Clinical trial results:
Pharmacokinetics of Haemocomplettan P in subjects with congenital fibrinogen deficiency

Summary

EudraCT number	2006-006023-39
Trial protocol	IT
Global end of trial date	13 May 2008

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	BI3023_2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00496262
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring-Strasse 76, Marburg, Germany, 35041
Public contact	Trial Disclosure Manager, CSL Behring GmbH, clinicaltrials@cslbehring.com
Scientific contact	Trial Disclosure Manager, CSL Behring GmbH, clinicaltrials@cslbehring.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 May 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare maximum clot strength (maximum clot firmness [MCF]) as a surrogate marker for hemostatic efficacy before and after administration of Haemocomplettan P in subjects with congenital fibrinogen deficiency and to demonstrate that MCF 1 hour after administration of 70 mg/kg b.w. of Haemocomplettan P is significantly higher compared to baseline.

To determine the single dose pharmacokinetics (PK) of Haemocomplettan P in subjects with congenital fibrinogen deficiency.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and standard operating procedures for clinical research and development at CSL Behring (CSLB).
The study protocol and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating centers.
Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	19 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	Italy: 8
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	15
EEA total number of subjects	8

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)	2
Adolescents (12-17 years)	3
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall, 17 subjects were screened for this study and 15 subjects were enrolled.

Period 1

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

Arms

Arm title	Human Fibrinogen Concentrate

Arm description:

All enrolled subjects received a single intravenous infusion of 70 mg/kg body weight of human fibrinogen concentrate.

Arm type	Experimental
Investigational medicinal product name	Human fibrinogen concentrate, pasteurized
Investigational medicinal product code	BI3023
Other name	Haemocomplettan® P
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single dose of 70 mg fibrinogen per kg body weight. Supplied as 1 g lyophilizate to be reconstituted in 50 mL of sterile water for injection. Final concentration for infusion was 20 mg/mL.

Number of subjects in period 1	Human Fibrinogen Concentrate
Started	15
Completed	15

Baseline characteristics

Reporting groups	
Reporting group title	Human Fibrinogen Concentrate
Reporting group description:	
All enrolled subjects received a single intravenous infusion of 70 mg/kg body weight of human fibrinogen concentrate.	

Reporting group values	Human Fibrinogen Concentrate	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
<16 years	4	4	
≥ 16 to < 65 years	11	11	
≥ 65 years	0	0	
Age continuous Units: years			
arithmetic mean	29.5		
standard deviation	± 15.9	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	10	10	

End points

End points reporting groups

Reporting group title	Human Fibrinogen Concentrate

Reporting group description:

All enrolled subjects received a single intravenous infusion of 70 mg/kg body weight of human fibrinogen concentrate.

Subject analysis set title	Pharmacokinetic Analysis Population
Subject analysis set type	Per protocol

Subject analysis set description:

The pharmacokinetics analysis population included all subjects in the ITT population who fulfilled all of the following conditions:
· Received 90% of the planned total dose of Haemocomplettan P.
· Did not meet any of the exclusion criteria.
· Did not receive any fibrinogen containing blood products between infusion of Haemocomplettan P and the end of the 14-day PK observation period.
· Provided sufficient PK data that allowed for a reliable PK analysis.

Subject analysis set title	Pre-infusion
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Less than or equal to 2 hours before start of infusion

Subject analysis set title	1 Hour Post-infusion
Subject analysis set type	Intention-to-treat

Subject analysis set description:

1 hour after end of infusion

Primary: Change From Pre-infusion to One-hour Post-infusion in Maximum Clot Firmness (MCF)

End point title	Change From Pre-infusion to One-hour Post-infusion in Maximum Clot Firmness (MCF)

End point description:

MCF is a functional parameter that depends on the activation of coagulation, the fibrinogen content of the sample (in plasma), and the polymerization and crosslinking of the fibrin network. MCF was determined by rotational thromboelastometry (ROTEM) testing.

The entire ITT population was used for a conservative analysis of the mean change in MCF. The mean change was set to 0 for any subject with missing MCF data.

End point type	Primary

End point timeframe:

Pre-infusion and one hour post-infusion

End point values	Pre-infusion	1 Hour Post-infusion		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: millimeters				
arithmetic mean (standard deviation)				
Maximum Clot Firmness (MCF)	0 (± 0)	8.9 (± 4.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Maximum Clot Firmness

Statistical analysis description:

The entire ITT population was used for a conservative analysis of the mean change in MCF. The mean change was set to 0 for any subject with missing MCF data.

Although the number of subjects included in analysis lists 30, the correct number is 15. Due to system constraints, this field is not able to be edited.

Comparison groups	Pre-infusion v 1 Hour Post-infusion
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided

Secondary: Terminal Elimination Half-life (t1/2) for Fibrinogen Activity

End point title	Terminal Elimination Half-life (t1/2) for Fibrinogen Activity

End point description:

Fibrinogen activity was measured using the Clauss assay. The detection limit for fibrinogen activity is 0.2 g/L.

End point type	Secondary

End point timeframe:

0.5 hours to 13 days post-infusion

End point values	Pharmacokinetic Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: hours				
arithmetic mean (standard deviation)	78.7 (± 18.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) for Fibrinogen Activity

End point title	Maximum Concentration (Cmax) for Fibrinogen Activity

End point description:

Fibrinogen activity was measured using the Clauss assay. The detection limit for fibrinogen activity is 0.2 g/L.

End point type	Secondary

End point timeframe:

Pre-infusion to 13 days post-infusion

End point values	Pharmacokinetic Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: g/L				
arithmetic mean (standard deviation)	1.4 (± 0.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve (AUC) Standardized for 70 mg/kg Body Weight Dose

End point title	Area Under the Concentration-time Curve (AUC) Standardized for 70 mg/kg Body Weight Dose

End point description:

Fibrinogen activity was measured using the Clauss assay. The detection limit for fibrinogen activity is 0.2 g/L.

End point type	Secondary

End point timeframe:

Pre-infusion to 13 days post-infusion

End point values	Pharmacokinetic Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: h*mg/mL				
arithmetic mean (standard deviation)	124.3 (± 24.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) for Fibrinogen Activity

End point title	Clearance (Cl) for Fibrinogen Activity

End point description:

Fibrinogen activity was measured using the Clauss assay. The detection limit for fibrinogen activity is 0.2 g/L.

End point type	Secondary

End point timeframe:

Pre-infusion to 13 days post-infusion

End point values	Pharmacokinetic Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: mL/h/kg				
arithmetic mean (standard deviation)	0.59 (± 0.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) for Fibrinogen Activity

End point title	Mean Residence Time (MRT) for Fibrinogen Activity

End point description:

Fibrinogen activity was measured using the Clauss assay. The detection limit for fibrinogen activity is 0.2 g/L.

End point type	Secondary

End point timeframe:

Pre-infusion to 13 days post-infusion

End point values	Pharmacokinetic Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: hours				
arithmetic mean (standard deviation)	92.8 (± 20.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss) for Fibrinogen Activity

End point title	Volume of Distribution at Steady State (Vss) for Fibrinogen Activity

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion to 13 days post-infusion

End point values	Pharmacokinetic Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: mL/kg				
arithmetic mean (standard deviation)	52.7 (± 7.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental In Vivo Recovery for Fibrinogen Activity

End point title	Incremental In Vivo Recovery for Fibrinogen Activity

End point description:

The maximum fibrinogen increase in plasma, per mg/kg body weight (b.w.). dosed, within 4 hours of infusion compared to pre-infusion.

End point type	Secondary

End point timeframe:

Pre-infusion to 4 hours post-infusion

End point values	Pharmacokinetic Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: mg/dL increase per mg/kg b.w.				
median (full range (min-max))	1.7 (1.3 to 2.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Classical In Vivo Recovery for Fibrinogen Activity

End point title	Classical In Vivo Recovery for Fibrinogen Activity

End point description:

The maximum fibrinogen increase in plasma, per mg/mL plasma volume dosed, within 4 hours of infusion.

End point type	Secondary

End point timeframe:
Pre-infusion to 4 hours post-infusion

End point values	Pharmacokinetic Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: percent				
median (full range (min-max))	61.8 (52.45 to 97.43)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose of study drug up until 44 days after administration of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	Human Fibrinogen Concentrate
Reporting group description:	
All enrolled subjects received a single intravenous infusion of 70 mg/kg body weight of human fibrinogen concentrate.	

Serious adverse events	Human Fibrinogen Concentrate		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Human Fibrinogen Concentrate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2007	Substantial Amendment No. 1 covered the following changes: 1. The time for the analysis of the screening sample was shortened from that given before (at least 4 weeks) to allow the subject to be treated as soon as the confirmed screening results were available. 2. A time specification (1 year prior to enrollment) was added for the exclusion criteria "presence or history of deep vein thrombosis or pulmonary embolism or of arterial thrombosis". This was justified as both conditions can be part of the underlying disease, and it is not medically indicated to exclude patients who have experienced these conditions more than 1 year prior to enrollment. Patients who have thromboembolic events in their medical history will also be in the population that is targeted to be treated with the product, because it is part of the underlying disease. 3. The last virus safety follow-up was changed to Day 45 instead of Month 3 because tests available (PCR) can already assess a potential virus transmission after 45 days. The shorter study period is more convenient for patients and investigators and the validity of the 45 days virus safety follow-up is scientifically equivalent to a 3-month virus safety follow-up. 4. Department name and staff changes were indicated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported