Clinical trial results:
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

Summary

EudraCT number	2013-004343-23
Trial protocol	IT
Global end of trial date	11 November 2019

Results information

Result version number	v1 (current)
This version publication date	23 October 2020
First version publication date	23 October 2020

Trial information

Trial identification

Sponsor protocol code	IG0902

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02281500
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols, S.A.
Sponsor organisation address	Can Guasch, 2, Parets del Vallès, Barcelona, Spain, 08150
Public contact	Bioscience Clinical and Pharmacovigilance, Instituto Grifols, S.A., 0034 935712000, IGregulatory.affairs@grifols.com
Scientific contact	Bioscience Clinical and Pharmacovigilance, Instituto Grifols, S.A., 0034 935712000, IGregulatory.affairs@grifols.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the pharmacokinetics (PK), efficacy, and safety of human plasma-derived fibrinogen concentrate FIB Grifols after a single-dose 70 milligrams/kilogram (mg/kg) body weight administration.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	India: 14
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	22
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	10
Adolescents (12-17 years)	1
Adults (18-64 years)	11
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in India, Lebanon, and the United States of America (USA) between 22 Jul 2016 (first subject first visit) and 11 Nov 2019 (last subject last visit).

Pre-assignment

Screening details:

A total of 26 subjects were screened, out of which 24 subjects were enrolled, of them 2 subjects withdrawal the consent prior to receiving the study treatment, and the remaining 22 subjects received the study treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	FIB Grifols 70 mg/kg body weight

Arm description:

Subjects received a single dose of slow intravenous infusion of Human Plasma-Derived Fibrinogen Concentrate Grifols (FIB Grifols) 70 milligram per kilogram (mg/kg) body weight, at a rate not exceeding 5 mL/minute, on Day 0.

Arm type	Experimental
Investigational medicinal product name	Fibrinogen Grifols
Investigational medicinal product code	FIB Grifols
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Subjects received a single dose of slow IV infusion of FIB Grifols 70mg/kg body weight, at a rate not exceeding 5 mL/minute, on Day 0.

Number of subjects in period 1	FIB Grifols 70 mg/kg body weight
Started	22
Completed	22

Baseline characteristics

Reporting groups	
Reporting group title	FIB Grifols 70 mg/kg body weight

Reporting group description:

Subjects received a single dose of slow intravenous infusion of Human Plasma-Derived Fibrinogen Concentrate Grifols (FIB Grifols) 70 milligram per kilogram (mg/kg) body weight, at a rate not exceeding 5 mL/minute, on Day 0.

Reporting group values	FIB Grifols 70 mg/kg body weight	Total	
Number of subjects	22	22	
Age categorical Units:			
Age continuous Units: Years arithmetic mean standard deviation	 16.65 ± 9.523	 -	
Gender categorical Units: Subjects			
Female	12	12	
Male	10	10	

End points

End points reporting groups

Reporting group title	FIB Grifols 70 mg/kg body weight

Reporting group description:

Subjects received a single dose of slow intravenous infusion of Human Plasma-Derived Fibrinogen Concentrate Grifols (FIB Grifols) 70 milligram per kilogram (mg/kg) body weight, at a rate not exceeding 5 mL/minute, on Day 0.

Primary: Area Under the Plasma Fibrinogen Concentration-time Curve (AUC) from Time Zero to 14 days (AUC0-14days) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Area Under the Plasma Fibrinogen Concentration-time Curve (AUC) from Time Zero to 14 days (AUC0-14days) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[1]

End point description:

AUC(0-14days) was calculated by a combination of linear and logarithmic trapezoidal methods and expressed in the unit of concentration × time. The linear trapezoidal method used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method used for those arising from decreasing concentrations. Plasma fibrinogen activity determined by the Clauss method in the central laboratory of the study. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The Pharmacokinetic (PK) analysis population included all subjects who have received study medication and had sufficient fibrinogen plasma concentration data to facilitate the calculation of pharmacokinetic parameters. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[2]			
Units: hour*gram per liter (h*g/L)				
arithmetic mean (standard deviation)	145.67 (± 43.441)			

Notes:

[2] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Fibrinogen Concentration-time Curve (AUC) from Time Zero to 14 days (AUC0-14days) of FIB Grifols Determined by Enzyme-Linked Immunosorbent Assay (ELISA) Method, Dose Normalized to 70 mg/kg and

Corrected for Baseline Concentration

End point title	Area Under the Plasma Fibrinogen Concentration-time Curve (AUC) from Time Zero to 14 days (AUC0-14days) of FIB Grifols Determined by Enzyme-Linked Immunosorbent Assay (ELISA) Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[3]

End point description:

AUC(0-14days) was calculated by a combination of linear and logarithmic trapezoidal methods and expressed in the unit of concentration × time. The linear trapezoidal method was used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method was used for those arising from decreasing concentrations. Plasma fibrinogen activity was determined by the ELISA method in the central laboratory of the study. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[4]			
Units: hour*milligram per milliliter (h*mg/mL)				
arithmetic mean (standard deviation)	186.63 (± 95.734)			

Notes:

[4] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: AUC from Time Zero To Infinite Time (AUC0-infinity) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	AUC from Time Zero To Infinite Time (AUC0-infinity) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[5]

End point description:

AUC0-infinity was calculated as AUC0-t + Ct/Kel, where (AUC0-t) was the area under the concentration vs. time curve from time 0 to the time of last quantifiable concentration (Ct), and Kel was the apparent terminal first-order elimination rate constant, determined by linear regression analysis of the natural log-linear segment of the plasma concentration-time curve, expressed in time-1 units (1/h). Plasma fibrinogen activity was determined by the Clauss method in the central laboratory of the study. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[6]			
Units: hours*gram per liter (h*g/L)				
arithmetic mean (standard deviation)	166.78 (± 54.081)			

Notes:

[6] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: AUC from Time Zero To Infinite Time (AUC0-infinity) of FIB Grifols Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	AUC from Time Zero To Infinite Time (AUC0-infinity) of FIB Grifols Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[7]

End point description:

AUC0-infinity was calculated as AUC0-t + Ct/Kel, where (AUC0-t) was the area under the concentration vs. time curve from time 0 to the time of last quantifiable concentration (Ct), and Kel was the apparent terminal first-order elimination rate constant, determined by linear regression analysis of the natural log-linear segment of the plasma concentration-time curve, expressed in time-1 units (1/h). Plasma fibrinogen activity was determined by the ELISA method in the central laboratory of the study. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	7[8]			
Units: h*mg/mL				
arithmetic mean (standard deviation)	242.94 (± 117.567)			

Notes:

[8] - PK analysis with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Peak Plasma Fibrinogen Concentration (Cmax) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Maximum Observed Peak Plasma Fibrinogen Concentration (Cmax) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[9]

End point description:

Cmax was obtained directly from the experimental data without interpolation. Plasma fibrinogen activity was determined by the Clauss method in the central laboratory of the study. PK analysis population included all subjects who have received study medication and had sufficient fibrinogen plasma concentration data to facilitate the calculation of pharmacokinetic parameters. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[10]			
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)	1.99 (± 0.404)			

Notes:

[10] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Peak Plasma Fibrinogen Concentration (Cmax) of FIB Grifols Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Maximum Observed Peak Plasma Fibrinogen Concentration (Cmax) of FIB Grifols Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[11]

End point description:

Cmax was obtained directly from directly from the experimental data without interpolation. Plasma fibrinogen activity was determined by the ELISA method in the central laboratory of the study. PK analysis population included all subjects who have received study medication and had sufficient fibrinogen plasma concentration data to facilitate calculation of pharmacokinetic parameters. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[12]			
Units: milligram per milliliter (mg/mL)				
arithmetic mean (standard deviation)	2.88 (± 0.859)			

Notes:

[12] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Plasma Fibrinogen Concentration (Tmax) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Time to Reach Maximum Plasma Fibrinogen Concentration (Tmax) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[13]

End point description:

Tmax was obtained directly from the experimental data without interpolation, expressed in time units (hour). Plasma fibrinogen activity was determined by the Clauss method in the central laboratory of the study. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	21[14]			
Units: hour (h)				
median (full range (min-max))	1.40 (1.0 to 24.5)			

Notes:

[14] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Plasma Fibrinogen Concentration (Tmax) of FIB Grifols Determined by ELISA Method

End point title	Time to Reach Maximum Plasma Fibrinogen Concentration (Tmax) of FIB Grifols Determined by ELISA Method[15]

End point description:

Tmax was obtained directly from the experimental data without interpolation, expressed in time units (hour). Plasma fibrinogen activity was determined by the ELISA method in the central laboratory of the study. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	21[16]			
Units: hour (h)				
median (full range (min-max))	1.80 (1.1 to 24.5)			

