Clinical trial results:
Clinical pharmacology, efficacy and safety study of FGTW in paediatric patients with severe congenital fibrinogen deficiency

Summary

EudraCT number	2013-000261-36
Trial protocol	FR Outside EU/EEA
Global end of trial date	11 December 2015

Results information

Result version number	v1 (current)
This version publication date	28 September 2016
First version publication date	28 September 2016

Trial information

Trial identification

Sponsor protocol code	FGTW-1004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02094430
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LFB Biotechnologies
Sponsor organisation address	3, Avenue des tropiques - BP 40305, 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)	EMEA-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 December 2015
Global end of trial reached?	Yes
Global end of trial date	11 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the efficacy of FGTW as a replacement therapy in paediatric patients with afibrinogenaemia or severe hypofibrinogenaemia:
▪ in preventing excessive bleeding in patients undergoing a surgical procedure,
▪ in treating bleeding of non-surgical origin

Protection of trial subjects:

Blood analyses required by the study procedures will be adapted to the body weight of the patient to take into consideration the Ethical Considerations and ICH Harmonised Tripartite Guideline "Clinical Investigation of Medicinal Products in the Paediatric Population".
The protocol-related blood withdrawal will not exceed 3 % of the total blood volume of the patient during a period of four weeks and will not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight; 3% is 2.4 mL blood per kg of body weight.
Patient confidentiality was maintained throughout the study.
The study was conducted in accordance with the with the principles laid down in the Declaration of Helsinki, the ICH guidelines for Good Clinical Practice (GCP) and all applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2014
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	Lebanon: 8
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Morocco: 7
Worldwide total number of subjects	16
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)	1
Children (2-11 years)	14
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

16 subjects were included in the TTS from 22/01/2014 to 11/12/2015 (LPO): 12 subjects participating in both PK and efficacy parts of the study and 4 subjects participating only in the efficacy part, all were analyzed for safety evaluation.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	16
Number of subjects completed	16

Period 1

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

Arms

Arm title	Experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	FibCLOT
Investigational medicinal product code	FGTW
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

No administration at inclusion

Number of subjects in period 1	Experimental
Started	16
Completed	16

Period 2

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

Arms

Arm title	Experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	FibCLOT
Investigational medicinal product code	FGTW
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

No administration at inclusion

Number of subjects in period 2[1]	Experimental
Started	12
Completed	12

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Pharmacokinetics at study entry was optional, and 12 of a total of 16 enrolled patients participated at PK study

Period 3

Period 3 title	Efficacy Study Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	FibCLOT
Investigational medicinal product code	FGTW
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

No administration at inclusion

Number of subjects in period 3	Experimental
Started	12
Completed	16

Joined	4
patients without pharmacology period	4

Baseline characteristics

Reporting groups	
Reporting group title	Inclusion visit

Reporting group description: -

Reporting group values	Inclusion visit	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	1	1	
Children (2-11 years)	14	14	
Adolescents (12-17 years)	1	1	
Age continuous Units: years			
median	6.5		
full range (min-max)	1 to 12	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	10	10	

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	
Subject analysis set title	TTS (Total treated set) - Surgical procedures
Subject analysis set type	Full analysis
Subject analysis set description:	
the TTS was defined as all subjects who received at least one administration of FGTW for any part of the study protocol.	
Subject analysis set title	TTS (Total treated Set) - Bleeding episodes
Subject analysis set type	Full analysis
Subject analysis set description:	
the TTS was defined as all subjects who received at least one administration of FGTW for any part of the study protocol.	

Primary: Proportion of Excellent/Good responses

End point title	Proportion of Excellent/Good responses[1]
End point description:	
End point type	Primary
End point timeframe:	
End point timeframe: Overall assessment of the hemostatic efficacy of FGTW done at least 6 hrs post-infusion for a bleeding episode/surgical procedure treated in an outpatient setting 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 analysis

End point values	TTS (Total treated set) - Surgical procedures	TTS (Total treated Set) - Bleeding episodes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[2]	11[3]		
Units: percentage				
Excellent/Good	100	97		
Moderate/None	0	3		

Notes:

[2] - 10 subjects underwent 11 surgical procedures.
The statistical unit was the treated event with FGTW
[3] - 11 subjects experienced 32 bleeding episodes.
The statistical unit was the treated event with FGTW

Statistical analyses

No statistical analyses for this end point

Primary: Incremental Recovery

End point title	Incremental Recovery[4]

End point description:

End point type	Primary

End point timeframe:

Incremental Recovery one hour post-infusion for fibrinogen activity after single IV infusion 0.06 g/kg FGTW in subjects with afibrinogenaemia

Notes:

[4] - 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 analysis

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: g/L per g/kg				
geometric mean (full range (min-max))	19.1 (14 to 30.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Half-life

End point title	Half-life[5]

End point description:

End point type	Primary

End point timeframe:

Half-life of FGTW for fibrinogen activity after a single IV infusion of 0.06 g/kg FGTW in pediatric subjects of 12 years or less with afibrinogenaemia

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 analysis

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
geometric mean (full range (min-max))	49 (41.1 to 57.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Clearance

End point title	Clearance[6]

End point description:

End point type	Primary

End point timeframe:

Clearance of FGTW for fibrinogen activity after a single IV infusion of 0.06 g/kg FGTW in pediatric subjects of 12 years or less with afibrinogenaemia

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 analysis

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mL/h/kg				
geometric mean (full range (min-max))	0.74 (0.47 to 1.03)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Experimental

Reporting group description: -

Serious adverse events	Experimental		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 16 (18.75%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Budd-Chiari syndrome			
subjects affected / exposed	1 / 16 (6.25%)		
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 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Experimental		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 16 (87.50%)		
Injury, poisoning and procedural complications			
Limb injury	Additional description: Not related to the study drug		
subjects affected / exposed	8 / 16 (50.00%)		
occurrences (all)	20		
Joint injury	Additional description: Not related to the study drug		
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	5		
Limb crushing injury	Additional description: Not related to the study drug		
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Head injury	Additional description: Not related to the study drug		
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	5		
Buttock crushing	Additional description: Not related to the study drug		
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Nervous system disorders			
Headache	Additional description: 2 adverse reactions in one subject		
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain	Additional description: Not related to the study drug		
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Pain in extremity	Additional description: Not related to the study drug		
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	6		
Bone pain	Additional description: Not related to the study drug		
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	7		
Infections and infestations			

rhinitis	Additional description: Not related to the study drug		
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	10		
Tonsillitis	Additional description: Not related to the study drug		
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2013	The principal aim of this amendment was to summarise the changes between study protocol version 3.0 dated 06 May 2013 and study protocol version 5.0 dated 10 July 2013 made during the assessment of the clinical trial by the French Authority (ANSM).
29 September 2014	This amendment increased the number of enrolled subjects from 12 to 16. The definition of ''major bleeding in nonsurgical subjects'' was revised to allow managing subjects in outpatient or inpatient setting. In previous protocol version, subjects were managed in inpatient setting only. The hospitalization was removed from the definition based on the current medical practice in fibrinogen congenital deficiency and the accurate definition from the ISTH Committee. The safety section "special rules for the study" was updated to capture any change in AE or SAE, in order to have as much information as possible on each AE or SAE.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported