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**
NCT Number:	NCT02281500
Document Date:	Protocol Version 3.0: 08 October 2018

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

Clinical Trial Sponsor:	Instituto Grifols, S.A. Can Guasch, 2 08150 Parets del Vallès Barcelona Spain
Product:	Human plasma-derived fibrinogen concentrate (FIB Grifols)
Study Phase:	I-II
Protocol Number:	IG0902
Version Number:	3.0 Includes IG0902/Version 2.3/12 Feb 2016, IG0902/Version 2.2/29 Sep 2015, IG0902/Versioni 2.1/08 Jul 2015 and IG0902/Version 2.0/21 Aug 2014
Date:	08 Oct 2018
EudraCT Number:	2013-004343-23

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

Protocol Number: IG0902

EudraCT Number: 2013-004343-23

Version Number: 3.0

Version Date: 8 Oct 2018

SPONSOR SIGNATURE/APPROVAL PAGE

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Signature: [redacted] Date: 09 OCTOBER 2018

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

Protocol Number: IG0902

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Version Date: 08 Oct 2018

INVESTIGATOR SIGNATURE PAGE

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol, Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable regulatory requirements.

_____	_____
INVESTIGATOR NAME (Please Print)	LOCATION
_____	_____
INVESTIGATOR SIGNATURE	DATE

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PROTOCOL SUMMARY

Protocol 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
Protocol Number:	IG0902
Protocol Version and Date:	Version 3.0, 08 Oct 2018
Sponsor:	Instituto Grifols, S.A. Can Guasch, 2 08150 Parets del Vallès Barcelona Spain
Coordinating Investigator:	Flora Peyvandi, MD Milano, Italy
Investigational Product (Test):	Human Plasma-Derived Fibrinogen Concentrate Grifols (FIB Grifols): – A Type II glass vial containing 1.0 g of Fibrinogen (powder for infusion). – A Type II glass vial containing 50 mL of sterile water for injection (SWFI) as solvent.
Indication:	Treatment of subjects with congenital afibrinogenemia (fibrinogen deficiency)
Trial Phase:	I/II
Trial Sites:	Multi-center study is planned to be conducted in multiple sites in multiple countries including India, Italy (European Union), Turkey, Lebanon, and the United States of America (USA).
Study Objectives:	To evaluate the pharmacokinetics, efficacy, and safety of human plasma-derived fibrinogen concentrate FIB Grifols after a single-dose 70 mg/kg body weight administration.
Trial Design:	This study is a phase I-II, multi-center, prospective, open-label, single-arm clinical study to evaluate the PK, efficacy, and safety of human plasma-derived fibrinogen concentrate FIB Grifols in adult and pediatric subjects with congenital afibrinogenemia. Approximately 10 adult subjects (≥18 years) with congenital afibrinogenemia will be administered a single dose of study drug

	at 70 mg/kg body weight and will be followed for PK, efficacy, and safety assessments. After the safety of fibrinogen concentrate FIB Grifols is assessed in at least 10 adult subjects and no safety issues are raised by the sponsor, the study will start to enroll approximately 10 pediatric subjects (<18 years) who will be dosed with study drug and followed for PK, efficacy, and safety assessments. All enrolled subjects (both adult and pediatric) will have documented congenital fibrinogen deficiency manifested as afibrinogenemia but will not have received any fibrinogen-containing product therapy within the preceding 21 days before the infusion of study drug. All subjects (both adult and pediatric) will be infused with the investigational product at 70 mg/kg body weight. PK parameters that will be calculated from plasma fibrinogen levels measured at different time points include: incremental in vivo recovery (IVR), area under the curve (AUC) calculated as AUC from zero to 14 days ($AUC_{0\text{-}14days}$) and AUC from zero to infinity ($AUC_{0\text{-}\infty}$), maximum plasma concentration (C_{max}), time to the observed maximum plasma concentration (t_{max}), half-life ($t_{1/2}$), mean residence time (MRT), volume of distribution (Vd), and clearance (Cl). Hemostatic efficacy of the investigational product will be assessed by means of rotational thromboelastometry (ROTEM) measure of maximum clot firmness (MCF) at baseline and 1-hour post-infusion. Other thromboelastographic measures as well as standard coagulation tests will be also determined pre- and post-infusion. Clinical safety, virus safety, and immunogenicity will be assessed in this clinical trial. Safety variables include adverse events (AEs), vital signs, physical assessments, laboratory tests, viral markers, and antibodies against human fibrinogen. Allergic/hypersensitivity reactions and thrombotic events will be monitored during the study. Stopping criteria have been established for immunogenic and thrombogenic events. Briefly, if a confirmed, single case of any of these events is reported after a subject has been dosed with study drug, any further enrollment and dosing of subjects in the study will be suspended until the event can be adequately assessed by the sponsor. The enrollment and dosing will only resume after explicit authorization by the sponsor.
Study Population and Sample Size:	Adult and pediatric subjects with congenital fibrinogen deficiency manifested as afibrinogenemia. Ten (10) evaluable adult subjects (≥18 years) will be sufficient for

	the purpose of establishing a PK profile of the investigational product. In order to allow for possible drop-outs, 11 subjects will be enrolled in the study. Only after the safety of the study drug has been assessed and established in the adult population, the study will start to enroll pediatric subjects. It is planned that 11 pediatric subjects will be enrolled to achieve 10 evaluable pediatric subjects.
Clinical Trial Duration:	Subjects' participation in this clinical trial will be approximately 3 months and 3 weeks: – Screening Visit: up to 21 days before study drug infusion visit (Day 0) – Study drug infusion visit: administration of study drug (Day 0) – PK, efficacy, and clinical safety follow-up period: Day 0 to Day 14 post-infusion – Safety follow-up period (Day 21, Week 4, and Month 3 Visits)
Main Subject Inclusion Criteria:	Subjects (both adult and pediatric) will be eligible for entry into the study once they meet ALL of the following inclusion criteria: 1. Male or female subjects less than 70 years old[a]. 2. Sign the written Informed Consent Form (ICF), or the subject's parent or legal guardian signs the ICF where applicable, and the Subject Authorization Form (SAF) where applicable. Pediatric subjects, as defined by local regulations, will be asked to sign an age appropriate assent form. 3. Subjects diagnosed with congenital fibrinogen deficiency manifested as afibrinogenemia. 4. Subjects with a fibrinogen level undetectable[1], or equal or less than 30 mg/dL determined by <u>both</u> Clauss and antigen methods at baseline[2] (samples drawn within 24 hours prior to infusion on Day 0 Visit will be tested locally) or at Screening Visit[3] (samples should be drawn at least 14 days prior to infusion on Day 0 Visit to be tested at central laboratory). [1] Limit of detection for fibrinogen level determination must be 30 mg/dL or lower for both methods. [2]For sites that have the capability of performing fibrinogen level determinations locally by both Clauss and antigen methods with a limit of detection of 30 mg/dL or lower. [3]For sites that do not have the capability of performing fibrinogen level determinations by both Clauss and antigen methods locally or have methods that are not sensitive enough

	(limit of detection: larger than 30 mg/dL). 5. Female subjects of child-bearing potential[b] must have a negative test for pregnancy blood or urine human chorionic gonadotropin (HCG-based assay) at baseline (sample drawn within 24 hours prior to infusion on Day 0 Visit). 6. Female subjects of child-bearing potential[b] and their partners have agreed to practice contraception using a method of proven reliability (ie, hormonal methods, barrier methods, intrauterine devices methods, or abstinence) to prevent a pregnancy during the course of the clinical trial. 7. Subjects must be willing to comply with all aspects of the clinical trial protocol, including blood sampling, for the whole duration of the study. [a]The enrollment of pediatric subjects (<18 years of age) will be initiated only after the safety of FIB Grifols in all adult subjects has been evaluated by the sponsor. [b]Women of child-bearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation or bilateral oophorectomy), or is not postmenopausal (post-menopausal is defined as amenorrhea for >12 consecutive months or women on hormone replacement therapy with documented serum follicle stimulating hormone level <35 mIU/mL). Even in women who are using oral, implanted, or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile, eg, vasectomy, should be considered to be of child bearing potential.
Main Exclusion Criteria:	Subjects will be ineligible for entry into the study if they meet ANY of the following exclusion criteria: 1. Subjects who received any fibrinogen-containing product within 21 days prior to Day 0 Visit. 2. Subjects who present with active bleeding within 10 days prior to infusion on Day 0. 3. Subjects with acquired (secondary) fibrinogen deficiency. 4. Subjects diagnosed with dysfibrinogenemia. 5. Subjects with documented history of deep vein thrombosis (DVT), pulmonary embolism, or arterial thrombosis within 1 year prior to enrolment in this clinical trial. 6. Subjects with known antibodies against fibrinogen. 7. Subjects with a history of severe anaphylactic reactions or

	reactions to any blood-derived product. 8. Subjects with a history of intolerance to any component of the investigational product. 9. Subjects with a documented history of IgA deficiency and antibodies against IgA. 10. Females who are pregnant or breastfeeding. 11. Subjects with renal impairment (ie, serum creatinine exceeds more than 2.0 times the upper limit of normal [ULN]) at baseline (sample drawn within 24 hours prior to infusion on Day 0 Visit). 12. Subjects with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding more than 2.5 times the ULN at baseline (sample drawn within 24 hours prior to infusion on Day 0 Visit). 13. Subjects with a history of chronic alcoholism or illicit drug addiction in the preceding 12 months prior to enrollment in this clinical trial. 14. Subjects with any medical condition which is likely to interfere with the evaluation of the study drug and/or the satisfactory conduct of the clinical trial according to the investigator's judgment (eg, congenital or acquired bleeding disorders other than congenital fibrinogen deficiency, planned surgery needing blood transfusion). 15. Subjects who received aspirin-containing products and nonsteroidal anti-inflammatory drugs (NSAIDs) within 7 days prior to the Day 0 Visit. 16. Subjects currently receiving, or having received within 3 months prior to enrolment into this clinical trial, any investigational drug or device. 17. Subjects who were previously administered the investigational product FIB Grifols during this clinical trial (ie, every subject can only participate in the study once). 18. Subjects who are unlikely to adhere to the protocol requirements, are likely to be uncooperative, or are unable to provide a storage serum sample prior to investigational drug infusion.
Pharmacokinetic Endpoints:	The following PK parameters will be calculated for fibrinogen by non-compartmental PK method determined from plasma levels before and at 30 minutes, 1 hour, 2 hour, 4 hour, 8 hour, 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. $AUC_{0\text{-}14days}$ 2. $AUC_{0\text{-}\infty}$

	3. C_{max} 4. t_{max} 5. $t_{1/2}$ 6. MRT 7. Vd 8. Cl 9. Incremental IVR
Primary Efficacy Endpoint:	Change in MCF measured by ROTEM MCF increase in subject's plasma samples from baseline to 1 hour post-infusion is the primary effect-variable in this clinical trial. MCF, as a functional parameter of blood's ability to coagulate, provides an indirect measure of hemostatic efficacy of replacement treatment with fibrinogen concentrates in subjects with fibrinogen deficiency.
Secondary [redacted] Efficacy Endpoints:	**Secondary Efficacy Endpoints:** 1. Difference (improvement) in other thromboelastographic parameters: • Clotting time (CT) • Clot formation time (CFT) • Alpha angle (α) Difference (improvement) in subject's plasma samples rotational thromboelastographic parameters from baseline to 1-hour post-infusion are secondary variables indicative of hemostatic efficacy of the treatment with a fibrinogen concentrate in subjects with fibrinogen deficiency. 2. Difference (improvement) in standard coagulation variables from baseline to 1-hour post-infusion. • Prothrombin time (PT) • Thrombin time (TT) • Activated partial thromboplastin time (aPTT) Difference in subject's plasma samples standard coagulation tests from baseline to 1-hour post-infusion are other secondary variables indicative of hemostatic efficacy of the treatment with a fibrinogen concentrate in subjects with fibrinogen deficiency. [redacted]

	[redacted]
Safety Endpoints:	1. Adverse events Adverse events (AEs) that occur at any time between signature of the informed consent to Week 4 Visit. AEs will be elicited by spontaneous reporting by study subjects and by a non-leading inquiry/observation by study staff. 2. Vital signs Clinically relevant (as defined in advance in the clinical trial protocol) variations in vital signs [temperature (T), respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP)] will be reported. Vital signs will be also monitored at baseline and at different time points after the infusion. 3. Physical assessment Physical assessments will be performed at baseline and at different time points and physical abnormalities will be recorded. 4. Laboratory panels The following clinical laboratory parameters will be measured at baseline and at different time points after infusion: Serum clinical chemistry: including creatinine, blood urea nitrogen (BUN), ALT, AST, alkaline phospatase (ALP), lactate dehydrogenase (LDH), total bilirubin (TB), glucose, sodium,

	potassium, chloride, and calcium. Hematological parameters: complete blood count (CBC), including platelet count and differential leukocyte count. Markers of activation of coagulation (not applicable for pediatric subjects): different measures indicative of activation in the coagulation pathway (D-dimer, antithrombin III [ATIII], thrombin-antithrombin III complex [TAT] prothrombin fragments [F_{1+2}]). 5. Antibodies against human fibrinogen (not applicable for pediatric subjects) Evidence of any possible immunogenicity of the investigational product will be assessed at the sponsor's laboratory. Samples from adult subjects will be assayed for generation of fibrinogen antibodies on an ongoing basis for the duration of the study. If a confirmed, single case of immunogenicity is reported after a subject was dosed with study drug, any further enrollment and dosing of subjects in the study will be suspended until the event can be adquately assessed by the sponsor. The enrollment and dosing will only resume after explicit authorization by the sponsor. 6. Allergic/hypersensitivity reactions Subjects will be carefully monitored for signs and symptoms of allergic/hypersensitivity reactions. The sponsor will routinely review reported AEs for possible allergic/hypersensitivity reactions. 7. Thrombotic events Subjects will be monitored for signs and symptoms of arterial and venous thrombotic events. If a confirmed, single case of a thrombotic event is reported by an investigator after a subject was dosed with study drug, any further enrollment and dosing of subjects in the study will be suspended until the event can be adequately assessed by the sponsor. The enrollment and dosing will only resume after explicit authorization by the sponsor. 8. Virus safety (not applicable for pediatric subjects) Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus, types 1 and 2 (HIV-1 and HIV-2), and parvovirus B19 (B19) will be monitored to assess virus safety.
Methodology:	Clinical trial procedures: After a Screening Visit, the enrolled subjects will undergo the Infusion Visit (Day 0), during which the subject will be administered study drug. After that, there will be a PK, efficacy,

	and clinical safety evaluation period (Day 0 to Day 14 Visits). There will be a follow-up period for safety and virology (visits at Day 21, Week 4, and Month 3) and immunogenicity (Day 0, Day 14, and Week 4). Medical history At Screening Visit, a complete medical history will be recorded for all study subjects. Physical assessments Several physical examinations by body systems will be performed at different time points throughout the study according to the schedules shown in adult (Table 4-1 and Table 4-3) and pediatric (Table 4-4 and Table 4-5) subjects. Height and weight Height and weight will be measured for all subjects at Baseline Visit. The weight value will be used for calculation of dose of IMP to be administered. Serum clinical chemistry Several serum clinical chemistry laboratory tests will be performed at different time points throughout the study according to the schedules shown in adult (Table 4-1 and Table 4-3) and pediatric (Table 4-4 and Table 4-5) subjects. Hematology Several hematology laboratory tests will be performed at different time points throughout the study according to the schedules shown in adult (Table 4-1 and Table 4-3) and pediatric (Table 4-4 and Table 4-5) subjects. Fibrinogen levels Plasma samples will be obtained for measurement of fibrinogen levels at several time points throughout the study according to the schedule shown in adult (Table 4-1 and Table 4-3) and pediatric (Table 4-4 and Table 4-5) subjects by two methods: 1. Fibrinogen activity (Clauss method) 2. Fibrinogen antigen Rotational Thromboelastometry ROTEM will be performed on frozen plasma samples taken at several time points throughout the study according to the schedules shown in adult (Table 4-1 and Table 4-3) and pediatric (Table 4-4 and Table 4-5) subjects by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

	Markers of activation of coagulation (not applicable for pediatric subjects) The following tests, indicative of activation of the coagulation: D-dimer, ATIII, thrombin-antithrombin III complex (TAT), and F_{1+2} will be performed on frozen plasma samples taken at several time points throughout the study according to the schedule shown in Table 4-1 and Table 4-3 by the central laboratory of the study. Immunogenicity (not applicable for pediatric subjects) Serum/plasma samples taken only from adult subjects at several time points throughout the study according to the schedule shown in Table 4-1 and Table 4-3 will be analyzed for the generation of antibodies to fibrinogen by using a stepwise approach starting with a functional screening assay to detect neutralizing activity. In the event neutralizing activity is detected, samples will be further assessed by a confirmatory ELISA for the presence of antibodies to fibrinogen. An additional aliquot of serum/plasma will be retained from all immunogenicity testing time points for re-testing if necessary. Viral panel (not applicable for pediatric subjects) Viral monitoring for each adult subject will be performed by means of serology and nucleic acid amplification technology (NAT) tests for following viruses: HAV, HBV, HCV, HIV-1 and HIV-2, and B19. Serum/plasma samples from all subjects will be examined at baseline (prior to infusion on Day 0) and at different time points according to the schedule shown in Table 4-1, Table 4-2, and Table 4-3. All serum/plasma samples will be sent to the central laboratory of the study for measurement of viral status. In case a subject is found to be positive for a particular virus at baseline, tests for this particular virus will not be performed at later time points during the study. An additional aliquot of serum/plasma will be retained from all viral time points for re-testing if necessary. Infusion and vital signs During the treatment infusion, all subjects' vital signs (T, RR, HR, SBP, and DBP) will be monitored. Monitoring will be performed within 60 minutes before the beginning of the infusion, at the completion of the infusion, and within 30 minutes after conclusion of each infusion. During the infusion, vitals signs will be recorded every 20 ± 5 minutes.

	The rate of infusion will be controlled by means of an infusion pump at a constant rate of not more than 5 mL/minute (it is acceptable to titrate up to this rate at the investigator's discretion). If an AE occurs during the infusion, the infusion rate may be reduced or the infusion may be interrupted until symptoms subside. Subsequently, the infusion may be resumed at a rate tolerated by the subject, but not exceeding 5mL/minute. Adverse events AEs occurring at any time between signature of the informed consent and the last day of the subject's participation in the safety follow-up period (Week 4 Visit) after investigational medicinal product infusion will be reported on the appropriate subject's case report form (CRF/eCRF). Nature, severity, seriousness (serious/non-serious) and causal-relationship to the study product will be assessed. Infusional AEs (ie, AEs temporally associated with an infusion of investigational product) will be defined and reported. Any AE occurred during infusion or within 24 and 72 hours after completion of infusion will be considered temporally associated with the infusion and labelled as infusional AEs. Monitoring of immunogenicity Evidence of any possible immunogenicity of the investigational product will be assessed by assaying for appearance of antibodies to fibrinogen. If a confirmed, single case of immunogenicity is reported after a subject was dosed with study drug, any further enrollment and dosing of subjects in the study will be suspended until the event can be adquately assessed by the safety group of the sponsor. The enrollment and dosing will only resume after explicit authorization by the sponsor. Monitoring of allergic/hypersensitivity reactions Subjects will be carefully monitored for signs and symptoms of allergic/hypersensitivity reactions. The Grifols Medical Monitor will routinely review reported AEs for possible allergic/hypersensitivity reactions. Monitoring of thrombotic events Subjects will be monitored for signs and symptoms of arterial and venous thromboses. In addition, the Grifols Medical Monitor will routinely review reported AEs for possible thromboses. Arterial and venous thromboses will be identified according to definitions in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Such thrombotic events include, but are not limited to, DVT, pulmonary embolism (PE), myocardial infarction, cerebrovascular accident, acute coronary

	syndrome, limb thrombosis, sagittal sinus thrombosis, and portal vein or mesenteric artery thrombosis. All thromboses will be recorded as AEs and reported accordingly. If a confirmed single case of thrombotic event is reported by an investigator after a subject was dosed with study drug, any further enrollment and dosing of subjects in the study will be suspended until the event can be adquately assessed by the sponsor. The enrollment and dosing will only resume after explicit authorization by the sponsor. Concomitant medication All medications, other than the investigational product, administered to subjects will be recorded during the clinical study.
Prohibited Concomitant Medications	Use of the following medications is prohibited during study participation: ▪ Aspirin-containing products and NSAIDs
Analytical Plan/Statistical Method:	The sample size in this study is based on the PK assessment. The sample size of 10 adult subjects is deemed sufficient for PK assessments. Assuming a 10% dropout rate, a total of 11 adult subjects need to be enrolled. In this study, the 10 adult subjects will be enrolled first. Only after the safety of the product has been assessed in these adults, will 10 pediatric subjects be enrolled into the study. Assuming a 10% dropout rate, a total of 11 pediatric subjects need to be enrolled. PK analysis 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. PK analysis will be performed independently for the adult and pediatric populations. All PK parameters will be calculated using non-compartmental methods using the fibrinogen concentration values obtained by both Clauss method and antigen (ELISA) methods. Efficacy analysis Primary efficacy analysis will be performed on the evaluable population. In addition, efficacy analysis will be also run on the per protocol (PP) population if it is different from the evaluable population. The evaluable population will include all individuals who received the investigational product of any amount and who have at least two measurements for the primary efficacy variable: one pre-infusion MCF and one 1-hour post-infusion MCF measurement by

ROTEM.

The PP population will include all subjects who received planned dose of investigational product (at least 90% of the planned dose), who have no major protocol violation(s), and who have at least two measurements for the primary efficacy variable: one pre-infusion MCF and one 1-hour post-infusion MCF measurements by ROTEM.

The primary efficacy endpoint will be the mean change (difference) of 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_o:$\Delta = 0$) 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 Wilcoxon signed rank test. In addition to this, the same analysis will be performed using the PP population. [redacted]

The following study variables will be examined in the evaluable and PP populations as secondary efficacy endpoints:

1. Mean change on other thromboelastographic variables
2. Mean change on standard coagulation tests

Similar analyses to those performed on the primary efficacy endpoint will be run on secondary efficacy endpoints.

[redacted]

Demographic (eg, sex, age, race, etc.) and baseline characteristics will be summarized using descriptive statistics.

All analyses on efficacy parameters (for the primary, secondary

	[redacted] efficacy endpoints) will be carried out in the overall study population (both adult and pediatric populations), and will also be conducted in the adult population and the pediatric population, separately. Primary efficacy analyses will be the ones performed on the overall study population. Safety analysis Safety analysis for FIB Grifols will be performed on the overall population (both adult and pediatric populations). FIB Grifols safety will also be assessed independently for both adult and pediatric populations. All AEs occurring in subjects who are infused with study drug will be listed in the clinical report of the study. Treatment-emergent AEs will be listed and tabulated by body system and they will be summarized by presenting individual incidences and percentages. In addition, treatment-emergent AEs will be also summarized by severity (intensity), seriousness (serious versus non-serious) and causal-relationship to the study product. Similarly, all treatment-emergent AEs potentially related to the investigational product will be summarized by presenting individual incidences and percentages, and will be also summarized by severity (intensity) and seriousness (serious versus non-serious). Infusional AEs will be defined as any AE that occurred during infusion or within 24 and 72 hours after completion of infusion. Infusional AEs will be summarized by presenting infusion's/subject's incidences and percentages (each subject contributes a single count to a category). AEs will be also tabulated by whether or not the AE occurred during the infusion or within 24 and 72 hours after completion of the infusion. Subjects who die, report a serious AE (SAE), or withdraw from the study because of AEs will be also individually listed and summarized. Events of special interest such as allergic/hypersensitivity reactions and thrombotic events will be individually listed and summarized. Vital signs (T, RR, HR, SBP, DBP) will be listed for each subject. Clinically relevant vital signs variations will be flagged. Clinical laboratory data for renal (creatinine, BUN), hepatic (ALT, AST, ALP, TB) and haematological parameters (CBC, including differential leukocyte count) will be listed for each subject. Values outside the upper or lower limit of the normal range for the respective testing laboratory will be flagged. For virus safety, the proportion of adult subjects who seroconverted during the study will be individually reported and

	discussed. Evidence of any possible immunogenicity will be assessed in the adult subjects by assaying for generation of antibodies to fibrinogen by using a stepwise approach starting with a functional screening assay to detect neutralizing activity. In the event neutralizing activity is detected, samples will be further assessed by a confirmatory ELISA for the presence of antibodies to fibrinogen.

ABBREVIATIONS

α	Alpha angle
ADR	Adverse drug reaction
aPTT	Activated partial thromoplastin time
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
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
B19	Parvovirus B19
BUN	Blood urea nitrogen
CBC	Complete blood count
CFT	Clot formation time
Cl	Clearance
C_{max}	Maximum plasma concentration
CRF/eCRF	Case report form/electronic case report form
CRO	Contract research organization
CT	Clotting time
DBP	Diastolic blood pressure
dL	Deciliter
DVT	Deep vein thrombosis
ELISA	Enzyme-linked immunosorbent assay
F_{1+2}	Prothrombin fragments F_{1+2}
FXIIIa	Activated factor XIII
GCP	Good clinical practice
HAV	Hepatitis A virus
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
Hct	Haematocrit
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus

Hgb	Haemoglobin
HIPAA	Health Information Portability and Accountability Act
HIV-1/HIV-2	Human immunodeficiency virus 1 and 2
HR	Heart rate
ICF	Informed consent form
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IgA	Immune globulin A
IRB	Institutional review board
IVR	In vivo recovery
kg	Kilogram
LDH	Lactate dehydrogenase
LSM	Least square mean
MCF	Maximum clot firmness
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
mm	Millimeter
mmHg	Arterial pressure in millimetres of mercury
mL	Milliliter
MRT	Mean residence time
NAT	Nucleic acid amplification technology
NSAID	Nonsteroidal anti-inflammatory drugs
PE	Pulmonary embolism
PK	Pharmacokinetic
PP	Per protocol
PT	Prothrombin time
QA	Quality assurance
RBC	Red blood cells
ROTEM	Rotational thromboelastometry
RR	Respiratory rate
SAE	Serious adverse event

SAF	Subjects authorization form
SBP	Systolic blood pressure
SWFI	Sterile water for injection
T	Temperature
$t_{1/2}$	Half-life
TAT	Thrombin-antithrombin III complex
TB	Total bilirubin
t_{max}	Time to the observed maximum plasma concentration
TRALI	Transfusion-related acute lung injury
TT	Thrombin time
ULN	Upper limit of normal
USA	United States of America
Vd	Volume of distribution
WBC	White blood cell

TABLE OF CONTENTS

IN-TEXT TABLES

IN-TEXT FIGURE

ANNEXES

1. GENERAL INFORMATION

1.1 PROTOCOL TITLE

Multicenter, prospective, open-label, single-arm trial to evaluate the pharmacokinetics, efficacy, and safety of Human Plasma derived Fibrinogen (FIB Grifols) in Subjects with Congenital Afibrinogenemia

1.2 PROTOCOL NUMBER, VERSION, DATE, AND EUDRACT NUMBER

Protocol Number: IG0902
Version Number: 3.0
Version Date: 08 Oct 2018
EudraCT Number: 2013-004343-23

1.3 NAME AND ADDRESS OF SPONSOR AND MONITOR

Sponsor:
Instituto Grifols, S.A.
Polígono Levante, C/ Can Guasch, 2
08150 - Parets del Vallès
Barcelona
Spain

1.4 NAME AND TITLE OF PEOPLE AUTHORIZED TO SIGN THE PROTOCOL AND THE PROTOCOL AMENDMENT(S) FOR SPONSOR

[redacted], Msc.
[redacted]

[redacted], MD
[redacted]

1.5 NAME, TITLE, ADDRESS, AND TELEPHONE NUMBER OF SPONSOR'S MEDICAL EXPERT FOR THE TRIAL

[redacted], MD
[redacted]
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Phone: [redacted]
Fax: [redacted]

1.6 NAME AND TITLE OF INVESTIGATORS WHO ARE RESPONSIBLE FOR CONDUCTING THE TRIAL, AND ADDRESS AND TELEPHONE NUMBER OF TRIAL SITES

Flora Peyvandi, MD
Coordinating Investigator

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Italy

Tel: [redacted]

Information for other centers and investigators can be found in the trial master file.

2. BACKGROUND INFORMATION

2.1 NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

The following investigational product will be used in this clinical trial:

Table 2-1 Investigational product

INVESTIGATIONAL PRODUCT	
FIB Grifols	Separate primary conditioning materials for lyophilized powder and solvent: - Vials containing 1.0 g of human FIB Grifols (powder for infusion) - Vials containing 50 mL of sterile water for injection (solvent)

FIB Grifols is a lyophilized and sterile preparation of fibrinogen highly purified from human plasma, subjected to three specific pathogen elimination steps (solvent/detergent, nanofiltration, and heat treatment) during its purification performed by Instituto Grifols, S.A. (Barcelona, Spain). FIB Grifols has not been tested in human subjects.

2.2 SUMMARY OF FINDINGS FROM NONCLINICAL STUDIES AND CLINICAL TRIALS THAT ARE RELEVANT TO THE TRIAL

All nonclinical data related to efficacy and safety of FIB Grifols is summarized in Human Plasma-derived Intravenous Fibrinogen Grifols Investigator's Brochure [1].

Regarding clinical data, the present clinical trial will constitute the first use of this product in human subjects.

2.3 SUMMARY OF THE KNOWN AND POTENTIAL RISKS AND BENEFITS TO HUMAN SUBJECTS

Intended benefit of fibrinogen concentrates is to avoid hemorrhagic manifestations in subjects with fibrinogen deficiencies. Already licensed products are indicated for treatment of acute bleeding episodes and as replacement therapy in subjects with congenital deficiency of fibrinogen and bleeding tendency, for peri-operative prophylaxis and before or during pregnancy and obstetrics. [2, 3, 4]

Fibrinogen concentrates are also indicated [5] as complementary therapy to management of life threatening bleeding in cases of acquired hypofibrinogenaemia, eg:

1. Increased consumption of fibrinogen associated with otherwise uncontrolled life threatening bleeding in obstetric complications
2. Dilutional hypofibrinogenemia in, for example, trauma-patients with severe blood loss after massive replacement therapy with colloid and crystalloid solutions
3. Disorders of synthesis of coagulation factors – eg, severe liver parenchyma damage with fibrinogen deficiency
4. Increased consumption of fibrinogen associated with otherwise uncontrolled life threatening bleeding due to disseminated intravascular coagulation syndrome and hyperfibrinolysis

Potential risks associated with the use of other fibrinogen products in the market include but are not limited to: thrombotic events, including myocardial infarction, pulmonary embolism (PE), deep vein thrombosis (DVT) and arterial thrombosis and allergic-anaphylactic reactions. [2, 3, 4, 5]

Thrombotic events may occur spontaneously in subjects with congenital deficiency with or without the use of fibrinogen replacement therapy. Thrombotic events have been reported in subjects treated with fibrinogen concentrates. Subjects receiving fibrinogen concentrates should be closely monitored for signs and symptoms of thrombosis.

Since FIB Grifols and other licensed fibrinogen concentrates are prepared from human plasma, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. In the case of FIB Grifols, the risk of transmission of infective agents is, however, reduced by: 1) selection of donors by a medical interview and screening of individual donations and plasma pools for hepatitis B surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV) and hepatitis C virus (HCV), 2) testing of plasma pools for HCV genomic material, and 3) inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV, hepatitis A virus (HAV), parvovirus B19 (B19), and hepatitis B virus (HBV). [1] As with all products containing human origin proteins, allergic reactions may occur. Symptoms of allergic or early signs of hypersensitivity reactions include hives, generalized urticaria, tightness of the chest, wheezing and hypotension. More serious hypersensitivity reactions cannot be ruled out, including anaphylactic shock, in the product administration, especially when immune globulin A (IgA) deficient subjects who present antibodies against IgA are administered. Fibrinogen concentrates should not be administered in subjects with selective IgA deficiency and who have antibodies against IgA or in subjects with known marked

hypersensitivity to the active substance or to any of the excipients contained in the product, described in FIB Grifols Investigator's Brochure [1].

In the case of replacement therapy with coagulation factors in other congenital deficiencies, antibody reactions have been observed, but there is currently no data with fibrinogen.

Other adverse reactions reported after treatment with fibrinogen concentrates are generalized reactions such as chills, fever, nausea and vomiting [2].

2.4 DESCRIPTION OF AND JUSTIFICATION FOR THE ROUTE ADMINISTRATION, DOSAGE, DOSAGE REGIMEN, AND TREATMENT PERIOD(S)

In order to exert its hemostatic properties, fibrinogen must be present intravascularly, therefore the product is to be administered by slow intravenous infusion. The dose to be administered in the study (single-dose intravenous infusion of FIB Grifols at a dosage of 70 mg/kg of body weight) is deemed sufficient to reach the generally accepted minimum threshold for hemostasis in subjects with congenital deficiency of not less than 1g of fibrinogen per liter [6].

The usual dosage and dosage regimen of chronic replacement therapy (prophylaxis in subjects with congenital fibrinogen deficiency and bleeding tendency) with human fibrinogen has not been yet clearly established. [5]

In this study, the rate of infusion is to be controlled by means of an infusion pump. Delivery will be performed at a rate not higher than 5 mL/minute (it is acceptable to titrate up to this rate at the investigator's discretion). If an adverse event (AE) occurs during the infusion, the infusion rate may be reduced or the infusion interrupted until symptoms subside. Subsequently, the infusion may be resumed at a rate tolerated by the subject, but not exceeding 5 mL/minute. All subjects will be monitored at different time points after the infusion ends for any signs of AE.

2.5 COMPLIANCE WITH THE PROTOCOL, GOOD CLINICAL PRACTICE AND THE APPLICABLE REGULATORY REQUIREMENTS

This clinical trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki of the 18th World Medical Assembly, June 1964, and consecutive updates, in compliance with the approved protocol of the study, with any approved amendment of the protocol, in compliance with International Conference on Harmonisation Good Clinical Practices (ICH GCP, Topic E6), and in compliance with other applicable regulatory requirements.

2.6 DESCRIPTION OF THE POPULATION TO BE STUDIED

Study population will be made up of adult and pediatric subjects with asymptomatic (non-bleeding) congenital fibrinogen deficiency (afibrinogenemia).

2.7 REFERENCE TO LITERATURE AND DATA THAT ARE RELEVANT TO THE TRIAL AND THAT PROVIDE BACKGROUND FOR THE TRIAL

Human fibrinogen (factor I) is a soluble plasma glycoprotein with a molecular weight of 330-340 kDa. The molecule is a hexamer containing two sets of three different chains (Aα, Bβ, γ)$_2$ with three parent chains, α, β and γ, and fibrinopeptide A and fibrinopeptide B, respectively. Both fibrinopeptides are cleaved from fibrinogen by thrombin. [7, 8]

Fibrinogen is synthesized by hepatocytes in the liver [9] and is essential for hemostasis, wound healing, fibrinolysis, inflammation, angiogenesis, cellular and matrix interactions, and neoplasia. These processes involve the conversion of fibrinogen to fibrin, and often the interaction of fibrinogen with various proteins and cells. Normal plasma levels are about 2.5 g fibrinogen/L of blood, however, concentrations of fibrinogen can increase by as much as 200-400% during times of physiological stress (primarily due to the actions of macrophage-derived interleukin-6, an acute phase reactant).

When fibrinopeptides A and B are cleaved from fibrinogen by thrombin, fibrin monomers are formed. The formed soluble fibrin monomers polymerize forming protofibrils. When protofibrils reach a sufficient length (usually about 600-800 nm), they aggregate laterally forming fibers. The fibrin clot is formed by branching of the fibers. [7]

Initially, the fibrin polymers are linked by hydrogen and electrostatic bonds and the structure (unstable or non-intercrossed clot) is easily dissolved by chaotropic agents such as 5M urea and proteolytic enzymes such as plasmin. The transglutaminase, activated factor XIII (FXIIIa), covalently binds specific glutamine residues in one fibrin molecule to lysine residues in another via isopeptide bonds, and covalent links are formed between the C-terminal of the γ-chains. Thus, fibrin polymers are formed. Stable or intercrossed clots are formed when the fibrin mesh is covalently linked. This intercrossing of the fibrin polymers delays proteolytic degradation of the meshed clot, reinforces its mechanical properties, and the clot is stabilized against mechanical, chemical, and proteolytic insults.[7]

The concentration of fibrinogen circulating in normal plasma ranges from 2.0 to 4.5 g/L however, in subjects with various congenital or acquired conditions, the levels of clottable fibrinogen are markedly reduced or undetectable. Conditions of congenital fibrinogen deficiency include afibrinogenemia (complete absence or extremely low levels of plasma fibrinogen), hypofibrinogenemia (reduced concentration (<150 mg/dL) of structurally normal plasma fibrinogen), and dysfibrinogenemia (normal plasma levels of abnormal or dysfunctional fibrinogen molecules). Qualitative and quantitative abnormalities can also co-exist as hypodysfibrinogenemia. [10, 11, 12]

Congenital afibrinogenemia is a rare coagulation disorder usually with an autosomal recessive mode of inheritance. According to the literature, in the Western countries its prevalence is estimated to be 1 subject per million people. In countries or regions with higher rates of consanguinity, this numbers may be increased. It is characterized by moderate to severe bleeding manifestations that often start at birth with uncontrolled umbilical cord hemorrhages. Bleeding may occur spontaneously or after minor trauma or small surgical intervention, into skin, mucosa, muscles, gastrointestinal tract or the central nervous system, with intracranial hemorrhage being the major cause of death.[10, 11, 13, 14, 15] Spontaneous spleen rupture has been also reported.[16] Affected women usually have menorrhagia and pregnancy is also frequently interrupted during the first trimester due

to the lack of proper stabilization of placental-maternal attachment by fibrinogen.[17, 18, 19, 20] In some cases, paradoxical arterial and venous thromboembolic complications may occur. [21, 22, 23, 24, 25] Typical laboratory findings in subjects with congenital afibrinogenemia include prolonged prothrombin time (PT), partial thromboplastin time, thrombin time (TT), and reptilase time. Mutations leading to congenital afibrinogenemia have been discovered in all three fibrinogen chains although the majority of subjects seem to have mutations in the Aα gene. [26, 27, 28, 29]

Clinical symptoms of hypofibrinogenemia are usually milder compared with afibrinogenemia, and the condition is frequently combined with a dysfibrinogenemia that is characterized with an abnormal fibrinogen variant (hypodysfibrinogenemia). Several missense mutations in the three fibrinogen genes have been identified as the cause of dysfibrinogenemia and hypofibrinogenemia that lead to abnormal gene expression resulting in the decreased fibrinogen concentration or dysfunctional fibrinogen molecules. [6, 12]

Subjects with any of these conditions are treated for bleeding either by substitution with a fibrinogen concentrate in countries where it is available, with cryoprecipitate (Cohn I fraction) or with fresh frozen plasma. [6, 10, 30]

Theoretically, fibrinogen concentrates would be the preferred option because of demonstrated and potential advantages when compared with cryoprecipitate and plasma in terms of safety, efficacy, access to timely intervention, and precise dosing.

Potential disadvantages associated with the use of cryoprecipitate and plasma would be:

1. Immune reactions including but not limited to allergic reactions, anaphylactic/anaphylactoid reactions, intravascular hemolysis and transfusion-related acute lung injury (TRALI)
2. Fluid overload due to the amount of volume needed for achieving required fibrinogen levels
3. Viral infection risks due to the lack of viral inactivation/removal steps
4. Precise dosing not feasible due to the lack of precise fibrinogen content and volume measurement
5. Preparation time as these products must be thawed, pooled and eventually ABO blood type matched prior to infusion.

Due to the low prevalence of this disease, there is an absolute lack of adequately well-designed, controlled studies in subjects with active bleeding and the only available data on fibrinogen concentrates' efficacy come from anecdotal case reports and retrospective studies and surveys. [13, 16, 19, 31, 32, 33, 34, 35, 36, 37, 38, 39] From these studies it can be concluded that the clinical efficacy of fibrinogen concentrates in achieving hemostasis in actively bleeding subjects and subjects at high risk situations (eg, undergoing surgery) is adequate and equivalent to those achieved by subjects treated with cryoprecipitate.

To date, the adequate prophylactic regimen to treat subjects with congenital deficiency and severe life-threatening bleeding tendency has not been yet clearly established and its efficacy remains controversial, although positive trends have been reported from retrospective studies and case reports. [6, 13, 18, 36]

Other clinical trials have studied the safety, pharmacokinetics and pharmacodynamics of fibrinogen concentrates in congenitally deficient subjects. [2, 40, 41] These studies showed a good correlation between fibrinogen levels determined by functional (Clauss) and antigen methods and confirmed previous data indicating a terminal half-life ($t_{1/2}$) of 3.0 to 5.3 days. For other PK parameters (volume of distribution [Vd], clearance [Cl], incremental in vivo recovery [IVR]), larger differences were found depending on the product used, reporting in vivo recoveries of 94% in one case and 54% in the other and 2-3 fold differences in Vd and Cl. For the same parameters, large differences (2-fold) were also found in terms of between-subject variability.

In all cases, fibrinogen capacity for restoring normal hemostasis was demonstrated by normalization of previously abnormal (prolonged) standard coagulation tests: TT, PT, and activated partial thromboplastin time (aPTT) values.

Hemostatic efficacy of treatment with fibrinogen concentrates has also been evaluated both in vitro and in vivo as well as in clinical studies in congenital and acquired fibrinogen deficiency. [42, 43, 44, 45, 46, 47, 48] Many of these studies have used pre-infusion and post-infusion rotational thromboelastometry (ROTEM) parameters, mainly maximum clot firmness (MCF) to demonstrate hemostatic efficacy. MCF is highly dependent on the concentration and activity of platelets and fibrinogen and is considered a functional marker/surrogate endpoint indicative of a subject's hemostatic competency. Many studies and papers have evaluated the correlation of thromboelastographic parameters with clinical bleeding occurrence and support the increasing use of this device for bedside monitoring of high-risk subjects in order to provide guidance for use of blood components and hemostatic products administration. [49, 50, 51, 52, 53, 54, 55, 56, 57, 58]

From these studies, as well as from years of clinical experience in the use of fibrinogen concentrates, it has been demonstrated that fibrinogen infusions were well tolerated and fibrinogen concentrates have a good safety profile.

The biggest concern with the use of this kind of product in subjects with congenital afibrinogenemia is the risk of thrombotic events. The occurrence of arterial and venous thromboembolism in this population with or without the use of fibrinogen-containing products has been extensively reported in the literature. [13, 14, 21, 22, 23, 24, 25, 59, 60] It has been speculated that in subjects lacking fibrinogen but with the hemostatic system otherwise intact, platelet aggregation can occur. Interestingly, a study performed on mice lacking fibrinogen demonstrated that clots rich in platelets and von Willebrand factor were formed with no differences with respect to wild type mice in platelet deposition or thrombus initiation phases. However, during the propagation phase, where fibrinogen is supposed to exert its function, growing clots did not resist shear stress and were stripped off and carried away causing downstream from the injury site embolization. [61]

Equally, thrombin generation is not disturbed in subjects suffering from isolated fibrinogen deficiency and the lack of fibrinogen to sequester the formed thrombin molecules into the fibrin (antithrombin I) clots would then cause elevated levels of circulating thrombin. In this regard, some studies and case reports have indicated that fibrinogen deficient subjects have increased levels of some markers of activation of coagulation as prothrombin activation fragments or thrombin-antithrombin complexes. This baseline overcoming of natural anticoagulation proteins as antithrombin III (ATIII) could explain the apparent reported lack of efficacy of heparins for prevention of thrombotic events in subjects with

fibrinogen congenital deficiency and the success when switching to treatment with direct thrombin inhibitors. [62, 63]

Due to the high frequency of fibrinogen-deficient subjects that suffer from life-threatening haemorrhagic events and the confines of having only a few approved products in the marketplace, Grifols has planned a clinical development program for FIB Grifols in subjects with congenital afibrinogenemia. The present study designed to obtain PK, safety, and hemostatic efficacy data is the first trial of the clinical program.

3. TRIAL OBJECTIVES AND PURPOSES

1. To evaluate the PK profile of FIB Grifols following single-dose administration of 70 mg/kg body weight.
2. To evaluate hemostatic efficacy of FIB Grifols by means of thromboelastographic MCF values' comparison at baseline and one hour after investigational product administration. Other thromboelastographic measures as well as standard coagulation tests measured at different time points will also serve as secondary [redacted] efficacy endpoints.
3. To evaluate the safety of FIB Grifols. Clinical safety, virus 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.

4. TRIAL DESIGN

4.1 PHARMACOKINETIC ENDPOINTS

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. Incremental in vivo recovery (IVR)

Incremental IVR will be calculated for fibrinogen levels from the peak level recorded within and including the first 4 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, and the actual volume infused to the subject will be used for calculating the dose administered to each subject.

The incremental 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 4 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) methods.

4.2 PRIMARY AND SECONDARY EFFICACY ENDPOINTS

Primary efficacy endpoint:

Difference (improvement) on plasma thromboelatographic MCF from baseline to 1-hour post-infusion. ROTEM measures will be performed at the central laboratory of the study.

Secondary efficacy endpoints:

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 (TT, PT and aPTT) from baseline to 1-hour post-infusion. Standard coagulation tests will be performed at the central laboratory of the study.

[redacted]

[redacted]

4.3 DESCRIPTION OF THE DESIGN OF THE TRIAL TO BE CONDUCTED

This is a phase I-II, multi-center, prospective, open-label, single-arm clinical trial to be carried out in subjects with congenital fibrinogen deficiency manifested as afibrinogenemia.

In this clinical trial, the PK profile of the investigational product 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 ROTEM measures of 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, 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), Turkey, Lebanon, and the United States of America (USA). It is planned to include 11 adult subjects 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 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.

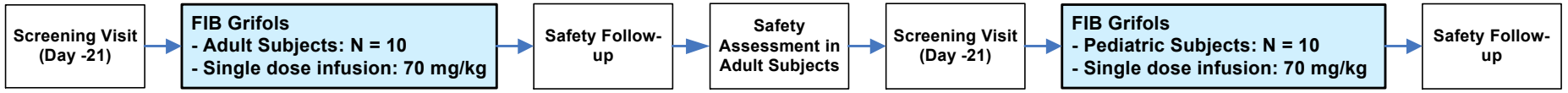
The principal investigator at each site must be aware of and explicitly authorize the use of home health nurses service.

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 (ie, 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 4-1**.

Overall Study Schema



Study Visits

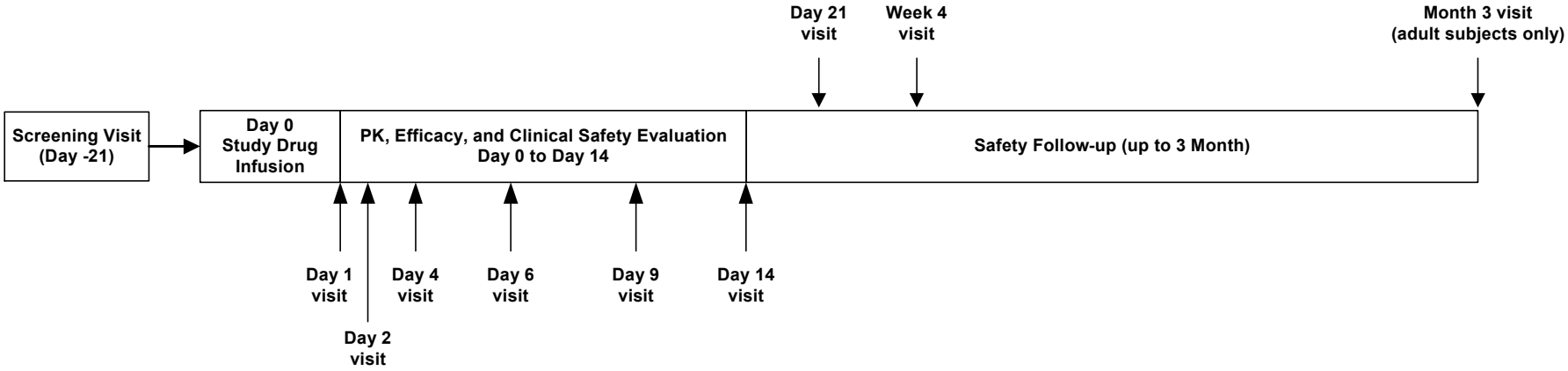


Figure 4-1 Overall Study Schema and Study Visits

4.4 MEASURES TO MINIMIZE/AVOID BIAS

4.4.1 RANDOMIZATION

This is a single-arm study and no randomization is applied.

4.4.2 BLINDING

This is an open-label study. No blinding is required.

4.5 DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

4.5.1 INVESTIGATIONAL PRODUCT IDENTIFICATION

Drug name:	FIB Grifols 1.0 g powder and solvent for infusion
ATC code:	B02BB01.
Active principle:	Human fibrinogen 1.0 g/vial.
Pharmaceutic form:	Vials containing 1.0 g of FIB Grifols powder and vials containing 50 ml of sterile water as solvent for infusion.
Manufacturer and sponsor:	Instituto Grifols, S.A. Can Guasch, 2. 08150 Parets del Vallès. Barcelona Spain

4.5.2 DOSAGE AND DOSAGE REGIMEN OF THE INVESTIGATIONAL PRODUCT

4.5.2.1 Dosage of investigational product

Dosage and regimen:	70 mg/kg body weight single dose
Administration via:	Intravenously
Administration form:	Investigational product will be prepared and administered as specified in the protocol Section 4.5.4

4.5.2.2 Dosage regimen of investigational product

A single infusion of fibrinogen concentrate at a dosage of 70 mg/kg body weight will be administered.

Only qualified health staff will administer the investigational product at the investigational site. Compliance with treatment will be recorded in the *Subject's Specific Administration Log* by the health staff.

During the treatment infusion, the subject's vital signs (temperature [T]; respiratory rate [RR]; heart rate [HR]; systolic blood pressure [SBP]; diastolic blood pressure [DBP]) will be monitored and recorded in the Day 0 Vital Signs worksheet as follows: 1) within 60

minutes before the beginning of the infusion; 2) at the beginning of the infusion, 3) every 20 ± 5 minutes during the infusion; 4) at the completion of the infusion and 5) within one hour after conclusion of the infusion.

The rate of infusion will be controlled by means of an infusion pump. The investigational medicinal product must be at room temperature and delivery will be performed at a constant rate not exceeding 5 mL/minute (it is acceptable to titrate up to this rate at the investigator's discretion). If an AE occurs during the infusion, the infusion rate may be reduced or the infusion may be interrupted until symptoms subside. Then, the infusion may be resumed up to a rate tolerated by the subject, but not exceeding 5 mL/minute.

4.5.3 PACKAGING AND LABELLING OF THE INVESTIGATIONAL PRODUCT

FIB Grifols will be supplied in type II glass vials containing 1 g of human fibrinogen (powder for infusion) and a vial containing 50 mL of water for injection (solvent).

Packaging and labeling of FIB Grifols supplies will comply with local regulatory requirements and will be translated into local languages when required per local regulations.

IMPORTANT:

INVESTIGATIONAL PRODUCT PACKAGINGS SHOULD BE STORED FOR ACCOUNTABILITY RECONCILIATION BY THE CLINICAL MONITOR BEFORE BEING DESTROYED.

4.5.4 STORAGE, PREPARATION, DISPENSATION AND ADMINISTRATION OF THE INVESTIGATIONAL PRODUCT

Instituto Grifols, S.A. will supply vials for intravenous administration of investigational product (FIB Grifols).

A drug repository company may be contracted for drug distribution to investigational sites where applicable. Investigational product will be maintained within respective recommended temperature conditions.

4.5.4.1 Storage and preparation of the investigational product

FIB Grifols must be stored between 2ºC and 25°C and must not be frozen. Moreover, FIB Grifols must be kept in a secure room with access restricted to necessary study site personnel.

The pharmacist must keep the investigational product accountability by means of the *Investigational Site Specific Drug Accountability Log*.

FIB Grifols solution preparation:

FIB Grifols solution will be prepared at investigational site pharmacy by the pharmacist responsible of the investigational product or by qualified personnel delegated, as indicated in the Human Plasma-derived Intravenous Fibrinogen Grifols Investigator's Brochure [1].

The product should be administered intravenously within 12 hours after reconstitution with the solvent supplied. Meanwhile, it should be stored between 2ºC and 25°C, for a maximum time of 12 hours.

Total dose or volume of the investigational product to be administered will be calculated according to the following formula:

Total dose (mg) = Body weight (kg) × 70 mg/ kg
Approximate total volume (mL) = Total dose (mg) × 0.05 mL/mg

IMPORTANT:

INVESTIGATIONAL PRODUCT PACKAGINGS SHOULD BE STORED FOR ACCOUNTABILITY RECONCILIATION BY THE CLINICAL MONITOR BEFORE BEING DESTROYED.

4.5.4.2 Dispensation and administration of the investigational product

Investigational product dispensation:

The pharmacist or the delegated qualified person is responsible for preparing the investigational product and must complete a dispensation register (*Subject Specific Dispensing Log*). The investigational product will be delivered to the staff performing the infusion.

Investigational product administration:

Qualified health staff will administer the investigational product, keeping maximum asepsis, at the investigational site. These qualified health staff must also complete an administration register in order to check treatment compliance (*Subject's Specific Administration Log*).

The investigational medicinal product to be administered must be at room temperature before administration and the administration should be performed by slow intravenous infusion at an infusion rate not exceeding 5 mL/minute. It is advisable to start the infusion with a slow rate and, if well-tolerated by the subject, then to incrementally increase it.

If the administration is problematic (ie, AEs or intolerance occurs), the rate of administration should be reduced, and even temporarily stopped until symptoms subside. In case of an anaphylactic shock, the administration of the product must be immediately discontinued, and the hospitals/centers current specific guidelines for shock therapy should be followed.

4.6 EXPECTED DURATION OF SUBJECT'S PARTICIPATION AND DESCRIPTION OF THE SEQUENCE AND DURATION OF THE TRIAL PERIOD

The total estimated maximum duration of subject's participation could be approximately 3 months and 3 weeks for adult subjects, starting with the Screening Visit (within 21 days

before Day 0). After infusion of the investigational product on Day 0, the PK, efficacy, and clinical safety evaluation period (Day 0 to Day 14) will commence. The subjects will be followed up for up to 3 months for safety, virology, and immunogenicity assessments. Pediatric subjects will not undergo Month 3 assessments and their study participation will conclude after the Week 4 Visit.

Clinical trial consists of:

1. Screening Visit: up to 21 days before the infusion visit (Day 0)
2. Infusion Visit: administration of the investigational medicinal product on Day 0
3. PK, Efficacy, and Clinical Safety Evaluation Visits: Day 0 to Day 14
4. Follow-Up Period up to 3 months: including safety follow-up visits (virology and immunogenicity assessments) on Day 21 ± 1 day, Week 4 ± 3 days
5. Month 3 ± 7 days (adult subjects only)

Clinical trial finalization will coincide with the last visit of the last subject included in the study.

Schedules of procedures for adult subjects are provided in Table 4-1, Table 4-2, and Table 4-3. Schedules of procedures for pediatric subjects are provided in Table 4-4 and Table 4-5.

Table 4-1 Schedule of Procedures of the Study in Adult Subjects

Visits Procedures and assessments	Screening Visit (up to 21 days prior to infusion visit)	Infusion Visit*	Pharmacokinetic, Efficacy, and Clinical Safety Evaluation Visits						Safety, Virology, and Immunogenicity Follow-Up Visits		
		Day 0	Day 1	Day 2	Day 4	Day 6	Day 9	Day 14	Day 21 ± 1 Day	Week 4 ± 3 Days	Month 3 ± 7 Days
Informed Consent	X										
HIPAA[1]	X										
Demographics[2]	X										
Medical History	X										
Height and Weight		X									
Inclusion/Exclusion Criteria	X	X									
Physical Assessment	X	X	X							X	
Medications[3]	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[4]		X[B]									
Serum Clinical Chemistry[5]		X[B]	X			X		X			
Hematology[6]		X	X			X		X			
Fibrinogen Levels (Clauss and Antigen)	X[A]	X[B,C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]			
Rotational Thromboelastometry[7]		X	X	X	X	X	X				
Standard Coagulation Tests[8]		X	X	X	X	X	X				
Markers of Activation of Coagulation[9]		X	X	X	X	X	X				
Immunogenicity Testing[10]		X						X		X	
Viral Panel[11]		X					X	X	X	X	X
Vital Signs[12]		X	X			X		X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	
Thrombotic Events Risk Assessment (including Wells Score)		X	X	X	X	X	X	X	X	X	
Allergic/hypersensitivity Reactions Risk Assessment		X	X	X	X	X	X	X	X	X	
Retention Sample[13]		X					X	X	X	X	X

* See specific Day 0 flowchart for adult subjects (Table 4-3)

1. Health Information and Accountability Act authorization form (if applicable).
2. Date of birth, gender, and ethnic origin.
3. Prior medications for the last 3 months (Screening Visit only) and concomitant medications.
4. Human chorionic gonadotropin-based blood or urine assay for women of childbearing potential.
5. 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.
6. Red blood cells (RBC) count, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count and differential, and platelet count.
7. Thromboelastographic parameters: clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), and alpha angle (α).
8. Thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (aPTT).
9. D-dimer, antithrombin III (ATIII), thrombin-antithrombin III complex (TAT), prothrombin fragments F_{1+2} (F_{1+2})
10. Antibodies to fibrinogen. Day 0 sample to be collected pre-infusion. For details, see specific Day 0 flowchart for adult subjects (Table 4-3).
11. Serology and nucleic acid amplification technology (NAT) testing for virus safety. For details, see the corresponding Schedule for Virology Testing (Table 4-2).
12. Heart rate (HR), respiration rate (RR), systolic and diastolic blood pressure (SBP and DBP), and temperature (T).
13. A serum/plasma retention sample will be kept frozen at -70ºC.

[A]Sites that cannot perform fibrinogen levels determinations (by both Clauss and antigen method) locally will have a blood sample taken at Screening Visit 14 days prior to Baseline Visit and have it analyzed for this parameter by both methods at the central laboratory of the study for verification of the eligibility against the Inclusion/Exclusion criteria. In these cases, the sample for assessing the Inclusion/Exclusion criteria will not be taken at Baseline Visit. Samples for pharmacokinetic (PK) will still be taken at Baseline Visit.

[B]Baseline pregnancy test (when applicable), serum clinical chemistry and fibrinogen levels (when applicable) results from samples drawn within 24 hours prior to the scheduled infusion and tested locally must be available prior to infusion for verification of the eligibility against the Inclusion/Exclusion criteria.

[C]Baseline (and subsequent) fibrinogen levels for PK calculations (Clauss and antigen methods [ELISA]) will be measured at the central laboratory of the study.

Table 4-2 Schedule for Virology Testing (Adult Subjects Only)

Visits	Viral Panel											
	Day 0 Baseline (within 60 min prior to the infusion)		Day 9[A]		Day 14[A]		Day 21 ± 1 Day [A]		Week 4 ± 3 Days [A]		Month 3 ± 7 Days [A]	
Viruses	**Serology**	**NAT***	**Serology**	**NAT**	**Serology**	**NAT**	**Serology**	**NAT**	**Serology**	**NAT**	**Serology**	**NAT**
Hepatitis A Virus (HAV)	X[1] (IgM&IgG)	X[1]				X	X (IgM&IgG)	X	X (IgM&IgG)	X		
Hepatitis B Virus (HBV)	X[1,2]	X[1]				X		X	X[4]	X	X[4]	
Hepatitis C Virus (HCV)	X[1]	X[1]								X	X[5]	X
Human Immunodeficiency Viruses, types 1 and 2 (HIV-1/2)	X[1]	X[1,3]								X[3]	X[6]	X[3]
Parvovirus B19	X[1] (IgM&IgG)	X[1]	X (IgM&IgG)	X	X (IgM&IgG)	X						

1. Sample will be always analyzed.
2. Total anti-HBc (IgM & IgG)
3. NAT for HIV-1 only
4. HBsAg
5. In case of HCV positive antibody screen, a recombinant immunoblot assay will be performed.
6. In case of HIV positive antibody screen, a Western blot assay for HIV-1 will be performed.

[A] Samples would be analyzed for a particular virus only in the event of negative results of analysis of NAT, IgM, and IgG for that particular virus performed on all previous samples.

* NAT = Nucleic acid amplification technology

Table 4-3 Schedule of Procedures During Day 0 (Infusion Visit) in Adult Subjects

Visits / Procedures and assessments	Baseline (prior to infusion)	During infusion	After Infusion				
			30 minutes	1 hour	2 hours	4 hours	8 hours
Inclusion/Exclusion Criteria	X						
Height and weight	X						
Physical Assessment	X						X
Medications[1]	X	X	X	X	X	X	X
Pregnancy Test[2]	X[A]						
Serum Clinical Chemistry[3]	X[A]						
Hematology[4]	X						
Fibrinogen Levels (Clauss and Antigen)	X[A,B]		X	X	X	X	X
Rotational Thromboelastometry[5]	X		X	X		X	
Standard Coagulation Tests[6]	X		X	X		X	
Markers of Activation of Coagulation[7]	X			X		X	
Immunogenicity Testing	X						
Viral Panel[8]	X						
Vital Signs[9]	X	X		X			
Adverse Events	X	X	X	X	X	X	X
Thrombotic Events Risk Assessment	X			X		X	
Allergic/hypersensitivity Reactions Risk Assessment	X			X		X	
Retention Sample[10]	X			X		X	
Footnotes continued on next page							

1. Concomitant medications.
2. Human chorionic gonadotropin (HCG)-based blood or urine assay for women of childbearing potential.
3. 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.
4. Red blood cells (RBC) count, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count and differential and platelet count.
5. Thromboelastographic parameters: clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), and alpha angle (α)
6. Thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (aPTT).
7. D-dimer, antithrombin III (ATIII), thrombin-antithrombin III complex (TAT), prothrombin fragments F_{1+2} (F_{1+2})
8. Serology and nucleic acid amplification technology (NAT) testing for virus safety. For details, see the corresponding Schedule for Virology Testing (Table 4-2).
9. Heart rate (HR), respiration rate (RR), systolic and diastolic blood pressure (SBP and DBP), and temperature (T).
10. A serum/plasma retention sample will be kept frozen at -70ºC.

[A] The results from baseline pregnancy test (when applicable), serum clinical chemistry and fibrinogen levels (when applicable) from samples drawn within 24 hours prior to the scheduled infusion and tested locally must be available prior to infusion for verification of the eligibility against the Inclusion/Exclusion criteria. In case fibrinogen levels determination for verification of the Inclusion/Exclusion criteria is performed at the Screening Visit, this sample will not be taken at Baseline Visit. Sample for PK will still be taken at Baseline Visit.

[B] Baseline fibrinogen levels for PK calculations (Clauss and antigen methods [ELISA]) will be measured at the central laboratory of the study.

Table 4-4 Schedule of Procedures of the Study in Pediatric Subjects

Visits Procedures and assessments	Screening Visit (up to 21 days prior to infusion visit)	Infusion Visit*	Pharmacokinetic, Efficacy, and Clinical Safety Evaluation Visits						Safety Follow-Up Visits[11]	
		Day 0	Day 1	Day 2	Day 4	Day 6	Day 9	Day 14	Day 21 ± 1 Day	Week 4 ± 3 Days
Informed Consent	X									
HIPAA[1]	X									
Demographics[2]	X									
Medical History	X									
Height and Weight		X								
Inclusion/Exclusion Criteria	X	X								
Physical Assessment	X	X	X							X
Medications[3]	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[4]		X[B]								
Serum Clinical Chemistry[5]		X[B]	X			X		X		
Hematology[6]		X	X			X		X		
Fibrinogen Levels (Clauss and Antigen)	X[A]	X[B,C]	X[C]	X[C,12]	X[C]	X[C]	X[C]	X[C,12]		
Rotational Thromboelastometry[7]		X								
Standard Coagulation Tests[8]		X								
Vital Signs[9]		X	X			X		X		
Adverse Events	X	X	X	X	X	X	X	X	X	X
Thrombotic Events Risk Assessment (including Wells Score)		X	X	X	X	X	X	X	X	X
Allergic/hypersensitivity Reactions Risk Assessment		X	X	X	X	X	X	X	X	X
Retention Sample[10]		X								

- See specific Day 0 flowchart for pediatric subjects (Table 4-5).

1. Health Information and Accountability Act (HIPAA) authorization form (if applicable).
2. Date of birth, gender, and ethnic origin.
3. Prior medications for the last 3 months (Screening Visit only) and concomitant medications.
4. Human chorionic gonadotropin (HCG)-based blood or urine assay for females of childbearing potential.
5. 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.
6. Red blood cells (RBC) count, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count and differential, and platelet count.
7. Thromboelastographic parameters: clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), and alpha angle (α).
8. Thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (aPTT).
9. Heart rate (HR), respiration rate (RR), systolic and diastolic blood pressure (SBP and DBP), and temperature (T).
10. A serum/plasma retention sample will be kept frozen at -70ºC.
11. Pediatric subjects will not undergo Month 3 virology and immunogenicity follow-up visits.
12. Not applicable for pediatric subjects weighing <30 kg.

[A]Sites that cannot perform fibrinogen levels determinations (by both Clauss and antigen method) locally will have a blood sample taken at Screening Visit 14 days prior to Baseline Visit and have it analyzed for this parameter by both methods at the central laboratory of the study for verification of the eligibility against the Inclusion/Exclusion criteria. In these cases, the sample for assessing the Inclusion/Exclusion criteria will not be taken at Baseline Visit. Samples for pharmacokinetic (PK) will still be taken at Baseline Visit.

[B]Baseline pregnancy test (when applicable), serum clinical chemistry and fibrinogen levels (when applicable) results from samples drawn within 24 hours prior to the scheduled infusion and tested locally must be available prior to infusion for verification of the eligibility against the Inclusion/Exclusion criteria.

[C]Baseline (and subsequent) fibrinogen levels for PK calculations (Clauss and antigen methods [ELISA]) will be measured at the central laboratory of the study.

Table 4-5 Schedule of Procedures During Day 0 (Infusion Visit) in Pediatric Subjects

Visits Procedures and assessments	Baseline (prior to infusion)	During infusion	After Infusion				
			30 minutes	1 hour	2 hours	4 hours	8 hours
Inclusion/Exclusion Criteria	X						
Height and Weight	X						
Physical Assessment	X						X
Medications[1]	X	X	X	X	X	X	X
Pregnancy Test[2]	X[A]						
Serum Clinical Chemistry[3]	X[A]						
Hematology[4]	X						
Fibrinogen Levels (Clauss and Antigen)	X[A,B]		X[9]	X	X[9]	X[9]	X
Rotational Thromboelastometry[5]	X			X			
Standard Coagulation Tests[6]	X			X			
Vital Signs[7]	X	X		X			
Adverse Events	X	X	X	X	X	X	X
Thrombotic Events Risk Assessment	X			X		X	
Allergic/hypersensitivity Reactions Risk Assessment	X			X		X	
Retention Sample[8]	X						
Footnotes continued on next page							

1. Concomitant medications.
2. Human chorionic gonadotropin (HCG)-based blood or urine assay for females of childbearing potential.
3. 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.
4. Red blood cells (RBC) count, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count and differential and platelet count.
5. Thromboelastographic parameters: clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), and alpha angle (α).
6. Thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (aPTT).
7. Heart rate (HR), respiration rate (RR), systolic and diastolic blood pressure (SBP and DBP), and temperature (T).
8. A serum/plasma retention sample will be kept frozen at -70ºC.
9. Not applicable for pediatric subjects weighing <30 kg.

[A] The results from baseline pregnancy test (when applicable), serum clinical chemistry and fibrinogen levels (when applicable) from samples drawn within 24 hours prior to the scheduled infusion and tested locally must be available prior to infusion for verification of the eligibility against the Inclusion/Exclusion criteria. In case fibrinogen levels determination for verification of the Inclusion/Exclusion criteria is performed at the Screening Visit, this sample will not be taken at Baseline Visit. Sample for PK will still be taken at Baseline Visit.

[B] Baseline fibrinogen levels for PK calculations (Clauss and antigen methods [ELISA]) will be measured at the central laboratory of the study.

4.6.1 DESCRIPTION OF THE CLINICAL TRIAL PROCEDURES

4.6.1.1 Medical history

A complete medical history will be carried out for all subjects at the Screening Visit.

4.6.1.2 Physical assessment

A physical assessment by body systems will be performed by the investigator or its designee (eg, a medical doctor designated as sub-investigator) at:

1. Screening Visit
2. Infusion Visit (Day 0): immediately prior (within 60 minutes prior) to the scheduled infusion and 8 hours post-infusion
3. Day 1 Visit (24 hours post-infusion)
4. Week 4 Visit

4.6.1.3 Height and weight

Height and weight will be measured for all subjects at Baseline Visit. The weight value will be used for calculation of dose of IMP to be administered.

4.6.1.4 Serum clinical chemistry

Laboratory test will include 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.

Blood specimens for laboratory tests will be collected for every subject at:

1. Infusion Visit (Day 0):
   A sample will be drawn within 24 hours prior to the scheduled infusion. In the case of the infusion, the sample will be also analyzed in due course locally in order to have the results available immediately prior to the scheduled infusion in order to verify that the subject fulfills the inclusion/exclusion criteria.
2. Day 1 (24 hours post-infusion)
3. Day 6 (144 hours post-infusion)
4. Day 14 (336 hours post-infusion)

All samples will be analyzed at the central laboratory.

4.6.1.5 Hematology

Laboratory test will include 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 cell (WBC) count and differential, and platelet count.

Blood specimens for laboratory tests will be collected for every subject at:

1. Infusion Visit (Day 0): within 24 hours prior to the scheduled infusion

2. Day 1 (24 hours post-infusion)
3. Day 6 (144 hours post-infusion)
4. Day 14 (336 hours post-infusion)

All samples will be analyzed at the central laboratory.

4.6.1.6 Fibrinogen Levels

Plasma samples will be obtained for measurement of fibrinogen levels by two methods:

1. Fibrinogen activity (Clauss method)
2. Fibrinogen antigen

Samples for fibrinogen determination will be taken at:

1. Screening Visit (up to 21 days prior to Infusion Visit): Sites that cannot perform fibrinogen levels determinations (by both Clauss and antigen method) locally will have a blood sample taken at Screening Visit and have it analyzed for this parameter by both methods at the central laboratory of the study for verification of the eligibility against the Inclusion/Exclusion criteria. In these cases, sample for the Inclusion/Exclusion criteria assessment will not be taken at Baseline Visit. Sample for PK will still be taken at Baseline Visit.

   In order to allow sufficient time for samples shipment and analysis and reporting of results back to the site, the sample for determination of the eligibility should be drawn at least 14 days prior to the planned infusion.

2. Infusion Visit (Day 0):

   i. For sites that have the capability of performing fibrinogen level determinations by both Clauss and antigen methods locally, a sample will be drawn within 24 hours of the scheduled infusion and analyzed at the local laboratory of the site in order to have the results available prior to the scheduled infusion in order to verify that the subject fulfills the inclusion criteria. In case fibrinogen levels determination for verification of the Inclusion/Exclusion criteria is performed at the screening visit, this sample will not be taken at Baseline Visit. Sample for PK as described below will still be taken at Baseline Visit.

   ii. Immediately prior (within 60 minutes prior) to the scheduled infusion a sample will be taken and analyzed at the central laboratory for fibrinogen levels. The value to be used for PK calculations as baseline value will be the central laboratory one, unless there is any technical issue with the PK central laboratory measurement that recommends not using this value, in which case the value for the Inclusion/Exclusion criteria assessment could be used for this purpose.

   iii. At 30 minutes (not applicable for pediatric subjects weighing <30 kg), 1 hour, 2 hours (not applicable for pediatric subjects weighing <30 kg), 4 hours (not applicable for pediatric subjects weighing <30 kg), and 8 hours after infusion end. These samples will be analyzed by central laboratory.

3. Day 1 (24 hours post-infusion): central laboratory testing only

4. Day 2 (48 hours post-infusion): central laboratory testing only (not applicable for pediatric subjects weighing <30 kg)
5. Day 4 (96 hours post-infusion): central laboratory testing only
6. Day 6 (144 hours post-infusion): central laboratory testing only
7. Day 9 (216 hours post-infusion): central laboratory testing only
8. Day 14 (336 hours post-infusion): central laboratory testing only (not applicable for pediatric subjects weighing <30 kg)

The exact time and date of taking the samples for the PK analysis will be recorded by the study staff for the PK analysis.

4.6.1.7 Rotational Thromboelastometry

ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

Samples for ROTEM will be taken at:

1. Infusion Visit (Day 0):
    i. Immediately prior (within 60 minutes prior) to the scheduled infusion
    ii. At 30 minutes (not applicable for pediatric subjects), 1 hour, and 4 hours (not applicable for pediatric subjects) after completion of the infusion
2. Day 1 (24 hours post-infusion, not applicable for pediatric subjects)
3. Day 2 (48 hours post-infusion, not applicable for pediatric subjects)
4. Day 4 (96 hours post-infusion, not applicable for pediatric subjects)
5. Day 6 (144 hours post-infusion, not applicable for pediatric subjects)
6. Day 9 (216 hours post-infusion, not applicable for pediatric subjects)

4.6.1.8 Standard coagulation tests

Following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

Samples for standard coagulation tests will be taken at:

1. Infusion Visit (Day 0):
    iii. Immediately prior (within 60 minutes prior) to the scheduled infusion
    iv. At 30 minutes (not applicable for pediatric subjects), 1 hour, and 4 hours (not applicable for pediatric subjects) after completion of the infusion
2. Day 1 (24 hours post-infusion, not applicable for pediatric subjects)
3. Day 2 (48 hours post-infusion, not applicable for pediatric subjects)
4. Day 4 (96 hours post-infusion, not applicable for pediatric subjects)
5. Day 6 (144 hours post-infusion, not applicable for pediatric subjects)
6. Day 9 (216 hours post-infusion, not applicable for pediatric subjects)

4.6.1.9 Markers of activation of coagulation

Following tests, indicative of activation of the coagulation: D-dimer, ATIII, thrombin-antithrombin III complex (TAT) and prothrombin fragments F_{1+2} (F_{1+2}) will be performed in adult subjects only on frozen plasma samples at the central laboratory of the study.

Samples for markers of activation of the coagulation tests will be taken at:

1. Infusion Visit (Day 0):
   i. Immediately prior (within 60 minutes prior) to the scheduled infusion
   ii. At 1 hour and 4 hours after completion of the infusion
2. Day 1 (24 hours post-infusion)
2. Day 2 (48 hours post-infusion)
3. Day 4 (96 hours post-infusion)
4. Day 6 (144 hours post-infusion)
5. Day 9 (216 hours post-infusion)

4.6.1.10 Immunogenicity testing

Serum/plasma samples from adult subjects only will be analyzed for the generation of antibodies to fibrinogen by using a stepwise approach starting with a functional screening assay to detect neutralizing activity. These samples will be analyzed at the sponsor's laboratory. In the event neutralizing activity is detected, samples will be further assessed by a confirmatory ELISA for the presence of antibodies to fibrinogen.

Samples for immunogenicity testing will be taken at:

1. Day 0, pre-infusion
2. Day 14 (± 1 day) post-infusion
3. Week 4 (± 3 days) post-infusion

4.6.1.11 Viral panel

Viral monitoring for each adult subject will be performed by means of serology and nucleic acid amplification technology (NAT) tests for the following viruses: HAV, HBV, HCV, HIV-1 and HIV-2, and B19.

Serum/plasma samples from all enrolled adult subjects will be examined at Baseline (prior to infusion on Day 0) and at different time points according to the schedule shown in Table 4-2.

All serum/plasma samples will be sent to the central laboratory of the study for measurement of serum viral status. If a subject is found to be positive for a particular virus at Baseline, tests for this particular virus would not be performed at later time points during the study.

4.6.1.12 Vital signs

Subject's following vital signs: T, RR, HR, SBP, and DBP will be monitored and recorded as follows:

1. Infusion Visit (Day 0):
    i. Immediately prior (within 60 minutes prior) to the scheduled infusion (baseline vital signs).
    ii. At the beginning of the infusion
    iii. Every 20 ± 5 minutes during the infusion
    iv. At the completion of the infusion
    v. 1 hour after infusion completion
2. Day 1 (24 hours post-infusion)
3. Day 6 (144 hours post-infusion)
4. Day 14 (336 hours post-infusion)

4.6.1.13 Adverse events

AEs that occurred at any time between signing of the informed consent and Week 4 post-infusion will be reported on the appropriate subject's case report form (CRF/eCRF) entry.

AEs assessment must be performed only by the investigator or its designee (eg, a medical doctor designated as sub-investigator). Under no circumstances should the assessment be performed by a study nurse (either site nurse or home health nurse).

4.6.1.14 Monitoring of allergic/hypersensitivity reactions

Subjects will be carefully monitored by the investigator and/or study staff for signs and symptoms of allergic/hypersensitivity reactions occuring between Baseline Visit and Week 4 Visit. The Grifols Medical Monitor will routinely review reported AEs for possible allergic/hypersensitivity reactions, according to algorithm described in Annex 2.

4.6.1.15 Monitoring of thrombotic events

Subjects will be monitored by the investigator and/or study staff for signs and symptoms of arterial and venous thromboses occuring between Baseline Visit and Week 4 Visit. The algorithms described in Annex 1, which include the Wells Score assessment, will be observed for evaluation and assessment of thrombotic events risk. In addition, the Grifols Medical Monitor will routinely review reported AEs for possible thrombotic events. Arterial and venous thromboses will be identified according to definitions in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Such thrombotic events include, but are not limited to, DVT, pumonary embolism (PE), myocardial infarction, cerebrovascular accident, acute coronary syndrome, limb thrombosis, sagittal sinus thrombosis, and portal vein or mesenteric artery thrombosis. All thromboses will be recorded as AEs and reported accordingly.

4.6.1.16 Retention sample

An additional appropriate volume of blood (specific volumes per visit indicated in Section 4.6.2) will be drawn in order to obtain a serum/plasma retention sample from each adult subject, with the exception of Day 0 pre-infusion sample, which will also be obtained from pediatric subjects. The retention sample will be frozen and stored in the event that additional testing is required in the future for purposes of this study only (ie, repeat testing, confirmation of virology results, or immunogenicity testing).

Retention samples will be drawn at:

1. Infusion Visit (Day 0): immediately prior (within 60 minutes prior) to the scheduled infusion. This sample will be also drawn from pediatric subjects. Additional samples will be drawn for enrolled adult subjects at 1 hour and 4 hours after completion of the infusion.
2. Day 9 (216 hours post-infusion, not applicable for pediatric subjects)
3. Day 14 (336 hours post-infusion, not applicable for pediatric subjects)
4. Day 21 ± 1 day post-infusion (not applicable for pediatric subjects)
5. Week 4 ± 3 days post-infusion (not applicable for pediatric subjects)
6. Month 3 ± 7 days post-infusion (not applicable for pediatric subjects)

4.6.1.17 Concomitant medication

All medications other than the investigational product administered to study subjects will be recorded during the conduct of the clinical trial.

4.6.1.18 Pregnancy test

Pregnancy test [human chorionic gonadotropin (HCG)-based blood or urine assay] for women of childbearing potential will be performed on a sample drawn within 24 hours of the scheduled infusion and analyzed at the local laboratory of the site in order to have the results available immediately prior to the scheduled infusion in order to verify that the subject fulfills the inclusion/exclusion criteria.

4.6.2 CLINICAL TRIAL VISITS

Screening Visit

This will be the first clinical trial visit for all subjects. The investigator will provide potential study participants with complete information about all clinical trial procedures as well as conditions of subject's participation.

During the Screening Visit, the investigator will determine subject's eligibility for the inclusion in this clinical trial.

The Screening Visit may take place for up to 21 days prior to the investigational medicinal product infusion (Day 0) to allow sufficient time for a wash-out period for those subjects that have recently received any administration of a fibrinogen-containing product (eg. fibrinogen concentrates, cryoprecipitate, fresh frozen plasma).

Assessments and procedures planned to be conducted during the Screening Visit will be performed only in the following order to avoid unnecessary assessments or procedures:

1. Information to be given to potential clinical trial subjects:

   – Subjects will be informed of the nature, purpose and procedures of the study, with a description of the possible risks involved.

- Subjects will be informed of the voluntary nature of participation, and of the right to withdraw from the study at any time, without this implying any negative consequences for the subject.
- Subjects will receive a *Patient Information Sheet* to take at home and they will be given enough time to think about their clinical trial participation.
- Investigator will make sure that potential subjects fully understand the elements of the *Patient Information Sheet*.

2. Clinical Trial Informed Consent:

   Before any study-specific screening procedures will be performed, and after completely understanding the nature of the clinical trial, potential subjects or their parents or legal guardian for those subjects not qualified to give legal consent, must sign and date a *Clinical Trial Informed Consent*. The investigator will also sign and date it, thus reflecting that *Clinical Trial Informed Consent* has been obtained, and that the subject has had the opportunity to ask questions, and has received adequate answers. The subject will receive a signed copy of the informed consent form (ICF) and the original will be filed along with the study documentation.

3. Health Information Portability and Accountability Act (HIPAA)

   The subject will be asked to sign HIPAA Authorization Form where necessary (Note: The HIPAA authorization may be included with the ICF).

4. Allocation of subject number:

   Following the signature of the *Clinical Trial Informed Consent*, the investigator will include the subject in the *Subject's Screening Log*, assignment of an individual inclusion number to each study subject.

5. Documentation of demography: date of birth, gender, and ethnic origin.

6. Documentation of the medical and surgical history for the last year.

7. Documentation of medications that the subject is taking or has taken within the last 3 months (it includes transfusion of blood or any blood-derived product).

8. Physical assessment by body systems.

9. Review of inclusion and exclusion criteria to confirm subject eligibility (see Sections 5.1 and 5.2).

   Subjects who do not fulfill all inclusion criteria (except laboratory criteria for which results may not be available at Screening Visit) or meet any exclusion criteria (except laboratory criteria for which results may not be available at Screening Visit) will be considered screening failures.

   Only subjects who fulfill all inclusion criteria (except laboratory criteria for which results may not be available at Screening Visit) and do not meet any of the exclusion criteria (except laboratory criteria for which results may not be available at Screening Visit) will be considered eligible to continue with the following assessments.

10. Assessment of AEs.

11. Fibrinogen levels: Plasma samples will be obtained for measurement of fibrinogen levels at those sites that cannot perform fibrinogen levels determinations by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen locally. In these cases the subject will have a blood sample taken at Screening Visit and have it analyzed for this parameter by both methods at the central laboratory of the study for verification of the eligibility against the Inclusion/Exclusion criteria. In these cases, samples for the Inclusion/Exclusion criteria assessment will not be taken at Baseline Visit. Samples for PK will still be taken at Baseline Visit.

    In order to allow sufficient time for samples shipment and analysis and reporting of results back to the site, the sample for the Inclusion/Exclusion criteria assessment should be drawn at least 14 days prior to the planned infusion.

Possible outcomes of the screening assessments:

Subjects who have undergone all Screening Visit assessments, fulfill all inclusion criteria (except laboratory criteria for which results may not be available at Screening Visit), and do not meet any exclusion criteria (except laboratory criteria for which results may not be available at Screening Visit) will be considered eligible to participate in the clinical trial. These subjects will be included in the *Subject's Identification Log*.

Subjects who have not undergone all Screening Visit assessments, do not fulfill all inclusion criteria (except laboratory criteria for which results may not be available at Screening Visit), and/or meet any exclusion criteria (except laboratory criteria for which results may not be available at Screening Visit) will be considered screening failures. If a subject is ineligible for the clinical trial, their demographic data and specific reason for ineligibility will be captured on the Screen Failure CRF/eCRF page and on the *Subject's Screening Log*.

If suitable for logistic reasons, the procedures scheduled at the Screening Visit may be performed during the Infusion Visit (Day 0) Baseline (within 24 hours prior to infusion). In this case, the Screening Visit will be combined with the Infusion Visit (Day 0) Baseline. In this case, assessments and procedures required during both visits (Screening Visit and Infusion Visit [Day 0] Baseline) have to be performed.

Infusion Visit (Day 0) – Baseline

The following assessments and/or procedures will be carried out on or before Day 0 as Baseline (within 24 hours prior to infusion, unless otherwise noted below):

1. Physical assessment by body systems performed by a medical doctor.

2. Laboratory testing:

   – Pregnancy test: pregnancy test [HCG-based blood or urine assay] will be performed for women of childbearing potential.

     Samples will be drawn within 24 hours prior to the scheduled infusion and analyzed by the local laboratory of the site in order to make these results available to the study team to verify compliance with Inclusion/Exclusion criteria before the infusion.

- Serum clinical chemistry: laboratory test will include creatinine, BUN, TB, ALP, ALT, AST, LDH, glucose, sodium, potassium, chloride, and calcium.

  Samples will be drawn within 24 hours prior to the scheduled infusion and analyzed by the local laboratory of the site in order to make these results available to the study team to verify compliance with Inclusion/Exclusion criteria before the infusion. Samples will also be analyzed by the central laboratory of the study.

- Hematology: laboratory test will include CBC: RBC count, Hgb, Hct, MCH, MCHC, MCV, WBC count and differential, and platelet count.

  Samples must be taken within 24 hours prior to the scheduled infusion to be analyzed by the central laboratory of the study.

- Fibrinogen levels: plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen.

For sites that have the capability of performing fibrinogen level determinations by both Clauss and antigen methods locally, samples will be drawn within 24 hours prior to the scheduled infusion and analyzed by the local laboratory of the site in order to have these results available to the study team to verify compliance with Inclusion/Exclusion criteria before the infusion. In case fibrinogen levels determination for verification of Inclusion/Exclusion criteria is performed at the Screening Visit, this sample will not be taken at Baseline Visit. Sample for PK as described below will still be taken at Baseline Visit.

Another sample for measuring baseline fibrinogen levels by both activity (Clauss) and antigen (ELISA) methods for PK calculations by the central laboratory of the study will be drawn within 60 minutes prior to the scheduled infusion.

- Rotational thromboelastometry: ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

  Samples must be taken within 60 minutes prior to the scheduled infusion to be analyzed by the central laboratory of the study.

- Standard coagulation tests: following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

  Samples must be taken within 60 minutes prior to the scheduled infusion to be analyzed by the central laboratory of the study.

- Markers of activation of coagulation (not applicable for pediatric subjects): following tests, indicative of activation of the coagulation: D-dimer, ATIII, TAT, and F_{1+2} will be performed on frozen plasma samples at the central laboratory of the study.

Samples must be taken within 60 minutes prior to the scheduled infusion to be analyzed by the central laboratory of the study.

– Immunogenicity testing (not applicable for pediatric subjects): serum/plasma samples must be taken prior to the scheduled infusion to be tested for antibodies to fibrinogen at the sponsor's laboratory.

– Viral panel (not applicable for pediatric subjects): viral monitoring for each subject will be performed at the central laboratory of the study by means of serology and NAT tests for the following viruses: HAV, HBV, HCV, HIV-1 and HIV-2, and B19. The following table (Table 4-6) provides a schedule of the virology testing on Day 0 (Baseline).

Table 4-6 Baseline Virology Schedule for Day 0

Virus	Serology	NAT
Hepatitis A virus (HAV)	X[1] (IgM & IgG)	X[1]
Hepatitis B virus (HBV)	X[1,2]	X[1]
Hepatitis C virus (HCV)	X[1]	X[1]
Human immunodeficiency virus type 1 and type 2 (HIV-1 & HIV-2)	X[1]	X[1,3]
Parvovirus B19	X[1] (IgM & IgG)	X[1]

[1] Sample will be always analyzed.
[2] Total anti-HBc (IgM & IgG).
[3] NAT for HIV-1 only.

Samples must be taken within 60 minutes prior to the scheduled infusion to be analyzed by the central laboratory of the study.

– Retention sample: An additional blood amount of approximately 20 mL will be drawn within 60 minutes prior to the scheduled infusion in order to obtain a serum/plasma retention sample from each subject. The retention sample will be frozen and stored at the central laboratory of the study in the event that additional testing is required in the future for purposes of this study only.

3. Vital signs: subject vital signs (T, RR, HR, SBP, DBP) will be monitored within 60 minutes before the beginning of the infusion (baseline vital signs).

4. Height and weight: Subject height and weight will be measured for all subjects at Baseline Visit. Weight value will be used for calculation of dose to be administered.

5. Assessment of AEs: AE occurring at any time between signature of *Clinical Trial Informed Consent* and the Week 4 Visit will be reported.

– Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions occurring between the Baseline Visit and Week 4 Visit.

– Subjects will be also monitored for signs and symptoms of arterial and venous thromboses occurring between the Baseline Visit and Week 4 Visit.

6. Assessment of concomitant medication: All concomitant medications, other than the investigational product, administered to the subject will be recorded.

The use of any concomitant medications during the PK study (between 1 week before the infusion and Day 14 post-infusion) should be avoided as much as possible. If clinical reasons make necessary the use of concomitant drugs, the treating physician will evaluate each case.

7. Review of inclusion and exclusion criteria to confirm subject eligibility (see Sections 5.1 and 5.2).

Subjects who do not fulfill all inclusion criteria (including laboratory criteria to be verified on Day 0 prior to the infusion) and/or fulfill any exclusion criteria (including laboratory criteria to be verified on Day 0 prior to the infusion) will be considered screening failures.

Only subjects who fulfill all inclusion criteria (including laboratory criteria to be verified on Day 0 prior to the infusion) and do not meet any exclusion criteria (including laboratory criteria to be verified on Day 0 prior to the infusion) will be considered eligible to continue with the following procedures of the study.

Infusion Visit (Day 0) - Infusion

After verification of compliance with all applicable Inclusion/Exclusion criteria, study staff may proceed with infusion of the investigational medicinal product according to the Section 4.5.4.2 *Dispensation and administration of the investigational product.*

If the subject had a bleeding requiring replacement therapy with any fibrinogen-containing product between Screening Visit and investigational medicinal product infusion then, the investigational medicinal product infusion should not be carried out and the 21-day washout period be observed, thus postponing investigational medicinal product infusion (Day 0 Visit) as appropriate. In this case, screening/baseline (pre-infusion) samples should be taken again, and laboratory inclusion/exclusion criteria verified with the results of the most recent sample.

Briefly, a 70 mg/kg body weight single-dose of FIB Grifols will be intravenously administered at a rate that must not exceed 5 mL/minute. Study staff should make sure that the product is at room temperature before being administered. The exact volume infused to the subject will be recorded in subject's source documents and CRF/eCRF. The exact date and time of start and completion of the infusion will be also recorded.

The following assessments and/or procedures will be carried out during infusion of the investigational medicinal product:

1. Vital signs: subject vital signs (T; RR; HR; SBP; DBP) will be monitored:
   i. At the beginning of the infusion
   ii. Every 20 ± 5 minutes during infusion
   iii. At the completion of the infusion

2. Assessment of AEs: Any AE occurred during infusion will be recorded, including the infusion time elapsed and the infusion rate at the time of onset.

3. Assessment of concomitant medication: all medications other than investigational product administered to the subject during infusion will be recorded.

Infusion Visit (Day 0) – Post-Infusion

Blood samples taken on Infusion Visit (Day 0) Post-infusion period should be taken from the contralateral arm where the investigational medicinal product has been infused.

Infusion Visit (Day 0) – 30 Minutes Post-Infusion

The following assessments and/or procedures will be carried out 30 minutes after the completion of the infusion of the investigational medicinal product (± 5 minutes):

1. Fibrinogen levels (not applicable for pediatric subjects weighing <30 kg): plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method), and fibrinogen antigen (ELISA).

   Fibrinogen levels for PK calculations will be made by the central laboratory of the study.

2. Rotational thromboelastometry (not applicable for pediatric subjects): ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

3. Standard coagulation tests (not applicable for pediatric subjects): following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

4. Assessment of AEs: any new AE occurred will be recorded.

5. Assessment of concomitant medication: all new medications other than investigational product administered to the subject will be recorded.

Infusion Visit (Day 0) – 1 Hour Post-Infusion

The following assessments and/or procedures will be carried out one (1) hour after the end of infusion of the investigational medicinal product (± 10 minutes):

1. Vital signs: subject vital signs (T; RR; HR; SBP; DBP) will be monitored.

2. Fibrinogen levels: plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA).

   Fibrinogen levels for PK calculations will be made by the central laboratory of the study.

3. Rotational thromboelastometry: ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

4. Standard coagulation tests: following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

5. Markers of activation of coagulation (not applicable for pediatric subjects): following tests, indicative of activation of the coagulation: D-dimer, ATIII, TAT, and F_{1+2} will be performed on frozen plasma samples at the central laboratory of the study.

6. Retention sample (not applicable for pediatric subjects): an additional blood amount of approximately 20 mL will be drawn in order to obtain a serum/plasma retention sample from each subject. The retention sample will be frozen and stored at the central laboratory of the study in the event that additional testing is required in the future for purposes of this study only.

7. Assessment of AEs: any new AE occurred will be recorded.

   – Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.

   – Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.

8. Assessment of concomitant medication: all new medications other than the investigational product administered to the subject will be recorded.

Infusion Visit (Day 0) – 2 Hours Post-Infusion

The following assessments and/or procedures will be carried out two (2) hours after the end of infusion of the investigational medicinal product (± 10 minutes):

1. Fibrinogen levels (not applicable for pediatric subjects weighing <30 kg): plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA).

   Fibrinogen levels for PK calculations will be made by the central laboratory of the study.

2. Assessment of AEs: any new AE occurred will be recorded.

3. Assessment of concomitant medication: all new medications other than the investigational product administered to the subject will be recorded.

Infusion Visit (Day 0) – 4 Hours Post-Infusion

The following assessments and/or procedures will be carried out four (4) hours after the end of infusion of the investigational medicinal product (± 10 minutes):

1. Fibrinogen levels (not applicable for pediatric subjects weighing <30 kg): plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA).

   Fibrinogen levels for PK calculations will be made by the central laboratory of the study.

2. Rotational thromboelastometry (not applicable for pediatric subjects): ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

3. Standard coagulation tests (not applicable for pediatric subjects): following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

4. Markers of activation of coagulation (not applicable for pediatric subjects): following tests, indicative of activation of the coagulation: D-dimer, ATIII, TAT, and F_{1+2} will be performed on frozen plasma samples at the central laboratory of the study.

5. Retention sample (not applicable for pediatric subjects): an additional blood amount of approximately 20 mL will be drawn in order to obtain a serum/plasma retention sample from each subject. The retention sample will be frozen and stored at the central laboratory of the study in the event that additional testing is required in the future for purposes of this study only.

6. Assessment of AEs: any new AE occurred will be recorded.

   – Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.

   – Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.

7. Assessment of concomitant medication: all new medications other than the investigational product administered to the subject will be recorded.

Infusion Visit (Day 0) – 8 Hours Post-Infusion

The following assessments and/or procedures will be carried out 8 hours after the end of infusion of the investigational medicinal product (± 10 minutes):

1. Physical assessment: physical examination by body systems performed by a medical doctor.

2. Fibrinogen levels: plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA).

   Fibrinogen levels for PK calculations will be made by the central laboratory of the study.

3. Assessment of AEs: any new AE occurred will be recorded.

   – Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.

   – Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.

4. Assessment of concomitant medication: all new medications other than investigational product administered to the subject will be recorded.

Day 1 Visit (24 hours Post-Infusion)

The following assessments and/or procedures will be carried out at Day 1 (24 hours after the infusion ± 30 minutes):

1. Physical assessment: physical examination by body systems performed by the investigator or its designee (eg, a medical doctor designated as sub-investigator).

2. Laboratory testing:

   – Serum clinical chemistry: laboratory test will include creatinine, BUN, TB, ALP, ALT, AST, LDH, glucose, sodium, potassium, chloride and calcium.

     Samples taken 24 hours after infusion will be analyzed by the central laboratory of the study.

   – Hematology: laboratory test will include CBC: RBC count, Hgb, Hct, MCH, MCHC, MCV, WBC count and differential, and platelet count.

     Samples taken within 24 hours after the infusion will be analyzed by the central laboratory of the study.

   – Fibrinogen levels: plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA).

     Samples taken 24 hours after the infusion will be analyzed for measuring fibrinogen levels for PK calculations by the central laboratory of the study.

   – Rotational thromboelastometry (not applicable for pediatric subjects): ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

     Samples taken 24 hours after the infusion will be analyzed by the central laboratory of the study.

     – Standard coagulation tests (not applicable for pediatric subjects): following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

     – Markers of activation of coagulation (not applicable for pediatric subjects): following tests, indicative of activation of the coagulation: D-dimer, ATIII, TAT, and F_{1+2} will be performed on frozen plasma samples at the central laboratory of the study.

   3. Vital signs: subject vital signs (T, RR, HR, SBP, DBP) will be monitored.

   4. Assessment of AEs: any new AE occurred will be recorded.

      – Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.

      – Subjects will be also monitored for signs and symptoms of arterial and venous thromboses.

5. Assessment of concomitant medication: all new medications administered to the subject will be recorded.

This visit will ALWAYS be performed at the study center by the investigative staff.

Day 2 Visit (48 hours Post-infusion)

The following assessments and/or procedures will be carried out at Day 2 (48 hours after the infusion ± 60 minutes):

1. Laboratory testing:
   - Fibrinogen levels (not applicable for pediatric subjects weighing <30 kg): Plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA).

     Samples taken 48 hours after the infusion will be analyzed for measuring fibrinogen levels for PK calculations by the central laboratory of the study.

