



## Clinical trial results:

### INTERNATIONAL NON -CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF FIBRINOGENE T-I IN ADOLESCENTS AND ADULTS WITH AFIBRINOGENAEMIA OR SEVERE HYPOFIBRINOGENAEMIA UNDERGOING SURGERY

#### Summary

EudraCT number	2007-001280-30
Trial protocol	FR
Global end of trial date	08 November 2013

#### Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	17 June 2015

#### Trial information

##### Trial identification

Sponsor protocol code	FGT1-A616
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	LFB Biotechnologies
Sponsor organisation address	3 Avenue des tropiques, BP 40305, Les Ulis, COURTABOEUF, France, 91958
Public contact	Global Clinical Development Leader, LFB Biotechnologies, 33 169825656,
Scientific contact	Global Clinical Development Leader, LFB Biotechnologies, 33 169825656,

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000457-PIP02-10
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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	19 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 November 2013
Global end of trial reached?	Yes
Global end of trial date	08 November 2013
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

The primary objective of the study is to assess the efficacy of FIBRINOGENE T-I in preventing excessive bleeding during surgical procedures or in treating bleeding of non surgical origin in patients with afibrinogenaemia or severe hypofibrinogenaemia.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Lebanon: 13
Country: Number of subjects enrolled	Morocco: 7
Country: Number of subjects enrolled	France: 2
Worldwide total number of subjects	22
EEA total number of subjects	2

Notes:

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**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)	8
Adolescents (12-17 years)	4
Adults (18-64 years)	10
From 65 to 84 years	0

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

20 subjects were included in the TTS from 2 july 2007 to 8 november2013 (LPO): 2 subjects in France, 6 subjects in Morocco and 12 subjects in Lebanon.

6 subjects participating only in the efficacy part, 4 subjects participating only in the Clinial Pharmacology part, 10 subjects participating in both part, all are analyzed for safety evaluation.

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

Number of subjects started	22
Number of subjects completed	20

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	not treated: 1
Reason: Number of subjects	sreening failure: 1

### Period 1

Period 1 title	before infusion
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	PK study only
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Clottafact
Investigational medicinal product code	FGT1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FGT1 (1.5 g/100 mL) a fibrinogen concentrate derived from human plasma was administered by intravenous infusion at a maximum rate of 4 mL/min.

For Pharmacokinetics:

A single dose of 0.06 g/kg body weight was administrated.

<b>Arm title</b>	PK + efficacy
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Clottafact
Investigational medicinal product code	FGT1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FGT1 (1.5 g/100 mL) a fibrinogen concentrate derived from human plasma was administered by

intravenous infusion at a maximum rate of 4 mL/min.

For Pharmacokinetics:

A single dose of 0.06 g/kg body weight was administrated.

For Efficacy:

Dose administered (g)= [desired Fg level (g/l) - baseline Fg level (g/l)] x 0,043 x body weight (Kg)  
(desired Fg level is at least 1,2 g/l for major bleeding and at least 1g/l for minor bleeding).

<b>Arm title</b>	Efficacy
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Clottafact
Investigational medicinal product code	FGT1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FGT1 (1.5 g/100 mL) a fibrinogen concentrate derived from human plasma was administered by intravenous infusion at a maximum rate of 4 mL/min.

For Efficacy:

Dose administered (g)= [desired Fg level (g/l) - baseline Fg level (g/l)] x 0,043 x body weight (Kg)  
(desired Fg level is at least 1,2 g/l for major bleeding and at least 1g/l for minor bleeding).

<b>Number of subjects in period 1<sup>[1]</sup></b>	PK study only	PK + efficacy	Efficacy
Started	4	10	6
Completed	4	10	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 2 patients in the worldwide number were not treated, 1 screening failure and 1 not treated by experimental product.

## Period 2

Period 2 title	FGT1 infusion
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	PK study only

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Clottafact
Investigational medicinal product code	FGT1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FGT1 (1.5 g/100 mL) a fibrinogen concentrate derived from human plasma was administered by

intravenous infusion at a maximum rate of 4 mL/min.  
For Pharmacokinetics:  
A single dose of 0.06 g/kg body weight was administrated.

<b>Arm title</b>	PK + efficacy
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Clottafact
Investigational medicinal product code	FGT1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FGT1 (1.5 g/100 mL) a fibrinogen concentrate derived from human plasma was administered by intravenous infusion at a maximum rate of 4 mL/min.

For Pharmacokinetics:

A single dose of 0.06 g/kg body weight was administrated.

For Efficacy:

Dose administered (g)= [desired Fg level (g/l) - baseline Fg level (g/l)] x 0,043 x body weight (Kg)  
(desired Fg level is at least 1,2 g/l for major bleeding and at least 1g/l for minor bleeding).

<b>Arm title</b>	Efficacy only
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Clottafact
Investigational medicinal product code	FGT1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FGT1 (1.5 g/100 mL) a fibrinogen concentrate derived from human plasma was administered by intravenous infusion at a maximum rate of 4 mL/min.

For Efficacy:

Dose administered (g)= [desired Fg level (g/l) - baseline Fg level (g/l)] x 0,043 x body weight (Kg)  
(desired Fg level is at least 1,2 g/l for major bleeding and at least 1g/l for minor bleeding).

<b>Number of subjects in period 2</b>	PK study only	PK + efficacy	Efficacy only
Started	4	10	6
Completed	4	10	6

**Period 3**

Period 3 title	Follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	PK study only

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Clottafact
Investigational medicinal product code	FGT1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FGT1 (1.5 g/100 mL) a fibrinogen concentrate derived from human plasma was administered by intravenous infusion at a maximum rate of 4 mL/min.

For Pharmacokinetics:

A single dose of 0.06 g/kg body weight was administered.

<b>Arm title</b>	PK + efficacy
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Clottafact
Investigational medicinal product code	FGT1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FGT1 (1.5 g/100 mL) a fibrinogen concentrate derived from human plasma was administered by intravenous infusion at a maximum rate of 4 mL/min.

For Pharmacokinetics:

A single dose of 0.06 g/kg body weight was administered.

For Efficacy:

Dose administered (g)= [desired Fg level (g/l) - baseline Fg level (g/l)] x 0,043 x body weight (Kg)  
(desired Fg level is at least 1,2 g/l for major bleeding and at least 1g/l for minor bleeding).

<b>Arm title</b>	Efficacy
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Clottafact
Investigational medicinal product code	FGT1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FGT1 (1.5 g/100 mL) a fibrinogen concentrate derived from human plasma was administered by intravenous infusion at a maximum rate of 4 mL/min.

For Efficacy:

Dose administered (g)= [desired Fg level (g/l) - baseline Fg level (g/l)] x 0,043 x body weight (Kg)  
(desired Fg level is at least 1,2 g/l for major bleeding and at least 1g/l for minor bleeding).

<b>Number of subjects in period 3</b>	PK study only	PK + efficacy	Efficacy
Started	4	10	6
Completed	4	10	6



## Baseline characteristics

### Reporting groups

Reporting group title	before infusion
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Reporting group description: -

Reporting group values	before infusion	Total	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
Children (2-11 years)	6	6	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	10	10	
Age continuous			
Units: years			
median	17.5		
full range (min-max)	7 to 37	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	13	13	

### Subject analysis sets

Subject analysis set title	TTS (Total Treated Set)
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Subject analysis set type	Full analysis
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Subject analysis set description:

the TTS was defined as all subjects who received at least one administration of FGT1 for any part of the study protocol.

Subject analysis set title	FAS (Full Analysis Set)
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Subject analysis set type	Full analysis
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Subject analysis set description:

the FAS consists of all subjects in the TTS who received at least one administration of FGT1 in the efficacy part of the study.

Subject analysis set title	PPS (Per Protocol Set)
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Subject analysis set type	Per protocol
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Subject analysis set description:

the PPS consists of all subject in the FAS who had a valid surgical or non surgical bleeding event. Analyses for the FAS and PPS were event-based, not subject based.

Subject analysis set title	CPS (Clinical Pharmacology Set)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

the CPS was defined as all subjects in the TTS who received FGT1 in the CP part (part I) of the study.

Reporting group values	TTS (Total Treated Set)	FAS (Full Analysis Set)	PPS (Per Protocol Set)
Number of subjects	20	16	15
Age categorical			
Units: Subjects			
Children (2-11 years)	6	5	4

Adolescents (12-17 years)	4	3	3
Adults (18-64 years)	10	8	8

Age continuous Units: years median full range (min-max)	17.5 7 to 37	17.5 7 to 37	
Gender categorical Units: Subjects			
Female	7	3	
Male	13	13	

<b>Reporting group values</b>	CPS (Clinical Pharmacology Set)		
Number of subjects	14		
Age categorical Units: Subjects			
Children (2-11 years)	1		
Adolescents (12-17 years)	4		
Adults (18-64 years)	9		
Age continuous Units: years median full range (min-max)	21.5 11 to 38		
Gender categorical Units: Subjects			
Female	6		
Male	8		

## End points

### End points reporting groups

Reporting group title	PK study only
Reporting group description: -	
Reporting group title	PK + efficacy
Reporting group description: -	
Reporting group title	Efficacy
Reporting group description: -	
Reporting group title	PK study only
Reporting group description: -	
Reporting group title	PK + efficacy
Reporting group description: -	
Reporting group title	Efficacy only
Reporting group description: -	
Reporting group title	PK study only
Reporting group description: -	
Reporting group title	PK + efficacy
Reporting group description: -	
Reporting group title	Efficacy only
Reporting group description: -	
Reporting group title	PK study only
Reporting group description: -	
Reporting group title	PK + efficacy
Reporting group description: -	
Reporting group title	Efficacy
Reporting group description: -	
Subject analysis set title	TTS (Total Treated Set)
Subject analysis set type	Full analysis
Subject analysis set description: the TTS was defined as all subjects who received at least one administration of FGT1 for any part of the study protocol.	
Subject analysis set title	FAS (Full Analysis Set)
Subject analysis set type	Full analysis
Subject analysis set description: the FAS consists of all subjects in the TTS who received at least one administration of FGT1 in the efficacy part of the study.	
Subject analysis set title	PPS (Per Protocol Set)
Subject analysis set type	Per protocol
Subject analysis set description: the PPS consists of all subject in the FAS who had a valid surgical or non surgical bleeding event. Analyses for the FAS and PPS were event-based, not subject based.	
Subject analysis set title	CPS (Clinical Pharmacology Set)
Subject analysis set type	Sub-group analysis
Subject analysis set description: the CPS was defined as all subjects in the TTS who received FGT1 in the CP part (part I) of the study.	

### Primary: overall assessment of the hemostatic efficacy of FGT1 Surgical procedures

End point title	overall assessment of the hemostatic efficacy of FGT1 Surgical procedures <sup>[1]</sup>
End point description: overall assessment was done using a 4-point scales (Excellent, Good, Moderate, None)	
End point type	Primary
End point timeframe: At the end of each treatment episode (24-48 hours after treatment when the subject was not hospitalized or on the day of hospital discharge when the subject was hospitalized)	

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: descriptive analyse

End point values	FAS (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	15 <sup>[2]</sup>			
Units: percentage				
Excellent / Good	100			
Moderate / None	0			

Notes:

[2] - 38 Surgical procedures done in 15 subjects.

## Statistical analyses

No statistical analyses for this end point

## Primary: Overall assessment of the hemostatic efficacy of FGT1 Non surgical bleeding events

End point title	Overall assessment of the hemostatic efficacy of FGT1 Non surgical bleeding events <sup>[3]</sup>
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End point description:

overall assessment was done using a 4-point scales (Excellent, Good, Moderate, None)

End point type	Primary
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End point timeframe:

At the end of each treatment episode (24-48 hours after treatment when the subject was not hospitalized or on the day of hospital discharge when the subject was hospitalized)

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: descriptive analyse

End point values	FAS (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	9 <sup>[4]</sup>			
Units: percentage				
Excellent / Good	100			
Moderate / None	0			

Notes:

[4] - 32 Non-surgical bleeding events in 9 subjects.

## Statistical analyses

No statistical analyses for this end point

## Primary: PK Analysis Fibrinogen antigen C max

End point title	PK Analysis Fibrinogen antigen C max <sup>[5]</sup>
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End point description:

End point type	Primary
End point timeframe:	
Plasma pharmacokinetic of Fibrinogen antigen after a single IV infusion of FGT1 in subjects with Afibrinogenemia.	
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: descriptive analyse	

<b>End point values</b>	CPS (Clinical Pharmacology Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: g/L				
median (full range (min-max))	1.5 (1.17 to 2.13)			

### Statistical analyses

No statistical analyses for this end point

### Primary: PK Analysis Fibrinogen antigen AUC 0-infinity

End point title	PK Analysis Fibrinogen antigen AUC 0-infinity <sup>[6]</sup>
End point description:	

End point type	Primary
End point timeframe:	
Plasma pharmacokinetic of Fibrinogen antigen after a single IV infusion of FGT1 in subjects with Afibrinogenemia.	
Notes:	
[6] - 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: descriptive analyse	

<b>End point values</b>	CPS (Clinical Pharmacology Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: g.h/L				
median (full range (min-max))	169 (111 to 260)			

### Statistical analyses

No statistical analyses for this end point

### Primary: PK Analysis Fibrinogen activity A max

End point title	PK Analysis Fibrinogen activity A max <sup>[7]</sup>
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End point description:

Plasma fibrinogen using the high calibration curve assay (Primary NCA)

End point type	Primary
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End point timeframe:

Plasma pharmacokinetic of Fibrinogen antigen after a single IV infusion of FGT1 in subjects with Afibrinogenemia.

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: descriptive analyse

End point values	CPS (Clinical Pharmacology Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: g/L				
median (full range (min-max))	1.34 (1.06 to 2.19)			

## Statistical analyses

No statistical analyses for this end point

## Primary: PK analysis Fibrinogen activity Recovery

End point title	PK analysis Fibrinogen activity Recovery <sup>[8]</sup>
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End point description:

Plasma fibrinogen using the high calibration curve assay (Primary NCA)

End point type	Primary
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End point timeframe:

Plasma pharmacokinetic of Fibrinogen antigen after a single IV infusion of FGT1 in subjects with Afibrinogenemia.

Notes:

[8] - 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: descriptive analyse

End point values	CPS (Clinical Pharmacology Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: (g/L)/(g/kg)				
median (full range (min-max))	22.2 (17.7 to 36.5)			

## Statistical analyses

No statistical analyses for this end point

**Primary: PK Fibrinogen activity AUC 0-infinity**

End point title	PK Fibrinogen activity AUC 0-infinity <sup>[9]</sup>
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End point description:

Plasma fibrinogen using the low calibration curve assay (secondary NCA)

End point type	Primary
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End point timeframe:

Plasma pharmacokinetic of Fibrinogen antigen after a single IV infusion of FGT1 in subjects with Afibrinogenemia.

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: descriptive analyse

End point values	CPS (Clinical Pharmacology Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: g.h/L				
median (full range (min-max))	105 (78.2 to 167)			

**Statistical analyses**

No statistical analyses for this end point

**Primary: PK fibrinogen activity Half-life**

End point title	PK fibrinogen activity Half-life <sup>[10]</sup>
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End point description:

Plasma fibrinogen using the low calibration curve assay (secondary NCA)

End point type	Primary
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End point timeframe:

Plasma pharmacokinetic of Fibrinogen antigen after a single IV infusion of FGT1 in subjects with Afibrinogenemia.

Notes:

[10] - 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: descriptive analyse

End point values	CPS (Clinical Pharmacology Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: hours				
median (full range (min-max))	67.9 (51 to 99.9)			

**Statistical analyses**





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12
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### Reporting groups

Reporting group title	Total treated Set
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Reporting group description: -

Serious adverse events	Total treated Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint dislocation	Additional description: Not Related		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transfusion-related circulatory overload			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Shock haemorrhagic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis superficial			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pilonidal cyst			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Total treated Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Limb injury			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	8		
Face injury			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Road traffic accident			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Gingival bleeding			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	15		
Bone pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Infections and infestations			
Rhinitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		

Postoperative wound infection subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2007	MSI for information. Addition of one principal investigator and one new site
11 June 2008	MSI for information. Addition of a new investigator.
18 August 2008	The activated protein C resistance test is not appropriated in afibrinogenaemic and hypofibrinogenaemic patients, reason why the test will be cancelled and replaced by genetic tests of factor V (Leiden) mutation and Factor II at the screening visit.
19 November 2008	Addition of 2 investigators
04 February 2009	MSI for information. To extend the duration if the study (without modification of patient participation).
10 April 2009	On AFSSAPS request on 20th October 2008 to provide "efficacy and safety data in treatment of major lifeor limb- threatening bleedings or in case of surgery in patient with fibrinogen inherited deficiency", LFB opted for the amendment of the study FGT1-A616 conducted in surgery. The major changes are the addition of a clinical pharmacology study (including a study of thrombogenicity) and an extension of the study in the treatment of bleedings. The modification impacts on the title, study objectives, study desing, study population and number of patients to enroll, the endpoints and evaluation parameters.
04 August 2009	This amendment will allow the recruitment of any possible paediatric patients respecting blood sampling constraints. This amendment is in line with the proposed PIP for this product, which was submitted to the EMEA end of May 2009.
23 September 2009	MSI for information Addition of a new investigational centre

08 June 2010	<p>The main changes proposed for the protocol are consecutive to the EMA scientific advice procedure that was held for this product in 2009 (extract of the EMA opinion attached).</p> <p>The main changes are the following:</p> <ul style="list-style-type: none"> <li>• To clarify the primary objective and the definition of type of bleedings and surgery.</li> <li>• To increase the number of included patient from 6 to 10 in order to get a sufficient number of events.</li> <li>• To precise for the inclusion criteria n° 4 that the minimum serological status necessary includes the vaccinations for hepatitis A and B</li> <li>• To precise for the exclusion criteria n°5 that only the personal history of venous or arterial thrombosis or thromboembolic event is an exclusion criteria.</li> <li>• The additional exclusion criteria n°16 has been added to exclude the patients with the treatments, which impact coagulation, could prolong bleeding and thus bias the evaluation of study endpoints.</li> <li>• The additional exclusion criteria specific to Clinical Pharmacology Part n°19 has been added to exclude patients with a recent bleeding(s) in order to have stable biological parameters.</li> <li>• The additional exclusion criteria specific to Clinical Pharmacology Part n°22 has been added in order to have enough time to perform all clinical pharmacology visits (during three weeks) to evaluate drug pharmacological and safety profile before the planned surgical procedure.</li> <li>• To prolong the study until Q2 2012 with no impact on duration of patient's exposure to the drug</li> <li>• To increase the level of minimal peri-operative "desired fibrinogen" level for minor surgery.</li> <li>• To add an ultrasonography of lower-limbs in order to monitor all thromboembolic events during the study and to evaluate their relation to the study drug.</li> <li>• Additional biological tests have been added for a better follow-up of safety.</li> </ul>
22 September 2010	<p>MSI for information.</p> <p>Change in the status of the investigational medicinal product FGT1.</p> <p>The IMP was granted a Marketing authorisation in France in May 2009</p>
19 September 2011	<p>substantial amendment: protocol amendment (modification of inclusion/exclusion criterias, primary and secondary endpoints...)</p>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported