# STATISTICAL ANALYSIS PLAN
# 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 fib1·inogen deficiency**

**Development Phase** III

Version 4

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The following approved this document:

| Name, | |
|---|---|
| [redacted] | |

**REVISION HISTORY**

| Version# | Version Date | Author | Description of Modifications from PrevJous Version |
|---|---|---|---|
| Final (1.0) | 12 March, 2015 | [redacted] | First issue |
| 2.0 | 15-Sept-2015 | | Change PK lime point Day 4 (96 hr) to Day 3 (72 hr)<br>Include FORMA 01 final mean IVR into dose calculation |

| | | | |
|---|---|---|---|
| 3.0 | 12-July-2016 | [redacted] | Change 90% to "two-sided 95%" confidence intervals<br>Change 6 to 12 patients undergoing PK |
| 4.0 | 2-June-2017 | | Interim analysis after at least 12 patients with PK data added |

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# 1 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ADR | Adverse drug reaction |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area under the concentration-time curve |
| AUMC | Area under the moment curve |
| BE | Bleeding Episode |
| BLEED | Analysis population of all treated bleeding episodes |
| b.w. | Body weight |
| CI | Confidence interval |
| Cl | Clearance |
| $C_{max}$ | Maximum concentration |
| CRF | Case report form |
| CSR | Clinical Study Report |
| EMA | European Medicines Agency |
| EU | European Union |
| FAS | Full analysis set |
| BLEED | Analysis population: includes all bleeding episodes |
| IDMEAC | Independent Data Monitoring & Endpoint Adjudication Committee |
| IMP | Investigational medicinal product |
| ITT | Intention-to-treat |
| IU | International Unit |
| IVR | In vivo recovery |
| MCF | Maximum clot firmness (‘clot strength’) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRT | Mean residence time |
| PDCO | Paediatric Committee of the EMA |
| PK | Pharmacokinetic(s) |
| PP | Per protocol |
| SAE | Serious adverse events |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| SOC | System organ class |
| SURG | Analysis population of all surgeries with IMP prophylaxis/treatment |
| $t_{1/2}$ | Half-life |
| TEM | Thromboelastometry |
| $T_{max}$ | Time of maximum concentration |
| US | United States |
| $V_{ss}$ | Volume of distribution at steady state |

# 2 PURPOSE

This Statistical Analysis Plan describes all statistical analyses to be performed on data collected in study FORMA-04 in full detail, and the resulting output that will be compiled for the integrated clinical study report.

No inferential statistics but only explorative and descriptive statistics are planned for this uncontrolled trial.

# 3 INTRODUCTION

*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.

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 deficiency.

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 and discussions with the Paul Ehrlich Institute and the Paediatric Committee (PDCO) of the EMA.

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 adult patients (FORMA-02), the main difference being the additional examination of PK properties in paediatric patients in FORMA-04.

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-01which was calculated using the Per protocol full analysis stet of data as 1.77 (mg/dL / mg/kg).

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

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

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. This is because the study will end once the 6th enrolled 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.

# 4 STUDY OBJECTIVES

## 4.1 Primary Objective

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

## 4.2 Secondary Objectives

Secondary objectives of this trial 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]) 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

## 4.3 Assessment of Study Objectives

### *4.3.1 Overall efficacy of Octafibrin for on-demand treatment of acute bleeding episodes (spontaneous or after trauma)*

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

Each subject will receive at least 1 infusion of *Octafibrin* for the treatment of acute bleeding 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.

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.

The individual subject observation and follow-up period for the first bleeding episode starts with the first dose of *Octafibrin* administered (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* for the first bleeding 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 for the first bleeding will be determined by the investigator based on his/her judgement of the subject's condition.

The investigator's overall clinical assessment of haemostatic efficacy for bleeding will be based on a 4-point haemostatic efficacy scale as described below:

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. |

The final efficacy assessment of each patient will be adjudicated by the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC).

### *4.3.2 Single-dose pharmacokinetics of* Octafibrin

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.

PK assessment will be done before single infusion of *Octafibrin,* at 1 and 3 hours post infusion, and on days 2, 4, 7, 10, and 14.

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)

#### *4.3.3 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])*

MCF will be assessed before first infusion and 1 hour after end of first infusion of each documented bleeding episode.

MCF (measured in mm) 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.

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.

#### *4.3.4 Peak target plasma fibrinogen level of 100 mg/dL in minor bleeds and 150 mg/dL for major bleeds 1 hour post-infusion*

Fibrinogen plasma level will be assessed 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).

#### *4.3.5 Response to Octafibrin based on incremental in vivo recovery (IVR)*

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 [[2] ].

Response is assessed by incremental IVR determined for each treated bleeding episode.

### *4.3.6 Efficacy of Octafibrin in preventing bleeding during and after surgery*

Efficacy of *Octafibrin* in preventing bleeding during and after surgery will be assessed at the end of surgery by the surgeon and post-operatively by the haematologist using two 4-point haemostatic efficacy scales.

An overall efficacy assessment taking both the intra- and post-operative assessment into account will be adjudicated by the IDMEAC.

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.

*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.

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.

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 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.

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

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.

The number of subjects per outcome category will be assessed and will include at least 2 surgeries.

The efficacy of *Octafibrin* in surgical prophylaxis will be assessed at the end of surgery by the surgeon using a 4-point intra-operative efficacy scale as defined below

4-point intra-operative efficacy scale

| 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)

Post-operatively an efficacy assessment will be made by the haematologist using a 4-point post-operative efficacy scale as defined below.

4-point post-operative efficacy scale

| 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 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.

The primary endpoint ('success' or 'failure') will be derived from the adjudicated intra- and post-operative assessments according to the agreed algorithm presented the table below:

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 indicated 'Primary adjudication' will be assigned following adjudication by the IDMEAC ('primary adjudication').

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 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').

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.

### *4.3.7 Clinical Safety*

Clinical safety and tolerability will be assessed by monitoring of vital signs, adverse events and laboratory parameters including inhibitors against FIX and Anti-FIX antibodies:

The following safety parameters will be calculated as secondary endpoints:

- Vital signs.
- Physical examination.
- 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

### Assessment of adverse events (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.

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.

The investigator responsible will grade

- the severity of all AEs or ADRs (mild, moderate, or severe)
  - 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.
- the causality of all AEs or ADRs (probable, possible, unlikely, not related, unclassified)
  - 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.

- o 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.
- o not related (unrelated): events for which sufficient information exists to conclude that the aetiology is unrelated to the IMP.
- o unclassified: reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

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.

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

- the outcome of all reported AEs
  - o recovered, resolved.
  - o recovering, resolving.
  - o not recovered, not resolved.
  - o recovered, resolved with sequelae.
  - o fatal.
  - o unknown.

  The responsible investigator will follow-up each AE until it is resolved or until the medical condition of the subject is stable.
- the action taken by the investigator
  - o in general:
    - none.
    - medication (other than IMP) or other (e.g., physical) therapy started.
    - test performed.
    - other (to be specified)
  - o regarding the IMP:
    - none.
    - product withdrawn.
    - dose reduced.
    - dose increased.
- the seriousness of all AEs or ADRs (non-serious or serious)

  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:
  - o 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.

The Sponsor is responsible to assess the expectedness of each ADR.

- 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.

# 5 STUDY DESIGN

## 5.1 Overall Design and Control Methods

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 here is currently ongoing in adult 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 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-01which was calculated using the Per protocol full analysis stet of data as 1.77 (mg/dL / mg/kg).

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 9.1). This is because the study will end once the 6th enrolled 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 9.4).

## 5.2 General Design and Plan

At least 12 male or female paediatric subjects with congenital fibrinogen deficiency will be enrolled into the study and undergo PK assessment; this will have duration of 14 days, after which a patient can be treated for a bleeding episode or planned surgical procedure when they occur. 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 observation period for each documented on-demand treatment of an acute bleeding episode starts with the first dose of *Octafibrin* administered for this episode and will be followed up to at least 30 days. The treatment observation period is depending on the demand for *Octafibrin* treatment after the first day of treatment. The demand will be determined by daily assessment of target and actual fibrinogen plasma level and will last at least 3 days for minor and at least 7 days for major bleedings.

The observation period for each documented elective surgery starts with the first dose of *Octafibrin* administered for this surgery and will be followed up until the last day treatment with *Octafibrin* was administered for this surgery. The surgical observation period will last at least 3 post-operative days for minor and at least 7 post-operative days for major surgeries or until the last post-operative infusion of *Octafibrin*, whichever comes last.

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. When the study is closed, all subjects having received any IMP will be asked to return for a Study Completion Visit.

## 5.3 Sample Size

The number of subjects is limited by the very small number of patients with this indication. 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.

## 5.4 Study Assessments

For assessments directly related to the evaluation of the primary and secondary endpoints please refer to section 10 and section 11.

The following parameters will be assessed to allow a meaningful characterisation of the study population and to collect background information required for medical evaluation of study events:

- Subject demographics and baseline characteristics: ethnicity, date of birth, gender, height, weight, date of diagnosis of fibrinogen deficiency, underlying gene defect, family history of fibrinogen deficiency and inhibitors against FIX, anti-FIX antibodies.
- Medical History including other congenital or acquired bleeding disorders
- Previous treatment with FIX concentrates
- Concomitant Medication will be recorded throughout the trial
- Physical examinations will be performed at screening and at the study completion visit.

# 6 STUDY POPULATIONS

## 6.1 Subject Disposition

For the analysis of this study, the following populations will be considered:

Safety Set: All subjects who received at least one infusion of *Octafibrin*. The analysis of safety will be based on this population.

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

Pharmacokinetic analysis set (PK): All patients of the FAS who started the PK assessment and have at least one valid post-baseline fibrinogen activity level.

Pharmacokinetik per protocol analysis set (PK-PP): All patients of the PK analysis set 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 dysfibrino-genaemia
- 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

First bleeding analysis set (firstBLEED): subjects of the FAS who have at least one episode of acute bleeding treated with *Octafibrin*.

First bleeding per protocol analysis set (BLEED-PP): All patients from the FirstBLEED analysis set 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

Bleeding analysis set (BLEED): all documented bleeding episodes treated with *Octafibrin* in subjects of the FAS.

Bleeding per protocol analysis set (BLEED-PP): all documented bleeding episodes with no major protocol deviations, i.e. fulfilling the following conditions:

- Fully documented haemostatic efficacy data available for the bleeding
- ≥90% of the planned total dose of the IMP was given for the bleeding
- ≥80% of the calculated dose (if no dose was calculated, 0% will be assumed) of the IMP was given over all further infusions of the bleeding according to the treatment schedule
- The patient with the respective bleeding 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.
- The patient with the respective bleeding 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

Surgery analysis set (SURG): all documented surgical interventions with a need for at least one infusion of the IMP during the time period from the day of surgery until day of overall clinical assessment of post-operative efficacy in subjects of the FAS.

Surgery per protocol analysis set (SURG-PP): all surgeries of the SURG analysis set, where the patients underwent the surgery fulfil the following conditions:

- Provide valid, i.e., non-missing, intra- and post-operative efficacy data for the surgery
- Received ≥90% of the planned total dose of the IMP in the first infusion prior to the surgery
- Received ≥80% of the calculated dose (if no dose was calculated, 0% will be assumed) of the IMP over all further infusions of the surgery 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

Subpopulations

Subpopulations based on the following categories will be examined:

- Severity of bleeding: minor versus major (subpopulations of the BLEED analysis set)
- Age 0 to <6 years versus 6 to <12 years (subpopulations of the BLEED-PP and the SURG-PP analysis set)

## 6.2 Major Protocol Deviations

Major protocol deviations will be assessed and listed as part of the database lock procedures prior to data analysis, and will include:

- Violation of inclusion or exclusion criteria
- Concomitant medication that may confound study results (see section "4.4.2 Forbidden Concomitant Therapy" of the protocol)
- Non-compliance issues raised by the investigator or sponsor
- Dosing errors (less than 80% or more than 120% of the planned dose of *Octafibrin*
- Treatment errors (fibrinogen treatment with therapies other than *Octafibrin* used for bleeding events or surgeries other than for emergency reasons)

The specific exclusion criteria for the study populations described in section 5.1 will be assessed together with the major protocol deviations prior to data analysis.

A list of major protocol deviations and the reasons for exclusion of patients from a study population will also be included in the CSR.

# 7 STATISTICAL ANALYSIS

The statistical analysis of the primary, secondary and safety endpoints is to be understood in the exploratory sense. No confirmatory hypothesis testing is planned.

The described analyses will be done if the number of patients is appropriate. Especially for the combination of age group and the subpopulations described in section 5.1 a frequency analysis may be replaced by a listing of the relevant data.

The efficacy analysis for the primary endpoint will be performed with the data from the first bleeding event of each patient using the FirstBLEED analysis set (ITT analysis) as the primary population and using the FirstBLEED-PP analysis set (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.

Please refer to section 13 for an overview of tables (marked "T"), listings ("L") and figures ("F").

## 7.1 Summary Tables

All collected efficacy and safety assessments will be presented by means of descriptive statistics. If not detailed otherwise, the parameters listed below will be tabulated according to the different types of data. The number of subjects in the analysis population (N) and the number of subjects contributing to each particular summary (n) will be included in every presentation.

- Binary data (whether or not an event has occurred): counts and proportions
- Count data (the frequency of an event in a set time period): rate (count per unit time)
- Continuous data (measurements on a continuous scale, including quasi-continuous variables): arithmetic mean, standard deviation, median, minimum, maximum
- Scales data (Ordinal and Non-ordinal): absolute and relative frequencies

Additional descriptive and exploratory statistics, such as confidence intervals, are included as appropriate. If not mentioned otherwise, confidence intervals are to be understood as two-sided, 95% confidence intervals.

## 7.2 Figures

Figures will always reference the number of subjects contained in the analysis population and the number of observations represented in the graphic. Various types of graphs, including bar charts, scatter plots, line plots, and plots showing means and standard deviations will be used to illustrate the statistical outcome.

## 7.3 Listings

Listings for the display of individual data summarized in tables and figures will be provided.

## 7.4 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 (Chapter 14: Tables 14.2.24-14.31, selected tables of 14.1, and related listings and graphs). The results of the interim analysis will have no impact on the further conduct of the study. There will be no additional SAP for the interim analysis.

## 7.5 Methods for Handling Missing Data

In general missing data values will not be replaced, except for the following:

- Body weight: In case of missing weight, the last available weight measurement will be used for calculation of the pharmacokinetic parameters in the PK phase of the study and recovery investigations (last observation carried forward).
- For the handling of missing FIX levels with regard to the PK analysis see Chapters 6.1 (PK-PP) and 6.2 (Major Protocol Deviations).

## 7.6 Dropouts

A complete list of dropouts will be presented, including the reason for dropout, the phase of the study (PK or non-PK phase) in which the patient dropped out and the duration of participation in the trial in terms of total days as well as exposure days to *Octafibrin*.

## 7.7 Statistical Analytical Issues

The statistical analysis of the primary, secondary and safety endpoints is to be understood in the exploratory sense. Therefore no confirmative statistical analysis is planned.

Subgroup analyses are planned for the two age strata (age groups < 6 years and ≥6 - 12 years) regarding PK results, in treatment of BEs and in surgical procedures as well as regarding adverse events.

# 8 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The following demographic data will be collected:

- Birth date (Age), Gender, Ethnic origin
  Age will be calculated from the date of birth and the start of the first PK administration

Further baseline characteristics are:

- Height, Weight
- Blood type
- Age when diagnosed with fibrinogen defiency
- Factor IX concentrate used prior to enrolment and respective total exposure days with any FIX concentrate
- FIX activity (%) at screening
- Pre-medication with FIX and concomitant medications
- Medical History and physical examination
- Family history of fibrinogen deficiency and inhibitors against FIX

All these demographic data and baseline characteristics will be presented in summary and/or frequency tables according to section 6.1 and as listed in section 13.

# 9 EVALUATION OF TREATMENT COMPLIANCE AND EXPOSURE

Pharmacokinetic assessments including Recovery:

- Schedule of PK assessments and deviations will be listed.
- Total dose and dose per kg body weight administered for PK assessments will be summarized.

Treatment of BEs and treatment during bleedings and surgeries: The following will be tabulated and/or summarized:

- Number of Injections
- Number of Exposure Days
- Total Dose, dose per indication (bleeding event, surgery)
- Doses (IU FIX/kg BW) per indication (bleeding event, surgery)

Furthermore the *Octafibrin* batches used will be listed.

# 10 EVALUATION OF TREATMENT EFFICACY

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 efficacy will be evaluated by descriptive statistics and all results will be presented stratified by the age groups (2-<6 years, 6-12 years), if appropriate, and in total. The stratification will be done according to the age of the patients at the screening assessment and patients will stay in the respective stratum for all analyses even when the age of the patient crosses the border of the first stratum.
Secondary endpoints are the clot strength after treatment of a bleeding episode with *Octafibrin,* the in-vivo recovery, the efficacy of *Octafibrin* in all bleeding episodes, and the surgical prophylaxis.

## 10.1 Treatment of first bleeding episode

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

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

The following will be presented following the manners of presentation described in section 7:

- Number of subjects with at least one bleeding episode
- Type of first bleeding episode (spontaneous, traumatic, post-operative, other)
- Site of first bleeding episode
- The duration of the first bleeding episode will be calculated.
  If the end time of a bleeding episode is missing it will be set to 23:59 of the same day, if the start time of a bleeding episode is missing it will be set to 0:00 of the same day.
- Severity of the first bleeding episodes (mild, moderate, severe)
- Efficacy assessment of the treatment made by the investigator (excellent, good, moderate, none) for the first bleeding episode.
  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 during or after the first bleeding episode
  - Subjects receiving cryoprecipitate or concentrates containing fibrinogen other than the IMP between first infusion and efficacy assessment for the first bleeding episode (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 after the first bleeding episode
- In addition to the four points scale the proportion of first bleeding episodes successfully treated with *Octafibrin* will be evaluated. "Successfully treated" are all "excellent" and "good" efficacy ratings of treated bleeding episodes. A two-sided 95% CI for the success rate in haemostatic efficacy ('excellent' or 'good') according to Clopper/Pearson will be computed.
- Treatment details: number of exposure days, number of injections, dosing incl. batch numbers., consumption of *Octafibrin* (IU/kg) for the first bleeding episode will be listed

- Any haemostatic co-medication will be listed.

## 10.2 Clot strength (MCF)

MCF and fibrinogen activity will be measured for each bleeding episode, once pre-infusion and once 1 hour after the first infusion. The analysis of MCF will be provided for the BLEED population.

The following will be presented following the manners of presentation described in section 7:

- Descriptive statistics of MCF and fibrinogen activity before and 1 hour after the end of the first infusion over all bleeding episodes, as well as changes between the two time points will be presented, together with 2-sided 95% CIs based on the paired t-test for the difference.
- If the number of bleedings is appropriate an analysis as described before will be provided separated by the 4-point haemostatic efficacy scale (excellent, good, moderate, none) and/or a dichotomised haemostatic efficacy scale (excellent/good, moderate/none). Otherwise listings with the patient data for MCF and fibrinogen activity will be given.
- If the number of bleedings is appropriate box plots will be provided separated by the 4-point haemostatic efficacy scale and/or the dichotomised haemostatic efficacy scale for MCF and fibrinogen activity.

## 10.3 In-vivo Recovery

IVR will be determined for the first infusion of each bleeding episode. The analysis population will be the BLEED population.

Incremental IVR (response) will be calculated as the increase in plasma fibrinogen (i.e., Clauss data) between the pre-infusion and the maximum of the 1-hour and 3-hour post-infusion measurement (expressed as absolute concentration in plasma [mg/dL]), divided by the exact dose of *Octafibrin* per body weight ([mg/kg]):

$$\text{Incremental IVR (response)} = IVR\left(\frac{\cancel{mg}\,\cancel{dl}}{\cancel{mg}\,\cancel{kg}}\right) = \frac{\Delta\, value\ \left(\frac{mg}{dL}\right)}{dose\ (mg)/body\ weight(kg)}$$

Classical IVR will be calculated as the increase in plasma fibrinogen (i.e., Clauss data) between the pre-infusion and the maximum of the 1-hour and 3-hour post-infusion measurement (expressed as absolute concentration in plasma [mg/mL]) multiplied with the plasma volume (mL, calculated according to the formula below), divided by the exact dose of *Octafibrin* (mg) (see also formula described by Nadler [2]):

Classical IVR (%) =100% x actual/expected increase =

100% x maximum increase in fibrinogen plasma level 1-hour and 3-hour post-infusion compared to pre-infusion [mg/dL] x plasma volume (dL)
divided by
exact dose of component in IMP administered [mg]:

$$classic\ \ IVR\ (\%) = \frac{100\ x\ \Delta\ value\ \left[\frac{mg}{dL}\right] \times plasma\ volume\ (dL)}{exact\ dose\ (mg)}$$

The formula for the calculation of the plasma volume is:

plasma volume (mL) = (1-hematocrit at pre-infusion (1)) x blood volume (mL)

with

blood volume (mL) = ((366.9 x (height in m)$^3$) + (32.19 x body weight in kg) + 640.1 for males and

blood volume (mL) = ((356.1 x height in m)$^3$) + (33.08 x body weight in kg) + 183.3 for females

If the number of bleedings is sufficient to be separated into minor and major bleedings descriptive statistics will be generated to show the distribution of IVRs separated by minor and major bleeding events.

Fibrinogen levels documented before, 1 hour and 3 hours after each infusion will be listed.

### 10.4 Efficacy of Octafibrin in all Bleeding Episodes

The same analyses as described for the first bleeding episode will be done for the total number of bleeding episodes.

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

The following will be presented following the manners of presentation described in section 7:

- Type of bleeding episodes (spontaneous, traumatic, post-operative, other)
- Site of bleeding episodes
- duration of bleeding episodes

  If the end time of a bleeding episode is missing it will be set to 23:59 of the same day, if the start time of a bleeding episode is missing it will be set to 0:00 of the same day.
- Severity of bleeding episodes (mild, moderate, severe)
- Efficacy assessment of the treatment of a bleeding episode made by the investigator (excellent, good, moderate, none)

  In the following situations 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: all bleeding episodes of that subject
  - 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]): the actual bleeding episode
  - Subjects with missing haemostatic efficacy assessment: the actual bleeding episode
- In addition to the four point scale the proportion of bleeding episodes successfully treated with *Octafibrin* will be evaluated. "Successfully treated" are all "excellent" and "good" efficacy ratings of treated bleeding episodes. A two-sided 95% CI for the success rate in haemostatic efficacy ('excellent' or 'good') according to Clopper/Pearson will be computed.
- The final efficacy assessment of each patient will be adjudicated by an Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC). The results of the adjudication will be shown together with the assessments of the investigator.

- Treatment details: number of exposure days, number of injections, dosing incl. batch numbers., consumption of *Octafibrin* (IU/kg per month, per year, per bleeding episode) will be listed
- Increase and decrease of doses of *Octafibrin* used to treat individual bleeding episodes will be listed.
- Any haemostatic co-medication will be listed.

## 10.5 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 (at the last post-operative day) by the haematologist using two 4-point efficacy scales.

The primary analysis regarding haemostatic efficacy will be done on the adjudicated assessments by the algorithm described above and by the IDMEAC.

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

- Number of subjects undergoing surgeries (minor, major, total)
- Number of surgeries, overall (minor, major, total)
- Surgery characteristics (type and site, pre-planned (yes/no), severity, expected and actual duration, expected and actual blood loss) will be listed.
- Details on treatment for surgical prophylaxis (number of exposure days and injections prior to surgery, dosing details, total amount of *Octafibrin)* will be listed.
- Pre-, intra-, and post-operative fibrinogen plasma levels, pre- and post-infusion will be listed.
- Efficacy evaluation by the surgeon at the end of the surgery and by the haematologist on the last post-operative day.
- Subjects who switch to another FIX product during a surgery will be considered treatment failures, i.e. the efficacy will be imputed to be “none” for each haemostatic efficacy assessment after the switch in the efficacy analyses for this surgery.
- Adjudicated overall efficacy assessment of the surgeries using the algorithm for the adjudicated intra- and post-operative assessments of haemostatic efficacy (as described in chapter 3.3.6 of this SAP). All assessments adjudicated by the IDMEAC will be listed together with the surgery details and the intra- and post-operative assessments of the surgeon and the haematologist.

# 11 EVALUATION OF PHARMACOKINETICS

The primary 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 study treatment (planned: single intravenous infusion of 70 mg/kg body weight of *Octafibrin)* and the potency of fibrinogen in the actually used batch.

The pharmacokinetic parameters will be determined from plasma fibrinogen levels taken before and at 1 hour and 3 hours after injection, as well as on days 2, 5, 7, 10 and 14.

For the additional recovery assessments blood samples for the calculation of the incremental recovery will be taken prior to the study drug injection, 1 hour and 3 hours post-infusion.

PK analysis on fibrinogen activity and antigen levels will be performed per patient with a non-compartmental model using standard PK software (Phoenix WinNonlin, Version 6.3 or higher [1]); 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 (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 ($V_{ss}$), and clearance (Cl)) will be summarized and presented as described for continuous variables in section 6.

Fibrinogen plasma levels below the limit of quantification will be set to 0 for PK calculations.

The following pharmacokinetic parameters will be estimated by non-compartmental analysis:

| | | |
|---|---|---|
| $C_{max}$ | Peak concentration observed | until the end of the 14 days PK period |
| $C_{max,norm}$ | Observed peak concentration normalised for the dose given | $C_{max,norm} = \frac{C_{max}}{D}$ where D is the dose in IU administered according to the actual potency of *Octafibrin* [a] |
| $T_{max}$ | Time when $C_{max}$ is observed | Timing starts at end of injection |
| $T_{1/2}$ | Elimination half-life | using linear regression on the terminal phase[b] of the logarithm of the concentration; $T_{1/2} = \frac{\ln(2)}{K}$ |

[a] The actual dose *D* based on the real potency of the batch of medication used will be calculated as D = $D_{nom}$ x Actual Potency/Labelled Potency where $D_{nom}$ stands for the nominal Dose according to the product label. For the determination of PK properties of *Octafibrin* this actual dose will be used.

[b] The non-compartmental approach does not presume that the plasma concentration follows a mono-exponential decay during the complete elimination phase ($t \geq T_{max}$). The appropriate time point when the terminal elimination phase starts will be determined automatically by the Software WinNonlin using the algorithm described in Appendix I: Determination of slope of elimination by non-compartmental PK analysis with WinNonlin® [1, Chapter 9, pages 218-219]. In addition visual examinations on the choice of the software will be performed on individual plots of the natural logarithm of the plasma levels *ln(C)* against time to determine whether linear regression yields a good approximation for *ln(C)* obtained at times $t \geq T_{max,}$ or whether it's more appropriate to assume a terminal elimination phase that starts later ($t \geq T_E$ , $T_E \geq T_{max}$).

| | | |
|---|---|---|
| | | (where *K,* the elimination rate constant, is determined as the slope of the regression line) |
| $AUC_{last}$ | Area under the curve from time point *t=0* [a] (i.e. the end of drug injection) to the last measured value | using the linear trapezoidal rule $$AUC_{last} = \sum \frac{(C_n + C_{n+1})}{2} \cdot \Delta t$$ |
| AUC | Area under the curve from baseline to infinity | $$AUC = \sum \frac{(C_n + C_{n+1})}{2} \cdot \Delta t + \frac{C_{last}}{K}$$ ($C_{last}$ is the last available measurement) |
| $AUC_{norm}$ | *AUC* normalised with respect to the dose administered | $$AUC_{norm} = \frac{AUC}{D}$$ where D is the dose in IU administered according to the actual potency of *Octafibrin* as described in [a]. |
| AUMC | Area under the moment curve (from baseline to infinity) | $$AUMC = \sum \frac{(t_n \cdot C_n + t_{n+1} C_{n+1})}{2} \cdot \Delta t + \frac{C_{last}}{K^2} + \frac{t_{last} \cdot C_{last}}{K}$$ |
| MRT | Mean residence time | $$MRT = \frac{AUMC}{AUC}$$ |
| CL | Clearance | $$CL = \frac{D}{AUC}$$ where *D* is the actual dose administered (see remark [a]) |
| Vss | Volume of distribution at steady state | $$V_{SS} = CL \cdot MRT$$ |

[a] For the extrapolation of the trapezoidal area under the concentration curve from time point *t=0* to the first measured fibrinogen value ($C_1$) the fibrinogen concentration at *t=0* ($C_0$) must be estimated. -To account for the presence of fibrinogen in the metabolism already during the infusion but before start of the clock used for the PK calculations (*t=0*), the PK software WinNonlin will automatically perform a log-linear regression of the first two data points to back-extrapolate $C_0$. However, in the instance that the regression yields a slope ≥ 0, then the first observed positive concentration (should in this study usually be $C_1$) will be used as an estimate for $C_0$ [1, Chapter 9, page 234].

# 12 EVALUATION OF SAFETY PARAMETERS

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 adverse events 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.

All adverse events for each subject will be listed in Appendix 16 of the CSR, featuring the following data:

- Subject identifier and characteristics (age, sex, weight)
- The adverse event (preferred term, reported term)
- Onset, date of resolution and duration of the adverse event
- Severity (mild, moderate, severe)
- Seriousness (serious/non-serious)
- Action taken - General (none, drug therapy, tests performed) and on study drug (dose not changed, product withdrawn, dose reduced, dose increased)
- Outcome (recovered, recovering, not recovered, recovered with sequelae, fatal, unknown)
- Causality assessment (probable, possible, unlikely, not related)
- Study treatment at time of event or most recent study treatment taken, including dose and batch number
- Previous exposure to fibrinogen treatment (exposure days and total amount used)

# 13 REFERENCES

[1] Phoenix™ WinNonlin® Copyright ©1998 - 2012, Certara L.P. WinNonlin Version 6.3 or higher.

[2] Nadler SB, Hidalgo JU, Bloch T: Prediction of blood volume in normal human adults. Surgery 1962; 51:224-232.

# 14 TABLES, FIGURES AND LISTINGS (SECTION 14 AND 16.2 OF THECSR)

The following tables, figures and lists will be generated.

All output will be headed with an appropriate heading specifying study ID and title.

All output will be dated and have page numbers in the form 'Page x of y'.

The order and numbering of the various parts of the Clinical Study Report may not necessarily follow the scheme used below.

All statistical output will identify the underlying analysis populations (see section 6), and indicate the number of subjects/ events in this population (N) and the number of subjects/events actually contributing to the particular output (n).

Due to the small number of patients some of the tables described below may be not generated in the final analysis and replaced by a listing comprising the same variables as in the respective table. If no patient is excluded from the PP population all tables, figures and listings will be done only for the ITT population.

| | | Analysis populations | |
|---|---|---|---|
| 14.1.1.1 | T | Subject Disposition and analysis populations<br>*Number of subjects enrolled, erroneously enrolled, treated, completed, withdrawn* | All |
| 14.1.1.2 | T | Bleeding episodes Analysis Populations | BLEED |
| 14.1.1.3 | T | Surgery Analysis Populations | SURG |
| 14.1.2 | L | Protocol Deviations<br>Listing of all major and minor protocol violations together with the reason of violation and exclusion from analysis populations | *SAF* |
| 14.1.3 | L | Compliance to Schedule of PK assessments<br>*PK assessments not performed according to the schedule* | ITT, PK-PP |

| | | Demographic Data | |
|---|---|---|---|
| 14.1.4 | T | Number of subjects per center, age-group and analysis population | SAF |
| 14.1.5 | T | Statistics on age, body height, body weight, body mass index, ethnicity and blood type | ITT, PP |
| 14.1.6 | T | Statistics on duration of treatment | ITT, PP |
| 14.1.7 | L | Underlying gene defects for FIX and family history of fibrinogen deficiency | ITT, PP |
| 14.1.8 | T | FIX activity (%) at screening | ITT, PP |
| 14.1.9 | T | Frequency of use of prior and concomitant medications by ATC class (without surgeries)<br>*(2 sub-tables: 1 for prior, 1 for concomitant)* | ITT, SAF |
| 14.1.10 | T | Use of Factor IX concentrates within ½ year before start of study treatment | ITT, SAF |

| | | Bleeding episodes | |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 14.2.1 | T | Subjects included in bleeding analysis (first, minor, major, total) and number of bleedings (minor, major, total) | ITT, PP |
| 14.2.2 | T | Number and frequency of bleeding episodes per subject | BLEED, BLEED-PP |
| 14.2.3 | T | Frequency of bleeding episodes per age group and in total | BLEED, BLEED-PP (age groups) |
| 14.2.4 | T | First bleeding episode per type of BE (spontaneous, traumatic, post-operative, other) | BLEED, BLEED-PP |
| 14.2.5 | T | Bleeding episodes per type of BE (spontaneous, traumatic, post-operative, other) | BLEED, BLEED-PP |
| 14.2.6 | T | Site of first bleeding episode | BLEED, BLEED-PP |
| 14.2.7 | T | Site of bleeding episodes | BLEED, BLEED-PP |
| 14.2.8 | T | Treatment duration of the first bleeding episode | BLEED, BLEED-PP |
| 14.2.9 | T | Treatment duration of bleeding episodes | BLEED, BLEED-PP |
| 14.2.10 | T | Severity of first bleeding episode (mild, moderate, severe) | BLEED, BLEED-PP |
| 14.2.11 | T | Severity of bleeding episodes (mild, moderate,severe) | BLEED, BLEED-PP |
| 14.2.12 | T | Efficacy assessment (final outcome) of treatment of first bleeding episode<br>a) Four point scale (14.2.11.1) (excellent, good, moderate, none)<br>b) Two point scale (successfully treated (excellent or good), not successfully treated (moderate or none) (14.2.11.2) | BLEED, BLEED-PP (age groups) |
| 14.2.13 | T | Statistics on successfully treated first bleeding episodes (two-sided 95% Clopper-Pearson confidence interval) | BLEED, BLEED-PP |
| 14.2.14 | T | Efficacy assessment (final outcome) of treatment of bleeding episodes<br>a) Four point scale (14.2.13.1) (excellent, good, moderate, none)<br>b) Two point scale (successfully treated (excellent or good), not successfully treated (moderate or none) (14.2.13.2) | BLEED, BLEED-PP (age groups) |
| 14.2.15 | L | Treatment details for each bleeding episode per patient (incl. exposure days, number of injections, dosing inc. batch numbers, consumption of Octafibrin, haemostatic co-medication) | BLEED, BLEED-PP |
| 14.2.16 | T | Statistics on successfully treated bleeding episodes (two-sided 95% Clopper-Pearson confidence interval) | BLEED, BLEED-PP |
| 14.2.17 | T | Statistics on MCF and fibrinogen activity for samples taken before and 1 hour after the end of the first infusion (including confidence interval for the difference) | BLEED, BLEED-PP |
| 14.2.18 | T | Statistics on MCF and fibrinogen activity for samples taken before and 1 hour after the end of the first infusion separated by four/two point efficacy scale | BLEED, BLEED-PP |
| 14.2.19 | F | Boxplot MCF and fibrinogen activity for samples taken before and 1 hour after the end of the first infusion separated by four/two point efficacy scale | BLEED, BLEED-PP |
| 14.2.20 | T | Statistics on final efficacy assessment of the IDMEAC and the efficacy assessment of the investigator | BLEED, BLEED-PP |

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| | | Surgeries | |
| 14.2.21 | T | Subjects included in surgery analysis (minor, major, total) and number of surgical procedures (minor, major, total) | ITT, PP |
| 14.2.22 | L | Surgery Characteristics (type and site, pre-planned, severity, expected and actual duration, expected and actual blood loss, age group) | Surg, Surg-PP |
| 14.2.23 | L | Fibrinogen levels pre-, intra- and post-operative, as well as pre- and post-infusion for each injection will be listed | Surg, Surg-PP |

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| 14.2.23 | L | Efficacy Evaluation of the Use of *Octafibrin* in Surgical Procedures<br>*a) at end of surgery (by the surgeon)*<br>*b) post-operatively (by the haematologist)*<br>*c) overall (by the IDMEAC)*<br>*using the four point scale (excellen, good, moderate, none) as described in chapter 3.3.6 of the SAP* | Surg, Surg-PP |

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| | | Pharmacokinetics | |
| 14.2.24 | T | Doses administered for PK and recovery assessments – PK-PP population<br>summary statistics for total dose and dose per kg b.w. for PK assessments<br>(inc. nominal dose and actual dose calculated from potency of the batch) | PK, PK-PP |
| 14.2.25 | F | Mean (+/- SD) fibrinogen levels (IU/mL) – PK-PP for each of the PK assessments<br>Summarized Plot of PK profiles mean (+/- SD) plots) | PK, PK-PP |
| 14.2.26 | T | Statistics on FIX concentrations (%), nominal time points - by age group and combined | PK, PK-PP<br>(age groups) |
| 14.2.27 | T | Statistics on $AUC_{last}$, AUC, $AUC_{norm}$, and AUMC of FIX, calculations based on actual time points<br>- by age group and combined | PK, PK-PP<br>(age groups) |
| 14.2.28 | T | Statistics on $C_{max}$, $C_{max,norm}$ and recovery of FIX (%) after injection of Octafibrin based on the actual potency, per performed recovery - by age group and combined | PK, PK-PP<br>(age groups) |
| 14.2.29 | T | Statistics on $T_{max}$ (h) after injection of Octafibrin per performed recovery - by age group and combined | PP, PK-PP<br>(age groups) |
| 14.2.30 | T | Statistics on $T_{1/2}$ and MRT after injection of Octafibrin based on the actual potency, - by age group and combined | PK, PK-PP<br>(age groups) |
| 14.2.31 | T | Statistics on CL and Vss after injection of Octafibrin based on the actual potency, - by age group and combined | PK, PK-PP<br>(age groups) |

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| | | Safety | |
| 14.3.1 | T | Extent of exposure SAF<br>*number of infusions, total dose (IU and IU/kg b.w.) per reason for administration and in total* | SAF |
| 14.3.2 | T | Summary of Adverse Events *number of subjects with any AE, SAE, Severe AE or possibly or probably related AE, AEs that begin within 24 hours of end of infusion* | SAF |
| 14.3.3 | T | Number of subjects with treatment-emergent adverse events by system organ class and preferred term – SAF | SAF |
| 14.3.4 | T | Number of subjects with treatment-emergent possibly/probably related to study drug by system organ class and preferred term – SAF | SAF |
| 14.3.5 | T | Number of subjects with treatment-emergent adverse events temporally related (within 24 hours after end of infusion) to study drug by system organ class and preferred term - SAF | SAF |
| 14.3.6 | T | Number of subjects with treatment-emergent adverse events by severity by system organ class and preferred term – SAF | SAF |

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| 14.3.7 | T | Summary of adverse events by age group (2-<6 years, 6 -<12 years) - SAF | SAF |
| 14.3.8 | L | Listing of treatment-emergent serious adverse events | SAF |
| 14.3.9 | L | Listing of deaths | SAF |
| 14.3.10 | L | Listing of adverse events leading to discontinuation of study medication or death | SAF |
| 14.3.11 | T | Statistics on laboratory values for each time point relative to bleeding and surgery events<br>(2 sub-tables: Hematology, Clinical chemistry) | SAF |
| 14.3.12 | L | Abnormal laboratory value listing<br>(2 sub-listings: Hematology, Clinical chemistry) | SAF |
| | T | Statistics on vital signs for each time point relative to bleeding and surgery events | SAF |
| 14.3.13 | L | Abnormal vital signs listing | SAF |
| 14.3.14 | L | Abnormal physical examination findings | SAF |

*Listings will generally be sorted by age group and subject number*

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| 16.2 | | *Subject Data Listings (section 16.2 of the CSR)* | |
| 16.2.1.1 | L | Prematurely discontinued subjects (inc. time in study and number of EDs) | All (enrolled subjects) |
| 16.2.1.2 | L | Study Completion – All enrolled subjects | All |
| 16.2.2 | L | Protocol violations and data issues *flagged by "minor" and "major"* | All |
| 16.2.3 | L | Disposition of subjects with respect to analysis populations | All screened subjects |
| 16.2.4.1 | L | Subject demographics – All enrolled subjects | All enrolled subjects |
| 16.2.4.2 | L | Medical history | All |
| 16.2.4.3.1 | L | Prior and concomitant medication | All |
| 16.2.4.3.2 | L | Co-medication used in the treatment of bleeding episodes | BLEED, BLEED-PP |
| 16.2.4.3.3 | L | Concomitant medication during surgery | Surg, Surg-PP |
| 16.2.5.1 | L | *Octafibrin* doses during study including reason for treatment | All |
| 16.2.5.2 | L | Deviations from the planned schedule of PK assessments | All |
| 16.2.5.3 | L | FIX concentrations (IU/mL) per assay during PK profile and recovery determination | All |
| 16.2.5.4 | L | PK parameters Octafibrin | All |
| 16.2.5.5 | L | Dose of Octafibrin for surgical reasons | Surg, Surg-PP |
| 16.2.5.6 | L | Pre-, intra-, and post-operative FIX plasma levels | Surg, Surg-PP |
| 16.2.6.1 | L | Bleeding episodes during study incl. efficacy assessment of treatment | BLEED, BLEED-PP |
| 16.2.6.2 | L | Bleeding episodes, doses and changes in dose per infusion for each bleeding episode during study | BLEED, BLEED-PP |
| 16.2.6.3.1 | L | Surgeries: Description and outcome of surgical procedures | Surg, Surg-PP |
| 16.2.6.3.2 | L | Surgeries: Description and assignment to SURG/SURG-PP populations including reasons for exclusion | Surg, Surg-PP |
| 16.2.6.3.3 | L | Surgeries: Blood loss (planned and actual), duration of surgery (planned and actual) | Surg, Surg-PP |
| 16.2.7.1 | L | Treatment emergent adverse Events (inc. indicator for phase of study: PK, surgery, bleeding) | All |

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| 16.2.7.2 | L | Possibly/probably related adverse events | All |
| 16.2.7.3 | L | Non-treatment emergent adverse events | All |
| 16.2.8.1 | L | Laboratory assessments (Haematology, Clinical chemistry)<br>*(2 sub-listings: hematology, clinical chemistry)* | All |
| 16.2.8.2 | L | FIX, inhibitor and FIX antibodies determinations at baseline and during study | All |
| 16.2.8.3 | L | Vital signs | SAF |
| 16.2.8.4.1 | L | Physical examination | All |
| 16.2.8.4.2 | L | Abnormal findings of physical examination | SAF |
| 16.2.9 | L | Additional comments provided in the CRF | All |
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| | | *Detailed PK analysis* | |
| 16.2.10 | F, PK | Graphs and WinNonlin outputs for individiual PK Analysis | |

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| 16.4 | | Individual Subject Data Listings (section 16.4 of the CSR) |
| | | *Note:* SAS datasets including individual subject data will be prepared. Datasets will be available on request, e.g. for an electronic submission according to CDISC /SDTM. Therefore no listings will be prepared for Section 16.4. |

## Appendix I: Determination of slope of elimination curve by non-compartmental PK analysis with WinNonlin®

The following is taken from the WinNonlin user's guide [1, Chapter 9, pages 218, 219], where K is the rate constant, associated with the terminal elimination phase and the slope of the terminal elimination phase on log scale = - K:

The user may specify the data points to be included in the calculation of K or choose that K not be estimated. If neither of these options is selected, WinNonlin determines the data points to be included, as follows. During the analysis, WinNonlin repeats regressions using the last three points with non-zero concentrations, then the last four, last five, etc. Points prior to $C_{max}$ or prior to the end of infusion are not used unless the user specifically requests that time range. Points with a value of zero for the dependent variable are excluded. For each regression, an adjusted $R^2$ is computed:

$$Adjusted R^2 = 1 - \frac{(1 - R^2) \cdot (n - 1)}{n - 2}$$

Where n is the number of data points in the regression and $R^2$ is the square of the correlation coefficient.

The regression with the largest adjusted $R^2$ is selected to estimate K with these caveats:

- If the adjusted $R^2$ does not improve, but is within 0.0001 of the largest adjusted $R^2$ value, the regression with the larger number of points is used.
- K must be positive, and calculated from at least three data points.