessments as detailed in the schedule for the **Last Post-Operative Day** should be performed instead.

Intra-operative assessments

The following assessments will be performed during or at the end of surgery:

- Blood draw for:
  - fibrinogen plasma levels (local lab–activity; central lab–antigen and activity)

Assessments at the end of surgery

- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma levels (local lab–activity; central lab–antigen and activity)
- Actual duration of surgical procedure (start and end times, i.e., skin to skin)
- Details of surgery
- Actual blood loss

- Details on concomitantly administered products, including any blood/blood product transfusions but excluding drugs given for routine anaesthesia
- Intra-operative efficacy assessment at the end of surgical procedure by the surgeon (see Section 7.2.2.4)
- AEs and concomitant medications

6.1.4.2 Any Post-Operative Day before the Last Post-Operative Day

On any post-operative day before the Last Post-Operative Day (see Section 6.1.4.3), the following assessments will be performed:

Daily post-operative assessments

The following assessments will be on every post-operative day:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma levels (local lab–activity; central lab–antigen and activity)
  - safety lab (local–haematology and clinical chemistry)
- Wound haematomas and oozing (noting whether surgical evacuation is required and severity and volume of oozing)
- AEs and concomitant medications

Octafibrin infusion, as required

Additional dosing should occur as required depending on the actual and target plasma level and based on the following criteria:

- If the actual fibrinogen plasma level is below the accepted lower limit of the target fibrinogen plasma level (80 mg/dL for minor surgery, 130 mg/dL for major surgery; see Section 5.4), the subject should receive another infusion of *Octafibrin*.
- If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, *Octafibrin* **should not** be administered on that day.

Pre- and post-infusion assessments

If the subject receives an infusion of *Octafibrin*, the following pre- and post-infusion assessments will be performed:

Pre-infusion assessments:

- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)

1 hour (±15 minutes) after the end of each infusion:

- Vital signs
- TEE questionnaire
- Blood draw for:
  - fibrinogen plasma level (local lab–activity; central lab–antigen and activity)
  - safety lab (local–haematology and clinical chemistry)
- AEs and concomitant medications.

6.1.4.3 Last Post-Operative Day

The Last Post-Operative Day is either at least post-operative day 3 for minor and post-operative day 7 for major surgery or the day of the last post-operative infusion, whichever comes last.

The assessments performed on the Last Post-Operative Day are identical to those performed on any other post-operative day (see Section 6.1.4.2).

In addition, the following assessments will be performed on the Last Post-Operative Day:

- post-operative efficacy assessment by the haematologist (see Section 7.2.2.4)
- brief narrative describing the details of hospitalisation (start and end date, details of the procedure), follow-up, outcome, and efficacy of the intervention

The assessments performed on the Last Post-Operative Day conclude the surgical observation period. No further study-related assessments will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up.

Patients may remain in the study until at least 12 patients have undergone PK assessments, the 6th patient (at least 3 patients each in the specified age groups) has at least one documented bleeding episode, and at least 2 surgical procedures have been documented. When the study is closed, all subjects having received any IMP will be asked to return for a Study Completion Visit as summarised in Section 6.1.5.

6.1.5 Study Completion Visit

At the end of the study duration, all subjects having received any IMP will be asked to return for a Study Completion Visit, during which the following assessments will be performed:

- Medical history since the last study visit
- Physical examination

After the Study Completion Visit, the clinical study is considered completed for the subject.

Patients who were screened for the study but did not receive any IMP throughout the study duration will be notified of the end of the study. No further assessments will need to be performed. These patients will be considered ‘no treatment’ patients and reported separately.

6.2 Duration of Study

6.2.1 Planned Duration for the Study as a Whole

The study will be considered completed when a minimum of 12 patients have had PK assessments, 6 subjects (at least 3 subjects aged between 0 and <6 years and 3 subjects aged between 6 and <12 years) have at least one documented bleeding episode, and a minimum of 2 surgical procedures have been documented. The study as a whole should be completed within 5 years.

The estimated start of the study (enrolment of first subject) is in the 3rd quarter of 2015, and the estimated end of the study (last visit of last subject) is in the 3rd quarter of 2020.

6.2.2 Planned Duration for an Individual Subject

All patients will undergo a PK study after screening. This will have a duration of 14 days, after which a patient can be treated for a bleeding episode or planned surgical procedure when they occur.

For subjects receiving on-demand treatment,

- the individual **subject observation and follow-up period** for each documented episode starts with the first dose of *Octafibrin* administered for on-demand treatment of an acute bleeding episode (Day 1) and will be followed up to at least Day 30.
- Each subject's **treatment observation period** is defined according to the severity of the event and will last at least 3 days for minor and 7 days for major bleeding episodes.

For subjects undergoing surgical prophylaxis,

- the **surgical observation period** starts with the first dose of *Octafibrin* administered prior to elective surgery (Day 1) and, depending on the severity of the event, will last 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, whichever comes last.

During the study observation period, enrolled patients will be treated for any bleeding episodes or planned surgeries that can be managed under the protocol. Patients may remain in the study until at least 12 patients have undergone PK assessment, the 6th patient (at least 3 patients each in the specified age groups) has at least one documented bleeding episode, and at least 2 surgical procedures have been documented.

As many bleeding episodes or surgeries as possible occurring throughout the study observation period will be documented. Only the first bleeding episodes will be used for the analysis of the primary endpoint (see Section 3.1.1). All bleeding episodes documented in the study will be assessed as a secondary endpoint (see Section 3.1.2).

Patients who were screened for the study but did not receive any IMP will be considered 'no treatment' patients and reported separately.

All patients completing the PK phase (i.e., at least 12 patients) will also be analyzed separately, regardless of whether they received any IMP for the treatment of a bleeding episode or surgery.

