Official Title:	**Multicenter, Prospective, Open-Label, Single-Arm Trial to Evaluate the Pharmacokinetics, Efficacy, and Safety of Human Plasma-Derived Fibrinogen (FIB Grifols) in Patients with Congenital Afibrinogenemia**
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STATISTICAL ANALYSIS PLAN (SAP)

FIB Grifols / IG0902

Title: Multicenter, Prospective, Open-Label, Single-Arm Trial to Evaluate the Pharmacokinetics, Efficacy, and Safety of Human Plasma-Derived Fibrinogen (FIB Grifols) in Patients with Congenital Afibrinogenemia

Author's Name and Address: [redacted], MS, MD

Grifols Therapeutics, LLC.

79 TW Alexander Drive

Research Triangle Park, NC 27709

Author's Telephone Number: [redacted]

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Approved by: [redacted] Date: 10 / Feb / 2020

Name: [redacted], PhD

Title: [redacted]

Approved by [redacted] Date: 10 / Feb / 2020

Name [redacted], MD

Title: [redacted]

Approved by: [redacted] Date: 11 / FEB / 2020

Name: [redacted], MSc

Title: [redacted]

Approved by: [redacted] Date: 11 / FEB / 2020

Name: [redacted]

Title: [redacted]

ABBREVIATIONS

α	Alpha angle
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromoplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATIII	Antithrombin III
AUC	Area under the curve
$AUC_{0\text{-}14days}$	Area under the curve from zero to 14 days
$AUC_{0\text{-}\infty}$	Area under the curve from zero to infinity
BUN	Blood urea nitrogen
CBC	Complete blood count
CFT	Clot formation time
CI	Confidence interval
Cl	Clearance
C_{max}	Maximum plasma concentration
CSR	Clinical Study Report
CT	Clotting time
CV	Coefficient of variation
DBP	Diastolic blood pressure
dL	Deciliter
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
F1+2	Prothrombin fragments F1+2
FIB	Fibrinogen
Hct	Hematocrit
Hgb	Hemoglobin
HR	Heart rate
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IP	Investigational product
IVR	In vivo recovery
K_{el}	Terminal first-order elimination rate constant
kg	Kilogram
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MCF	Maximum clot firmness
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRT	Mean residence time
NAT	Nucleic acid amplification technology
Q1	25th percentile
Q3	75th percentile
PK	Pharmacokinetic
PP	Per-protocol
PT	Prothrombin time (according to the context)
PT	Preferred term (according to the context)
RBC	Red blood cells
ROTEM	Rotational thromboelastometry
RR	Respiration rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System Organ Class
SOI	Start of Infusion
T	Temperature
$t_{1/2}$	Half-life
TAT	Thrombin-antithrombin III complex
TB	Total bilirubin
TEAE	Treatment emergent adverse event
t_{max}	Time to the observed maximum plasma concentration
TI	Time of infusion (i.e. length of infusion)
TT	Thrombin time
USA	United States of America
Vd	Volume of distribution
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

TABLE OF CONTENTS

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol IG0902 Version 2.3, dated 12Feb2016 and eCRF Version 5.0, dated 07Feb2017. The purpose of this SAP is to ensure that the statistical methodologies that will be used, and the data listings, summary tables and figures which will be produced, are appropriate and complete to support valid conclusions regarding the study objectives and the completion of the Clinical Study Report (CSR). Additional post-hoc or unplanned analyses, which are not defined in this SAP, may be performed to support the clinical development program. Such analyses will be documented in the CSR.

2 STUDY DESIGN AND OBJECTIVES

2.1 Study Design

This is a phase I-II, multi-center, prospective, open-label, single-arm clinical trial to evaluate the pharmacokinetics (PK), efficacy, and safety of human plasma-derived fibrinogen concentrate FIB Grifols in subjects with congenital fibrinogen deficiency manifested as afibrinogenemia.

In this clinical trial, the PK profile of the investigational product (IP) FIB Grifols will be established by measuring fibrinogen levels at different time points after a single-dose infusion of 70 mg/kg body weight. The hemostatic efficacy of FIB Grifols will be also established by means of rotational thromboelastometry (ROTEM) measures of maximum clot firmness (MCF) at baseline and 1-hour post-infusion.

Comparison of other thromboelastographic measures and standard coagulation tests before and after infusion at different time points will serve as secondary [redacted] endpoints indicative of hemostatic efficacy of the product. Safety of the product will be also studied by assessment of infusion tolerability, adverse events (AEs), and laboratory tests, including immunogenicity and virology testing.

This clinical trial is planned to be performed at sites in multiple countries including India, Italy (European Union), and the United States of America (USA). It is planned to include 11 adult subjects (≥18 years) with congenital fibrinogen deficiency in order to provide at least 10 evaluable adult subjects. Only after the safety of FIB Grifols in adult subjects has been assessed and established by the sponsor, will the study start to enroll 11 pediatric subjects (<18 years) to achieve 10 evaluable pediatric subjects.

During the Screening Visit, the investigator will determine subject's eligibility for inclusion in the study. After giving informed consent and assent if applicable to participate in the clinical trial, subjects will be included in the *Subject's Screening Log* and they will be assessed using screening examinations. Eligible subjects will be treated with the investigational medicinal product under study and they will be included in the *Subject's Identification Log* by the investigator.

Throughout the clinical trial, several visits will be scheduled. Initial visits including Infusion Visit (Day 0) and Day 1 Visit will always be performed at the study center; however, the following visits may be performed by home health nurses at the subject's convenience: Day 2, Day 4, Day 6, Day 9, Day 14, Day 21 and Month 3 Visit (Month 3 Visit is applicable only for adult subjects).

It is required that Week 4 Visit is performed at the respective study center by the site investigative staff. Study assessments will comprise physical assessments, blood analysis, vital signs, and recording of AEs and concomitant medications.

The principal investigator at each site must be aware of and explicitly authorize the use of home health nurses service.

Home health nurses will not perform procedures or assessments that only a medically qualified physician (either the principal investigator or the designated sub-investigator) could do (i.e., physical assessment, AEs assessment or serious adverse events [SAEs] assessment). Home health nurses will only perform activities as indicated on the delegation of duties form. These will be limited to:

- Blood extraction and sample processing for shipment.
- Vital signs measurement (including heart rate [HR], respiration rate [RR], systolic and diastolic blood pressure [SBP and DBP], and temperature [T]).
- Subject interview and recording of potential AEs to be communicated to the principal investigator.
- Concomitant medications recording.

The overall study schema is shown in Figure 2-1.

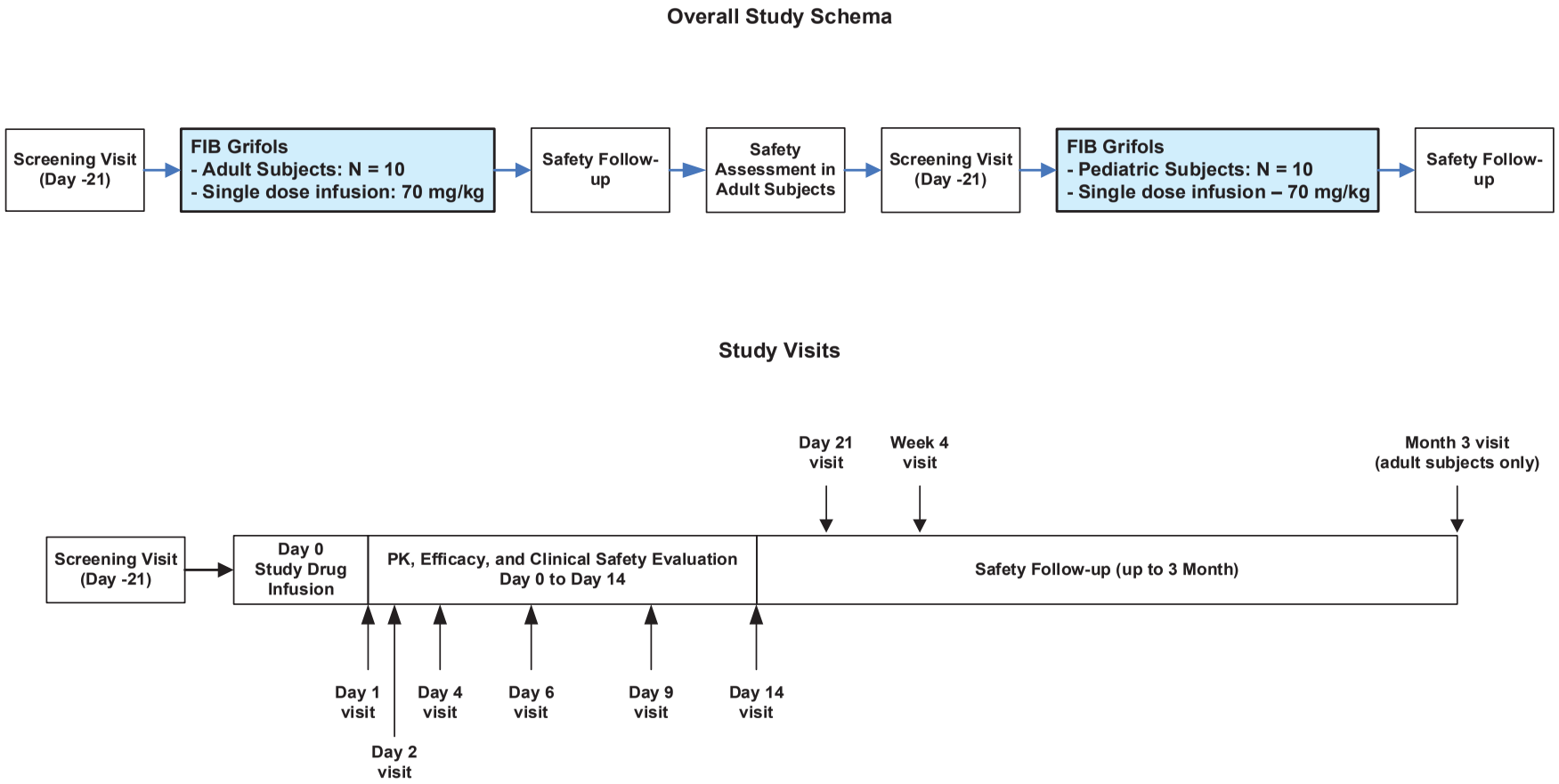

Figure 2-1 Overall Study Schema and Study Visits

2.2 Study Objectives

2.2.1 Pharmacokinetic (PK) Objectives

To evaluate the PK profile of FIB Grifols following single-dose administration of 70 mg/kg body weight.

2.2.2 Efficacy Objectives

To evaluate hemostatic efficacy of FIB Grifols by means of thromboelastographic MCF values' comparison at baseline and one hour after IP administration. Other thromboelastographic measures as well as standard coagulation tests measured at different time points will also serve as secondary [redacted] efficacy endpoints.

2.2.3 Safety Objectives

To evaluate the safety of FIB Grifols, clinical safety, viral safety, and immunogenicity will be assessed in this clinical trial. Safety variables include AEs, vital signs, physical assessments, laboratory tests, viral markers, and antibodies against human fibrinogen.

3 STUDY VARIABLES

3.1 PK Variables

Plasma fibrinogen activity will be determined by the activity (Clauss) method and antigen method (enzyme-linked immunosorbent assay [ELISA]) in the central laboratory of the study. Fibrinogen activity levels will be determined immediately before infusion and at different time points after infusion.

The following PK parameters will be calculated for fibrinogen by a non-compartmental PK method determined from plasma levels before and at 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 1 day (24 hours), 2 days (48 hours), 4 days (96 hours), 6 days (144 hours), 9 days (216 hours), and 14 days (336 hours) after the end of the infusion:

1. Area under the curve (AUC) including AUC from zero to 14 days ($AUC_{0\text{-}14days}$) and AUC from zero to infinity ($AUC_{0\text{-}\infty}$)
2. Maximum plasma concentration (C_{max})
3. Time to the observed maximum plasma concentration (t_{max})
4. Half-life ($t_{1/2}$)
5. Mean residence time (MRT)
6. Volume of distribution (Vd)
7. Clearance (Cl)
8. In vivo recovery (IVR)

Incremental IVR will be calculated for fibrinogen levels from the peak level recorded within and including the first four hours after the end of infusion and reported as [mg/dL]/[mg/kg]. For the calculation of recovery, the declared potency of the investigational medicinal product actually administered to the subject will be considered in the calculation of dose administered, and the actual volume infused to the subject will also be used for calculating the dose administered to each subject.

The *IVR* will be determined for every subject using the following formula:

([*FIB max* (mg/dL)] - [*FIB pre-infusion* (mg/dL)])/*FIB administered* (mg)/Body weight (kg)

where the *FIB max* is the peak FIB activity within the first four hours after the end of infusion and *FIB pre-infusion* is the baseline FIB activity level of the subject. *FIB administered* will be the actual administered dose calculated using the actual volume administered to the subject, the declared potency, and the true concentration of FIB in the batch used.

All PK parameters will be estimated using the fibrinogen concentration values obtained by both functional (Clauss) method and antigen (ELISA) method.

3.2 Efficacy Variables

3.2.1 Primary Efficacy Variable

The primary efficacy variable is difference (improvement) on plasma thromboelastographic MCF from baseline to 1-hour post-infusion. ROTEM measures will be performed at the central laboratory of the study.

3.2.2 Secondary Efficacy Variables

Secondary efficacy variables assessed in this study are:

1. Difference (improvement) on other plasma thromboelastographic variables (clotting time [CT], clot formation time [CFT], and alpha angle [α]) from baseline to 1-hour post-infusion. ROTEM measures will be performed at the central laboratory of the study.
2. Difference (improvement) on standard coagulation tests (thrombin time [TT], prothrombin time [PT], and activated partial thromboplastin time [aPTT]) from baseline to 1-hour post-infusion. Standard coagulation tests will be performed at the central laboratory of the study.

[redacted]

[redacted]

3.3 Safety Variables

The following safety variables will be assessed in this study:

1. AEs
2. Vital signs
3. Physical assessments
4. Laboratory panels
5. Antibodies against fibrinogen (immunogenicity testing)
6. Allergic/hypersensitivity reaction
7. Thrombotic event
8. Viral safety

4 GENERAL STATISTICAL CONSIDERATIONS

Statistical analyses and data presentations will be generated using SAS version 9.4 or higher.

Unless otherwise noted, for continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. All statistical inference will be tested at 2-sided with α=0.05.

Unless otherwise noted, all data collected in the electronic case report forms (eCRFs) or electronically transferred (such as central laboratory data) will be presented in data listings. Subjects will be identified in the data listings by subject number (which includes site number) and grouped by adult and pediatric populations.

For table summaries, the data will be presented at the scheduled visits according to protocol. Any data collected at the unscheduled visits will be listed.

4.1 Data Handling

Unless otherwise noted, if an observation is missing at a specific scheduled visit/timepoint, the value at that visit will not be imputed and will be set to missing.

Baseline will be defined as the last measurement taken prior to the start of the infusion on Day 0 (Infusion Visit).

4.1.1 PK Data Handling

4.1.1.1 Time Window for Pharmacokinetic Analysis

The scheduled time points specified in the protocol will be used in the tables for presenting the individual and summary data of plasma fibrinogen concentrations. The nominal time (hours post start of infusion) will be used in figures for presenting the mean or median measured concentration vs. time curve. Due to the variable infusion durations in individual subjects and the considerable difference of mean infusion durations between the adult and pediatric groups, the nominal time will be adjusted by using the mean infusion duration of 1 hour and 0.5 hour for the adult and pediatric groups, respectively.

If PK blood samples are not drawn exactly at the protocol specified time, the samples will still be included in the PK analysis as long as the actual sample collection date and clock time for each sample is recorded and the actual elapsed time from the start of infusion can be calculated.

The actual elapsed time between the start of the infusion and each PK blood sample draw will be calculated and used as the PK time point. In addition, the actual duration of the infusion will be calculated to determine the time of the end of infusion. The PK parameter calculation for each subject will be based on the actual elapsed time from the start of infusion instead of the scheduled time or nominal time post end of infusion.

An example of actual elapsed time calculated from the time of the start of infusion is shown below.

Scheduled Time	**Nominal Time (Hours post SOI) for Adult**	**Nominal Time (Hours post SOI) for Pediatric**	**Example Actual Elapsed Time (Hours post SOI)**
Pre-infusion	**	**	**
Start of infusion	0	0	0
End of infusion*	1	0.5	1.25
30 minutes post-infusion	1.5	1	1.75
1 hour post-infusion	2	1.5	2.20
2 hours post-infusion	3	2.5	3.35
4 hours post-infusion	5	4.5	5.30
8 hours post-infusion	9	8.5	9.56
Day 1 (24 hours post-infusion)	25	24.5	25.90
Day 2 (48 hours post-infusion)	49	48.5	49.80
Day 4 (96 hours post-infusion)	97	96.5	97.67
Day 6 (144 hours post-infusion)	145	144.5	145.50

Day 9 (216 hours post-infusion)	217	216.5	217.75
Day 14 (336 hours post-infusion)	337	336.5	337.20

*End of infusion is not a defined time point in order to facilitate the different infusion times required per patient and serves as a relative measure for the calculation of nominal times of the post-infusion time points.
SOI – Start of infusion
**The pre-infusion concentration will be used for the baseline concentration regardless of actual time taken so long as it occurs before the SOI.

4.1.1.2 Plasma Concentration Values Below the Quantification Limit

If any plasma concentration values of fibrinogen are below the lower limit of quantification (LLOQ) for either the activity (Clauss) method or the antigen (ELISA) method, in general the values will be replaced with a value of zero for the PK analysis. If necessary, alternative methods may be used to impute the values below LLOQ based on PK principle, and such methods will be documented in the CSR.

4.1.1.3 Plasma Concentration Missing Values

For PK analysis, any invalid plasma concentration values of fibrinogen will be treated as missing. If necessary, invalid or missing values will be interpolated or extrapolated using PK principle, as appropriate, and such interpolations or extrapolations will be documented in the CSR.

4.1.2 Efficacy Data Handling

For the ROTEM measurements, undetectable values of MCF and alpha angle are set to 0, and undetectable values of CFT and CT are set to missing.

4.2 Analysis Populations

Safety population

The Safety population consists of all subjects who receive infusion (at any dose) of the IP. This will be the analysis population for the safety data.

PK population

The PK population will consist of all subjects who have received study medication and have sufficient fibrinogen plasma concentration data to facilitate calculation of PK parameters. The PK population will be used for the analyses of the PK parameters.

Adequate treatment compliance will be considered when determining valid concentration-time data for inclusion in the PK analyses. The values or profiles deemed not reliable due to treatment non-compliance or other reasons will be excluded from the PK analyses and flagged in the listing. Any subject who has at least one major protocol deviation which might

have impact on the PK analyses (to be defined in a data review meeting prior to database lock) will be excluded from the PK population.

Evaluable population (efficacy)

The Evaluable population will include all subjects who received IP at any amount and who have at least two measurements for the primary efficacy variable: one pre-infusion MCF and 1-hour post-infusion MCF measurements by ROTEM.

Per-protocol population (efficacy)

The Per-protocol (PP) population will include all subjects who received planned dose of the IP (at least 90% of the planned dose based on the prepared volume), who have no major protocol violation that might have impact on the primary efficacy assessment (to be defined in a data review meeting prior to database lock), and who have at least two measurements for the primary efficacy variable: one baseline (pre-infusion) MCF measurement by ROTEM and 1-hour post-infusion MCF measurement by ROTEM for the investigational medicinal product.

Any deviations from the protocol will be recorded in the protocol deviation list. The validity of a subject for inclusion in each of these four populations (Safety, PK, Evaluable, and PP) will be assessed at a data review meeting that will take place before database lock. The data review meeting will review the protocol deviation list, as well as data listings. If additional protocol deviations are identified which justify removing a subject from any population, then these decisions will be documented.

4.3 Sample Size Considerations

The sample size in this study is based on the PK assessment. The sample size of 10 adult subjects was selected to establish a PK profile of the IP. In order to allow for possible drop-outs, 11 adult subjects will be enrolled in the study.

Only after the safety of the product has been assessed and established in the adult subjects population, will 10 pediatric subjects be enrolled into the study. Assuming a 10% dropout rate, a total of 11 pediatric subjects need to be enrolled.