   - Rotational thromboelastometry (not applicable for pediatric subjects): ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

     Samples taken 48 hours after the infusion will be analyzed by the central laboratory of the study.

   - Standard coagulation tests (not applicable for pediatric subjects): following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

   - Markers of activation of coagulation (not applicable for pediatric subjects): following tests, indicative of activation of the coagulation: D-dimer, ATIII, TAT, and F_{1+2} will be performed on frozen plasma samples at the central laboratory of the study.

2. Assessment of AEs: any new AE occurred will be recorded.
   - Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.

   - Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.

3. Assessment of concomitant medication: all new medications administered to the subject will be recorded.

This visit, and all subsequent follow-up visits except Week 4 Visit may be conducted in the subject's home by designated study staff (eg, homecare nurses) if approved by the study subject and the investigator.

Day 4 Visit (96 Hours Post-Infusion)

The following assessments and/or procedures will be carried out at Day 4 (96 hours after the infusion ± 60 minutes):

1. Laboratory testing:
   - Fibrinogen levels: plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA)

     Samples taken 96 hours after the infusion will be analyzed for measuring fibrinogen levels for PK calculations by the central laboratory of the study.

   - Rotational thromboelastometry (not applicable for pediatric subjects): ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

     Samples taken 96 hours after the infusion will be analyzed by the central laboratory of the study.

   - Standard coagulation tests (not applicable for pediatric subjects): following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

   - Markers of activation of coagulation (not applicable for pediatric subjects): following tests, indicative of activation of the coagulation: D-dimer, ATIII, TAT, and F_{1+2} will be performed on frozen plasma samples at the central laboratory of the study.

2. Assessment of AEs: any new AE occurred will be recorded.
   - Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.

   - Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.

3. Assessment of concomitant medication: all new medications administered to the subject will be recorded.

Day 6 Visit (144 Hours Post-Infusion)

The following assessments and/or procedures will be carried out at Day 6 (144 hours after the infusion ± 60 minutes):

1. Laboratory testing:
   - Serum clinical chemistry: laboratory test will include creatinine, BUN, TB, ALP, ALT, AST, LDH, glucose, sodium, potassium, chloride, and calcium.

     Samples taken 144 hours after the infusion will be analyzed by the central laboratory of the study.

   - Hematology: laboratory test will include CBC: RBC count, Hgb, Hct, MCH, MCHC, MCV, WBC count and differential, and platelet count.

Samples taken 144 hours after the infusion will be analyzed by the central laboratory of the study.

- Fibrinogen levels: plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA).

  Samples taken 144 hours after the infusion will be analyzed for measuring fibrinogen levels for PK calculations by the central laboratory of the study.

- Rotational thromboelastometry (not applicable for pediatric subjects): ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

  Samples taken 144 hours after the infusion will be analyzed by the central laboratory of the study.

- Standard coagulation tests (not applicable for pediatric subjects): following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

- Markers of activation of coagulation (not applicable for pediatric subjects): following tests, indicative of activation of the coagulation: D-dimer, ATIII, TAT, and F_{1+2} will be performed on frozen plasma samples at the central laboratory of the study.

2. Vital signs: subject vital signs (T, RR, HR, SBP, and DBP) will be monitored

3. Assessment of AEs: any new AE occurred will be recorded.

   - Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.

   - Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.

4. Assessment of concomitant medication: all new medications administered to the subject will be recorded.

Day 9 Visit (216 Hours Post-Infusion)

The following assessments and/or procedures will be carried out at Day 9 (216 hours after the infusion ± 60 minutes):

1. Laboratory testing:

   - Fibrinogen levels: plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA).

     Samples taken 216 hours after the infusion will be analyzed for measuring fibrinogen levels for PK calculations by the central laboratory of the study.

- Rotational thromboelastometry (not applicable for pediatric subjects): ROTEM will be performed on frozen plasma samples by the central laboratory and following parameters measured: CT, CFT, MCF, and α.

  Samples taken 216 hours after the infusion will be analyzed by the central laboratory of the study.

- Standard coagulation tests (not applicable for pediatric subjects): following standard coagulation tests: TT, PT, and aPTT will be performed on frozen plasma samples at the central laboratory of the study.

- Markers of activation of coagulation (not applicable for pediatric subjects): following tests, indicative of activation of the coagulation: D-dimer, ATIII, TAT, and F_{1+2} will be performed on frozen plasma samples at the central laboratory of the study.

- Viral panel (not applicable for pediatric subjects): viral monitoring for each adult subject will be performed at the central laboratory of the study according to the following table (Table 4-7), which provides a schedule of the virology testing on Day 9 (216 hours after the infusion).

Table 4-7 Virology Schedule for Day 9

Virus	Serology	NAT
Parvovirus B19[1]	X (IgM & IgG)	X

[1] The samples drawn on Day 9 will be analyzed only in the event of negative results of NAT, IgM, and IgG analysis for the presence of B19 performed on Baseline sample.

- Retention sample (not applicable for pediatric subjects): an additional blood amount of approximately 5 mL will be drawn on Day 9 (216 hours after the infusion) in order to obtain a serum/plasma retention sample from each adult subject. The retention sample will be frozen and stored at the central laboratory of the study in the event that additional testing is required in the future for purposes of this study only.

2. Assessment of AEs: any new AE occurred will be recorded.
   - Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.
   - Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.
3. Assessment of concomitant medication: all new medications administered to the subject will be recorded.

Day 14 Visit (336 Hours Post-Infusion)

The following assessments and/or procedures will be carried out at Day 14 (336 hours after the infusion ± 60 minutes):

1. Laboratory testing:

– Serum clinical chemistry: laboratory test will include creatinine, BUN, TB, ALP, ALT, AST, LDH, glucose, sodium, potassium, chloride, and calcium.

  Samples taken 336 hours after the infusion will be analyzed by the central laboratory of the study.

– Hematology: laboratory test will include CBC: RBC count, Hgb, Hct, MCH, MCHC, MCV, WBC count and differential, and platelet count.

  Samples taken 336 hours after the infusion will be analyzed by the central laboratory of the study.

– Fibrinogen levels (not applicable for pediatric subjects weighing <30 kg): plasma samples will be obtained for measurement of fibrinogen levels by two methods: fibrinogen activity (Clauss method) and fibrinogen antigen (ELISA).

  Samples taken 336 hours after the infusion will be analyzed for measuring fibrinogen levels for PK calculations by the central laboratory of the study.

– Immunogenicity testing (not applicable for pediatric subjects): Serum/plasma samples to be tested for antibodies to fibrinogen

– Viral panel (not applicable for pediatric subjects): viral monitoring for each adult subject will be performed at the central laboratory of the study according to the following table (Table 4-8), which provides a schedule of the virology testing on Day 14 (336 hours after the infusion).

Table 4-8 Virology Schedule for Day 14

Virus	Serology	NAT
HAV[1]		X
HBV[1]		X
Parvovirus B19[1]	X (IgM & IgG)	X

[1] The samples drawn on Day 14 will be analyzed for a particular virus only in the event of negative results of analysis of NAT, IgM, and IgG for that particular virus performed on the samples from all previous visits.

– Retention sample (not applicable for pediatric subjects): An additional blood amount of approximately 20 mL will be drawn on Day 14 (336 hours after the infusion) in order to obtain a serum/plasma retention sample from each adult subject. The retention sample will be frozen and stored at the central laboratory of the study in the event that additional testing is required in the future for purposes of this study only.

2. Vital signs: Subject vital signs (T, RR, HR, SBP, DBP) will be monitored.

3. Assessment of AEs: Any new AE occurred will be recorded.

   – Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.
   – Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.

4. Assessment of concomitant medication: all new medications administered to the subject will be recorded.

Day 21 ± 1 Day Visit

The following assessments and/or procedures will be carried out at Day 21 ± 1 days after the infusion:

1. Laboratory testing:
   - Viral panel (not applicable for pediatric subjects): viral monitoring for each adult subject will be performed at the central laboratory of the study according to the following table (Table 4-9), which provides a schedule of the virology testing on Day 21 ± 1 day after the infusion.

Table 4-9 Virology Schedule for Day 21 ± 1 Day Visit

Virus	Serology	NAT
HAV[1]	X (IgM & IgG)	X
HBV[1]		X

[1]The samples drawn on Day 21 will be analyzed for a particular virus only in the event of negative results of analysis of NAT, IgM, and IgG for that particular virus performed on the samples from all previous visits.

   - Retention sample (not applicable for pediatric subjects): an additional blood amount of approximately 10 mL will be drawn on Day 21 ± 1 day after the infusion in order to obtain a serum/plasma retention sample from each adult subject. The retention sample will be frozen and stored at the central laboratory of the study in the event that additional testing is required in the future for purposes of this study only.

2. Assessment of AEs: any new AE occurred will be recorded.
   - Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.
   - Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.

3. Assessment of concomitant medication: all new medications administered to the subject will be recorded.

Week 4 ± 3 Days Visit

The following assessments and/or procedures will be carried out at Week 4 ± 3 days after the infusion:

1. Physical assessment: physical examination by body systems performed by the investigator or its designee (eg, a medical doctor designated as sub-investigator).
2. Laboratory testing:
   - Immunogenicity testing (not applicable for pediatric subjects): serum/plasma samples to be tested for antibodies to fibrinogen.

– Viral panel (not applicable for pediatric subjects): viral monitoring for each adult subject will be performed at the central laboratory of the study according to the following table (Table 4-10), which provides a schedule of the virology testing on Week 4 ± 3 days after the Infusion Visit.

Table 4-10 Virology Schedule for Week 4 ± 3 Days

Virus	Serology	NAT
HAV[1]	X (IgM & IgG)	X
HBV[1]	X[2]	X
HCV[1]		X
HIV-1[1]		X

[1] The samples drawn on Week 4 ± 3 Days will be analyzed for a particular virus only in the event of negative results of analysis of NAT, IgM, and IgG for that particular virus performed on the samples from all previous visits.

[2] HBsAg

– Retention sample (not applicable for pediatric subjects): an additional blood amount of approximately 10 mL will be drawn on Week 4 ± 3 days after the Infusion Visit in order to obtain a serum/plasma retention sample from each adult subject. The retention sample will be frozen and stored at the central laboratory of the study in the event that additional testing is required in the future for purposes of this study only.

3. Assessment of AEs: Any new AE occurred will be recorded.

– Subjects will be monitored for signs and symptoms of allergic/hypersensitivity reactions.
– Subjects will also be monitored for signs and symptoms of arterial and venous thromboses.

4. Assessment of concomitant medication: all new medications administered to the subject will be recorded.

This visit will always be performed at the study center by the investigator.

Month 3 ± 7 Days Visit

This visit is not applicable to pediatric subjects. The following assessments and/or procedures will be carried out at Month 3 ± 7 days after the infusion:

1. Laboratory testing:

– Viral panel: viral monitoring for each subject will be performed at the central laboratory of the study according to the following table (Table 4-11), which provides a schedule of the virology testing on Month 3 ± 7 days after the Infusion Visit.

Table 4-11 Virology Schedule for Month 3 ± 7 Days

Virus	Serology	NAT
HBV[1]	X[2]	
HCV[1]	X[3]	X
HIV-1[1] and HIV-2[1]	X[4]	X[5]

[1] The samples drawn on Month 3 ± 7 Days will be analyzed for a particular virus only in the event of negative results of analysis of NAT, IgM, and IgG for that particular virus performed on the sample from Day 0 Visit (Baseline).
[2] HBsAg
[3] In case of HCV positive antibody screen, a recombinant immunoblot assay will be performed.
[4] In case of HIV positive antibody screen, a Western blot assay for HIV-1 will be performed.
[5] NAT for HIV-1 only.

- Retention sample: an additional blood amount of approximately 10 mL will be drawn on Month 3 ± 7 days after the Infusion Visit in order to obtain a serum/plasma retention sample from each subject. The retention sample will be frozen and stored at the central laboratory of the study in the event that additional testing is required in the future for purposes of this study only.

2. Assessment of concomitant medication: a registry of medications, other than the investigational product, administered to the subject.

4.7 PREMATURE DISCONTINUATION OF PARTICIPATING SUBJECTS

Study participation is strictly voluntary. Study subjects have the right to withdraw from the study at any time for any reason. Likewise the investigator can withdraw a subject from the clinical trial at any time if it is deemed in the subject's best interest

In any case, the investigator must document the reason(s) for withdrawal of each subject in the medical history and in the CRF/eCRF. Moreover, after subject's withdrawal it is suggested to perform a last visit as soon as possible so that all study-related information can be recorded. The sponsor will have access to all data gathered on subjects prior to termination.

Since premature discontinuations could lead to missing data, it will be possible to substitute certain discontinued subjects for new ones in order to get number of evaluable subjects. These substitutions will be only allowed when premature discontinuations happen before the infusion of investigational product during the enrolment period.

Subject withdrawal criteria and procedures are described in Section 5.3.

4.8 ACCOUNTABILITY PROCEDURES FOR THE INVESTIGATIONAL PRODUCT

The investigational site must keep accurate drug accountability records. These will include: 1) dates of receipt for investigational product; 2) when and how much investigational product was dispensed; 3) when and how much investigational product was administered to each study subject.

In addition, reasons for deviations from the expected dispensing/administration regimen must also be recorded.

All study medication will be reconciled before completion of the clinical trial within each clinical site.

4.9 SOURCE DATA

All information contained in the medical history, complementary exploration reports including laboratory test will be considered as clinical trial source data.

Any data entered in the CRF/eCRF should have written or electronic record in the subject's medical records. These written or electronic records will be considered source data and should be dated and signed by the investigator or by the qualified delegated person (eg, results of physical examinations, vital signs testing, or the investigational product administration procedure).

For every single subject enrolled, the investigator will write into his/her medical history that he/she has been enrolled in a clinical trial, specifying its title, study number and sponsor (Instituto Grifols, S.A.), as well as the inclusion date.

The investigator is responsible for maintaining complete and adequate case histories in source records of each subject. All study-specific data necessary to be recorded in the CRF/eCRF that cannot be found in subject's past medical records (such as medical history, past medications, etc, to be recorded at screening visit) should be recorded by the investigator or its designee in subject's medical file, dating and signing all new entries.

Source data must be preserved for the maximum period of time permitted by local regulations and made available by the investigator in the cases described above.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 SUBJECT INCLUSION CRITERIA

Subject eligibility will be based on the presence of congenital fibrinogen deficiency manifested as afibrinogenemia and the willingness to participate the study.

Subjects fulfilling the following inclusion criteria are eligible for participation in the study:

1. Male or female subjects less than 70 years old[a].
2. Sign the written ICF, or the subject's parent or legal guardian signs the ICF where applicable, and the Subject Authorization Form (SAF) where applicable. Pediatric subjects, as defined by local regulations, will be asked to sign an age appropriate assent form.
3. Subjects diagnosed with congenital fibrinogen deficiency manifested as afibrinogenemia.
4. Subjects with a fibrinogen level undetectable[1], or equal or less than 30 mg/dL determined by both Clauss and antigen methods at baseline[2] (sample drawn within 24 hours prior to infusion on Day 0 Visit will be tested locally) or at Screening Visit[3] (sample should be drawn at least 14 days prior to infusion on Day 0 Visit to be tested at central laboratory).

[1] Limit of detection for fibrinogen level determination must be 30 mg/dL or lower for both methods.

[2]For sites that have the capability of performing fibrinogen level determinations locally by both Clauss and antigen methods with a limit of detection of 30 mg/dL or lower.

[3]For sites that do not have the capability of performing fibrinogen level determinations by both Clauss and antigen methods locally or have methods that are not sensitive enough (limit of detection: 30 mg/dL).

5. Female subjects of child-bearing potential[b] must have a negative test for pregnancy blood or urine HCG-based assay at baseline (sample drawn within 24 hours prior to infusion on Day 0 Visit)
6. Female subjects of child-bearing potential[b] and their partner have agreed to practice contraception using a method of proven reliability (ie, hormonal methods, barrier methods, intrauterine devices methods) to prevent a pregnancy during the course of the clinical trial
7. Subjects must be willing to comply with all aspects of the clinical trial protocol, including blood sampling, for the whole duration of the study

[a]The enrollment of pediatric subjects (below 18 years of age) will be initiated only after the safety of FIB Grifols in the adult subjects has been evaluated by the sponsor.

[b]Women of child-bearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (post-menopausal is defined as amenorrhea for >12 consecutive months or women on hormone replacement therapy with documented serum follicle stimulating hormone level <35 mIU/mL). Even in women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile, eg, vasectomy, should be considered to be of child bearing potential.

5.2 SUBJECT EXCLUSION CRITERIA

Subjects who meet any of the following exclusion criteria are to be excluded from study participation:

1. Subjects who received any fibrinogen-containing product within 21 days prior to Day 0 Visit -infusion day.
2. Subjects who present with active bleeding within 10 days prior to infusion on Day 0 Visit.
3. Subjects with acquired (secondary) fibrinogen deficiency.
4. Subjects diagnosed with dysfibrinogenemia.
5. Subjects with documented history of DVT, PE, or arterial thrombosis within 1 year prior to enrolment in this clinical trial.
6. Subjects with known antibodies against fibrinogen.

7. Subjects with a history of anaphylactic reactions or severe reactions to any blood-derived product.
8. Subjects with a history of intolerance to any component of the investigational product.
9. Subjects with a documented history of IgA deficiency and antibodies against IgA
10. Females who are pregnant or are breastfeeding.
11. Subjects with renal impairment [ie, serum creatinine exceeds more than 2.0 times the upper limit of normal (ULN) for the expected normal range for the testing laboratory] at baseline (sample drawn within 24 hours prior to infusion on Day 0 Visit) .
12. Subjects with AST or ALT levels exceeding more than 2.5 times the ULN for the expected normal range for the testing laboratory at baseline (sample drawn within 24 hours prior to infusion on Day 0 Visit).
13. Subjects with a history of chronic alcoholism or illicit drug addiction in the preceding 12 months prior to enrolment in this clinical trial.
14. Subjects with any medical condition which is likely to interfere with the evaluation of the study drug and/or the satisfactory conduct of the clinical trial according to the investigator's judgment (eg, congenital or acquired bleeding disorders other than congenital fibrinogen deficiency, planned surgery needing blood transfusion).
15. Subjects who received aspirin-containing products and nonsteroidal anti-inflammatory drugs (NSAIDs) within 7 days prior to Day 0 Visit.
16. Subjects currently receiving, or having received within 3 months prior to enrolment into this clinical trial, any investigational drug or device.
17. Subjects who were previously administered the investigational product FIB Grifols during this clinical trial (ie, every subject can only participate in the study once).
18. Subjects who are unlikely to adhere the protocol requirements, or are likely to be uncooperative, or unable to provide a storage serum sample prior to investigational drug infusion.

5.3 SUBJECT WITHDRAWAL CRITERIA AND PROCEDURES

Subjects have the right to withdraw from the study at any time for any reason, either before or after the infusion of the investigational product. The investigator can withdraw a subject from the clinical trial at any time.

The investigator will document the reason(s) for withdrawal of each subject in source documents and in the CRF/eCRF. All data gathered on the subject prior to termination will be made available to the sponsor.

Subject participation in the study may be terminated early under the following circumstances:

1. The subject withdraws his/her informed consent to participate in the clinical trial or for pediatric subjects, subject withdraw informed consent at his/her own request or at the request of the legally accepted representatives (eg, parent or legal guardian).
2. The subject discontinues his/her participation in the clinical trial without withdrawing his/her informed consent.

3. The subject does not meet all inclusion criteria and is deemed a screen failure.
4. The subject meets any of the exclusion criteria and is deemed a screen failure.
5. The subject is not able to adhere to the main protocol requirements (major protocol violations).
6. The occurrence of an AE which in the investigator's opinion requires the withdrawal of the subject from the clinical trial.
7. The subject is lost to follow-up.
8. Subject's death.
9. Any event which in the opinion of the investigator impedes the subject's participation in the study.

For subjects who are screen failures or early discontinue the clinical trial, study completion procedures will be completed as per Section 6.4.

If the reason for early discontinuation is an AE, in so far as is possible, the subject will be followed-up until the event resolves, or has been stabilized, and no further change is expected.

Subjects who early discontinue the clinical trial once any amount of investigational product has been already administered cannot be replaced.

6. TREATMENT OF SUBJECTS

6.1 TREATMENT TO BE ADMINISTERED

During this clinical trial, each subject will receive a single-dose intravenous infusion of investigational product 70 mg/kg body weight. The investigational product should be administered by slow intravenous infusion, at a rate not exceeding 5 mL/minute. The actual doses (volumes) actually administered to the subject will be recorded.

6.2 MEDICATION(S)/TREATMENT(S) PERMITTED (INCLUDING RESCUE MEDICATION) AND NOT PERMITED BEFORE AND/OR DURING THE TRIAL

Study subjects should not receive other fibrinogen-containing products to treat their signs/symptoms of congenital afibrinogenemia during the study course. Nevertheless, the use of any non-study medication or any change in long term therapy during the course of the study should be avoided when possible. Any other non-study medications are allowed only if treatment becomes medically necessary according to the investigator judgment. In all cases, the investigator must record all medication administered during the clinical trial in the subject's CRF/eCRF.

In case the study subject receives any fibrinogen-containing product during the course of the PK follow-up period (up to Day 14), PK and efficacy results will not be taken into account for PK and efficacy analyses in the PK period starting with the actual time of the alternative fibrinogen-containing product administration and going forward.

No drug-drug interactions have been previously reported with the use of fibrinogen products. The subjects who are currently receiving other investigational drug or device (as specified in the exclusion criteria) will be excluded.

The following medications are prohibited during study participation:

- Aspirin-containing products and NSAIDs

6.3 PROCEDURES FOR MONITORING SUBJECT COMPLIANCE

Since all investigational product administration will be performed only at investigational sites by qualified staff, compliance with the clinical trial treatment will be assessed by means of the infusion logs. Investigational sites will be provided with logs where to register investigational product administration, both volume and rate of administration. (*Subject Specific Administration Log*). These forms will be available for clinical trial monitors to check clinical trial treatment compliance.

6.4 STOPPING RULES AND DISCONTINUATION CRITERIA

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

A subject may leave the study at any time for any reason and will be permitted to do so without penalty. Instituto Grifols, S.A. will be notified by the investigator if a subject terminates or is terminated from the study early. The reason for early termination will be clearly documented in subject's medical records and the CRF/eCRF and reasonable efforts to perform study completion procedures will be made when appropriate. The investigator can withdraw a subject from the clinical trial at any time.

For subjects who are screen failures because they do not meet all inclusion criteria or they meet any of the exclusion criteria, it is not necessary to perform additional study completion procedures other than recording all the study data gathered until the moment when the subjects is deemed to be a screen failure, including the reasons for the screen failure.

For subjects who are not screen failures and withdraw from the clinical trial before the beginning of the investigational medicinal product infusion, study completion procedures consisting of a physical assessment, recording of vital signs (T, RR, HR, SBP, and DBP,) and concomitant medications, and assessment of AEs will be performed during their last visit at the site, if possible.

For subjects administered any amount of investigational medicinal product (infusion) who discontinue the clinical trial early, study procedures and assessments scheduled on Infusion Visit (Day 0) – 1-Hour Post-Infusion time point (see Section 4.6.2) will be performed as study completion procedures when discontinuation is before, or on, Infusion Visit (Day 0) - 1-Hour Post-Infusion time point. If early discontinuation occurs after Infusion Visit (Day 0) – 1-Hour Post-Infusion time point has occurred, then the assessments for the next required scheduled visit/time point will be performed as study completion procedures.

For subjects who withdraw their informed consent to participate in the clinical trial, it is not necessary to perform additional study completion procedures other than recording all the study data gathered until the moment when the subjects withdraw their informed consent.

7. ASSESSMENT OF EFFICACY

7.1 SPECIFICATION OF EFFICACY PARAMETERS

Primary efficacy endpoint will be:

Change on MCF from baseline to 1-hour post-infusion.

Secondary efficacy endpoints will be:

1. Change on other thromboelastographic variables (CT, CFT, and α from baseline to 1-hour post-infusion.

2. Change on standard coagulation tests (TT, PT, and aPTT) from baseline to 1-hour post-infusion.

[redacted]

7.2 METHODS AND TIMING FOR ASSESSING, RECORDING, AND ANALYSING OF EFFICACY PARAMETERS

7.2.1 CHANGE ON MAXIMUM CLOT FIRMNESS (MCF) MEASURED BY ROTATIONAL THROMBOESLATOGRAPHY (ROTEM)

The primary efficacy endpoint will be the mean change on MCF from baseline to 1 hour after the end of the infusion.

All rotational thromboelastographic measures on frozen plasma samples will be analyzed at a central laboratory using ROTEM, Pentapharm GmbH, Munich, Germany).

MCF is a functional parameter indicative of blood's ability to clot and is mainly dependent on platelet concentration and functionality and fibrinogen concentration and activity. On frozen plasma samples, where platelet function is considered to be abolished, MCF will be almost exclusively dependent on fibrinogen concentration and functionality, thus providing a surrogate measure of hemostatic efficacy of the study drug.

7.2.2 CHANGE ON OTHER THROMBOELASTOGRAPHIC VARIABLES

Secondary efficacy endpoints will be mean change on other thromboelastographic variables (CT, CFT, and α) from baseline to 1-hour post-infusion.

These variables provide information about different phases of the clotting process: initiation phase (CT) and propagation phase (CFT and α) and both of them should be improved in the plasma of a subject with fibrinogen deficiency by the treatment with a fibrinogen concentrate.

7.2.3 CHANGE ON STANDARD COAGULATION TESTS

Secondary efficacy endpoints will be mean change on standard coagulation tests (TT, PT, and aPTT) from baseline to 1-hour post-infusion.

It is expected that these values indicative of the extrinsic and intrinsic coagulation pathways are abnormal (prolonged) in subjects with fibrinogen deficiency and that treatment with a fibrinogen concentrate will restore to some extent these values.

All standard coagulation tests on frozen plasma samples will be analyzed at a central laboratory.

[redacted]

8. ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Aspects of clinical safety, virus safety, and immunogenicity will be considered in this clinical trial.

Safety endpoints will include:

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. Virus safety

8.2 METHODS AND TIMING FOR ASSESSING, RECORDING, AND ANALYSING OF SAFETY PARAMETERS

8.2.1 ADVERSE EVENTS

The occurrence and follow-up details of all AEs experienced by any of the subjects during the clinical trial, from the signature of the informed consent to Week 4 Visit will be recorded in source documents and in the CRF/eCRF.

It is investigator's responsibility to ensure that all AEs are appropriately recorded.

AEs will be elicited by spontaneous reporting by the study subject or by a non-leading inquiry or direct observation by the study staff.

8.2.2 VITAL SIGNS

During the infusion and at different time points throughout the study, vital signs will be monitored by the investigator or by qualified staff.

Clinically relevant vital signs (T, BP, HR, RR) abnormalities will be reported as AEs.

A vital sign will be considered clinically relevant if it represents a change from the baseline value that meets the following criteria:

1. HR increase or decrease of ≥30 bpm
2. SBP increase or decrease of ≥30 mm Hg
3. DBP increase or decrease of ≥30 mm Hg
4. T change of ≥1ºC

8.2.3 PHYSICAL ASSESSMENT

A physical assessment by body systems will be performed at different time points throughout the study by the investigator or a medical doctor designated sub-investigator. The investigator will be required to classify the physical finding abnormalities as clinically relevant or not according to his/her judgment. Results will be recorded in the source documents and on the subject's CRF/eCRF. Physical assessments abnormalities judged by the investigator as clinically relevant will be considered AEs.

8.2.4 LABORATORY PANELS

Laboratory tests will include:

1. Serum clinical chemistry: including creatinine, BUN, ALT, AST, ALP, LDH, TB, glucose, sodium, potassium, chloride and calcium.

2. Hematological parameters: CBC, including platelet count and differential leukocyte count.

3. Markers of activation of coagulation: different measures indicative of activation in the coagulation pathway (D-dimer, ATIII, TAT, F_{1+2}).

Blood specimens for laboratory tests will be collected at different time points throughout the study. Laboratory tests results will be collected in the corresponding CRF/eCRF entry. Abnormal (out of range) results will be flagged by the reporting laboratory. The investigator will be required to indicate the clinical relevance of out of range (abnormal) results. Laboratory results out of the normal range judged by the investigator as clinically relevant will be considered AEs.

In the case of markers of activation of coagulation, their relationship with plasma fibrinogen levels pre- and post-infusion will be studied.

In case of pediatric sampling, pediatric tubes would be provided to reduce the amount of blood drawn for lab works, including the complete elimination of virology, immunogenicity, and markers of activation of coagulation lab works. Pediatric subjects will not undergo Month 3 virology and immunogenicity follow-up visits, and their participation in the study will finish at the Week 4 Visit. Pediatric subjects weighing less than 30 kg will also have an even more reduced blood sampling schedule as detailed in Table 4-4 and Table 4-5:

- Day 0 - baseline (including the retention sample)
- Day 0 - 1 hour post-infusion
- Day 0 - 8 hours post-infusion
- Day 1 - 24 hours post-infusion
- Day 4 - 96 hours post-infusion
- Day 6 - 144 hours post-infusion and
- Day 9 - 216 hours post-infusion

8.2.5 ANTIBODIES AGAINST FIBRINOGEN DETERMINATION (IMMUNOGENICITY TESTING)

Evidence of any possible immunogenicity of the investigational product will be assessed at the sponsor's laboratory. Samples from adult subjects will be assayed for the generation of antibodies to fibrinogen by using a stepwise approach starting with a functional screening assay to detect neutralizing activity. In the event neutralizing activity is detected, samples will be further assessed by a confirmatory ELISA for the presence of antibodies to fibrinogen.

If a confirmed, single case of immunogenicity is reported after a subject has been dosed with study drug, any further enrollment and dosing of subjects in the study will be suspended until the event can be adequately assessed by the safety group of the sponsor. The enrollment and dosing will only resume after explicit authorization by the sponsor.

8.2.6 MONITORING OF ALLERGIC/HYPERSENSITIVITY REACTIONS

Subjects will be carefully monitored by the investigator or study staff for signs and symptoms of allergic/hypersensitivity reactions occurring between the Baseline Visit and the Week 4 Visit. The Grifols Medical Monitor will routinely review reported AEs for possible allergic/hypersensitivity reactions according to the algorithm described in Annex 2.

8.2.7 MONITORING OF THROMBOTIC EVENTS

Subjects will be monitored by the investigator and/or study staff for signs and symptoms of arterial and venous thromboses occurring between the Baseline Visit and the Week 4 Visit. The algorithms described in Annex 1, which include the Wells Score assessment, will be observed for evaluation and assessment of thrombotic events risk. In addition, the Grifols Medical Monitor will routinely review reported AEs for possible thromboses. Arterial and venous thromboses will be identified according to definitions in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM [66]). Such thrombotic events include, but are not limited to, DVT, PE, myocardial infarction, cerebrovascular accident, acute coronary syndrome, limb thrombosis, sagital sinus thrombosis, and portal vein or mesenteric artery thrombosis. All thromboses will be recorded as AEs and reported accordingly.

If a confirmed single case of thrombosis is reported after a subject has been dosed with study drug, any further enrollment and dosing of subjects in the study will be suspended until the event can be adequately assessed by the safety group of the sponsor. The enrollment and dosing will only resume after explicit authorization by the sponsor.

8.2.8 VIROLOGY TESTING

Viral monitoring for each adult subject will be performed by mean of serology and nucleic acid amplification technology tests.

Serum/plasma samples from all subjects will be drawn at baseline (prior to the scheduled infusion). An additional aliquot of serum/plasma will be retained from all viral time points for re-testing if necessary.

During follow-up, viral monitoring will be limited to those subjects and viruses where all previous tests were non-reactive (negative) for the target virus at baseline (prior to the infusion of the investigational medicinal product) and previous visits. If there is a positive virology test result at baseline, laboratory testing for this particular virus will no longer be performed during the course of the clinical trial.

If there is a change from baseline (prior to the infusion of the investigational medicinal product) viral status during clinical trial, it must be confirmed by repeating the virology test, using the same technique and/or other techniques as deemed appropriate by the sponsor (eg, more sensitive techniques), such as nucleic acid amplification technology tests. Moreover, if considered necessary by the sponsor, re-analysis of any sample could be ordered, including storage samples, by an independent laboratory.

8.3 PROCEDURES FOR ELICITING REPORTS OF AND FOR RECORDING AND REPORTING ADVERSE EVENT AND INTERCURRENT ILLNESSES

8.3.1 ADVERSE EVENT

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory findings, for instance), symptoms, or disease temporally associated with the use of a medicinal product or study treatment, whether or not considered related to the medicinal product or study treatment.

Any AE that occurs at any time between signature of the informed consent and last day of the subject's participation in the clinical safety period of the study (Week 4 Visit) must be reported on the AE CRF/eCRF entry.

8.3.2 CAUSALITY OF ADVERSE EVENT

The investigator will be asked to assess the causal relationship of the AE to the study treatment according to the following classification based on Karch FE et al [64]:

- **Definite:** An event that follows a reasonable temporal sequence from administration of the treatment or in which the treatment level has been established in body fluids or tissues; that follows a known response pattern to the suspected treatment; and that is confirmed by improvement on stopping the treatment (dechallenge), and reappearance of the event on repeated exposure (rechallenge).

- **Probable:** An event that follows a reasonable temporal sequence from administration of the treatment; that follows a known response pattern to the suspected treatment; that is confirmed by dechallenge; and that could not be reasonably explained by the known characteristics of the subject's clinical state.

- **Possible:** An event that follows a reasonable temporal sequence from administration of the treatment; that follows a known response pattern to the suspected treatment; but that could have been produced by the subject's clinical state or other modes of therapy administered to the subject.

- **Doubtful/Unlikely:** An event that follows a reasonable temporal sequence from administration of the treatment; that does not follow a known response pattern to the suspected treatment; but that could not be reasonably explained by the known characteristics of the subject's clinical state.

- **Unrelated:** Any event that does not meet the criteria above.

The operational tool to decide the AE causal relationship is based on algorithms by Karch-Lasagna and Naranjo [64, 65].

When an AE is classified, assessing causal relationship by the investigator, as definitive, probable, possible, or doubtful/unlikely, the event will be defined as suspected adverse drug

reaction (ADR). When the causal relationship is labeled “Unrelated”, then it will be considered that the AE is not imputable to the study treatment and it is not an ADR.

Any AE experienced by the subject prior to the investigational product infusion on Day 0 will be labeled as Unrelated to the investigational medicinal product.

8.3.3 SUSPECTED ADVERSE DRUG REACTION

All noxious and unintended responses to a medicinal product or study treatment related to any dose should be considered a suspected ADR. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product or study treatment and an AE is at least a reasonable possibility, that is, the relationship cannot be ruled out. In the framework of this study, a suspected ADR with a causal relationship of “definite” will be named as Adverse Reaction. Adverse reactions are a subset of suspected ADR.

The sponsor is responsible for assessing the suspected ADR expectedness during the clinical trial.

8.3.4 SEVERITY OF ADVERSE EVENT OR SUSPECTED ADVERSE DRUG REACTION

AE and suspected ADR will be classified depending on their severity (intensity) according to the following definition:

1. Mild: awareness of sign or symptom, but easily tolerated (acceptable)

2. Moderate: discomfort to interfere with usual activity (disturbing)

3. Severe: incapacity to work or to do usual activity (unacceptable)

AE and suspected ADR severity (intensity) gradation must be distinguished from AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, a headache could be mild, moderate or severe but unusually is serious in all these cases.

The investigator will be responsible for assessing the AE or suspected ADR severity (intensity) during the clinical trial, taking into account currently criteria detailed in this section.

8.3.5 SERIOUS ADVERSE EVENT

An SAE is an AE or a suspected ADR, occurring at any dose that fulfils one or more of the following:

1. Results in death.

2. Is immediately life-threatening (life-threatening in the definition of SAE refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).

3. Requires in-subject hospitalisation or requires prolongation of existing hospitalization*.

4. Results in persistent or significant disability/incapacity.

5. Is a congenital anomaly/ birth defect.

6. Is an important medical event: important medical event in the definition of "serious" refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization. Development of cancer or drug dependency or drug abuse will normally be considered serious by this criterion.

   *Hospitalization is to be considered only hospital stay for equal or more than 24 hours. The following hospitalizations should not be reported as SAEs:

   - Hospitalization or prolongation of hospitalization needed for procedures required by the clinical trial protocol.

   - Hospitalization or prolongation of hospitalization as part of a routine procedure followed by the center.

   - Hospitalization for a survey visit, annual physicals, or social reasons.

   - Elective (pre-planned) hospitalizations for a pre-existing condition that had not worsened from Baseline (eg, elective or scheduled surgery arranged prior to start of the study).

   - Admissions not associated with an AE (eg, social hospitalization for purposes of respite care).

A distinction should be drawn between serious and severe AEs. The term "severe" is used to describe the severity of a specific event; the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious", which is defined on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) is a medical term while severity is a subjective term.

According to the medical criteria, an AE, or a suspected ADR, can be classified as serious, although it does not fulfill the conditions detailed in this section, if it is considered important from a medical point of view. The investigator is responsible for assessing the AE, or suspected ADR, seriousness during the clinical trial, taking into account currently criteria detailed in this section.

8.3.6 COLLECTION AND REPORTING OF ADVERSE EVENTS AND SUSPECTED ADVERSE DRUG REACTIONS

AEs will be collected from the time of the subject´s signature of the *Clinical Trial Informed Consent* until Week 4 Visit. All reported AEs will be recorded on the AE CRF/eCRF entry.

An identical entry should be also present in the subject's hospital record. If no AE has occurred during the study period, this should also be indicated in the CRF/eCRF.

At each visit/time point, the occurrence of AEs will be assessed by the study staff. If it is possible, AEs will be elicited by asking the subject a non-leading question such as "Do you feel different in any way since the last assessment?" Moreover, AE will also be collected through directly observed events or spontaneously volunteered by the subject. Signs observed by the study staff should also be considered to elicit AEs especially when the subjects cannot be asked (eg, the subject is anesthetized). Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible. It is responsibility of the investigator to ensure that AEs are appropriately recorded.

Infusional AEs (ie, AEs temporally associated with an infusion of investigational medicinal product) will be defined as any AE occurred during the infusion or within 24 after completion of the infusion. For example, it will include any clinically relevant abnormalities in vital signs during the infusion, as previously defined.

Other safety variables comprise blood laboratory tests. A clinically relevant deviation from normal/reference laboratory ranges based on each individual pre-study (baseline) value (as judged by the investigator) may also constitute an AE and should be recorded on the AE CRF/eCRF entry. Abnormalitites in laboratory results, vital signs and physical exams should not be recorded as AEs if they are known to be a symptom or sign of a syndrome or diagnosis that is also being reported as an AE.

The following variables must be recorded on the AE CRF/eCRF entry:

1. The verbatim term (a diagnosis is preferred)
2. Date/time of onset
3. Date/time of resolution
4. Severity (mild, moderate, severe)
5. Causality (unrelated, doubtful/unlikely, possible, probable, definite)*
6. Seriousness (yes, no)
7. Action taken (with regard to study drug)
8. Other action (to treat the event)
9. Outcome and sequel (follow-up on AE)

** Causality assessment will be only made when the AE occurs after the subject has been administered the investigational product (at any dose). AE occurring before subject's exposure to study treatment will be always labeled as "Unrelated".*

In addition to the investigator's own description of the AEs, each AE will be encoded by the sponsor or designated (eg, contract research organization [CRO]) according to the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary of medical codes.

A pregnancy not verified before enrollment but occurring during the course of the study will not be considered an AE, unless a causal relationship to the study drug is at least suspected. In any case, a Pregnancy Report Form must be completed and sent within 24

hours to the sponsor. A copy of the form should be filled at the study site for follow-up until the end of the pregnancy.

8.3.7 TIMELINES AND REPORTING OF SERIOUS ADVERSE EVENTS

All SAEs must be reported, whether or not considered attributable to the study drug, on the AE CRF/eCRF entry and in a separate *SAE Report Form*.

When the investigator becomes aware of a SAE, she/he must submit by email a completed, signed and dated SAE Report Form **within 24 hours** to the sponsor.

After the initial report, all relevant information for SAE follow up, and for the outcome, must be also supplied to the sponsor in a timely manner (within 3 days from its identification or within 24 hours for relevant new information) by mean of the SAE Report Form. In addition, the sponsor or CRO may request additional information and/or reports.

All SAE Report Forms must be submitted to:

Grifols Global Pharmacovigilance E-mail: [redacted] FAX (back-up only): [redacted] (US/Canada) and [redacted] (International)

In order to be promptly assessed by the sponsor, any thrombotic event (regardless of fulfilling or not fulfilling seriousness criteria) will be always expeditiously communicated to the sponsor by means of the SAE Report Form.

8.4 TYPE AND DURATION OF THE FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

In so far as is possible, all subjects will be followed up until the AE or the suspected ADR has been resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study, the course of the event should be followed until the final outcome is known, or the event has been stabilized and no further change is expected and the investigator decides that no further follow-up is necessary.

Any pregnancy should be followed by the investigator until delivery or to the end of pregnancy.

9. STATISTICS

9.1 STATISTICAL METHODS TO BE EMPLOYED AND TIMING OF PLANNED INTERIM ANALYSIS(SES)

9.1.1 STATISTICAL ANALYSIS OF DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics, for the safety population (see Section 9.7.1), will be presented in tabular form and summarized by both adult and pediatric populations using descriptive statistics.

9.1.2 STATISTICAL ANALYSIS OF PHARMACOKINETICS

PK analyses will be assessed on the PK population (see Section 9.7.1). PK analyses will be performed on both the adult and pediatric populations independently.

9.1.2.1 Analysis of PK concentration and dosing data

Plasma concentrations of fibrinogen will be summarized by visit/time point and by both adult and pediatric populations. The summaries will include n, mean (standard deviation [SD]), 90% confidence interval (CI) for mean, coefficient of variation (% CV), median, minimum, and maximum as well as geometric mean. Plasma fibrinogen concentration versus time curves will be presented by both adult and pediatric populations.

9.1.2.2 Calculation of PK parameters

The PK profiles of the investigational product following single administration will be characterized by PK parameters, including IVR, AUC calculated as $AUC_{0\text{-}14days}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, MRT, Vd, and Cl.

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

9.1.2.3 Analyses of PK parameters

Descriptive statistics (summarized by both adult and pediatric populations), including n, mean, SD, 90% CI for mean, % CV, median, minimum, maximum, and geometric mean (except t_{max}) will be calculated for all PK parameters including AUC $_{0\text{-}14\ days}$, and $AUC_{0\text{-}\infty}$. PK analysis will be independently performed for adult and pediatric populations.

9.1.3 STATISTICAL ANALYSIS OF EFFICACY

Primary efficacy analyses will be assessed on the evaluable population (see Section 9.7.1) and in addition on the per protocol (PP) population (see Section 9.7.1). Unless otherwise specified, the test is two-sided and the significance level is 0.05. All analyses on efficacy parameters (for the primary, secondary [redacted] efficacy endpoints) will be carried out in the overall study population (adults 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.

9.1.3.1 Analysis of primary efficacy endpoint

Primary efficacy endpoint will be 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 (see Section 9.7.1).

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 ranked sign test. In addition to this, the same analysis will be performed using the PP population.

[redacted]

9.1.3.2 Analysis of secondary efficacy endpoints

Secondary study variables will be examined in the evaluable and PP populations.

1. Mean change on other thromboelastographic variables:

   Mean change (difference) in thromboelastographic variables: CT, CFT, and α in plasma samples pre-infusion and 1-hour post-infusion will be analyzed.

   Similar analyses to those performed on the primary efficacy endpoint will be run on secondary efficacy endpoints.

2. Mean change on standard coagulation tests:

   Mean difference in standard coagulation tests: TT, PT, and aPTT in plasma samples pre-infusion and 1-hour post-infusion will be analyzed.

   Similar analyses to those performed on the primary efficacy endpoint will be run on secondary efficacy endpoints.

[redacted]

9.1.4 STATISTICAL ANALYSIS OF SAFETY

Adverse events:

Safety analyses for FIB Grifols will be performed on the overall population (both adult and pediatric age groups). FIB Grifols safety will also be assessed independently for both adult and pediatric populations.

Any AE that occurs at any time between signing of the *Clinical Trial Informed Consent* and Week 4 Visit will be reported on the appropriate subject's CRF/eCRF entry for any subject who received at least 1 infusion (at any dose) of investigational product.

Treatment-emergent AEs (ie, AEs occurring after the start of the investigational product infusion) will be listed and tabulated by body system with subject identification code, and they will be also presented as subject incidences and percentages. In addition, treatment-emergent AEs will be summarized by both adult and pediatric populations as well as severity (intensity), seriousness (serious versus non-serious), and causal-relationship to the study product.

Similarly, all treatment-emergent AEs potentially related to the investigational product will be listed and tabulated by body system with subject identification code, and they will be also presented as subject incidences and percentages. In addition, these will be also summarized by both adult and pediatric populations as well as severity (intensity) and seriousness (serious versus non-serious).

For AEs temporally associated to the infusion, listings of AEs will be presented. AEs will be also split between AEs occurring during the infusion or after the infusion completion but within 24 and 72 hours after completion of the infusion. For an AE that occurs during an infusion, the infusion rate in effect at the time of onset of the AE, the time the AE is first reported and the time the AE changes materially in intensity and/or resolves are all to be reported and tabulated.

Subjects who die, report a serious AE (SAE), or withdraw from the study because of AEs will be also individually listed and summarized.

AEs will be coded according to the AEs classification of the MedDRA, and will be described by a synonym (Preferred Term) and the affected organ / system, the intensity, causality and seriousness.

Vital signs:

Vital signs (T, RR, HR, SBP, DBP) will be listed for each clinical trial subject. In case a subject presents a clinically relevant variation of vital signs during an infusion will be flagged and discussed as an AE temporally associated to the infusion.

Clinically relevant vital signs, as defined in advance in the clinical trial protocol (see Section 8.2.2) will be flagged and discussed as an AE.

Physical assessment:

Physical findings (normal and abnormal) will be listed for each clinical trial subject. Subjects who acquire clinically relevant abnormalities, which were not already present at baseline, will be flagged and discussed as an AE.

Serum clinical chemistry:

All clinical laboratory data for serum clinical chemistry (creatinine, BUN, TB, ALP, ALT, AST, LDH, glucose, sodium, potassium, chloride and calcium) will be listed for each clinical trial subject and clinically relevant abnormalities (abnormal values are those out of the normal range reported by the respective laboratory), as judged by the investigator, will be flagged.

Hematology:

All clinical laboratory data for hematology (CBC): RBC count, Hgb, Hct, MCH, MCHC, MCV, WBC count and differential, and platelet count) will be listed for each clinical trial subject and clinically relevant abnormalities (abnormal values are those out of the normal range reported by the respective laboratory), as judged by the investigator, will be flagged.

Markers of activation of coagulation:

All clinical laboratory data for markers of activation of coagulation (D-dimer, ATIII, TAT, and F_{1+2}) will be listed for each adult clinical trial subject and clinically relevant abnormalities (abnormal values are those out of the normal range reported by the respective laboratory), as judged by the investigator, will be flagged.

Immunogenicity testing:

All results of testing for antibodies to fibrinogen will be listed for each adult clinical trial subject.

In the event a subject becomes positive for antibodies to fibrinogen during the study period, the case will be evaluated and discussed.

Events of special interest - allergic/hypersensitivity reactions and thrombotic events

Events of special interest such as allergic/hypersensitivity reactions and thrombotic events (results of the Wells Score will be utilized to assess thrombotic events risk) will be individually listed and summarized. These events will be individually summarized and evaluated taking into account all available information about predisposing factors in the clinical history of the subject, infusion rate at onset (if applicable), time elapsed since infusion, fibrinogen levels at/close to onset, markers of activation of coagulation levels (not applicable for pediatric subjects) pre-infusion, post-infusion and at/close to onset (if available) and any other relevant factors.

Virus safety:

All results of viral markers will be listed for each adult clinical trial subject.

In case of a potential seroconversion during the study, it will be reported and discussed.

9.1.5 TIMING OF PLANNED 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.

9.2 SAMPLE SIZE DETERMINATION

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 investigational product. 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.

9.3 LEVEL OF SIGNIFICANCE

Unless otherwise specified, all statistical tests will be two-sided, for which an alpha level of 0.05 will be considered to indicate statistical significance.

9.4 CRITERIA FOR THE TERMINATION OF THE TRIAL

Not anticipated.

9.5 PROCEDURES FOR ACCOUNTING FOR MISSING, UNUSED, AND SPURIOUS DATA

For the PK analysis, any missing or not valid values for fibrinogen concentration will be treated as missing, or if necessary, will be interpolated or extrapolated using PK principle, as appropriate, and will be documented in the clinical study report.

For primary efficacy endpoint analysis, the missing value in change from baseline in MCF will be set to zero.

9.6 PROCEDURES FOR REPORTING ANY DEVIATION FROM THE ORIGINAL STATISTICAL PLAN

In case of any deviations from the original statistical plan, these will be documented in the final study report.

9.7 SELECTION OF SUBJECTS TO BE INCLUDED IN THE ANALYSES

9.7.1 POPULATION FOR PHARMACOKINETIC ANALYSIS

The PK analysis population will consist of all subjects who have received study medication and have sufficient fibrinogen plasma concentration data to facilitate calculation of

pharmacokinetic parameters. The PK population will be used for the analyses of the PK parameters.

9.7.2 POPULATION FOR STATISTICAL ANALYSIS OF EFFICACY

Two study populations for statistical analysis of efficacy will be used: evaluable population and PP population. All efficacy analysis will be primarily run on the evaluable population and then they will be also run on PP.

Definition of evaluable population:

The evaluable population will include all subjects who received investigational product 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.

Definition of PP:

The PP population will include all subjects who received planned dose of the investigational product (at least 90% of the planned dose), who have no major protocol violation (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.

9.7.3 POPULATION FOR STATISTICAL ANALYSIS OF SAFETY

All subjects who receive infusion (at any dose) of the investigational product will be included in the safety population.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will permit study-related monitoring, sponsor audits, Institutional Review Board's (IRB) review and health authorities' inspection(s), providing direct access to source data and documents. A person designated by the sponsor will monitor the study to ensure that all required documentation is available, and that collected data on the CRF/eCRF precisely reflect data on source documents. Access to the history and clinical course of the study subjects by the monitor will be granted. A trial quality assurance audit may be conducted at any time during the course of the study or after its conclusion at the site or vendor.

For each enrolled subject, the investigator or designee will write into the subject's medical history that he/she is enrolled in this study sponsored by Instituto Grifols, S.A., a well as all safety and efficacy information. The investigator is responsible for maintaining complete and adequate case histories in source records of each subject. Source data must be preserved for the maximum period of time permitted by local regulations and made available by the investigator in the cases described below.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The present clinical trial will be conducted in accordance with the GCP/ICH guidelines. Clinical trial monitoring team will systematically control the clinical trial essential documents. All clinical trial phases will be monitored and they may be subjected to internal audits by quality assurance (QA). All monitoring visits and internal audits will be followed by internal reports and corrective actions, if needed. Follow-up letters will be forwarded to sites after all clinical visits.

11.1 QUALITY CONTROL BY THE CLINICAL TRIAL MONITORING TEAM

The clinical trial monitoring team will monitor data collected throughout the study. The investigator will be available for clinical trial monitors during their visits and will ensure that the monitor has access to all documents that they require, including to the subject's files (direct access). The investigator agrees to cooperate with the monitor to make certain that any problems detected in the course of these monitoring visits are resolved. Subject's anonimity must be safeguarded and all data checked during these monitoring visits must remain confidential.

11.2 QUALITY ASSURANCE BY THE CLINICAL TRIAL AUDIT TEAM

Any study site or vendor may be selected for audit at any moment by a clinical trial audit team, originating from the sponsor or from the external CROs acting on behalf of the sponsor.

The investigator and audited staff agree to cooperate with the auditor to ensure that any problems detected in the course of these audit visits are resolved. Subject's anonymity must be safeguarded and data checked during these audit visits must remain confidential.

12. ETHICS

12.1 ETHICAL CONSIDERATIONS AND ETHICS COMMITTEE

The ethical standards adopted by the XVIII World Medical Assembly (Helsinki, 1964) (and subsequent revisions) will be strictly observed. The clinical trial likewise will be performed in compliance with standards of ICH GCP guideline relating to trials involving investigational drugs (ICH Topic E6).

The study cannot begin until an independent ethics committee (IEC)/IRB and the health authorities (when necessary) have approved the protocol, the informed consent document, and the patient information sheets. The investigator will provide the sponsor/CRO with a copy of the communication from the IEC/IRB to the investigator indicating approval of the protocol and consent form/information sheets before the clinical trial is started.

The IEC/IRB must be informed of all relevant protocol amendments that may affect the safety of the participating subjects or conduction of the clinical trial. All substantial amendments to the protocol must be reviewed and approved prior to implementation as applicable per local regulations in force, except where necessary to eliminate apparent immediate hazards to human subjects. SAEs, unexpected adverse reactions, and other

relevant information that may alter the study design or entail subject risk will be reported to the IEC/IRB when required per applicable local regulations. Equally, protocol deviations and violations may be submitted to IRB according to the requirements of each of these institutions.

The investigator will be responsible for obtaining annual IEC/IRB renewal when applicable and submitting SAE reports to the IEC/IRB for the duration of the study (as per site policies and procedures). Copies of the investigator's report and/or copies of the IEC/IRB extension approval must be made available to the sponsor or designee (eg, CRO).

12.2 INFORMED CONSENT AND INFORMATION SHEETS

The investigator (or designee) will obtain written informed consent from each subject participating in this clinical trial, after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study, and prior to initiating any study related procedure to a subject.

For subjects not qualified to give legal consent, written consent must be obtained from the parent or legal guardian.

Each subject will be also informed that his/her source medical records may be scrutinized by the clinical trial monitor team, the clinical trial audit team, inspectors from the health authorities or reviewers from the IEC/IRB, in accordance with applicable regulations; that the investigator will protect any personal information not related to the study; and that these persons are bound by the same confidentiality obligations as the subject's family doctor.

The investigator (or designee) will explain that subjects are completely free to refuse to enter into the clinical trial or to withdraw from it at any time, without any consequences for their further care and without the need for them to justify their decision.

After the subject has had time to read the information and feels all their questions have been answered, they will be asked to sign the *Clinical Trial Informed Consent*. The investigator will also sign and date the *Clinical Trial Informed Consent*, thus reflecting that informed consent has been obtained, and that the subject (and his/her representative) has had the opportunity to ask questions, and has received adequate answers. The subject will receive a signed copy of the *Clinical Trial Informed Consent* and of the *Patient Information Sheet*. The original *Clinical Trial Informed Consent* will be filed along with the study documentation.

12.3 CONFIDENTIALITY

All data related to procedures, medications, patents, scientific information, and other data on materials will be considered confidential, and are sponsor's property. However, the study protocol and other important documents may be submitted to the IEC/IRB and health authorities to obtain approval for conducting the study.

The investigator will ensure that the subjects' anonymity will be maintained. Applicable privacy rules will be followed to obtain authorization for most uses and disclosures of Protected Health Information. On CRF/eCRFs or other documents submitted to the sponsor or its designee, subjects will not be identified by their names, but by a numeric identification code. Documents not for submission to Instituto Grifols, S.A. or its designee,

(eg, the site confidential subject enrolment log and original subjects' consent forms) will be maintained by the investigator in strict confidence.

The investigator will accept that the sponsor may use the clinical trial results, including CRF/eCRF data, sheets or their copies, or reports with or without comments, and with or without analyses, to submit them to regulatory authorities, and may reveal them if needed to other investigators. To allow use of the information obtained in the clinical trial, the investigator will understand that he/she will be obliged to supply the sponsor with full results of the tests and all the information developed during the study.

13. DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT

The study data will be recorded and kept current in the CRF/eCRF by the site study personnel directly responsible for the information.

The data in the CRF/eCRF will be monitored at the site by Grifols representatives or designee and reviewed for completeness and compared with the available source documents. Examples of source documents include individual subject medical records or laboratory reports, which are separate from the CRF/eCRFs.

Coding of AEs will be performed automatically by the data management team using the MedDRA dictionary. Similarly, coding of all medications will occur using the WHODrug dictionary. SAEs will be also coded using MedDRA.

13.2 RECORD KEEPING

The investigator is responsible for maintaining all records pertaining to the clinical trial and for ensuring complete and accurate documentation.

The investigator is responsible for maintaining a nominative subject enrollment log. This confidential subject identification code provides the link between named subject source records in the subject file and anonymous CRF/eCRF data provided to sponsor.

Essential documents of the study will be retained by the investigator according to what is established in the ICH GCP (ICH E6), or as per local regulations, whichever is longer.

No study documents will be destroyed without prior written agreement between the investigator and Instituto Grifols, S.A. Should the investigator wish to assign the study records to another party, or move them to another location, Instituto Grifols, S.A., must be notified in writing.

14. FINANCING AND INSURANCE

The sponsor will acquire an insurance policy to cover possible damage to the subject resulting from their participation in the study, in accordance with applicable local legislation; such coverage will be renewed periodically for the full duration of the study.

15. PUBLICATION POLICY

Institution and the investigator agree that the first publication shall be made in conjunction with the presentation of a joint, multi-center publication of the study results from all appropriates sites. If such a multi-center publication is not submitted within twelve (12) months after conclusion of the study at all sites or after Grifols confirms there will be no joint, multi-center publication, then institution and/or investigator shall have the right, at their discretion, to publish, either in writing or orally, the results of the study performed under the protocol, subject to the conditions outlined below:

1. The results of the study will be reported in the publicly accessible registry(ies).
2. Institution and/or investigator shall furnish Grifols with a copy of any proposed publication at least thirty (30) days in advance of the date of submission for publication.
3. Within said thirty (30) day period, Grifols shall:
   - Review such proposed publication for confidential information (other than study results) and for subject information subject to the HIPAA and other applicable privacy laws;
   - Review such proposed publication for the unauthorized use of the name, symbols and/or trademarks of Grifols;
   - By written notice to the investigator, identify with specificity the text or graphics in such proposed publication that Grifols contends contains confidential information, protected subject information, or the unauthorized use of Grifols' name, symbols and/or trademarks so that the proposed publication may be edited appropriately to remove such text or graphics before publication; and
   - By written request, Grifols may delay proposed publications up to sixty (60) days to allow Grifols to protect its interests in Grifols Inventions described in such publications.
4. Institution and/or investigator shall give Grifols the option of receiving an acknowledgment for its sponsorship of the study in all such publications or presentation.

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