Notes:

[16] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Terminal Half-life (t1/2) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Apparent Terminal Half-life (t1/2) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[17]

End point description:

t1/2 was the time measured for the concentration to decrease by one half. t1/2 calculated by natural log 2 divided by Kel and expressed in time units (hour). PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[18]			
Units: hour (h)				
arithmetic mean (standard deviation)	76.94 (± 20.215)			

Notes:

[18] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Terminal Half-life (t1/2) of FIB Grifols Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Apparent Terminal Half-life (t1/2) of FIB Grifols Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[19]

End point description:

t1/2 was the time measured for the concentration to decrease by one half. t1/2 calculated by natural log 2 divided by Kel and expressed in time units (hour). PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	7[20]			
Units: hour (h)				
arithmetic mean (standard deviation)	66.92 (± 16.789)			

Notes:

[20] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Mean Residence Time (MRT) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Mean Residence Time (MRT) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[21]

End point description:

MRT was calculated by AUC0-inf/AUC0-inf - (TI/2), where AUC0-inf was the area under the first moment of the concentration vs. time curve from time 0 extrapolated to infinite time and T1/2 was the apparent terminal half-life of infusion. PK analysis population included all subjects who have received study medication and had sufficient fibrinogen plasma concentration data to facilitate the calculation of pharmacokinetic parameters. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[22]			
Units: hour (h)				
arithmetic mean (standard deviation)	72.67 (± 12.185)			

Notes:

[22] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Mean Residence Time (MRT) of FIB Grifols Assessed Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Mean Residence Time (MRT) of FIB Grifols Assessed Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[23]

End point description:

MRT was calculated by AUC0-inf/AUC0-inf - (TI/2), where AUC0-inf was the area under the first moment of the concentration vs. time curve from time 0 extrapolated to infinite time and T1/2 was the apparent terminal half life of infusion. PK analysis population included all subjects who have received study medication and had sufficient fibrinogen plasma concentration data to facilitate calculation of pharmacokinetic parameters. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[24]			
Units: hour (h)				
arithmetic mean (standard deviation)	62.64 (± 19.142)			

Notes:

[24] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution (Vd) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Volume of Distribution (Vd) of FIB Grifols Determined by Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[25]

End point description:

Volume of distribution was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[26]			
Units: milliliter per kilogram (mL/kg)				
arithmetic mean (standard deviation)	47.932 (± 7.5997)			

Notes:

[26] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution (Vd) of FIB Grifols Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Volume of Distribution (Vd) of FIB Grifols Determined by ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[27]

End point description:

Volume of distribution was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	7[28]			
Units: mL/kg				
arithmetic mean (standard deviation)	31.264 (± 10.9702)			

Notes:

[28] - PK analysis with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Clearance (Cl) of FIB Grifols Determined By Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Clearance (Cl) of FIB Grifols Determined By Clauss Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[29]

End point description:

Clearance of a drug was a measure of the rate at which a drug was metabolized or eliminated by normal biological processes. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	10[30]			
Units: mL/h/kg				
arithmetic mean (standard deviation)	0.454 (± 0.1216)			

Notes:

[30] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Clearance (Cl) of FIB Grifols Determined By ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration

End point title	Clearance (Cl) of FIB Grifols Determined By ELISA Method, Dose Normalized to 70 mg/kg and Corrected for Baseline Concentration[31]

End point description:

Clearance of a drug was a measure of the rate at which a drug was metabolized or eliminated by normal biological processes. PK parameters adjusted for baseline fibrinogen level calculated by deducting the pre-infusion fibrinogen concentration from the post-infusion concentrations before the calculation. The PK population used for the analyses of the PK parameters. Here, the "number of subjects analyzed" signifies subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	7[32]			
Units: mL/h/kg				
arithmetic mean (standard deviation)	0.341 (± 0.1360)			

Notes:

[32] - PK analysis with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: In Vivo Recovery (IVR) of FIB Grifols Determined by Clauss Method

End point title	In Vivo Recovery (IVR) of FIB Grifols Determined by Clauss Method[33]

End point description:

Incremental IVR was calculated for fibrinogen levels from the peak level recorded within and included the first four hours after the end of infusion and reported as milligram per deciliter per milligram per

kilogram [mg/dL]/[mg/kg]. IVR was determined for every subject using the following formula: ([FIB max (mg/dL)] - [FIB pre-infusion (mg/dL)])/FIB administered (mg)/Body weight (kg), where the FIB max is the peak FIB activity within the first four hours after the end of infusion and FIB pre-infusion was the baseline FIB activity level of the subject. FIB administered was 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. The PK population used for the analyses of the PK parameters.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	21[34]			
Units: (mg/dL)/(mg/kg)				
arithmetic mean (standard deviation)	2.380 (± 0.6689)			

Notes:

[34] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: In Vivo Recovery (IVR) of FIB Grifols Determined by ELISA Method

End point title	In Vivo Recovery (IVR) of FIB Grifols Determined by ELISA Method[35]

End point description:

Incremental IVR was calculated for fibrinogen levels from the peak level recorded within and included the first four hours after the end of infusion and reported as milligram per deciliter per milligram per kilogram [mg/dL]/[mg/kg]. IVR was determined for every subject using the following formula: ([FIB max (mg/dL)] - [FIB pre-infusion (mg/dL)])/FIB administered (mg)/Body weight (kg), where the FIB max is the peak FIB activity within the first four hours after the end of infusion and FIB pre-infusion was the baseline FIB activity level of the subject. FIB administered was 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. The PK population used for the analyses of the PK parameters.

End point type	Primary

End point timeframe:

Pre-infusion, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 336 hours post-infusion

Notes:

[35] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since the descriptive statistical analysis was only planned for this endpoint.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	21[36]			
Units: (mg/dL)/(mg/kg)				
arithmetic mean (standard deviation)	3.474 (±			

	1.3607)

Notes:

[36] - PK population with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change on Maximum Clot Firmness (MCF) from Baseline to 1-hour Post-infusion

End point title	Mean Change on Maximum Clot Firmness (MCF) from Baseline to 1-hour Post-infusion[37]

End point description:

MCF was 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. Rotational thromboelastography (ROTEM) was performed on frozen plasma samples by the central laboratory to measure MCF. Undetectable MCF values were set to 0. The Evaluable population included all subjects who received Investigational Product (IP) at any amount and who had at least two measurements, pre-infusion MCF and 1-hour post-infusion MCF measurements by ROTEM.

End point type	Primary

End point timeframe:

Baseline to 1 hour post-infusion

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT database does not allow to report only one treatment group in the statistical analyses section. Due to this format constraint, inferential statistical analysis was not presented for this end-point.

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: millimeter (mm)				
arithmetic mean (standard deviation)	10.71 (± 4.122)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Clotting Time (CT) from Baseline to 1-hour Post-infusion

End point title	Mean Change in Clotting Time (CT) from Baseline to 1-hour Post-infusion

End point description:

Improvement in adult subjects' plasma samples in CT from baseline to 1-hour post-infusion indicated the hemostatic efficacy of the treatment with fibrinogen concentrate in subjects with fibrinogen deficiency. The Evaluable population was used for the analyses. Here "99999" signifies that standard deviation could not be estimated as there was only 1 subject with detectable baseline CT value and thus analyzed, undetectable CT values were set to missing.

End point type	Secondary

End point timeframe:

Baseline to 1-hour post-infusion

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	1[38]			
Units: Second (sec)				
arithmetic mean (standard deviation)	-3462.0 (± 99999)			

Notes:

[38] - Evaluable population analysis with evaluable subject for this end-point.

Statistical analyses

No statistical analyses for this end point

Secondary: Clot Formation Time (CFT) at 1-hour Post-infusion

End point title	Clot Formation Time (CFT) at 1-hour Post-infusion

End point description:

Improvement in subjects plasma samples in CFT at 1-hour post-infusion indicated the hemostatic efficacy of the treatment with fibrinogen concentrate in subjects with fibrinogen deficiency. The Evaluable population was used for the analyses. Here "99999" signifies that standard deviation could not be estimated as there was only 1 subject with detectable baseline CFT value and thus analyzed, undetectable CFT values were set to missing.

End point type	Secondary

End point timeframe:

1 hour post-infusion

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	1[39]			
Units: sec				
arithmetic mean (standard deviation)	68.0 (± 99999)			

Notes:

[39] - Evaluable population analysis with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Alpha angle (α) from Baseline to 1-hour Post-infusion

End point title	Mean Change in Alpha angle (α) from Baseline to 1-hour Post-infusion

End point description:

Improvement in subjects plasma samples in alpha angle from baseline to 1-hour post-infusion indicated the hemostatic efficacy of the treatment with fibrinogen concentrate in subjects with fibrinogen deficiency. The Evaluable population was used for the analyses.

End point type	Secondary

End point timeframe:

Baseline to 1 hour post-infusion

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	21[40]			
Units: degree				
arithmetic mean (standard deviation)	34.9 (± 34.52)			

Notes:

[40] - Evaluable population analysis with the eligible subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Prothrombin Time (PT) from Baseline to 1-hour Post-infusion

End point title	Mean Change in Prothrombin Time (PT) from Baseline to 1-hour Post-infusion

End point description:

Improvement in the subject’s plasma samples standard coagulation tests from baseline to 1-hour post-infusion indicated hemostatic efficacy of the treatment with fibrinogen concentrate in subjects with fibrinogen deficiency. The Evaluable population was used for the analyses.

End point type	Secondary

End point timeframe:

Baseline to 1 hour post-infusion

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	17[41]			
Units: sec				
arithmetic mean (standard deviation)	-102.79 (± 2.101)			

Notes:

[41] - Evaluable population with eligible subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Thrombin time (TT) from Baseline to 1-hour Post-infusion

End point title	Mean Change in Thrombin time (TT) from Baseline to 1-hour Post-infusion

End point description:

Improvement in the subject's plasma samples standard coagulation tests from baseline to 1-hour post-infusion indicated hemostatic efficacy of the treatment with fibrinogen concentrate in subjects with fibrinogen deficiency. The Evaluable population was used for the analyses.

End point type	Secondary

End point timeframe:

Baseline to 1 hour post-infusion

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	19[42]			
Units: sec				
arithmetic mean (standard deviation)	-200.41 (± 58.178)			

Notes:

[42] - Evaluable population analysis with evaluable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Activated Partial Thromboplastin Time (aPTT) from Baseline to 1-hour Post-infusion

End point title	Mean Change in Activated Partial Thromboplastin Time (aPTT) from Baseline to 1-hour Post-infusion

End point description:

Improvement in subject's plasma samples standard coagulation tests from baseline to 1-hour post-infusion indicated hemostatic efficacy of the treatment with a fibrinogen concentrate in subjects with fibrinogen deficiency. The Evaluable population was used for the analyses.

End point type	Secondary

End point timeframe:

Baseline to 1 hour post-infusion

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	19[43]			
Units: sec				
arithmetic mean (standard deviation)	-97.16 (± 10.580)			

Notes:

[43] - Evaluable population analysis with evaulable subjects for this end-point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a study drug which may or may not have a causal relationship with the study drug. SAE was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-subject hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Treatment-emergent defined as adverse events/serious adverse events that started or worsened on or after the start of the investigational product infusion. The safety population included all subjects who received infusion (at any dose) of the IP.

End point type	Secondary

End point timeframe:

From the start of the investigation product infusion up to Week 4

End point values	FIB Grifols 70 mg/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: subjects				
number (not applicable)				
Subjects with AEs	9			
Subjects with Serious AEs	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the start of the investigational product infusion up to Week 4	
Adverse event reporting additional description:	
The safety population included all subjects who received infusion (at any dose) of the IP.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	FIB Grifols 70 mg/kg body weight
Reporting group description:	
Subjects received a single dose of slow IV infusion of FIB Grifols 70 mg/kg body weight, at a rate not exceeding 5 mL/minute, on Day 0.	

Serious adverse events	FIB Grifols 70 mg/kg body weight		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	FIB Grifols 70 mg/kg body weight		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 22 (40.91%)		
Investigations			
Blood pressure diastolic decreased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Blood pressure systolic decreased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	3		

Heart rate increased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Injury, poisoning and procedural complications Traumatic haematoma subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Vascular disorders Phlebitis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Reproductive system and breast disorders Menorrhagia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2016	Amendment #2.3 included clarification regarding subject eligibility determination and included additional details. 1. 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. 2. 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. The subject discontinues his/her participation in the clinical trial without withdrawing his/her informed consent. Any AE occurred during infusion or within 24 and 72 hours after completion of infusion will be considered temporally associated with the infusion and labeled as infusional AEs. Thrombotic Events Risk Assessment included Wells Score which will be observed for evaluation and assessment of thrombotic events risk.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported