



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 |
|-----------------------|-----------|

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:

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:

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:

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:

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 |
|-------------------|---|

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 |
| Arm title | 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.

| | |
|------------------|---------------|
| Arm title | 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).

| | |
|--|---------------------------------------|
| Arm title | 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).

| Number of subjects in period 1^[1] | 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 |
| Arm title | 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.

| | |
|--|---------------------------------------|
| Arm title | 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).

| | |
|--|---------------------------------------|
| Arm title | 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).

| Number of subjects in period 2 | 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 |
| Arm title | 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.

| | |
|------------------|---------------|
| Arm title | 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 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).

| | |
|------------------|----------|
| Arm title | 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).

| Number of subjects in period 3 | PK study only | PK + efficacy | Efficacy |
|---------------------------------------|---------------|---------------|----------|
| Started | 4 | 10 | 6 |
| Completed | 4 | 10 | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | before infusion |
|-----------------------|-----------------|

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) |
|----------------------------|-------------------------|

| | |
|---------------------------|---------------|
| 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.

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

| | | | |
|-------------------------------|---------------------------------|--|--|
| Reporting group values | 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 | 21.5 | | |
| full range (min-max) | 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 |
| 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 ^[1] |
| 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 ^[2] | | | |
| 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 ^[3] |
|-----------------|---|

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:

[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 ^[4] | | | |
| 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 ^[5] |
|-----------------|---|

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

| | | | | |
|-------------------------------|---------------------------------|--|--|--|
| 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)) | 1.5 (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 ^[6] |
|-----------------|--|

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

| | | | | |
|-------------------------------|---------------------------------|--|--|--|
| End point values | 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 ^[7] |
|-----------------|--|

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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 ^[8] |
|-----------------|---|

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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 ^[9] |
|-----------------|--|

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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 ^[10] |
|-----------------|--|

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 12 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Total treated Set |
|-----------------------|-------------------|

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 %

| Non-serious adverse events | 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 | | |
|---|----------------------|--|--|

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"> • To clarify the primary objective and the definition of type of bleedings and surgery. • To increase the number of included patient from 6 to 10 in order to get a sufficient number of events. • To precise for the inclusion criteria n° 4 that the minimum serological status necessary includes the vaccinations for hepatitis A and B • 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. • 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. • 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. • 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. • To prolong the study until Q2 2012 with no impact on duration of patient's exposure to the drug • To increase the level of minimal peri-operative "desired fibrinogen" level for minor surgery. • 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. • Additional biological tests have been added for a better follow-up of safety. |
| 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