4.4 Interim Analysis

An interim safety analysis will be performed with the adult population in order to assess the safety of FIB Grifols prior to starting enrollment of pediatric subjects. PK and efficacy interim analyses of the investigational medicinal product may also be performed in the adult population.

5 SUBJECT DISPOSITION

Subject disposition will be summarized by adult and pediatric populations separately and on the overall population (adult and pediatric populations combined).

Subject disposition will include the number of subjects screened, number of subjects enrolled, number and percentage of subjects in each analysis population, number and percentage of subjects completing the study.

The number and percentage of subjects discontinuing early from the study will be summarized for primary reasons of discontinuation. Also, the number and percentage of screening failures will be summarized for primary reasons of ineligibility.

Disposition status will be listed for all subjects.

6 PROTOCOL DEVIATIONS

Protocol deviations will be identified during the study and evaluated before the database lock. The type/category of protocol deviations and severity (i.e., minor or major) will be summarized by adult and pediatric populations and overall.

7 DEMOGRAPHY AND MEDICAL HISTORY

7.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics including sex, race, ethnicity, age, age categories (<2, ≥2 - <12, ≥12 - <18, ≥18 - <65, ≥65 - <70), baseline pregnancy test, height, weight, and body mass index will be summarized by adult and pediatric populations and overall. The congenital fibrinogen deficiency history will be summarized.

All demographic and baseline characteristics data will be listed.

7.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized/listed by adult and pediatric populations and overall.

8 CONCOMITANT MEDICATION AND TREATMENT

8.1 Prior and Concomitant Medication

All medications as documented by the investigator will be coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug classification Dictionary (WHO-DD). All medications will be summarized by adult and pediatric populations and overall and sorted alphabetically by medication class (i.e., ATC level 2) and medication sub-class (i.e., ATC level 4). If the ATC level 4 term is missing, the ATC level 3 term will be used in the medication summary table and data listing.

The following convention will be used for missing or partial end date information in order to determine whether a medication is prior or concomitant:

The unknown portions of a medication end date will be assumed to be as late as possible. If a medication end date is incomplete but the month/year of medication end date is prior to the month/year of the start of study treatment, then the medication will be considered a prior medication. If a medication end date is incomplete but the month/year of medication end date is the same as the month/year of the start of study treatment, then the medication will be considered a concomitant medication. All other incomplete medication end dates and all medications with missing end dates will be assumed to be concomitant medications. Start/end dates reported in the eCRFs will be presented in the listings.

Prior medications are defined as any medication ended prior to the start of study treatment (i.e., start of the infusion on Day 0).

Concomitant medications are defined as any medication started on or after the start of study treatment or any medication taken prior to the start of study treatment and continued after the start of study treatment during the study.

8.2 Extent of Study Treatment Exposure and Compliance

The total volume infused (mL) and duration of infusion (minutes) will be summarized. Further, exposure information along with infusion interruptions will also be summarized. Duration of infusion will be calculated as stop time of infusion – start time of infusion.

Treatment compliance will be calculated as (total volume infused / total volume prepared) * 100% during the study. The total volume prepared and dispensed by pharmacist is the intended dose volume a subject should be given based on the body weight. The treatment compliance will be listed and summarized. The number of subjects with at least 90% compliance will be calculated.

Considering different potencies from different lots are administered, the actual dose in mg/kg body weight may deviate from the planned or target dose of 70 mg/kg. The lot number, potency, actual dose infused (mg), and planned dose calculated (mg) based on the planned amount of 70 mg/kg body weight will be listed.

Additional consideration regarding treatment compliance will be given when determining legitimacy for inclusion of fibrinogen concentration data for calculation of the PK parameters. Reasons for excluding fibrinogen concentration data or a subject from the analysis of PK parameters will be documented in the CSR.

9 PK ANALYSIS

PK analyses will be based on the PK population and will be performed on the adult and pediatric populations independently. PK analyses will be performed using the fibrinogen concentration values obtained by both Clauss method and antigen (ELISA) method.

9.1 Analysis of PK concentration and dosing data

Plasma concentrations of fibrinogen will be presented in a listing by subject, study day, date, and scheduled/nominal sampling time point. The data listing will provide details of all planned plasma collection time points relative to the start of infusion (scheduled and nominal times as shown in Section 4.1.1.1), actual collection date and clock times and actual elapsed times from the start of the infusion, as well as plasma fibrinogen concentrations. If any concentration values are excluded from the PK analyses, they will be flagged in the listing. The lot number, potency, actual dose infused (mg), and planned dose calculated (mg) based on the planned amount of 70 mg/kg body weight will also be listed. .

Plasma concentrations of fibrinogen will be summarized by adult and pediatric populations and the scheduled/nominal time point. The summaries will include n, mean, SD, 90% confidence interval (CI) for mean, coefficient of variation (%CV), median, minimum, maximum, and geometric mean. [redacted]

Plasma fibrinogen concentration vs. time curves for individual subjects will be presented with the actual elapsed time from the start of the infusion plotted on the x-axis. Individual concentration vs. time plots will also be presented for all subjects on the same figure (so called spaghetti plot) for the adult and pediatric populations separately. For all subjects combined (separately for the adult and pediatric populations), mean or median plasma fibrinogen concentration vs. time curves will be presented in one figure with the nominal time (see Section 4.1.1.1) plotted on the x-axis. All plasma fibrinogen concentration vs. time curves will be plotted on both the linear and the semi-log scale.

9.2 Calculation of PK parameters

The PK parameters of plasma fibrinogen following single-dose administration in individual subjects will be determined as appropriate and as data permit. The PK parameters will include IVR, AUC calculated as $AUC_{0\text{-}14days}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, MRT, Vd, and Cl.

The PK parameters will be calculated using non-compartmental methods with WinNonlin software.

All PK parameters will be calculated using the fibrinogen concentration values obtained by both Clauss method and antigen (ELISA) method.

The pharmacokinetic parameters of interest will be determined as follows:

IVR	incremental in vivo recovery, calculated as ([FIB max (mg/dL)] - [FIB pre-infusion (mg/dL)])/FIB administered (mg)/Body weight (kg), where the FIB max is the peak FIB activity during the first four hours of sampling after the end of infusion and FIB pre-infusion is the baseline FIB activity of the subject, expressed as mg/dL per

	mg/kg. FIB administered will be the actual administered dose calculated using the actual volume administered to the subject, the potency, and the true concentration of FIB in the batch used.
$AUC_{0\text{-}14days}$	area under the concentration vs. time curve from time 0 to 14 days, calculated by a combination of linear and logarithmic trapezoidal methods and expressed in the unit of concentration × time (e.g., mg × h/dL). The linear trapezoidal method will be used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
$AUC_{0\text{-}\infty}$*	area under the concentration vs. time curve from time 0 extrapolated to infinite time, calculated as $AUC_{0\text{-}t} + C_t/K_{el}$, where $AUC_{0\text{-}t}$ is the area under the concentration vs. time curve from time 0 to the time of last quantifiable concentration (C_t), and K_{el} is the apparent terminal first-order elimination rate constant, determined by linear regression analysis of the natural log-linear segment of the plasma concentration-time curve, expressed in $time^{-1}$ units (1/h). At least 3 time points will be included in the determination of K_{el}.
C_{max}	the first observed peak plasma fibrinogen concentration following the end of drug infusion obtained directly from the experimental data without interpolation, expressed in concentration units (mg/dL).
t_{max}	the observed time to reach peak plasma fibrinogen concentration obtained directly from the experimental data without interpolation, expressed in time units (hour).
$t_{½}$*	the terminal half-life, calculated as $\ln(2)/K_{el}$, expressed in time units (hour).
MRT*	mean residence time, calculated as $AUMC_{0\text{-}\infty}/AUC_{0\text{-}\infty}–(TI/2)$, expressed in time units (hour), where $AUMC_{0\text{-}\infty}$ is the area under the first moment of the concentration vs. time curve from time 0 extrapolated to infinite time, and TI is the length of infusion.*
Cl*	clearance, calculated as $Dose/AUC_{0\text{-}\infty}$, expressed in units dL/h/kg.
Vd*	volume of distribution, calculated as Cl × MRT, expressed in units dL/kg.

*Parameters relying on the determination of the apparent terminal first-order elimination rate constant (K_{el}) will not be reported if $R^2<0.8$ or the extrapolated AUC to infinity is >20%.

Considering different potencies from different lots are administered, the actual dose amount (mg/kg) infused may deviate from the planned or target dose of 70 mg/kg. All appropriate PK parameters, such as AUC and C_{max}, will be dose normalized to 70 mg/kg body weight after taking into account the actual potency. In addition, PK parameters corrected for the baseline fibrinogen level of the subject will be calculated for all the PK parameters above. The correction will be based on the fibrinogen concentration measured pre-infusion. The calculations will be the same as those described above for the un-corrected PK parameters, except the fibrinogen concentration measured pre-infusion will be deducted from the concentrations of each post-infusion sample before the calculations.

9.3 Descriptive Statistics of PK Parameters

Descriptive statistics (summarized separately for adult and pediatric populations, including n, mean, SD, 90% CI for mean, %CV, median, minimum, and maximum will be calculated for all PK parameters. Geometric mean and 90% CI for geometric mean will also be calculated for all PK parameters (except t_{max}). If data allow, PK parameters for the pediatric population will also be summarized by age group as appropriate (e.g. <2, ≥2 - <12, ≥12 - <18 years).

10 EFFICACY ANALYSIS

Efficacy analyses will be performed on the Evaluable population. As sensitivity analyses, the efficacy analyses will also be assessed on the PP population (if different from the Evaluable population).

All analyses on efficacy parameters (including the primary, secondary, [redacted] efficacy endpoints) will be carried out in the overall study population (adult subjects plus pediatric subjects), and will also be conducted in the adult population and the pediatric population separately. The primary efficacy analyses will be the ones performed on the overall study population.

All efficacy variables and their changes from baseline (pre-infusion) will be summarized descriptively by planned day and time. Other than number of non-missing values, mean, SD, median, minimum and maximum, 25th percentile (Q1) and 75th percentile (Q3) will also be calculated. Summary tables and figures will be provided.

10.1 Primary Efficacy Analysis

The primary efficacy endpoint is the mean change (difference) on the MCF variable measured on pre-infusion and 1-hour post-infusion plasma samples by ROTEM in the Evaluable population.

For the primary efficacy endpoint, the change (difference) between the pre-infusion and 1-hour post-infusion MCF, the statistical null hypothesis (H_0: $\Delta = 0$) of no difference will be tested against two-sided alternative hypothesis (H_1: $\Delta \neq 0$) with a one sample t-test for paired observations. The maximum permitted type 1 error will be 5%, two-sided.

The same analysis will be performed using the median value by the Wilcoxon signed rank test. In addition to this, the two analyses above will be performed using the PP population. [redacted]

10.2 Secondary Efficacy Analyses

Secondary efficacy analyses will be performed in the Evaluable and PP populations. Secondary efficacy variables including change (difference) in other thromboelastographic variables (CT, CFT, α) and standard coagulation tests (TT, PT, aPTT) in plasma samples pre-

infusion and 1-hour post-infusion will be summarized by adult and pediatric populations and overall.

Statistical analyses using the one sample t-test for paired observations and the Wilcoxon signed rank test will be performed on the secondary efficacy endpoints, similar to the analyses on the primary efficacy endpoint.

11 SAFETY ANALYSIS

Safety analyses are based on the Safety population. Safety analyses will be performed in the adult and the pediatric population separately and in the overall population (adult and pediatric populations combined).

11.1 Adverse Events

All reported AEs will be coded and summarized by system organ class (SOC) and preferred term (PT) according to MedDRA.

AE causality will be classified and assessed by the investigator. If the causality is definitive, probable, possible, or doubtful/unlikely, the event will be defined as a suspected adverse drug reaction (ADR). If the causal relationship is labeled as "Unrelated", then it will be considered that the AE is not imputable to the investigational medicinal product and it is not a suspected ADR. In the framework of this study, a suspected ADR with a causal relationship of "definite" are named as adverse reaction. Adverse reactions are a subset of suspected ADR.

For summary purposes, AEs will be classified as treatment emergent AEs (TEAEs) or non-treatment emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start of study treatment. A TEAE will be defined as an AE which occurred on or after the start of study treatment. For AEs with incomplete start dates, the same algorithm for missing or partial date information described in Section 8.1 (Prior and Concomitant

Medication) will be used for determination of treatment emergent or not. Non-TEAEs and TEAEs will be summarized separately.

The incidence of AEs, suspected ADRs, non-serious AEs, SAEs, and AEs by severity and causal-relationship to the IP will be summarized using descriptive statistics. At each level of summarization, a subject will only be counted once per SOC or PT using the most severe or highest causal relationship AE. Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed.

Temporally-associated AEs defined as during infusion or within 24 hours and within 72 hours following the end of IP infusion will be separately summarized. For AEs that occur during study drug infusion, the infusion rate in effect at the time of onset of the AE, the time when the AE is first reported and the time when the AE changes materially in intensity and/or resolves will be listed.

Adverse events of special interest including allergic/hypersensitivity reactions and arterial and venous thrombotic events according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) will be separately summarized. The results of the Wells Score utilized to assess thrombotic events risk will also be listed.

All AEs will be presented in a data listing.

11.2 Laboratory Assessments

Serum clinical chemistry (creatinine, blood urea nitrogen [BUN], total bilirubin [TB], alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], glucose, sodium, potassium, chloride, and calcium), hematology (complete blood count [CBC]) (red blood cells [RBC] count, hemoglobin [Hgb], hematocrit [Hct], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], mean corpuscular volume [MCV], white blood cells [WBC] count and differential, and platelet count), and markers of activation of coagulation (D-dimer, anti-thrombin III [ATIII], thrombin-antithrombin III comples [TAT], and prothrombin fragments F1+2 (F1+2) will be collected for all subjects at the assigned visits according to the protocol. Immunogenicity testing for antibodies to fibrinogen and virology (hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus type 1 and type 2, and parvovirus B19) will be done on adult subjects only. The pregnancy, serum clinical chemistry, and fibrinogen samples drawn within 24 hours of the scheduled infusion for determination of subjects' eligibility will be stored and analyzed by a local laboratory. All other laboratory panels above will be stored and/or analyzed by a central laboratory.

The hematology and clinical chemistry parameters will be summarized with number of subjects, mean, SD, median, minimum, and maximum values at each visit. Change from baseline will be descriptively summarized. Shift tables, based on the high/low flags, will also be summarized for each parameter with normal ranges at each visit. Clinically relevant laboratory abnormalities in hematology and clinical chemistry parameters, as judged by the investigators, will be reported, analyzed, and discussed as AEs.

Fibrinogen immunogenicity data with neutralizing antibody and antibodies to fibrinogen will be summarized and listed for evaluation if applicable.

Blood samples for viral nucleic acid amplification technology (NAT) and viral serology will always be analyzed at Baseline (pre-infusion on Day 0). Samples at later time points would be analyzed for a particular virus only in the event of negative results of analysis for that particular virus performed on all previous samples. All available virology testing results will be listed.

All laboratory data will be presented in data listings.

11.3 Vital Signs

Vital sign data (T, RR, HR, SBP, and DBP) and their changes from baseline will be summarized with the number of subjects, mean, SD, median, minimum, and maximum values. The vital sign data collected at the pre-infusion time point on Day 0 (Infusion Visit) will be defined as the baseline values.

All vital sign data will be listed.

Clinically relevant vital sign abnormalities as defined in protocol Section 8.2.2 will be reported, analyzed, and discussed as AEs.

11.4 Physical Assessments

Physical assessment findings at the Screening Visit will be summarized with numbers and percentages by body system. Entries for 'Other' body systems will be grouped together; a subject with 2 or more 'Other' entries will be counted only once. Physical assessment change findings after the Screening Visit will be summarized with numbers and percentages for each response category to the question ‘Were there any findings or existing findings that worsened?’ (‘No’, ‘Yes, not clinically significant’, ‘Yes, clinically significant’).

All physical assessment data will be listed.

Clinically relevant physical assessment abnormalities, as judged by the investigators and which were not already present at baseline, will be reported, analyzed, and discussed as AEs.

12 CHANGES IN PLANNED ANALYSIS IN PROTOCOL

The evaluation of at least 90% of the planned dose was administered for the PP population will use the prepared volume per the pharmacy manual as the reference. The reason is that different potencies from different lots are administered, the actual dose in mg/kg body weight may deviate from the planned or target dose of 70 mg/kg automatically.

Incremental IVR will be calculated for fibrinogen levels from the peak level recorded within and including the first four hours after the end of infusion and reported as [mg/dL]/[mg/kg], not just the first hour. Based on preliminary data review of the fibrinogen levels, it seems that

C_{max} occurs between 1 and 2 hours after the end of infusion, later than the previously planned 1 hour. So in order to ensure the C_{max} was captured the time duration is extended. Also, for RiaSTAP™, a fibrinogen concentrate (human), the incremental IVR was determined from fibrinogen levels obtained up to 4 hours post-infusion and we want to match that.

PK parameters corrected for the baseline fibrinogen level of the subject will be calculated, in addition to the uncorrected PK parameters as planned.

All appropriate PK parameters, such as AUC and C_{max}, will be dose normalized to 70 mg/kg body weight after taking into account the actual potency.

13 SUMMARY OF CHANGES IN SAP AMENDMENTS

13.1 Amendment 1

Cover page

[redacted] title was updated.

The external PK consultant who revises and reviews this version of the SAP and who derives the PK parameters was added as an approver.

Section 1

The versions of protocol and eCRF were updated.

Section 3.1

The four paragraphs about IVR and its definition were revised so that the peak FIB activity within the first four hours after the end of infusion will be included, not just the first hour. And necessary detailed for clarification purpose were also added.

Section 4.1.1.1

The original first and second paragraphs were switched.

The current first and third paragraphs were revised after more details were added for clarification purpose.

The nominal time (hours post start of infusion) was updated from 2 to 1 hour, the mean infusion duration of the adult population in this study.

Footnotes were added for the table of scheduled time points.

The original last paragraph of ‘In addition, the actual duration of the infusion will be calculated.’ was removed, since it was already mentioned in the third paragraph.

Section 4.2

In the definition of PP population, the requirement of at least 90% of the planned dose will be based on the prepared volume.

Section 8.2

A third paragraph was added.

Section 9.1

The following was added to the end of the first paragraph:

The lot number, potency, actual dose infused (mg), and planned dose calculated (mg) based on the planned amount of 70 mg/kg body weight will also be listed.

The original second paragraph was deleted.

The following was added to the end of the current second paragraph:

Section 9.2

In the list of 'pharmacokinetic parameters of interest ', the definitions of these parameters were revised: IVR, C_{max}, t_{max}, MRT.

Units for Cl and Vd were revised, and unit for IVR was added.

A footnote starting with '*' was added for the list of PK parameters of interest.

Other than a few revisions were made for the sake of clarification and/or completeness to the last paragraph, the following was also added:

Considering different potencies from different lots are administered, the actual dose amount (mg/kg) infused may deviate from the planned or target dose of 70 mg/kg. All appropriate PK parameters, such as AUC and C_{max}, will be dose normalized to 70 mg/kg body weight after taking into account the actual potency.

Section 9.3

Added this sentence 'If data allow, PK parameters for the pediatric population will also be summarized by age group as appropriate (e.g. <2, ≥2 - <12, ≥12 - <18 years). '

Section 10

The following was added:

Other than number of non-missing values, mean, SD, median, minimum and maximum, 25th percentile (Q1) and 75th percentile (Q3) will also be calculated. Summary tables and figures will be provided.

Section 11.1

'Suspected' was added in front of all 'adverse drug reaction(s)'.

The following was added:

In the framework of this study, a suspected ADR with a causal relationship of "definite" are named as adverse reaction. Adverse reactions are a subset of suspected ADR.

Section 12

Added this new section.

13.2 Amendment 2

Cover page

Study physician was changed from [redacted] to [redacted].

The external PK consultant was changed from [redacted] to [redacted].

Section 4.1.1.1

The method of adjusting the nominal time (hours post start of infusion) was changed from using 1 hour (i.e., the mean infusion duration for adult) for all subjects to using 1 hour and 0.5 hour for the adult and pediatric groups, respectively.

A new column of nominal time for pediatric was added in the table of scheduled time points.

Section 4.1.2

Added this new section.

STATISTICAL ANALYSIS PLAN (SAP)

FIB Grifols / IG0902

Title: Multicenter, Prospective, Open-Label, Single-Arm Trial to Evaluate the Pharmacokinetics, Efficacy, and Safety of Human Plasma-Derived Fibrinogen (FIB Grifols) in Patients with Congenital Afibrinogenemia

Author's Name and Address: [redacted], MS, MD

Grifols Therapeutics, LLC.

79 TW Alexander Drive

Research Triangle Park, NC 27709

Author's Telephone Number: [redacted]

Version/Date: Final V3.0 Amendment 2 / 10Feb2020

Approved by: [redacted] Date: 10 / Feb / 2020

Name: [redacted], PhD

Title: [redacted]

Approved by [redacted] Date: 10 / Feb / 2020

Name [redacted], MD

Title: [redacted]

Approved by: [redacted] Date: 11 / FEB / 2020

Name: [redacted], MSc

Title: [redacted]

Approved by: [redacted] Date: 11 / FEB / 2020

Name [redacted]

Title: [redacted]

ABBREVIATIONS

α	Alpha angle
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromoplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATIII	Antithrombin III
AUC	Area under the curve
$AUC_{0\text{-}14days}$	Area under the curve from zero to 14 days
$AUC_{0\text{-}\infty}$	Area under the curve from zero to infinity
BUN	Blood urea nitrogen
CBC	Complete blood count
CFT	Clot formation time
CI	Confidence interval
Cl	Clearance
C_{max}	Maximum plasma concentration
CSR	Clinical Study Report
CT	Clotting time
CV	Coefficient of variation
DBP	Diastolic blood pressure
dL	Deciliter
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
F1+2	Prothrombin fragments F1+2
FIB	Fibrinogen
Hct	Hematocrit
Hgb	Hemoglobin
HR	Heart rate
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IP	Investigational product
IVR	In vivo recovery
K_{el}	Terminal first-order elimination rate constant
kg	Kilogram
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MCF	Maximum clot firmness
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRT	Mean residence time
NAT	Nucleic acid amplification technology
Q1	25th percentile
Q3	75th percentile
PK	Pharmacokinetic
PP	Per-protocol
PT	Prothrombin time (according to the context)
PT	Preferred term (according to the context)
RBC	Red blood cells
ROTEM	Rotational thromboelastometry
RR	Respiration rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System Organ Class
SOI	Start of Infusion
T	Temperature
$t_{1/2}$	Half-life
TAT	Thrombin-antithrombin III complex
TB	Total bilirubin
TEAE	Treatment emergent adverse event
t_{max}	Time to the observed maximum plasma concentration
TI	Time of infusion (i.e. length of infusion)
TT	Thrombin time
USA	United States of America
Vd	Volume of distribution
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

TABLE OF CONTENTS

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol IG0902 Version 2.3, dated 12Feb2016 and eCRF Version 5.0, dated 07Feb2017. The purpose of this SAP is to ensure that the statistical methodologies that will be used, and the data listings, summary tables and figures which will be produced, are appropriate and complete to support valid conclusions regarding the study objectives and the completion of the Clinical Study Report (CSR). Additional post-hoc or unplanned analyses, which are not defined in this SAP, may be performed to support the clinical development program. Such analyses will be documented in the CSR.

2 STUDY DESIGN AND OBJECTIVES

2.1 Study Design

This is a phase I-II, multi-center, prospective, open-label, single-arm clinical trial to evaluate the pharmacokinetics (PK), efficacy, and safety of human plasma-derived fibrinogen concentrate FIB Grifols in subjects with congenital fibrinogen deficiency manifested as afibrinogenemia.

In this clinical trial, the PK profile of the investigational product (IP) FIB Grifols will be established by measuring fibrinogen levels at different time points after a single-dose infusion of 70 mg/kg body weight. The hemostatic efficacy of FIB Grifols will be also established by means of rotational thromboelastometry (ROTEM) measures of maximum clot firmness (MCF) at baseline and 1-hour post-infusion.

Comparison of other thromboelastographic measures and standard coagulation tests before and after infusion at different time points will serve as secondary [redacted] endpoints indicative of hemostatic efficacy of the product. Safety of the product will be also studied by assessment of infusion tolerability, adverse events (AEs), and laboratory tests, including immunogenicity and virology testing.

This clinical trial is planned to be performed at sites in multiple countries including India, Italy (European Union), and the United States of America (USA). It is planned to include 11 adult subjects (≥18 years) with congenital fibrinogen deficiency in order to provide at least 10 evaluable adult subjects. Only after the safety of FIB Grifols in adult subjects has been assessed and established by the sponsor, will the study start to enroll 11 pediatric subjects (<18 years) to achieve 10 evaluable pediatric subjects.

During the Screening Visit, the investigator will determine subject's eligibility for inclusion in the study. After giving informed consent and assent if applicable to participate in the clinical trial, subjects will be included in the *Subject's Screening Log* and they will be assessed using screening examinations. Eligible subjects will be treated with the investigational medicinal product under study and they will be included in the *Subject's Identification Log* by the investigator.

Throughout the clinical trial, several visits will be scheduled. Initial visits including Infusion Visit (Day 0) and Day 1 Visit will always be performed at the study center; however, the following visits may be performed by home health nurses at the subject's convenience: Day 2, Day 4, Day 6, Day 9, Day 14, Day 21 and Month 3 Visit (Month 3 Visit is applicable only for adult subjects).

It is required that Week 4 Visit is performed at the respective study center by the site investigative staff. Study assessments will comprise physical assessments, blood analysis, vital signs, and recording of AEs and concomitant medications.

The principal investigator at each site must be aware of and explicitly authorize the use of home health nurses service.

Home health nurses will not perform procedures or assessments that only a medically qualified physician (either the principal investigator or the designated sub-investigator) could do (i.e., physical assessment, AEs assessment or serious adverse events [SAEs] assessment). Home health nurses will only perform activities as indicated on the delegation of duties form. These will be limited to:

- Blood extraction and sample processing for shipment.
- Vital signs measurement (including heart rate [HR], respiration rate [RR], systolic and diastolic blood pressure [SBP and DBP], and temperature [T]).
- Subject interview and recording of potential AEs to be communicated to the principal investigator.
- Concomitant medications recording.

The overall study schema is shown in Figure 2-1.

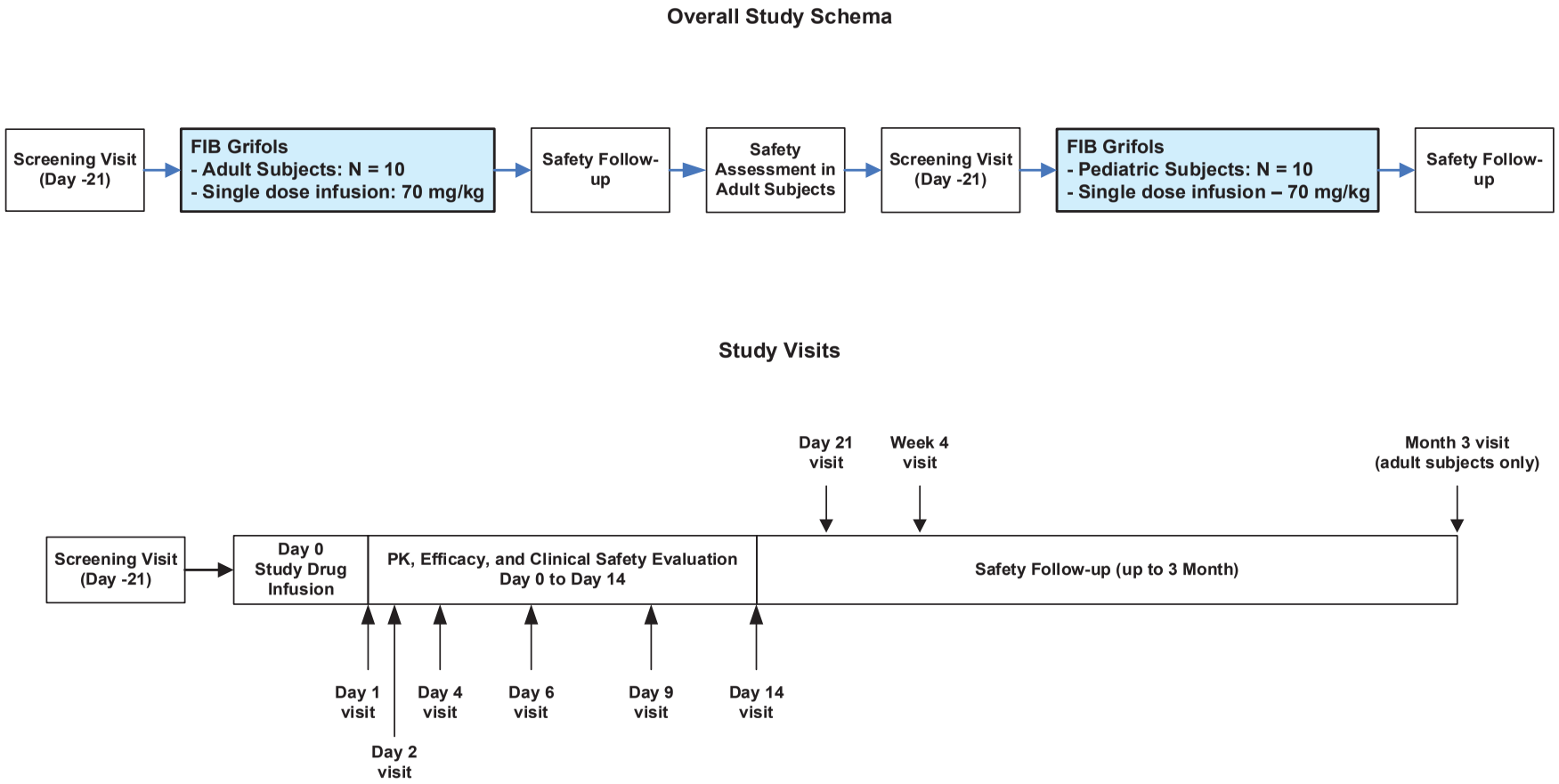

Figure 2-1 Overall Study Schema and Study Visits

2.2 Study Objectives

2.2.1 Pharmacokinetic (PK) Objectives

To evaluate the PK profile of FIB Grifols following single-dose administration of 70 mg/kg body weight.

2.2.2 Efficacy Objectives

To evaluate hemostatic efficacy of FIB Grifols by means of thromboelastographic MCF values' comparison at baseline and one hour after IP administration. Other thromboelastographic measures as well as standard coagulation tests measured at different time points will also serve as secondary [redacted] efficacy endpoints.

2.2.3 Safety Objectives

To evaluate the safety of FIB Grifols, clinical safety, viral safety, and immunogenicity will be assessed in this clinical trial. Safety variables include AEs, vital signs, physical assessments, laboratory tests, viral markers, and antibodies against human fibrinogen.

3 STUDY VARIABLES

3.1 PK Variables

Plasma fibrinogen activity will be determined by the activity (Clauss) method and antigen method (enzyme-linked immunosorbent assay [ELISA]) in the central laboratory of the study. Fibrinogen activity levels will be determined immediately before infusion and at different time points after infusion.

The following PK parameters will be calculated for fibrinogen by a non-compartmental PK method determined from plasma levels before and at 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 1 day (24 hours), 2 days (48 hours), 4 days (96 hours), 6 days (144 hours), 9 days (216 hours), and 14 days (336 hours) after the end of the infusion:

1. Area under the curve (AUC) including AUC from zero to 14 days ($AUC_{0\text{-}14days}$) and AUC from zero to infinity ($AUC_{0\text{-}\infty}$)
2. Maximum plasma concentration (C_{max})
3. Time to the observed maximum plasma concentration (t_{max})
4. Half-life ($t_{1/2}$)
5. Mean residence time (MRT)
6. Volume of distribution (Vd)
7. Clearance (Cl)
8. In vivo recovery (IVR)

Incremental IVR will be calculated for fibrinogen levels from the peak level recorded within and including the first four hours after the end of infusion and reported as [mg/dL]/[mg/kg]. For the calculation of recovery, the declared potency of the investigational medicinal product actually administered to the subject will be considered in the calculation of dose administered, and the actual volume infused to the subject will also be used for calculating the dose administered to each subject.

The *IVR* will be determined for every subject using the following formula:

([*FIB max* (mg/dL)] - [*FIB pre-infusion* (mg/dL)])/*FIB administered* (mg)/Body weight (kg)

where the *FIB max* is the peak FIB activity within the first four hours after the end of infusion and *FIB pre-infusion* is the baseline FIB activity level of the subject. *FIB administered* will be the actual administered dose calculated using the actual volume administered to the subject, the declared potency, and the true concentration of FIB in the batch used.

All PK parameters will be estimated using the fibrinogen concentration values obtained by both functional (Clauss) method and antigen (ELISA) method.

3.2 Efficacy Variables

3.2.1 Primary Efficacy Variable

The primary efficacy variable is difference (improvement) on plasma thromboelastographic MCF from baseline to 1-hour post-infusion. ROTEM measures will be performed at the central laboratory of the study.

3.2.2 Secondary Efficacy Variables

Secondary efficacy variables assessed in this study are:

1. Difference (improvement) on other plasma thromboelastographic variables (clotting time [CT], clot formation time [CFT], and alpha angle [α]) from baseline to 1-hour post-infusion. ROTEM measures will be performed at the central laboratory of the study.
2. Difference (improvement) on standard coagulation tests (thrombin time [TT], prothrombin time [PT], and activated partial thromboplastin time [aPTT]) from baseline to 1-hour post-infusion. Standard coagulation tests will be performed at the central laboratory of the study.

[redacted]

[redacted]

3.3 Safety Variables

The following safety variables will be assessed in this study:

1. AEs
2. Vital signs
3. Physical assessments
4. Laboratory panels
5. Antibodies against fibrinogen (immunogenicity testing)
6. Allergic/hypersensitivity reaction
7. Thrombotic event
8. Viral safety

4 GENERAL STATISTICAL CONSIDERATIONS

Statistical analyses and data presentations will be generated using SAS version 9.4 or higher.

Unless otherwise noted, for continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. All statistical inference will be tested at 2-sided with α=0.05.

Unless otherwise noted, all data collected in the electronic case report forms (eCRFs) or electronically transferred (such as central laboratory data) will be presented in data listings. Subjects will be identified in the data listings by subject number (which includes site number) and grouped by adult and pediatric populations.

For table summaries, the data will be presented at the scheduled visits according to protocol. Any data collected at the unscheduled visits will be listed.

4.1 Data Handling

Unless otherwise noted, if an observation is missing at a specific scheduled visit/timepoint, the value at that visit will not be imputed and will be set to missing.

Baseline will be defined as the last measurement taken prior to the start of the infusion on Day 0 (Infusion Visit).

4.1.1 PK Data Handling

4.1.1.1 Time Window for Pharmacokinetic Analysis

The scheduled time points specified in the protocol will be used in the tables for presenting the individual and summary data of plasma fibrinogen concentrations. The nominal time (hours post start of infusion) will be used in figures for presenting the mean or median measured concentration vs. time curve. Due to the variable infusion durations in individual subjects and the considerable difference of mean infusion durations between the adult and pediatric groups, the nominal time will be adjusted by using the mean infusion duration of 1 hour and 0.5 hour for the adult and pediatric groups, respectively.

If PK blood samples are not drawn exactly at the protocol specified time, the samples will still be included in the PK analysis as long as the actual sample collection date and clock time for each sample is recorded and the actual elapsed time from the start of infusion can be calculated.

The actual elapsed time between the start of the infusion and each PK blood sample draw will be calculated and used as the PK time point. In addition, the actual duration of the infusion will be calculated to determine the time of the end of infusion. The PK parameter calculation for each subject will be based on the actual elapsed time from the start of infusion instead of the scheduled time or nominal time post end of infusion.

An example of actual elapsed time calculated from the time of the start of infusion is shown below.

Scheduled Time	**Nominal Time (Hours post SOI) for Adult**	**Nominal Time (Hours post SOI) for Pediatric**	**Example Actual Elapsed Time (Hours post SOI)**
Pre-infusion	**	**	**
Start of infusion	0	0	0
End of infusion*	1	0.5	1.25
30 minutes post-infusion	1.5	1	1.75
1 hour post-infusion	2	1.5	2.20
2 hours post-infusion	3	2.5	3.35
4 hours post-infusion	5	4.5	5.30
8 hours post-infusion	9	8.5	9.56
Day 1 (24 hours post-infusion)	25	24.5	25.90
Day 2 (48 hours post-infusion)	49	48.5	49.80
Day 4 (96 hours post-infusion)	97	96.5	97.67
Day 6 (144 hours post-infusion)	145	144.5	145.50

Day 9 (216 hours post-infusion)	217	216.5	217.75
Day 14 (336 hours post-infusion)	337	336.5	337.20

*End of infusion is not a defined time point in order to facilitate the different infusion times required per patient and serves as a relative measure for the calculation of nominal times of the post-infusion time points.
SOI – Start of infusion
**The pre-infusion concentration will be used for the baseline concentration regardless of actual time taken so long as it occurs before the SOI.

4.1.1.2 Plasma Concentration Values Below the Quantification Limit

If any plasma concentration values of fibrinogen are below the lower limit of quantification (LLOQ) for either the activity (Clauss) method or the antigen (ELISA) method, in general the values will be replaced with a value of zero for the PK analysis. If necessary, alternative methods may be used to impute the values below LLOQ based on PK principle, and such methods will be documented in the CSR.

4.1.1.3 Plasma Concentration Missing Values

For PK analysis, any invalid plasma concentration values of fibrinogen will be treated as missing. If necessary, invalid or missing values will be interpolated or extrapolated using PK principle, as appropriate, and such interpolations or extrapolations will be documented in the CSR.

4.1.2 Efficacy Data Handling

For the ROTEM measurements, undetectable values of MCF and alpha angle are set to 0, and undetectable values of CFT and CT are set to missing.

4.2 Analysis Populations

Safety population

The Safety population consists of all subjects who receive infusion (at any dose) of the IP. This will be the analysis population for the safety data.

PK population

The PK population will consist of all subjects who have received study medication and have sufficient fibrinogen plasma concentration data to facilitate calculation of PK parameters. The PK population will be used for the analyses of the PK parameters.

Adequate treatment compliance will be considered when determining valid concentration-time data for inclusion in the PK analyses. The values or profiles deemed not reliable due to treatment non-compliance or other reasons will be excluded from the PK analyses and flagged in the listing. Any subject who has at least one major protocol deviation which might

have impact on the PK analyses (to be defined in a data review meeting prior to database lock) will be excluded from the PK population.

Evaluable population (efficacy)

The Evaluable population will include all subjects who received IP at any amount and who have at least two measurements for the primary efficacy variable: one pre-infusion MCF and 1-hour post-infusion MCF measurements by ROTEM.

Per-protocol population (efficacy)

The Per-protocol (PP) population will include all subjects who received planned dose of the IP (at least 90% of the planned dose based on the prepared volume), who have no major protocol violation that might have impact on the primary efficacy assessment (to be defined in a data review meeting prior to database lock), and who have at least two measurements for the primary efficacy variable: one baseline (pre-infusion) MCF measurement by ROTEM and 1-hour post-infusion MCF measurement by ROTEM for the investigational medicinal product.

Any deviations from the protocol will be recorded in the protocol deviation list. The validity of a subject for inclusion in each of these four populations (Safety, PK, Evaluable, and PP) will be assessed at a data review meeting that will take place before database lock. The data review meeting will review the protocol deviation list, as well as data listings. If additional protocol deviations are identified which justify removing a subject from any population, then these decisions will be documented.

4.3 Sample Size Considerations

The sample size in this study is based on the PK assessment. The sample size of 10 adult subjects was selected to establish a PK profile of the IP. In order to allow for possible drop-outs, 11 adult subjects will be enrolled in the study.

Only after the safety of the product has been assessed and established in the adult subjects population, will 10 pediatric subjects be enrolled into the study. Assuming a 10% dropout rate, a total of 11 pediatric subjects need to be enrolled.

4.4 Interim Analysis

An interim safety analysis will be performed with the adult population in order to assess the safety of FIB Grifols prior to starting enrollment of pediatric subjects. PK and efficacy interim analyses of the investigational medicinal product may also be performed in the adult population.

5 SUBJECT DISPOSITION

Subject disposition will be summarized by adult and pediatric populations separately and on the overall population (adult and pediatric populations combined).

Subject disposition will include the number of subjects screened, number of subjects enrolled, number and percentage of subjects in each analysis population, number and percentage of subjects completing the study.

The number and percentage of subjects discontinuing early from the study will be summarized for primary reasons of discontinuation. Also, the number and percentage of screening failures will be summarized for primary reasons of ineligibility.

Disposition status will be listed for all subjects.

6 PROTOCOL DEVIATIONS

Protocol deviations will be identified during the study and evaluated before the database lock. The type/category of protocol deviations and severity (i.e., minor or major) will be summarized by adult and pediatric populations and overall.

7 DEMOGRAPHY AND MEDICAL HISTORY

7.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics including sex, race, ethnicity, age, age categories (<2, ≥2 - <12, ≥12 - <18, ≥18 - <65, ≥65 - <70), baseline pregnancy test, height, weight, and body mass index will be summarized by adult and pediatric populations and overall. The congenital fibrinogen deficiency history will be summarized.

All demographic and baseline characteristics data will be listed.

7.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized/listed by adult and pediatric populations and overall.

8 CONCOMITANT MEDICATION AND TREATMENT

8.1 Prior and Concomitant Medication

All medications as documented by the investigator will be coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug classification Dictionary (WHO-DD). All medications will be summarized by adult and pediatric populations and overall and sorted alphabetically by medication class (i.e., ATC level 2) and medication sub-class (i.e., ATC level 4). If the ATC level 4 term is missing, the ATC level 3 term will be used in the medication summary table and data listing.

The following convention will be used for missing or partial end date information in order to determine whether a medication is prior or concomitant:

The unknown portions of a medication end date will be assumed to be as late as possible. If a medication end date is incomplete but the month/year of medication end date is prior to the month/year of the start of study treatment, then the medication will be considered a prior medication. If a medication end date is incomplete but the month/year of medication end date is the same as the month/year of the start of study treatment, then the medication will be considered a concomitant medication. All other incomplete medication end dates and all medications with missing end dates will be assumed to be concomitant medications. Start/end dates reported in the eCRFs will be presented in the listings.

Prior medications are defined as any medication ended prior to the start of study treatment (i.e., start of the infusion on Day 0).

Concomitant medications are defined as any medication started on or after the start of study treatment or any medication taken prior to the start of study treatment and continued after the start of study treatment during the study.

8.2 Extent of Study Treatment Exposure and Compliance

The total volume infused (mL) and duration of infusion (minutes) will be summarized. Further, exposure information along with infusion interruptions will also be summarized. Duration of infusion will be calculated as stop time of infusion – start time of infusion.

Treatment compliance will be calculated as (total volume infused / total volume prepared) * 100% during the study. The total volume prepared and dispensed by pharmacist is the intended dose volume a subject should be given based on the body weight. The treatment compliance will be listed and summarized. The number of subjects with at least 90% compliance will be calculated.

Considering different potencies from different lots are administered, the actual dose in mg/kg body weight may deviate from the planned or target dose of 70 mg/kg. The lot number, potency, actual dose infused (mg), and planned dose calculated (mg) based on the planned amount of 70 mg/kg body weight will be listed.

Additional consideration regarding treatment compliance will be given when determining legitimacy for inclusion of fibrinogen concentration data for calculation of the PK parameters. Reasons for excluding fibrinogen concentration data or a subject from the analysis of PK parameters will be documented in the CSR.

9 PK ANALYSIS

PK analyses will be based on the PK population and will be performed on the adult and pediatric populations independently. PK analyses will be performed using the fibrinogen concentration values obtained by both Clauss method and antigen (ELISA) method.

9.1 Analysis of PK concentration and dosing data

Plasma concentrations of fibrinogen will be presented in a listing by subject, study day, date, and scheduled/nominal sampling time point. The data listing will provide details of all planned plasma collection time points relative to the start of infusion (scheduled and nominal times as shown in Section 4.1.1.1), actual collection date and clock times and actual elapsed times from the start of the infusion, as well as plasma fibrinogen concentrations. If any concentration values are excluded from the PK analyses, they will be flagged in the listing. The lot number, potency, actual dose infused (mg), and planned dose calculated (mg) based on the planned amount of 70 mg/kg body weight will also be listed. .

Plasma concentrations of fibrinogen will be summarized by adult and pediatric populations and the scheduled/nominal time point. The summaries will include n, mean, SD, 90% confidence interval (CI) for mean, coefficient of variation (%CV), median, minimum, maximum, and geometric mean. [redacted]

Plasma fibrinogen concentration vs. time curves for individual subjects will be presented with the actual elapsed time from the start of the infusion plotted on the x-axis. Individual concentration vs. time plots will also be presented for all subjects on the same figure (so called spaghetti plot) for the adult and pediatric populations separately. For all subjects combined (separately for the adult and pediatric populations), mean or median plasma fibrinogen concentration vs. time curves will be presented in one figure with the nominal time (see Section 4.1.1.1) plotted on the x-axis. All plasma fibrinogen concentration vs. time curves will be plotted on both the linear and the semi-log scale.

9.2 Calculation of PK parameters

The PK parameters of plasma fibrinogen following single-dose administration in individual subjects will be determined as appropriate and as data permit. The PK parameters will include IVR, AUC calculated as $AUC_{0\text{-}14days}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, MRT, Vd, and Cl.

The PK parameters will be calculated using non-compartmental methods with WinNonlin software.

All PK parameters will be calculated using the fibrinogen concentration values obtained by both Clauss method and antigen (ELISA) method.

The pharmacokinetic parameters of interest will be determined as follows:

IVR	incremental in vivo recovery, calculated as ([FIB max (mg/dL)] - [FIB pre-infusion (mg/dL)])/FIB administered (mg)/Body weight (kg), where the FIB max is the peak FIB activity during the first four hours of sampling after the end of infusion and FIB pre-infusion is the baseline FIB activity of the subject, expressed as mg/dL per

	mg/kg. FIB administered will be the actual administered dose calculated using the actual volume administered to the subject, the potency, and the true concentration of FIB in the batch used.
$AUC_{0\text{-}14days}$	area under the concentration vs. time curve from time 0 to 14 days, calculated by a combination of linear and logarithmic trapezoidal methods and expressed in the unit of concentration × time (e.g., mg × h/dL). The linear trapezoidal method will be used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
$AUC_{0\text{-}\infty}$*	area under the concentration vs. time curve from time 0 extrapolated to infinite time, calculated as $AUC_{0\text{-}t} + C_t/K_{el}$, where $AUC_{0\text{-}t}$ is the area under the concentration vs. time curve from time 0 to the time of last quantifiable concentration (C_t), and K_{el} is the apparent terminal first-order elimination rate constant, determined by linear regression analysis of the natural log-linear segment of the plasma concentration-time curve, expressed in $time^{-1}$ units (1/h). At least 3 time points will be included in the determination of K_{el}.
C_{max}	the first observed peak plasma fibrinogen concentration following the end of drug infusion obtained directly from the experimental data without interpolation, expressed in concentration units (mg/dL).
t_{max}	the observed time to reach peak plasma fibrinogen concentration obtained directly from the experimental data without interpolation, expressed in time units (hour).
$t_{½}$*	the terminal half-life, calculated as $\ln(2)/K_{el}$, expressed in time units (hour).
MRT*	mean residence time, calculated as $AUMC_{0\text{-}\infty}/AUC_{0\text{-}\infty}–(TI/2)$, expressed in time units (hour), where $AUMC_{0\text{-}\infty}$ is the area under the first moment of the concentration vs. time curve from time 0 extrapolated to infinite time, and TI is the length of infusion.*
Cl*	clearance, calculated as $Dose/AUC_{0\text{-}\infty}$, expressed in units dL/h/kg.
Vd*	volume of distribution, calculated as Cl × MRT, expressed in units dL/kg.

*Parameters relying on the determination of the apparent terminal first-order elimination rate constant (K_{el}) will not be reported if $R^2<0.8$ or the extrapolated AUC to infinity is >20%.

Considering different potencies from different lots are administered, the actual dose amount (mg/kg) infused may deviate from the planned or target dose of 70 mg/kg. All appropriate PK parameters, such as AUC and C_{max}, will be dose normalized to 70 mg/kg body weight after taking into account the actual potency. In addition, PK parameters corrected for the baseline fibrinogen level of the subject will be calculated for all the PK parameters above. The correction will be based on the fibrinogen concentration measured pre-infusion. The calculations will be the same as those described above for the un-corrected PK parameters, except the fibrinogen concentration measured pre-infusion will be deducted from the concentrations of each post-infusion sample before the calculations.

9.3 Descriptive Statistics of PK Parameters

Descriptive statistics (summarized separately for adult and pediatric populations, including n, mean, SD, 90% CI for mean, %CV, median, minimum, and maximum will be calculated for all PK parameters. Geometric mean and 90% CI for geometric mean will also be calculated for all PK parameters (except t_{max}). If data allow, PK parameters for the pediatric population will also be summarized by age group as appropriate (e.g. <2, ≥2 - <12, ≥12 - <18 years).

10 EFFICACY ANALYSIS

Efficacy analyses will be performed on the Evaluable population. As sensitivity analyses, the efficacy analyses will also be assessed on the PP population (if different from the Evaluable population).

All analyses on efficacy parameters (including the primary, secondary, [redacted] efficacy endpoints) will be carried out in the overall study population (adult subjects plus pediatric subjects), and will also be conducted in the adult population and the pediatric population separately. The primary efficacy analyses will be the ones performed on the overall study population.

All efficacy variables and their changes from baseline (pre-infusion) will be summarized descriptively by planned day and time. Other than number of non-missing values, mean, SD, median, minimum and maximum, 25th percentile (Q1) and 75th percentile (Q3) will also be calculated. Summary tables and figures will be provided.

10.1 Primary Efficacy Analysis

The primary efficacy endpoint is the mean change (difference) on the MCF variable measured on pre-infusion and 1-hour post-infusion plasma samples by ROTEM in the Evaluable population.

For the primary efficacy endpoint, the change (difference) between the pre-infusion and 1-hour post-infusion MCF, the statistical null hypothesis (H_0: $\Delta = 0$) of no difference will be tested against two-sided alternative hypothesis (H_1: $\Delta \neq 0$) with a one sample t-test for paired observations. The maximum permitted type 1 error will be 5%, two-sided.

The same analysis will be performed using the median value by the Wilcoxon signed rank test. In addition to this, the two analyses above will be performed using the PP population. [redacted]

10.2 Secondary Efficacy Analyses

Secondary efficacy analyses will be performed in the Evaluable and PP populations. Secondary efficacy variables including change (difference) in other thromboelastographic variables (CT, CFT, α) and standard coagulation tests (TT, PT, aPTT) in plasma samples pre-

infusion and 1-hour post-infusion will be summarized by adult and pediatric populations and overall.

Statistical analyses using the one sample t-test for paired observations and the Wilcoxon signed rank test will be performed on the secondary efficacy endpoints, similar to the analyses on the primary efficacy endpoint.

11 SAFETY ANALYSIS

Safety analyses are based on the Safety population. Safety analyses will be performed in the adult and the pediatric population separately and in the overall population (adult and pediatric populations combined).

11.1 Adverse Events

All reported AEs will be coded and summarized by system organ class (SOC) and preferred term (PT) according to MedDRA.

AE causality will be classified and assessed by the investigator. If the causality is definitive, probable, possible, or doubtful/unlikely, the event will be defined as a suspected adverse drug reaction (ADR). If the causal relationship is labeled as "Unrelated", then it will be considered that the AE is not imputable to the investigational medicinal product and it is not a suspected ADR. In the framework of this study, a suspected ADR with a causal relationship of "definite" are named as adverse reaction. Adverse reactions are a subset of suspected ADR.

For summary purposes, AEs will be classified as treatment emergent AEs (TEAEs) or non-treatment emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start of study treatment. A TEAE will be defined as an AE which occurred on or after the start of study treatment. For AEs with incomplete start dates, the same algorithm for missing or partial date information described in Section 8.1 (Prior and Concomitant

Medication) will be used for determination of treatment emergent or not. Non-TEAEs and TEAEs will be summarized separately.

The incidence of AEs, suspected ADRs, non-serious AEs, SAEs, and AEs by severity and causal-relationship to the IP will be summarized using descriptive statistics. At each level of summarization, a subject will only be counted once per SOC or PT using the most severe or highest causal relationship AE. Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed.

Temporally-associated AEs defined as during infusion or within 24 hours and within 72 hours following the end of IP infusion will be separately summarized. For AEs that occur during study drug infusion, the infusion rate in effect at the time of onset of the AE, the time when the AE is first reported and the time when the AE changes materially in intensity and/or resolves will be listed.

Adverse events of special interest including allergic/hypersensitivity reactions and arterial and venous thrombotic events according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) will be separately summarized. The results of the Wells Score utilized to assess thrombotic events risk will also be listed.

All AEs will be presented in a data listing.

11.2 Laboratory Assessments

Serum clinical chemistry (creatinine, blood urea nitrogen [BUN], total bilirubin [TB], alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], glucose, sodium, potassium, chloride, and calcium), hematology (complete blood count [CBC]) (red blood cells [RBC] count, hemoglobin [Hgb], hematocrit [Hct], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], mean corpuscular volume [MCV], white blood cells [WBC] count and differential, and platelet count), and markers of activation of coagulation (D-dimer, anti-thrombin III [ATIII], thrombin-antithrombin III comples [TAT], and prothrombin fragments F1+2 (F1+2) will be collected for all subjects at the assigned visits according to the protocol. Immunogenicity testing for antibodies to fibrinogen and virology (hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus type 1 and type 2, and parvovirus B19) will be done on adult subjects only. The pregnancy, serum clinical chemistry, and fibrinogen samples drawn within 24 hours of the scheduled infusion for determination of subjects' eligibility will be stored and analyzed by a local laboratory. All other laboratory panels above will be stored and/or analyzed by a central laboratory.

The hematology and clinical chemistry parameters will be summarized with number of subjects, mean, SD, median, minimum, and maximum values at each visit. Change from baseline will be descriptively summarized. Shift tables, based on the high/low flags, will also be summarized for each parameter with normal ranges at each visit. Clinically relevant laboratory abnormalities in hematology and clinical chemistry parameters, as judged by the investigators, will be reported, analyzed, and discussed as AEs.

Fibrinogen immunogenicity data with neutralizing antibody and antibodies to fibrinogen will be summarized and listed for evaluation if applicable.

Blood samples for viral nucleic acid amplification technology (NAT) and viral serology will always be analyzed at Baseline (pre-infusion on Day 0). Samples at later time points would be analyzed for a particular virus only in the event of negative results of analysis for that particular virus performed on all previous samples. All available virology testing results will be listed.

All laboratory data will be presented in data listings.

11.3 Vital Signs

Vital sign data (T, RR, HR, SBP, and DBP) and their changes from baseline will be summarized with the number of subjects, mean, SD, median, minimum, and maximum values. The vital sign data collected at the pre-infusion time point on Day 0 (Infusion Visit) will be defined as the baseline values.

All vital sign data will be listed.

Clinically relevant vital sign abnormalities as defined in protocol Section 8.2.2 will be reported, analyzed, and discussed as AEs.

11.4 Physical Assessments

Physical assessment findings at the Screening Visit will be summarized with numbers and percentages by body system. Entries for 'Other' body systems will be grouped together; a subject with 2 or more 'Other' entries will be counted only once. Physical assessment change findings after the Screening Visit will be summarized with numbers and percentages for each response category to the question ‘Were there any findings or existing findings that worsened?’ (‘No’, ‘Yes, not clinically significant’, ‘Yes, clinically significant’).

All physical assessment data will be listed.

Clinically relevant physical assessment abnormalities, as judged by the investigators and which were not already present at baseline, will be reported, analyzed, and discussed as AEs.

12 CHANGES IN PLANNED ANALYSIS IN PROTOCOL

The evaluation of at least 90% of the planned dose was administered for the PP population will use the prepared volume per the pharmacy manual as the reference. The reason is that different potencies from different lots are administered, the actual dose in mg/kg body weight may deviate from the planned or target dose of 70 mg/kg automatically.

Incremental IVR will be calculated for fibrinogen levels from the peak level recorded within and including the first four hours after the end of infusion and reported as [mg/dL]/[mg/kg], not just the first hour. Based on preliminary data review of the fibrinogen levels, it seems that

C_{max} occurs between 1 and 2 hours after the end of infusion, later than the previously planned 1 hour. So in order to ensure the C_{max} was captured the time duration is extended. Also, for RiaSTAP™, a fibrinogen concentrate (human), the incremental IVR was determined from fibrinogen levels obtained up to 4 hours post-infusion and we want to match that.

PK parameters corrected for the baseline fibrinogen level of the subject will be calculated, in addition to the uncorrected PK parameters as planned.

All appropriate PK parameters, such as AUC and C_{max}, will be dose normalized to 70 mg/kg body weight after taking into account the actual potency.

13 SUMMARY OF CHANGES IN SAP AMENDMENTS

13.1 Amendment 1

Cover page

[redacted] title was updated.

The external PK consultant who revises and reviews this version of the SAP and who derives the PK parameters was added as an approver.

Section 1

The versions of protocol and eCRF were updated.

Section 3.1

The four paragraphs about IVR and its definition were revised so that the peak FIB activity within the first four hours after the end of infusion will be included, not just the first hour. And necessary detailed for clarification purpose were also added.

Section 4.1.1.1

The original first and second paragraphs were switched.

The current first and third paragraphs were revised after more details were added for clarification purpose.

The nominal time (hours post start of infusion) was updated from 2 to 1 hour, the mean infusion duration of the adult population in this study.

Footnotes were added for the table of scheduled time points.

The original last paragraph of ‘In addition, the actual duration of the infusion will be calculated.’ was removed, since it was already mentioned in the third paragraph.

Section 4.2

In the definition of PP population, the requirement of at least 90% of the planned dose will be based on the prepared volume.

Section 8.2

A third paragraph was added.

Section 9.1

The following was added to the end of the first paragraph:

The lot number, potency, actual dose infused (mg), and planned dose calculated (mg) based on the planned amount of 70 mg/kg body weight will also be listed.

The original second paragraph was deleted.

The following was added to the end of the current second paragraph:

Section 9.2

In the list of 'pharmacokinetic parameters of interest ', the definitions of these parameters were revised: IVR, C_{max}, t_{max}, MRT.

Units for Cl and Vd were revised, and unit for IVR was added.

A footnote starting with '*' was added for the list of PK parameters of interest.

Other than a few revisions were made for the sake of clarification and/or completeness to the last paragraph, the following was also added:

Considering different potencies from different lots are administered, the actual dose amount (mg/kg) infused may deviate from the planned or target dose of 70 mg/kg. All appropriate PK parameters, such as AUC and C_{max}, will be dose normalized to 70 mg/kg body weight after taking into account the actual potency.

Section 9.3

Added this sentence 'If data allow, PK parameters for the pediatric population will also be summarized by age group as appropriate (e.g. <2, ≥2 - <12, ≥12 - <18 years). '

Section 10

The following was added:

Other than number of non-missing values, mean, SD, median, minimum and maximum, 25th percentile (Q1) and 75th percentile (Q3) will also be calculated. Summary tables and figures will be provided.

Section 11.1

'Suspected' was added in front of all 'adverse drug reaction(s)'.

The following was added:

In the framework of this study, a suspected ADR with a causal relationship of "definite" are named as adverse reaction. Adverse reactions are a subset of suspected ADR.

Section 12

Added this new section.

13.2 Amendment 2

Cover page

Study physician was changed from [redacted] to [redacted].

The external PK consultant was changed from [redacted] to [redacted].

Section 4.1.1.1

The method of adjusting the nominal time (hours post start of infusion) was changed from using 1 hour (i.e., the mean infusion duration for adult) for all subjects to using 1 hour and 0.5 hour for the adult and pediatric groups, respectively.

A new column of nominal time for pediatric was added in the table of scheduled time points.

Section 4.1.2

Added this new section.