6.2.3 Premature Termination of the Study

Both the investigator and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

Furthermore, the investigator should promptly inform the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

Early termination of the study as a whole or centre-wise may apply for the following reasons:

- **Clinical Study:** At any time the study as a whole may be terminated prematurely if new toxicological or pharmacological findings or serious adverse events (SAEs) invalidate the earlier positive benefit-risk-assessment.
- **Study Centre:** At any time the study may be terminated at an individual study centre if:
  - The centre cannot comply with the requirements of the protocol.
  - The centre cannot comply with Good Clinical Practice (GCP) standards.
  - The required recruitment rate is not met.

Should the study be prematurely terminated, all study materials (completed, partially completed, and blank CRFs, IMPs etc.) must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Background and Screening Information

The following information will be captured on at screening:

Demographics: sex, age, weight and height (calculated body mass index), and ethnic origin

Medical history: obtained by interviewing the subject/legal guardian and by performing a physical examination

Previous and concomitant medication: obtained by interviewing the subject/legal guardian

7.2 Efficacy Assessments

7.2.1 Assessments for Primary Efficacy Endpoint

The primary endpoint is the overall clinical assessment of the haemostatic efficacy of *Octafibrin* in treating the first documented bleeding episode of each patient.

- The **first bleeding episode** covers the time period from the 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.
- The **investigator's overall clinical assessment** covers the entire time period of the first bleeding episode as defined above. The assessment includes the clinical condition of the subject, laboratory values such as haematocrit and haemoglobin, as well as any additional haemostatic treatments.

The investigator's overall clinical assessment of haemostatic efficacy will be based on a 4-point haemostatic efficacy scale (Table 2). The final efficacy assessment of each patient will be adjudicated by the IDMEAC.

Table 2: Overall clinical assessment of haemostatic efficacy

Category	Definition
Excellent	Immediate and complete cessation of bleeding in the absence of other haemostatic intervention as clinically assessed by the treating physician; and/or <10% drop in haemoglobin compared to pre-infusion.
Good	Eventual complete cessation of bleeding in the absence of other haemostatic intervention as clinically assessed by the treating physician; and/or <20% drop in haemoglobin compared to pre-infusion.
Moderate	Incomplete cessation of bleeding and additional haemostatic intervention required, as clinically assessed by the treating physician; and/or between 20 and 25% drop in haemoglobin compared to pre-infusion.
None	No cessation of bleeding and alternative haemostatic intervention required, as clinically assessed by the treating physician; and/or >25% drop in haemoglobin compared to pre-infusion.

7.2.2 Assessments for Secondary Endpoints

7.2.2.1 Pharmacokinetics

The PK endpoints (i.e., AUC, incremental and classical IVR, terminal elimination half-life ($t_{1/2}$), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), mean residence time (MRT), volume of distribution (Vss), and clearance (Cl) will be assessed after a single intravenous infusion of 70 mg/kg body weight of *Octafibrin.*

7.2.2.2 Clot Strength

MCF will be determined using thromboelastometry (ROTEM) and will be used as a surrogate marker for haemostatic efficacy. 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 is the continuous registration of blood clot firmness during the entire coagulation process (Figure 1).

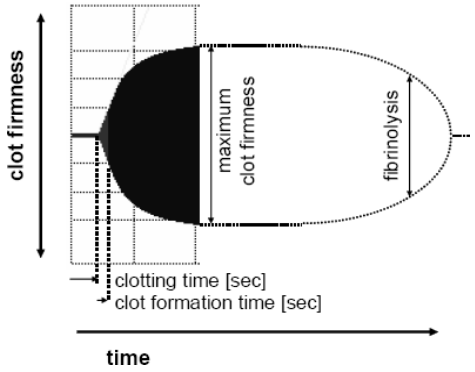

Figure 1: Example of thromboelastogram

MCF (measured in mm) is a functional parameter which depends on the activation of coagulation, the platelet and fibrinogen content of the blood sample, and the polymerisation and cross-linking of the fibrin network.

ROTEM has been shown in various studies to be predictive of clinical coagulopathy [16, 17, 18, 19, 20]. ROTEM has been used as a functional marker for the assessment of fibrinogen content, and for the effects of fibrinogen supplementation on the clinical efficacy [21, 22, 23, 24, 25, 26]. Therefore, the MCF parameter is regarded as an adequate surrogate marker for the haemostatic efficacy of fibrinogen supplementation in patients with congenital fibrinogen deficiency.

To obtain consistent results across all study centres, with minimal centre-to-centre variability, MCF blood samples will be forwarded to the central laboratory. MCF will be assessed from frozen citrated plasma samples.

The MCF (units: mm) at 1 hour post-infusion will be regarded as surrogate efficacy criterion.

7.2.2.3 Recovery

For the first infusion of each treated bleeding episode, IVR will be determined using the following approaches:

- Incremental IVR (response): 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* (expressed as mg/kg dosed)
- Classical 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 total dose of *Octafibrin* per expected plasma volume (expressed as mg/dL), with expected plasma volume being estimated based on the blood volume formula described by Nadler [27]

7.2.2.4 Surgical Prophylaxis

The efficacy of *Octafibrin* in surgical prophylaxis will be assessed at the end of surgery by the surgeon and post-operatively by the haematologist as described in Table 3. The efficacy of *Octafibrin* in surgical prophylaxis will be based on an overall assessment. The overall surgical efficacy will be adjudicated by the IDMEAC who will evaluate the surgeons' and investigators' assessments in conjunction with a review of the surgical case.

Table 3: Clinical assessment of surgical prophylaxis

Category	Definition
Intra-operative efficacy as assessed by surgeon (at end of the surgery = after last suture)	
Excellent	Intra-operative blood loss* was lower than or equal to the average expected blood loss for the type of procedure performed in a subject with normal haemostasis and of the same sex, age, and stature.
Good	Intra-operative blood loss* was higher than average expected blood loss but lower or equal to the maximal expected blood loss for the type of procedure in a subject with normal haemostasis.
Moderate	Intra-operative blood loss* was higher than maximal expected blood loss for the type of procedure performed in a subject with normal haemostasis, but haemostasis was controlled.
None	Haemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.

*Excludes unexpected blood loss due to surgical complications, i.e.,
- direct injury of a vessel (artery or vein)
- vessel injury not adequately responding to routine surgical procedures achieving haemostasis
- accidental injury of parenchymatous tissue (e.g., liver, lung)

Category	Definition
Post-operative efficacy as assessed by haematologist	
Excellent	No post-operative bleeding or oozing that was not due to complications of surgery. All post-operative bleeding (due to complications of surgery) was controlled with *Octafibrin* as anticipated for the type of procedure.
Good	No post-operative bleeding or oozing that was not due to complications of surgery. Control of post-operative bleeding due to complications of surgery required increased dosing with *Octafibrin* or additional infusions, not originally anticipated for the type of procedure.
Moderate	Some post-operative bleeding and oozing that was not due to complications of surgery; control of post-operative bleeding required increased dosing with *Octafibrin* or additional infusions, not originally anticipated for the type of procedure.
None	Extensive uncontrolled post-operative bleeding and oozing. Control of post-operative bleeding required use of an alternate fibrinogen concentrate.

The IDMEAC will conduct an independent adjudication of all haemostatic efficacy results and adjudicate the investigator's assessments of the intra- and post-operative assessments ('secondary adjudication').

The primary endpoint ('success' or 'failure') will be derived from the adjudicated intra- and post-operative assessments according to the agreed algorithm presented in Table 4.

Table 4: Algorithm for the adjudicated intra- and post-operative assessments of haemostatic efficacy

Intra-operative assessment	Post-operative assessment			
	Excellent	**Good**	**Moderate**	**None**
Excellent	Success	Success	Success	Primary adjudication
Good	Success	Success	Primary adjudication	Failure
Moderate	Success	Primary adjudication	Failure	Failure
None	Primary adjudication	Failure	Failure	Failure

Outcomes designated as 'primary adjudication' will be assigned following adjudication by the IDMEAC.

In documenting the adjudication process for the assessment of surgical prophylaxis, the IDMEAC will explicitly identify any subjects for whom they considered there to be '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 will be analyzed both including (as a sensitivity analysis) and excluding the unexpected blood loss.

In the event that any intra- or post-operative endpoint data differ between the investigator's assessment and the adjudicated assessment by the IDMEAC, the endpoint will be that based on the adjudicated assessments. The efficacy of *Octafibrin* in surgical prophylaxis will be evaluated by descriptive statistics based on an overall assessment.

In addition, the location, severity, and type of surgery will be documented. Expected and actual duration of surgical procedure and details of administered dose(s) of *Octafibrin* (pre-, intra- and/or post-operatively) will be recorded. Fibrinogen plasma levels (pre-, intra-, and post-operatively) will be measured. Details of concomitantly administered products (except standard anaesthesia), along with a brief narrative describing the outcome of the intervention, will be recorded.

7.3 Laboratory Assessments

Table 5 summarises all test parameters and the laboratories responsible for analysis.

Table 5: Test Parameters and Laboratories

Test	Material needed	Responsible laboratory
Fibrinogen activity (Clauss)	Citrated plasma	Local and central
Fibrinogen:Ag	Citrated plasma	Central
Fibrinogen inhibitor testing	Citrated plasma	Central
Clinical chemistry	Serum	Local
Haematology	EDTA blood	Local
Maximum clot strength	Citrated plasma	Central
Thrombogenicity (D-dimer, prothrombin fragment 1+2)[1]	Citrated plasma	Central

[1] Any thromboembolic events reported from Day 1 to Day 30 will be documented as AEs. A final clinical evaluation of any signs or symptoms of potential thromboembolic events will be done at Day 30.

All remaining serum and plasma volumes will be labelled and stored as retention samples at the central laboratory for at least 24 months after the completion of the study and until Octapharma's written authorisation to destroy these samples. These samples may be used for additional coagulation and viral testing, if needed.

The flow chart of assessments for on-demand treatment is provided on page xxii. The flow chart of assessments for surgical prophylaxis is provided on page xxiii.

7.3.1 Blood Sampling

The *actual* time of blood sampling must be recorded in the CRF and on the corresponding laboratory requisition forms.

If several blood samples have to be taken at one time point, the blood sampling will be done in the following sequence:

1. Coagulation (citrated plasma)
2. Haematology and virology serology (EDTA blood and serum, respectively)
3. Clinical chemistry (serum)

7.3.2 Citrated Plasma

Blood samples taken for plasma will be centrifuged after collection as instructed in the laboratory manual provided by the Sponsor. Aliquots of the supernatant are subsequently transferred into the tubes provided by the Sponsor and stored or shipped under conditions described in the laboratory manual.

For the analysis performed in the central laboratory, samples of citrated blood will be collected for coagulation factor analysis and antibody testing. After collection and centrifugation as instructed in laboratory manual, the plasma will be aliquoted into cryo-resistant tubes. Samples will be stored frozen and shipped to the central laboratory on dry-ice.

For analyses performed locally, citrated blood as required by the local laboratory will be collected and processed in accordance with local requirements.

Retention samples will be taken at described time points in the study for possible retesting if needed.

7.3.3 EDTA Blood

A sample of EDTA blood will be collected for the measurement of haematology parameters (red blood cell count, RBCC; white blood cell count, WBCC; haemoglobin, HB; haematocrit, HCT; and platelet count, PC).

All tests will be done at the local laboratory.

7.3.4 Serum

For the determination of clinical chemistry (total bilirubin, BILI; alanine aminotransferase, ALT; aspartate aminotransferase, AST; blood urea nitrogen, BUN; serum creatinine, CREA; lactate dehydrogenase, LDH), a serum blood sample will be collected.

All tests will be done at the local laboratory.

Retention samples will be taken at entry into the study and at the Study Completion Visit for potential viral testing if there is a suspicion of infection.

7.3.5 Recording of Clinically Significant Abnormal Laboratory Values as AEs/ADRs

The investigator must assess the clinical significance of abnormal laboratory values outside the normal range as specified by the reference laboratory. Any clinically significant abnormalities should be fully investigated.

Only laboratory abnormalities that have been rated as being clinically significant and occurred after the first IMP administration in the study, will be documented as AEs/ADRs. Clinically significant is defined as any laboratory abnormality that the investigator feels is of clinical concern and/or requires medical intervention and/or follow-up. Additional tests and other evaluations required to establish the significance or aetiology of an abnormal result or to monitor the course of an AE should be obtained if clinically indicated.

Any abnormal laboratory value that persists should be followed until resolution or for 14 days after the Study Completion Visit, whichever occurs first. Preferably, clinically significant laboratory abnormalities should be medically diagnosed and entered as a diagnosis into the AE form.

7.4 Safety Assessments

Any of the following drug safety information shall be collected:

- All AEs occurring between the start of the first *Octafibrin* infusion and the end of the PK phase, the end of each 30-day observation and follow-up period for on-demand treatment, or the end of the surgical observation period will be recorded.
- All SAEs occurring after the first *Octafibrin* infusion will be documented and reported for a patient throughout the duration of the patient's participation in the study or as required to meet local regulations (definitions and reporting requirements, see Section 7.4.1).
- Post study related safety reports, drug overdose, interaction, abuse, misuse, or medication error (see Section 7.6).

7.4.1 Adverse Events (AEs)

7.4.1.1 Definitions

- AE: An AE is any untoward medical occurrence in a study subject receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.
- Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- Other significant AEs: Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy.
- Withdrawal due to AE/ADR: Subject whose treatment with IMP is discontinued because of an AE or ADR. Any such events will be followed up by the investigator until the event is resolved or until the medical condition of the subject is stable. All follow-up information collected will be made available to the Sponsor.

7.4.1.2 Collection of AEs

The condition of the subject will be monitored throughout the **PK phase**, each **30-day observation and follow-up period** for on-demand treatment or each **surgical observation period** for surgical interventions. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as 'How have you been since the last visit?'

Only AEs or ADRs which occur during the PK phase, any 30-day observation and follow-up period for on-demand treatment, or any surgical observation period for surgical interventions will be recorded in detail on the appropriate pages of the CRF. If the subject reports several signs or symptoms which represent a single syndrome or diagnosis, the latter should be recorded in the CRF.

The investigator responsible will grade the severity of all AEs or ADRs (mild, moderate, or severe; see Section 7.4.1.3), the seriousness (non-serious or serious; see Section 7.4.2), and causality (see Section 7.4.1.4). The Sponsor is responsible to assess the expectedness of each ADR (expected or unexpected; see Section 7.4.1.5).

In the event of clinically significant abnormal laboratory findings, the tests will be repeated and followed up until they have returned to normal and/or an adequate explanation is available.

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of IMP are not considered as AEs when observed at a later stage unless they represent an exacerbation in intensity or frequency (worsening).

The investigator responsible should always provide detailed information concerning any abnormalities and the nature of, and reasons for any necessary action(s), as well as any other observations or comments, which are useful for the interpretation and understanding of the subjects' AEs or ADRs.

7.4.1.3 Severity of AEs

The intensity/severity of all AEs will be graded as follows:

- Mild: an AE, usually transient, which causes discomfort but does not interfere with the subject's routine activities.
- Moderate: an AE which is sufficiently discomforting to interfere with the subject's routine activities.
- Severe: an AE which is incapacitating and prevents the pursuit of the subject's routine activities.

Grading of an AE is up to the medical judgement of the investigator and will be decided on a case-by-case basis.

7.4.1.4 Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the investigator responsible:

- Probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the subject's clinical state.
- Possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- Unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the subject's clinical state or by environmental factors or other therapies administered.
- Not related (unrelated): events for which sufficient information exists to conclude that the aetiology is unrelated to the IMP.
- Unclassified: reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

7.4.1.5 Classification of ADRs

ADRs will be classified by the Sponsor as either expected or unexpected:

- Expected: an AE that is listed in the current edition of the Investigator's Brochure
- Unexpected: an AE that is not listed in the current edition of the Investigator's Brochure, or that differs because of greater severity or greater specificity

7.4.1.6 Outcome of AEs

The outcome of all reported AEs has to be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A subject's **death** per se is not an event, but an outcome. The event which resulted into subject's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end, and without respect of being considered treatment-related or not.

7.4.1.7 Action(s) Taken

AEs requiring action or therapy must be treated with recognised standards of medical care to protect the health and wellbeing of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

The action taken by the investigator must be documented:

1. In general:
   - None
   - Medication (other than IMP) or other (e.g., physical) therapy started
   - Test performed
   - Other (to be specified)
2. Regarding the IMP:
   - None
   - Product withdrawn
   - Dose reduced
   - Dose increased

The responsible investigator will follow-up each AE until it is resolved or until the medical condition of the subject is stable; all relevant follow-up information will be reported to the Sponsor.

7.4.2 Serious Adverse Events

All reported SAEs occurring after the first administration of IMP in the study will be documented and reported for a patient throughout the duration of the patient's participation in the study. This will be designated as occurring in either an "active period" (i.e., during the treatment observation and follow-up period) or an "inactive period" between treatment events (i.e., bleeding or surgery).

All related concomitant medications will also be collected for these events.

No SAEs will be collected between screening and the first treatment unless required by local regulations.

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is another important medical event

NOTE: The term 'life-threatening' refers to an event in which the subject was — in the view of the reporting investigator — at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

In other situations, medical judgement should be exercised in deciding whether an AE/ADR is serious: Important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the subject. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.4.3 SAE Reporting Timelines

All SAEs, whether suspected to be related to study treatment or not, are to be reported by telephone, fax or e-mail immediately to the Clinical Project Manager or designee. Contact details will be communicated at the study initiation visit.

An Octapharma 'Serious Adverse Event Report' must be completed and submitted within 24 hours after recognition of the event.

In any case, all SAEs should also be reported to

Octapharma's Central Drug Safety Unit:
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: +43 1 61032 9949
E-mail: cdsu@octapharma.com

24 hours emergency telephone number: +43 1 40 80 500

Waiver from SAE expedited reporting requirement

The following SAEs do not require expedited reporting:

- Hospitalisation for the treatment of disease-related conditions assessed as unrelated to IMP treatment
- Prolongation of an existing hospitalization due to economic or social reasons, but not medical reasons

7.5 Vital Signs and Physical Examination, including Thromboembolic Event (TEE) Questionnaire

Vital signs including systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature should be recorded using standard clinical procedures at the study centres. Vital signs will be assessed after 3 minutes of rest in the supine or semi-recumbent position.

Physical examination will consist of checking the general appearance, skin condition, eyes, ears, nose and throat examination, heart auscultation, chest, breast and abdomen examination, neurological assessment, lymph node palpation, spine, and extremities examination.

The **TEE questionnaire** will be completed at all study visits for the treatment of bleeding episodes and for surgeries.

The flow chart of assessments for on-demand treatment is provided on page xxii. The flow chart of assessments for surgical prophylaxis is provided on page xxiii.

7.6 Other Relevant Safety Information

7.6.1 Post-study Related Safety Reports

Any ADR (i.e., any AE with a suspected causal relationship to the IMP) which occurs after the completion of the study should be reported by the investigator. The usual procedure for reporting post marketing safety information should be followed, but relation to the clinical study should be stated on the report.

If a subject/patient dies within 4 weeks after the last IMP administration, this should be reported as well, without being considered treatment related or not.

7.6.2 Overdose, Interaction, Misuse, Medication Error

The following safety relevant information should be reported as an AE or, if the reaction fulfils one of the criteria for seriousness, as a SAE.

- Drug overdose: An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than that specified in the protocol, and higher than the known therapeutic dose and of clinical relevance. The reaction must be clearly identified as an overdose.
- Interaction: A drug interaction is a situation in which a substance/medicinal product affects the activity of an IMP, i.e., the effects are increased or decreased, or they produce an effect that none of the products exhibits on its own. The reaction must be clearly identified as drug interaction.
- Misuse: Misuse is the deliberate administration or use of the medicinal product outside its described indication or outside the current state of the art medical practice (off-label-use). The reaction must be clearly identified as misuse.
- Medication error: Medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, and/or instructions for use/labelling. The reaction must be clearly identified as a medication error.

7.7 Other Assessments

Not applicable.

7.8 Appropriateness of Measurements

The clinical and laboratory measurements used to assess the efficacy and safety of *Octafibrin* are generally accepted and in accordance with published recommendations. All laboratory parameters will be evaluated by accredited laboratory facilities using standardised and validated methods.

The key laboratory investigations of the study (Clauss assay, fibrinogen specific enzyme linked immunosorbent assay, and MCF) will be performed by a central laboratory specialised in the determination of coagulation parameters.

8 DATA HANDLING AND RECORD KEEPING

8.1 Source Data and Records

Source data are defined as all the information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records allowing reconstruction and evaluation of the clinical study.

The investigator will maintain adequate source records (e.g., case histories or subject files for each subject enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each subject enrolled, the investigator will indicate in the source record(s) that the subject participates in this study.

All data entered in the CRF must be supported by source data in the subject records with the exceptions listed in Section 8.2.

The investigator will permit study-related monitoring, audit(s), IEC/IRB review(s) and regulatory inspection(s), by providing direct access to source data/records.

The investigator may authorise site staff (e.g., sub-investigators, nurses) to enter study data into the CRF. This must be documented in the 'Delegation of Authority Log,', filled in and signed by the investigator responsible.

8.2 Case Report Forms

For each subject enrolled, a CRF will be completed. The Principal Investigator or authorised investigators will sign the CRF as required on the forms.

All forms will be filled out using an indelible (black or blue) pen, and must be legible. The following data will be recorded directly on the CRFs, without prior written or electronic record of source data, turning the CRF into source:

- Vital signs
- Physical examination results
- Date and time of blood sampling

8.3 Changes to Case Report Form Data

Errors occurring in CRFs will be crossed out without obscuring the original entry, the correction will be written alongside the initial entry, and the change will be initialled and dated by the investigator or authorised study site personnel. When changes to CRF data are necessary following removal of the original CRF from the study site, any such changes will be documented on data clarification/resolution forms, which will be submitted to the investigator for signature.

If reason for the change is not obvious, then a reason should be given. The Principal Investigator must, as a minimum, sign the final CRF page to attest the accuracy and completeness of all the data. Once the data have been entered onto the database, they will be checked and any discrepancies will be raised and returned to the investigator for resolution. Data will be monitored and tabulated in accordance with the Data Management Plan.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management for incomplete or ambiguous resolutions. If the query response provided confirms the data as correct, the discrepancy will be closed based on the query response. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, source data verification will be confirmed as complete by the monitor, and all CRFs and resolved data discrepancies will be approved by the investigator prior to database lock.

8.4 Information of Investigators

An Investigator's Brochure will be handed out to the investigator before the start of the study. This Brochure contains all information in the Sponsor's possession necessary for the investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The Investigator's Brochure will be updated by the Sponsor at regular intervals and in case new information concerning the IMP becomes available.

The investigators will be informed about the methods for rating relevant study outcomes and for completing CRFs in order to reduce discrepancies between participating investigators and study sites.

The investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.5 Responsibilities

The investigator is accountable for the conduct of the clinical study. If any responsibilities are delegated, the investigator should maintain a list of appropriately qualified persons to whom he/she has delegated significant study-related duties.

A Delegation of Authority Log will be filled in and signed by the investigator responsible. In accordance with this authority log study site staff (e.g., sub-investigators, nurses) is authorized to perform study related tasks and to enter specific data into the CRF.

8.5.1 Co-ordinating Investigator

The co-ordinating investigator of this study is:

8.5.2 External Parties

Central laboratory testing, monitoring, data management, and biostatistics will be delegated under an agreement of transfer of responsibilities to a central laboratory or an external Contract Research organisation (CRO).

All Octapharma procedures and policies have to be met by external parties (CROs and central laboratories), discrepancies or exceptions are to be approved by Octapharma. All parties involved in the study are responsible to comply with local and international obligations, regulatory requirements and duties in accordance with local laws, GCP guidelines, SOPs and other applicable regulations.

8.6 Investigator's Site File

At each study site, the investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the investigator for the maximum period of time required by local regulations.

The investigator is responsible for maintaining a confidential subject identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the investigator and the Sponsor. Should the investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.7 Provision of Additional Information

On request, the investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the subject's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the subject's confidentiality is protected in accordance with applicable regulations.

8.8 Independent Data Monitoring & Endpoint Adjudication Committee

An Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC) will be established by the Sponsor. The IDMEAC will be composed of recognised experts in the field of clinical care who are not actively recruiting subjects.

The IDMEAC will review relevant data periodically during the study and will give advice on the continuation, modification, or termination of the study. This committee will also be responsible for adjudicating the primary and secondary efficacy endpoints in the study.

A IDMEAC charter will define in detail the composition, responsibilities and procedures of the IDMEAC.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external Contract Research Organization (CRO). All Octapharma procedures and policies have to be met by this CRO. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics.

A statistical analysis plan (SAP) describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor before the start of the study.

Due to the low number of patients, all statistical analysis will be descriptive only.

Continuous variables will be summarised using descriptive statistics (including arithmetic mean, standard deviation (SD), median, minimum and maximum, number of observations and missing observations). Categorical variables will be summarised with counts and percentages.

9.1 Sample Size

The number of subjects is limited by the very small number of patients with this indication. At least 12 patients will undergo PK assessments in this study. The minimum number of paediatric patients with a haemostatic outcome assessment for the on-demand treatment of a bleeding episode will be 6 and has been agreed upon with the paediatric committee of the EMA. No confirmatory test is provided. Therefore, no sample size estimation is provided.

9.2 Populations for Analysis

9.2.1 Safety Population

The safety population will include all subjects who received at least one infusion of the IMP. The analysis of safety will be based on this population.

9.2.2 Full Analysis Set

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 (second inclusion criterion; see Section 4.2)

9.2.3 PK Analysis Population

The PK analysis population includes all patients of the FAS who started the PK assessment and have at least one valid post-baseline fibrinogen activity level.

9.2.4 PK-PP Population

The PK-PP population includes patients in the PK analysis population who completed the PK sampling phase without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results:

Especially patients will be excluded from this population, if they meet the following protocol deviations:

- Bleeding disorder other than congenital fibrinogen deficiency, including dysfibrinogenaemia
- Any fibrinogen concentrate or other fibrinogen-containing blood product within 2 weeks prior to start of treatment for the PK phase
- Diagnosis or suspicion of a neutralising anti-fibrinogen inhibitor currently or at any time in the past
- Patients who use concomitant medication before or during the PK phase that may confound study results
- Patients who receive less than 90% of the planned dose (nominal)
- Fibrinogen baseline measurement for PK assessment missing
- More than 2 post-baseline blood samples missing for PK assessment

9.2.5 FirstBLEED Population

The FirstBLEED population will include subjects of the FAS who fulfil the following condition:

- Presented with at least one episode of acute bleeding (third inclusion criterion; see Section 4.2) treated with *Octafibrin*

9.2.6 FirstBLEED-PP Population

The FirstBLEED-PP population will include subjects of the FirstBLEED population who fulfil the following conditions:

- Provide valid, i.e., non-missing, haemostatic efficacy data for their first bleeding
- Received ≥90% of the planned total dose of the IMP in the first infusion for their first bleeding
- Received ≥80% of the calculated dose (if no dose was calculated, 0% will be assumed) of the IMP over all further infusions of the first bleeding according to the treatment schedule

- Did not meet any of the following exclusion criteria:
  - Bleeding disorder other than congenital fibrinogen deficiency
  - End-stage liver disease (i.e., Child-Pugh-score B or C)
  - Suspicion of an anti-fibrinogen inhibitor as indicated by previous IVR, if available <0.5 (mg/dL)/(mg/kg)
  - Treatment with any fibrinogen concentrate or other fibrinogen-containing blood product within 2 weeks prior to start of treatment for the bleeding episode
- Did not use any coagulation-active drug (i.e., non-steroidal anti-inflammatory drugs, warfarin, coumarin derivatives, platelet aggregation inhibitors) within 1 week prior to start of treatment for the first bleeding episode, or as a planned or expected medication during the time period from Day 1 until 24 hours (i.e., 1 day) after the last *Octafibrin* infusion

9.2.7 BLEED Population

The BLEED population will include all documented bleeding episodes treated with *Octafibrin* in subjects of the FAS.

9.2.8 BLEED-PP Population

A BLEED-PP population comprising bleeding episodes with no major protocol deviations will be defined in the SAP, with criteria similar to the FirstBLEED-PP population.

9.2.9 SURG population

The SURG population will include all surgical interventions with a need for at least one infusion of the IMP during the time period from the day of surgery until overall clinical assessment of haemostatic efficacy (third inclusion criterion; see Section 4.2) in subjects of the FAS.

A SURG-PP population comprising surgical interventions with no major protocol deviations will be defined in the SAP with criteria similar to the FirstBLEED-PP population.

NOTE: Any protocol deviations which will lead to the exclusion from an analysis population other than those mentioned above must be agreed upon in writing by the Sponsor and the study statistician, and in any case, before database closure.

The efficacy analysis for the primary endpoint will be performed with the data from the first bleeding event of each patient using the FirstBLEED population (ITT analysis) as the primary population and using the FirstBLEED-PP population (PP analysis) as a secondary population. An additional analysis will be performed for all bleeding events on the BLEED and BLEED-PP population. The primary analysis population for the PK analysis will be the PK-PP population.

9.2.10 Subpopulations

Subpopulations based on the following categories will be examined:

- Severity of bleeding: minor versus major (subpopulations of the BLEED population)
- Age 0 to <6 years versus 6 to <12 years

9.3 Efficacy Analysis Plan

9.3.1 Primary Endpoint

The primary endpoint is the overall clinical assessment of haemostatic efficacy of *Octafibrin* in treating the first documented bleeding episode of each patient (FirstBLEED population). The first bleeding episode covers the time period from the first *Octafibrin* infusion until 24 hours (i.e., 1 day) after the last infusion or the end of the treatment observation period, whichever comes last (see Section 3.1.1). The final efficacy assessment of each patient will be adjudicated by an Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC).

Frequency distribution will be provided for the haemostatic efficacy scale data. In addition, the assessment made by the investigator on the 4-point rating scale will be transformed to a dichotomous endpoint with success defined as a rating of 'excellent' or 'good'. A 2-sided 95% CI for the success rate in haemostatic efficacy ('excellent' or 'good') according to Clopper/Pearson will be computed.

For the following subjects, the haemostatic efficacy outcome will be set to the worst efficacy category, i.e., 'none':

- Subjects who withdraw from the study due to lack of efficacy
- Subjects receiving cryoprecipitate or concentrates containing fibrinogen other than the IMP between first infusion and efficacy assessment (unless it is clearly documented that these products were administered for reasons unrelated to IMP efficacy [e.g., pharmacy error])
- Subjects with missing haemostatic efficacy assessment

Haemostatic efficacy will be displayed by covariables (sex, age groups, weight, type of bleeding) in tables or with covariables in listings depending on the number per subgroup.

9.3.2 Secondary Endpoints

9.3.2.1 Pharmacokinetics (PK)

The primary PK analysis will be based on the PK-PP population.

The exact applied dose of fibrinogen concentrate (expressed as mg/kg dosed) will be calculated for each subject, based upon the actually administered amount of each study treatment and the potency of fibrinogen in the actually used batch.

PK analysis on fibrinogen activity and antigen levels will be performed per patient with a non-compartmental model using standard PK software (Phoenix [28]); this includes graphical displays of individual elimination curves. Individual endogenous baseline concentrations, if any, will be taken into account by subtraction from post-baseline values. The resulting PK parameters will be summarized and presented as described for continuous variables.

The PK endpoints (i.e., area under the concentration-time curve (AUC), incremental IVR, classical IVR, terminal elimination half-life ($t_{1/2}$), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (Tmax), mean residence time (MRT), volume of distribution (V_{ss}), and clearance (Cl)) will be assessed after a single intravenous infusion of 70 mg/kg body weight of *Octafibrin*.

9.3.2.2 Clot strength (MCF)

The analysis of MCF will be provided for the BLEED population.

MCF before as well as MCF and fibrinogen activity 1 hour after the end of the first infusion, as well as changes in MCF from pre-infusion will be summarised over all bleeding episodes using descriptive statistics. The course of laboratory data will be presented graphically. Mean changes in MCF will be described with 2-sided 95% CIs based on the paired t-test.

The same analyses or respective listings (depending on the number of observations per subgroup) will be provided separated for the predefined subgroups as well as separated for the subjects' clinical outcome represented by each step of the 4-point haemostatic efficacy scale (excellent, good, moderate, none) and the dichotomised haemostatic efficacy scale (excellent/good, moderate/none). Boxplots will show MCF by haemostatic efficacy outcome, if applicable.

9.3.2.3 In-vivo recovery

IVR will be determined for the first infusion of each bleeding episode (see Section 7.2.2.3). The analysis population will be the BLEED population.

Incremental IVR (response) will be 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* (expressed as mg/kg dosed):

Incremental IVR (response) (mg/dL increase/[mg/kg b.w.]) =

> Maximum increase in fibrinogen plasma level up to the 3-hour measurement post-infusion compared to pre-infusion (mg/dL) /
> (exact dose of component in IMP administered [mg]/b.w. [kg])

Classical IVR will be 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 total dose of *Octafibrin* per expected plasma volume (expressed as mg/dL, expected plasma volume being estimated based on the blood volume formula described by Nadler [27]):

Classical IVR (%) =

> 100% x actual/expected increase =
> 100% x maximum increase in fibrinogen plasma level 1 and 3 hours post-infusion compared to pre-infusion (mg/dL) x plasma volume (dL) / (exact dose of component in IMP administered [mg]).

Descriptive tables will show the distribution of IVRs separated by minor and major bleeding events. Fibrinogen levels before and 1 hour after each infusion will be listed.

9.3.2.4 Efficacy of Octafibrin in All Bleeding Episodes

The efficacy of *Octafibrin* in the treatment of all bleeding episodes recorded throughout the study observation period will be assessed in the same way as the efficacy of *Octafibrin* in the treatment of the first bleeding episode per patient (see Section 9.3.1).

In addition to the 'first BE per patient approach,' haemostatic efficacy (4-point scale) and success rates for the treatment of bleeding episodes will be presented descriptively for all bleeding episodes (BLEED population) by frequency tables.

Success rate estimates will also be provided with two-sided 95% CIs, considering both

- the assessments of each bleeding episode as an independent case within each subject and
- outcomes of assessments as repeated measurements within the same patient, if applicable (e.g., by general estimation equations with intra-subject correlation structure).

9.3.2.5 Surgical Prophylaxis

Efficacy of *Octafibrin* in surgical prophylaxis will be assessed intra-operatively (at the end of surgery = after last suture) by the surgeon and post-operatively by the haematologist using two 4-point efficacy scales (see Section 7.2.2.4). The primary analysis regarding haemostatic efficacy will be done on the adjudicated assessments using the algorithm described in Table 4 and by the IDMEAC.

