



## 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)                          | 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? | 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**

|  |   |
|--|---|
| <b>Arm title</b>                       | 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

|   |              |
|---|--------------|
| <b>Number of subjects in period 2<sup>[1]</sup></b> | 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**

|  |   |
|--|---|
| <b>Arm title</b>                       | 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

| <b>Number of subjects in period 3</b> | 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:<br>the TTS was defined as all subjects who received at least one administration of FGWT 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:<br>the TTS was defined as all subjects who received at least one administration of FGWT for any part of the study protocol. |   |

### Primary: Proportion of Excellent/Good responses

|                        |   |
|------------------------|---|
| End point title        | Proportion of Excellent/Good responses <sup>[1]</sup> |
| End point description: |   |

|  |         |
|--|---------|
| End point type   | Primary |
| End point timeframe:   |         |
| End point timeframe:<br>Overall assessment of the hemostatic efficacy of FGWT 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 <sup>[2]</sup>                             | 11 <sup>[3]</sup>                           |  |  |
| 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 FGWT

[3] - 11 subjects experienced 32 bleeding episodes.  
The statistical unit was the treated event with FGWT

### Statistical analyses

No statistical analyses for this end point



## Primary: Incremental Recovery

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Incremental Recovery <sup>[4]</sup> |
|-----------------|-------------------------------------|

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 <sup>[5]</sup> |
|-----------------|--------------------------|

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

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**Primary: Clearance**

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|                 |                          |
|-----------------|--------------------------|
| End point title | Clearance <sup>[6]</sup> |
|-----------------|--------------------------|

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

|                                       |                     |  |  |  |
|---------------------------------------|---------------------|--|--|--|
| <b>End point values</b>               | 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) |  |  |  |

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**Statistical analyses**

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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 %

|   |  |  |  |
|---|--|--|--|
| <b>Non-serious adverse events</b>                     | 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported