STATISTICAL ANALYSIS PLAN

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

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AUTHORIZATION DOCUMENT

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REVISION HISTORY

Version #	Version Date	Author	Description of Modifications from Previous Version
1.0	13-Jan-2015	[redacted]	First issue
1.1	09-April-2015		Reference to IDMEAC charter regarding statistical algorithm Clarification of pediatric subgroup Inclusion of analysis by race
2.0	11-July-2016		Changes to statistical analysis

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
CSR	Clinical Study Report
EU	European Union
EMA	European Medicines Agency
FAS	Full Analysis Set
IVR	In Vivo Recovery
IDMEAC	Independent Data Monitoring & Endpoint Adjudication Committee
IMP	Investigational Medicinal Product
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
MCF	Maximum Clot Firmness
PP	Per Protocol
PDCO	Paul Ehrlich Institute and the Pediatric Committee
PK	Pharmacokinetic
SOC	System Organ Class
SAP	Statistical Analysis Plan
SD	Standard Deviation
SAE	Serious Adverse Event
TEG	Thromboelastography
TLG's	Tables Listings Graphs
US	United States

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a comprehensive and detailed description of statistical methods to be used to analyze the data for protocol FORMA-02, Version 6.0, 31-Oct-2014, as amended on 08-July-2016 (Version 7.0).

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol FORMA-02. In addition, this SAP will describe any clarifications or modifications to the endpoints and statistical methods in the protocol. The planned analyses identified in this SAP will supersede the statistical sections in protocol and will be included in regulatory submissions and/or future manuscripts. In addition, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Additional exploratory analyses may be added as addendums to this SAP after the signoff. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.

2 DESCRIPTION OF THE PROTOCOL

2.1 Protocol Number and Version

FORMA-02, Version 7.0

2.2 Protocol Title

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

2.3 Protocol Date

The date of protocol Version 7.0 is 08-July-2016.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is:

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

3.1.2 Secondary Objectives

- To show 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 Thromboelastography (TEG) in the pivotal Pharmacokinetic (PK) study FORMA-01. Therefore, MCF as surrogate efficacy parameter will be determined before first infusion and 1 hour after the end of first and last infusion.
- To achieve 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.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is:

- The primary endpoint is the overall clinical assessment of 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 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.

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.

3.2.2 Secondary Endpoints

The secondary efficacy endpoints are:

- MCF assessment before first infusion and 1 hour after end of first and last 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 of each documented bleeding episode).
- Response as indicated by incremental IVR, calculated as the maximum increase in plasma fibrinogen (Clauss data) between pre-infusion and 1 and 3 hours post-infusion.
- 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.
*All 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	
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 ofprocedure.
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. 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 based on an agreed algorithm as indicated in the IDMEAC charter .

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.

The safety endpoints are:

- Vital signs.
- Physical examination.
- Check of Wells criteria for deep venous thrombosis (DVT) and PE (pulmonary embolism).
- Routine clinical laboratory assessment, including coagulation parameters.
- Adverse events (AEs), including thromboembolic complications and early signs of allergic or hypersensitivity reactions.
- Immunogenicity testing at Day 14 and Day 30 after the administration of Octafibrinfor bleeding.

4 STUDY METHODS

4.1 Study Design

This is a multinational, multi-centre, prospective, open-label, uncontrolled, Phase III study to assess the efficacy and safety of Octafibrin for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in subjects with congenital fibrinogen deficiency

A minimum of 24 subjects will be enrolled in the study to assess on-demand treatment of at least one bleeding episode. This will include at least 4 subjects aged between 12 and 18 years (only 18 and above in Russia). This will also include an assessment of at least 4 surgical procedures, 2 of which should be performed in subjects aged between 12 and 18 years (only 18 and above in Russia). The study will be conducted in approximately 15 centres worldwide.

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 24th patient has at least one documented bleeding episode. The study will be considered completed when a minimum of 24 subjects have at least one documented bleeding episode. The study as a whole should be completed within 5 years.

4.2 Study Rationale

It is estimated that there are 500 to 1000 subjects with congenital fibrinogen deficiency in the European Union (EU). Historically, the principal source for the treatment of congenital fibrinogen deficiency has been cryoprecipitate. 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.

The introduction of Octafibrin will present an additional and safe option, providing more choices of supply for the benefit of the medical community and subjects 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 and safety of Octafibrin for on-demand treatment of acute bleeding in 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” (CHMP/BPWP/144552/2009) and discussions with the Paul Ehrlich Institute and the Paediatric Committee (PDCO) of the EMA.

4.3 Study Duration

4.3.1 Planned Duration for an Individual Subject

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 for up to 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 epi-sodes or planned surgeries that can be managed under the protocol. Patients may remain in the study until the 24th patient has at least one documented bleeding episode.

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 3.2.1). All bleeding episodes documented in the study will be assessed as a secondary endpoint (see Section 3.2.2).

Patients who were screened for the study but do not present with a bleeding episode or planned surgery during the study observation period will be considered 'no treatment' patients.

The individual observation period by subject starts with the first dose of Octafibrin administered for on-demand treatment of an acute bleeding episode or prior to elective surgery (Day 1). Subjects enrolled will be treated for any bleeding episodes or planned surgeries during the study observation period. They may remain in the study until the 24th subject has at least one documented bleeding episode.

4.3.2 Planned Duration for the Study as a Whole

The study will be considered completed when a minimum of 24 subjects have at least one documented bleeding episode. The study as a whole should be completed within 5 years.

The estimated start of the study (enrolment of first subject) is in the 4th quarter of 2014, and the estimated end of the study (last visit of last subject) is in the 4th quarter of 2019.

4.4 Study Population

4.4.1 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 the safety population.

4.4.2 Full Analysis Set (FAS)

The full analysis set defined according to the intention-to-treat (ITT) principle will include subjects who fulfill 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).
- Presented with an episode of acute bleeding (third inclusion criterion).
- And/or plan to undergo a surgical procedure with a need for at least one infusion of the IMP (third inclusion criterion).

4.4.3 The Per Protocol (PP) Population

The per-protocol (PP) population will include all subjects of the full analysis set who fulfill all of the following conditions:

- Provide valid, i.e., non-missing haemostatic efficacy data.
- Provide a 1-hour post-infusion MCF value.
- Received ≥90% of the planned total dose of the IMP in the first infusion.
- Received ≥80% of the calculated dose (no dose was calculated, 0% will be assumed) of the IMP over all further infusions 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 or surgery.
- 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 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.
- Surgical procedure with a need for at least one infusion of the IMP with an overall clinical assessment of haemostatic efficacy.

Any protocol deviations other than those with respect to the above conditions for the PP population must be agreed upon in writing by the Sponsor and the study statistician, and in any case, before database closure.

The efficacy analysis will be performed for bleeding events using the full analysis set (ITT analysis) and for the PP population (PP analysis). An additional analysis will also be performed for the surgical population.

4.4.4 Surgical Prophylaxis Population

The full analysis set defined according to the intention-to-treat (ITT) principle will include subjects who fulfill 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).
- Presented with an episode of acute bleeding (third inclusion criterion).
- And plan to undergo a surgical procedure with a need for at least one infusion of the IMP (third inclusion criterion).

4.4.5 Subpopulations

Subpopulations based on the following categories will be examined:

- Severity of bleeding: minor versus major.
- Age: Paediatric (≤18 years) versus adult (18–64) versus elderly patients (≥65), if appropriate.
- Sex.

4.5 Flow Chart of Assessments

4.5.1 Flow Chart of Assessments for On-Demand Treatment of Acute Bleeding

	Screening	Observations performed for each bleeding episode												Study Completion Visit
		Day 1			All study days after Day 1 (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	Day 14 (± 2 days)	Day 30 (± 1 week)	
		Pre-infusion	Post-infusion		Daily	Pre-infusion [a]	1 h post-infusion [a] (± 15 min)	Pre-infusion	Post-infusion					
			1 h (± 15 min)	3 h (± 15 min)					1 h (± 15 min)	3 h (± 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	x			
Wells criteria for DVT and PE		x	x	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]**	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]**	x **[d]**			
MCF **[d]**		x **[b]**	x						x					
Thrombogenicity **[d]**		x	x	x			x		x	x	x			
Immunogenicity **[d]**		x										x	x	
Safety lab (haematology and clinical chemistry) **[c]**		x	x	x	x **[i]**		x		x	x	x			
Retention plasma samples **[e]**		x **[b]**	x	x	x	x	x	x	x	x	x	x	x	
Retention serum samples **[e]**		x												x
Urine or blood pregnancy test		x												
Infusion of *Octafibrin*		x **[f]**				x **[f,g]**			x					
Final haemostatic efficacy assessment											x			
AEs [h]		>	>	>	>	>	>	>	>	>	>	>	>	>
Concomitant medications		>	>	>	>	>	>	>	>	>	>	>	>	>

DVT = deep venous thrombosis; PE = pulmonary embolism; 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] Plasma retain sample for potential retesting; serum retain 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 completion of the Wells criteria for assessment of possible DVT and PE or any thromboembolic events or hypersensitivity reactions.

[i] Haematology only

4.5.2 Flow Chart of Assessments for Surgical Prophylaxis

	Screening	Observations performed for each surgical intervention											Study Completion Visit
		Before surgery		Day 1 Surgery			Any POP day (i.e., up to 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	Pre-infusion	1 h post-infusion (± 15 min)	Daily	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											
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			
Wells criteria for DVT and PE		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]**	
Thrombogenicity **[c]**			x			x			x			x	
Safety lab (haematology and clinical chemistry) **[b]**		x					x		x	x		x	
Retention plasma samples **[d]**			x		x **[a]**	x	x	x	x	x	x	x	
Retention serum samples **[d]**		x											x
Urine or blood pregnancy test		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		>	>	>	>	>	>	>	>	>	>	>	>

DVT = deep venous thrombosis; PE = pulmonary embolism; 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 completion completion of the Wells criteria for assessment of possible DVT and PE or any thromboembolic events and hypersensitivity reactions.

4.5.3 Schedule of Visits/Summary of Study Procedures

Refer to Section 6.1 of protocol – Observations performed throughout the study.

5 SEQUENCE OF PLANNED ANALYSES

An interim analysis will be performed after the data is available for the first bleeding episode of 10 subjects. Two of these subjects should be between 12 and 18 years old. Results will be included in the submission for registration. Descriptive efficacy and safety analysis will be performed and presented to IDMEAC.

6 GENERAL CONSIDERATIONS FOR STATISTICAL ANALYSIS

The descriptive statistics for continuous variables will be presented with number (n) of non-missing observations, mean, Standard Deviation (SD), median, minimum and maximum (or range). For categorical variables, descriptive statistics will be presented with number of eligible subjects and number (n) with percentage of observations in the various categories of the endpoint, where percentage will be based on the eligible subjects in the respective analysis set.

6.1 Study Population

6.1.1 Number of Subjects

A minimum of 24 subjects will be enrolled in the study to assess on-demand treatment of at least one bleeding episode. This will include at least 4 subjects aged between 12 and 18 years (only 18 and above in Russia). This will also include an assessment of at least 4 surgical procedures, 2 of which should be performed in subjects aged between 12 and 18 years (only 18 and above in Russia). The study will be conducted in approximately 15 centres worldwide.

6.1.2 Subpopulations

Subpopulations based on the following categories will be examined:

- Severity of bleeding: minor versus major.
- Age: Paediatric (<18 years) versus adult (18–64) versus elderly patients (≥65), if appropriate.
- Sex
- Race
- Surgical population

6.1.3 Sample Size Rationale

The number of subjects is limited by the very small number of subjects in this indication. Therefore no real sample size estimation is provided. Instead, the probabilities for different outcomes are provided, given a success rate of 95% for a total number of 24 subjects together with respective confidence intervals (CIs).

6.2 Derived and Computed Variables

It is expected that variables will be derived and computed. The SAP will not be amended for additional variables that are not related to the primary or key secondary variables.

For analysis purpose the assessment made by the investigator on the 4-point rating scale will be transformed to a dichotomous endpoint with success as “Yes” defined as a rating of excellent or good and “No” as Moderate or Non or Missing). The success rate will be calculated as the proportion of patients with success.

Any additional derived variables will be identified and documented in the Statistical Analysis System (SAS®) programs that create analysis files.

The following variable will be calculated for the analysis tables: BMI

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes, or Equation(s)
BMI	Body Mass Index	—	BMI = {Weight (in Kg) / (Height (in meters))^2}
Success	Overall clinical assessment of haemostatic efficacy	Yes/No	if value is ‘excellent; or ‘good’, then Success = “Yes” if value is ‘Moderate ‘or ‘None’ or ‘Missing’, then Success = “No”

Body Mass Index (BMI) = {Weight (in Kg) / (Height (in meters)) 2}

6.3 Handling of Drop-outs and Missing Values

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 per-protocol PP population. LOCF (Last observation carried forward) approach will be used for body weight measurement for all analysis involving dose/kg BW.

Missing MCF and IVR values will not be replaced.

6.4 Analysis Software

All the Statistical Reports including Summary Tables, Listings and Graphs (TLGs) will be generated using a customized reporting SAS Version 9.3 for windows, SAS Institute, Cary, North Carolina, United States of America (USA).

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The following information will be captured on enrolment:

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.

7.1 Demographics

Demographic variables and will be summarized descriptively. Demographic variables will include age, weight, sex, height, BMI and ethnic origin. Variables that are measured on a continuous scale, such as the age of the subject at the time of enrollment, the number of non-missing observations (n), mean, median, SD, minimum, and maximum will be tabulated for Octafibrin. Variables that are measured on a categorical scale will be summarized using frequencies and percentages of Octafibrin.

7.2 Medical History

Medical history will be listed by body system coded by MedDRA version 17.1 or higher with Preferred Term.

8 EFFICACY ANALYSIS

8.1 Primary Efficacy Analysis

For bleeding efficacy, 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 until 24 hours (i.e., 1 day) after the last infusion or the end of the treatment observation period, whichever comes last. Frequency distribution will be provided for the haemostatic efficacy scale data. In addition, a 95% CI for the success rate in haemostatic efficacy (excellent or good) according to Casella (Blyth-Still-Casella interval) will be computed using StatXact® software.

For the following subjects the haemostatic efficacy outcome will be set to the worst 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 efficacy [e.g., pharmacy error]).
- Subjects with missing haemostatic efficacy assessment.

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

8.2 Hypothesis Testing and Determination of Sample Size

The following hypothesis will be tested:

H_0: $p \leq 0.6$

Against the alternative

H_A: $p > 0.6$

Where p is the proportion of subjects with successful haemostatic efficacy (i.e.; 'excellent' or 'good').

The null hypothesis will be tested against the alternative by comparing the lower limit of the two-sided 95% Blyth-Still-Casella confidence interval for the proportion of patients with successful haemostatic efficacy with the predefined threshold of 0.6.

Due to practical limitations in subject enrolment and total study duration due to the very small number of patients with this indication, no real sample size calculation was performed on basis of statistical power considerations. Instead, the probabilities and associated confidence intervals (CIs) for different outcomes are provided, assuming a true success rate of 0.95.

Assuming that the study treatment is successful (i.e. the haemostatic efficacy assessment is 'excellent' or 'good') in 95% of the subjects, the success rates given in Table 1 will be observed in the 24 study subjects with the following probabilities:

Table 1: Overall clinical assessment of haemostatic efficacy

Outcome (n/N)	Percentage	Probability for the outcome (binomial)	95% (2-sided) confidence interval[a]
≥19/24	≥79.1%	0.999	0.594–0.914
≥20/24	≥83.3%	0.994	0.633–0.941
≥21/24	≥87.5%	0.970	0.691–0.965
≥22/24	≥91.7%	0.884	0.744–0.985

n = number of subjects with 'excellent' and 'good' haemostatic efficacy; N = total number of subjects.

[a] Blyth-Still-Casella interval, realised by StatXact® software.

Hence, assuming that treatment with Octafibrin is associated with a true success rate of 95% of the 24 subjects, there will be a 99.4% probability that at least 20 of 24 subjects will have a successful assessment. In case of 20 successful assessments, the lower boundary of the 95% CI will be 0.633, i.e., > 60%.

For the purpose of analysis, the efficacy assessment made by the investigator on the 4-point rating scale will be transformed to a dichotomous endpoint, with 'treatment success—yes' defined as a rating of 'excellent' or 'good' and 'treatment success—no' defined as a rating of 'moderate,' 'none,' or a missing rating. The success rate will be calculated as the proportion of patients with treatment success.

8.3 Secondary Efficacy Analyses

8.3.1 Clot strength (MCF)

- Fibrinogen levels 1 hour after infusions of the IMP, MCF at baseline and at 1 hour after first and last infusion as well as changes of MCF from baseline will be summarized using descriptive statistics and displayed graphically. The course of laboratory data will be presented graphically. Mean changes in MCF will be described with 2-sided 95% CIs.
- Statistical analyses will also be performed separately 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 dichotomized haemostatic efficacy scale (excellent/good, moderate/none). Scatter plots will show MCF by haemostatic efficacy outcome.

Correlation with MCF and MCF Change:

- In addition, a correlation analysis between MCF and the haemostatic efficacy assessment will be performed. To evaluate the correlation between MCF and the primary efficacy variable Spearman correlation coefficients will be estimated for the correlation of the 4-point haemostatic efficacy with MCF and with MCF change.

Note: If there is almost no variation in haemostatic efficacy outcomes (e.g., if almost all of the outcomes are "excellent") there will be only low discriminatory power to show an association between MCF and haemostatic efficacy.

Octafibrin use

- The dose of the IMP used per dayand in total will be summarized using descriptive statistics for minor and major bleeding events. Frequency of infusions and duration of treatment will also be summarized. The frequency of unscheduled infusions will be summarized descriptively.

8.3.2 Fibrinogen Levels

Fibrinogen plasma level before and 1 hour after the end of each subsequent infusion and at the time of the overall clinical assessment of haemostatic efficacy.

Fibrinogen at baseline and at 1 hour after first and last infusion as well as changes of Fibrinogen from baseline will be summarized using descriptive statistics and displayed graphically.

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

8.3.3 In-Vivo Recovery

- Calculation and analysis of IVR will be performed for the Clauss method only.
- Response (incremental IVR) will be calculated as the maximum increase in plasma fibrinogen (i.e., Clauss data) as compared to pre-infusion, within the 12 hours (will usually refer either to the 60 minutes or the 3 hours after the first and the last infusion and refer to the 60 minutes time point after the other infusions) following infusion (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 within 12 hours 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) as compared to pre-infusion, within 12 hours (will usually refer either to the 60 minutes or the 3 hours after the first and the last infusion and refer to the 60 minutes time point after the other infusions) following infusion (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.

Classical IVR (%) =

100% x actual/expected increase =
100% x maximum increase in fibrinogen plasma level within 12 hours compared to pre-infusion (mg/dL) x plasma volume (dL) / (exact dose of component in IMP administered [mg]):

$$IVR\left(\frac{IU/dL}{IU/kg}\right) = \frac{\Delta\ value\left(\frac{IU}{dL}\right)}{dose\,(IU)\ /\ body\ weight\ (kg)}$$

Response and classical IVR will be calculated for each infusion of each subject. Descriptive tables will show the distributions of the 2 parameters per infusion day separated for minor and major bleeding. An exploratory analysis using a repeated-measures analysis of covariance model will analyze whether the response/classical IVR changed over time. The dose (mg/kg) associated with the respective IVR will be held as covariate in the model. The response/IVR over time and dose will also be presented in scatter plots for all subjects and by major/minor bleeding.

8.3.4 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 9.4.1).

8.3.5 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. 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 primary 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 the documentation of the adjudication process for the assessment of surgical prophylaxis the DMEAC will explicitly identify any subjects for whom they considered there to be "unexpected blood loss due to surgical complications" and if that consideration altered the 4-point assessment of surgical prophylaxis. This information will be analyze both including (as a sensitivity analysis) and excluding unexpected blood loss if it occurs.

9 SAFETY ANALYSES

AEs and SAEs will be coded by latest version 17 or higher of MedDRA body system and preferred term, and tabulated by indicating number and percentage of subjects and number of events. Number and percentage of subjects who experience any Adverse Drug Reaction (ADR) will be summarized.

AEs will be collected and evaluated for relation to test article, seriousness, intensity, frequency, measures taken and outcome.