The following will be presented in frequency tables with descriptive statistics or in listings, depending on the number of surgeries:

- Adjudicated overall efficacy assessment by the described algorithm and the IDMEAC
- Efficacy evaluation by the surgeon and the haematologist (intra- and post-operatively)
- Number of patients undergoing surgeries and number of surgeries (minor, major, total)
- Surgery characteristics (type and site, pre-planned (yes/no), reason, severity, expected and actual duration, expected and actual blood loss)
- Details on treatment with *Octafibrin* (before, during, and after the surgical procedure (number of infusions, dosing details, amount of IMP)
- Pre-, intra-, and post-operative fibrinogen plasma levels, pre- and post-infusion

In documenting the adjudication process for the assessment of surgical prophylaxis, the IDMEAC will explicitly identify any subjects for whom they considered there to be '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 will be analyzed both including (as a sensitivity analysis) and excluding the unexpected blood loss.

9.4 Safety Analysis Plan

The analysis of safety will be based on the safety population.

All AEs (including events likely to be related to the underlying disease, or a concomitant illness or medication or clinically significant abnormalities in laboratory parameters or vital signs) will be displayed in summary tables and listings.

Incidences of AEs will be given as numbers and percentages of subjects with:

- Any AE
- Any SAE
- Any AE probably or possibly related to the IMP
- Any AE temporally related (within 24 hours after end of infusion) to the IMP
- Any severe AE
- Any withdrawal due to AE
- Any AE by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (descending frequency)
- Any AE temporally related (within 24 hours after end of infusion) by MedDRA preferred term (descending frequency)
- Any AE by MedDRA system organ class (SOC)
- Any AE temporally related (within 24 hours after end of infusion) by MedDRA SOC

Summary tables for AEs will be given by SOC and preferred term. Additionally, AEs will be summarised by severity and relationship to the IMP

The MedDRA coded terms and the corresponding original (verbatim) terms used by the investigator will be listed.

For laboratory variables (analyses of haematology, clinical chemistry, and thrombogenicity), the mean, standard deviation, median, and range will be presented per time point. Laboratory variables will also be presented graphically. Intra-individual changes between pre-infusion and the respective post-infusion time points will be analysed using shift tables and graphical presentations. Fibrinogen inhibitor testing data will be summarized in frequency tables.

For vital signs, the mean, standard deviation, median, and range will be presented per time point (original values and intra-individual changes between pre-infusion and the respective post-infusion time points). Physical examination data will be presented in frequency tables.

9.5 Additional Analyses

Octafibrin use

Octafibrin will be individually dosed to achieve a recommended target fibrinogen plasma level dependent on the bleeding type (minor or major). Individual doses, achieved FVIII level after dosing, the target level as well as the difference between target level and achieved level will be listed, summarized using descriptive statistics and displayed graphically.

The dose of the IMP used per day and in total will be summarised using descriptive statistics for minor and major bleeding events. Frequency of infusions and duration of treatment will also be summarised.

9.6 Handling of Missing Data

In general, if not stated differently, missing data will not be imputed.

If the haemostatic efficacy assessment is missing, it will be set to 'none' in the ITT analysis. Subjects with missing haemostatic efficacy assessment will be excluded from the PP population.

Missing PK parameters, MCF and IVR values will not be replaced.

9.7 Randomisation

Not applicable.

9.8 Interim Analysis

An administrative interim analysis will be performed after at least 12 patients have undergone PK assessment within the study. The interim analysis will focus on the PK data only. The results of the interim analysis will have no impact on the further conduct of the study.

10 ETHICAL, REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical and Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP regulations and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO), as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the subject information and informed consent form, any other materials provided to the subjects, and further requested information will be submitted by the Sponsor or the investigator to the appropriate IEC/IRB and the Regulatory Authority. The study approval letter must be available before any subject is exposed to a study-related procedure.

The Sponsor, the investigator and any third party (e.g., CRO) involved in obtaining approval, must inform each other in writing that all ethical and legal requirements have been met before the first subject is enrolled in the study.

10.3 Subject Information and Informed Consent

At screening, the investigator will obtain a freely given written consent from each subject's legal guardian after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which is relevant to the legal guardian's decision to have the subject participate. The informed consent form must be signed, with name and date and time noted by the subject's legal guardian and the investigator, before the subject is exposed to any study-related procedure, including screening tests for eligibility.

If the period between screening and treatment is more than 3 months, informed consent will be reviewed and confirmed prior to treatment, and details of the review process will be recorded in the patient chart and indicated by the investigator.

The investigator will explain that the legal guardian is completely free to refuse to have the subject enter the study or to withdraw the subject from it at any time, without any consequences for the further care of the subject and without the need to justify. The investigator will complete the informed consent section of the CRF for each subject enrolled.

Each legal guardian will be informed that the subject's medical (source) records may be reviewed by the study monitor, a quality assurance auditor or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the investigator (co-ordinating investigator in multi-centre studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the IEC(s/IRB) and/or competent authority responsible as required by applicable regulations. IEC(s)/IRB approval will at a minimum be requested for any change to this protocol which could affect the safety of the subjects, the objective/design of the study, any increase in dosage or duration of exposure to the IMP an increase in the number of subjects treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Subjects Data

The investigator will ensure that the subject's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the subjects will not be identified by their names, but by a unique subject number. Documents not for submission to the Sponsor, i.e., the confidential subject identification code list, original consent forms and source records will be maintained by the investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the start of treatment of the first subject. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

11.2 Audit and Inspection

The investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and Sponsor's SOPs) will be prepared by the Sponsor after the completion of the study. The co-ordinating investigator will approve the final study report after review. The clinical study report will be available for the submission to the competent authorities in the 2nd quarter of 2021.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is envisaged by an investigator, the investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-centre studies only in their entirety and not as individual centre data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a subject in association with the IMP or the participation in the study, Octapharma AG will contract insurance in accordance with local regulations.

The investigator is responsible for dispensing the IMP according to this protocol, and for its secure storage and safe handling throughout the study.

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15 APPENDICES

None.