Descriptive statistics and subject listing will be presented for concomitant medications.

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

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

Treatment emergent AEs will be those occurring during infusion or in the 45-day observation period after the first infusion. ADRs will be classified by the Sponsor as either expected or unexpected

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 summarized 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, biochemistry, and thrombogenicity), the mean, standard deviation, median, and range will be presented. Laboratory variables will also be presented graphically. Intra-individual changes between baseline and the respective post-baseline time points will be analyzed using shift tables and graphical presentations. Virus safety variables and physical examination will be evaluated via frequency tables.

9.1 Vital Signs

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

9.2 Physical Exam

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 **Wells criteria for assessing the probability for possible DVT and PE** will be documented for all study and planned follow-up visits of any patients treated in the study (see Section 7.6 of the study protocol).

10 ADDITIONAL ANALYSES

If any additional statistical analyses required during the final analysis, appropriate methods will be used, and any changes, including the rationale for use, will be documented in the Clinical Study Report (CSR).

11 DATA LISTINGS

All Case Report Form (CRF) data, as well as any outcomes derived from the data, will be summarized in detailed data listings. Subject data listings will be presented for all subjects randomized into the study.

12 PLOTS AND GRAPHS

- The plots and graphs will be presented to illustrate the efficacy variables.
- A bar graph will be prepared for Haemostatic Efficacy.
- A line graph will be prepared for mean MCF at baseline and at 1 hour after first and last infusion as well as mean change of MCF from baseline.
- A line graph will be prepared for mean Fibrinogen at baseline and at 1 hour after first and last infusion as well as mean change of Fibrinogen from baseline.
- A line graph will be prepared for mean MCF Vs Time and Fibrinogen levels Vs Time.
- A bar graph will be prepared for Intra-operative efficacy as assessed by surgeon (at the end of the surgery = after last suture).
- A bar graph will be prepared for Post-operative efficacy as assessed by haematologist.
- A scatter plot will be prepared for MCF and the haemostatic efficacy.
- A scatter plot will be prepared for response/IVR over time and dose for all subjects and by major/minor bleeding.

13 REPORTING CONVENTIONS

13.1 Reporting of Numeric Values

All raw data will be presented to the original number of decimal places. The mean and medians will be presented with 1 decimal place more than raw data. The SD will be presented with two decimal places more than raw data. Percentages will be presented in xx.x % format. Precision of p-values will be four decimal places. p-values less than 0.0001 will be presented as <.0001 and if equal to 1 then ≥ 0.9999. Missing values for both numeric and character variables will be presented as blanks in a table or data listing.

13.2 Output (Tables, Listings and Graphs) Considerations

The ICH numbering convention is to be used for all tables, figures and data listings. The default Tables, Listings and Graphs layout will be as follows:

Orientation	As per the size of the tables page orientation will be landscape
Paper Size	Letter size (11” x 8.5”)
Margins	Top: 1.25 in, if landscape [1.0 in, if Portrait] Bottom: 0.75 in, if landscape [0.75 in, if Portrait] Left: 0.75 in, if landscape [1.25 in, if Portrait] Right: 0.5 in, if landscape [0.5 in, if Portrait]
Font	Font style (preferably Courier New) of the Text with size 8 or higher
Headers	Titles of Table/Listing will be center **Left:** Sponsor: Study Name: Protocol No: **Right:** Status: Draft or Final Data Status/Date: Eg. Draft, Dummy Treatment Code, Datalock Date
Footers	**Left:** Analysts Initials: Program Name: Program Run date: time: **Right:** Datasets used: Page XXX of YYY

The margin may be reduced as necessary to allow additional rows to be presented, but not at the expense of clarity. Also the orientation may be changed to portrait if appropriate. The date format for all presentations will be 'DDMMMYYYY'.

Population(s) represented on the tables or listings will be clearly identified in the title as "Population: <name of population>" where <name of population> is any of the analysis population names or abbreviations defined in the SAP.

All observed time values and time durations will be reported using a 24-hour clock HH:MM format. The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5min) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.

14 REFERENCES

- ICH E3: Structure and content of Clinical Study Reports, July, CPMP.
- ICH E9: Statistical Principles for Clinical Trials, September 1998, CPMP.