Clinical trial results:
Efficacy and safety of two dose regimens of Octaplex in patients with intracranial haemorrhage related to oral anticoagulant therapy: a multicentre, prospective, randomised, open-label study.

Summary

EudraCT number	2007-000602-73
Trial protocol	FR
Global end of trial date	16 April 2011

Results information

Result version number	v1 (current)
This version publication date	04 January 2017
First version publication date	04 January 2017

Trial information

Trial identification

Sponsor protocol code	LEX-206

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Octapharma France SAS
Sponsor organisation address	62bis Avenue André Morizet, Boulogne-Billancourt, France, 92100
Public contact	Mag. Friedrich W. Kursten , Octapharma Pharmazeutika Produktionsges.m.b.H. , +43 161 032 1245, friedrich.kursten@octapharma.com
Scientific contact	Mag. Friedrich W. Kursten , Octapharma Pharmazeutika Produktionsges.m.b.H. , +43 161 032 1245, friedrich.kursten@octapharma.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 January 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to compare the efficacy of two dose regimens of Octaplex on the INR at 10 ± 5 minutes after the end of injection in patients with intracranial haemorrhage related to oral anticoagulant therapy.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP, and national regulatory requirements. In- and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and safety factors associated with the investigational medicinal product. Throughout the study safety was assessed, such as occurrence of adverse events, lab values, vital signs and physical examinations.

Background therapy:

Octaplex was administered as a single dose, by intravenous infusion. All patients were also given 5 mg vitamin K.

Evidence for comparator:

N.A.

Actual start date of recruitment	07 November 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 59
Worldwide total number of subjects	59
EEA total number of subjects	59

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)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	7
From 65 to 84 years	38
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

Studied Period: FPI 07-NOV-2008 and LPO 16-APR-2011.
In total 59 patients suffering from intracranial haemorrhage related to oral anticoagulant therapy were enrolled from 15 active study sites in France.

Pre-assignment

Screening details:

Patients of 18 years of age or older, Intracranial haemorrhage (intracerebral and acute subdural) confirmed by medical imaging (CT-scan only), use of oral anticoagulant, vitamin K antagonists only, written informed consent from the patient or a legally acceptable representative.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Octaplex 25 IU/kg

Arm description:

Octaplex was administered as a single dose by intravenous infusion (at the standard dose) in accordance with the randomisation. All patients were also given 5 mg vitamin K.
Throughout the stay in the hospital, efficacy and safety assessments were performed at precise time points calculated from the end of Octaplex infusion: The medical part of the study ended on Day 30 (or the last day of hospitalisation if the patient was discharged earlier) after the Octaplex infusion. Three months after the Octaplex infusion, patients had to complete a quality of life (SF-36) and a pharmaco-economic self-questionnaire.

Arm type	Experimental
Investigational medicinal product name	Octaplex
Investigational medicinal product code	ATC B02BD01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard dose (25 IU/kg).
There were only two infusion speed groups: the low (≥3 mL/min and <8 mL/min) and the high (≥8 mL/min) infusion speed group, which included 20 and 39 patients, respectively, in the FAS and 18 and 35 patients, respectively, in the PP Set.

Arm title	Octaplex 40 IU/kg

Arm description:

Octaplex was administered as a single dose by intravenous infusion (at the high dose) in accordance with the randomisation. All patients were also given 5 mg vitamin K. Throughout the stay in the hospital, efficacy and safety assessments were performed at precise time points calculated from the end of Octaplex infusion: The medical part of the study ended on Day 30 (or the last day of hospitalisation if the patient was discharged earlier) after the Octaplex infusion. Three months after the Octaplex infusion, patients had to complete a quality of life (SF-36) and a pharmaco-economic self-questionnaire. less

Arm type	Experimental
Investigational medicinal product name	Octaplex
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

High dose (40 IU/kg).
There were only two infusion speed groups: the low (≥3 mL/min and <8 mL/min) and the high (≥8 mL/min) infusion speed group, which included 20 and 39 patients, respectively, in the FAS and 18 and 35 patients, respectively, in the PP Set.

Number of subjects in period 1	Octaplex 25 IU/kg	Octaplex 40 IU/kg
Started	29	30
Completed	23	22
Not completed	6	8
Adverse event, serious fatal	4	4
Patient transfer	1	2
No benefit to stay at hospital	-	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Octaplex 25 IU/kg

Reporting group description:

Octaplex was administered as a single dose by intravenous infusion (at the standard dose) in accordance with the randomisation. All patients were also given 5 mg vitamin K.
Throughout the stay in the hospital, efficacy and safety assessments were performed at precise time points calculated from the end of Octaplex infusion: The medical part of the study ended on Day 30 (or the last day of hospitalisation if the patient was discharged earlier) after the Octaplex infusion. Three months after the Octaplex infusion, patients had to complete a quality of life (SF-36) and a pharmaco-economic self-questionnaire.

Reporting group title	Octaplex 40 IU/kg

Reporting group description:

Octaplex was administered as a single dose by intravenous infusion (at the high dose) in accordance with the randomisation. All patients were also given 5 mg vitamin K. Throughout the stay in the hospital, efficacy and safety assessments were performed at precise time points calculated from the end of Octaplex infusion: The medical part of the study ended on Day 30 (or the last day of hospitalisation if the patient was discharged earlier) after the Octaplex infusion. Three months after the Octaplex infusion, patients had to complete a quality of life (SF-36) and a pharmaco-economic self-questionnaire. less

Reporting group values	Octaplex 25 IU/kg	Octaplex 40 IU/kg	Total
Number of subjects	29	30	59
Age categorical Units: Subjects			
Adults (18-64 years)	8	4	12
From 65-84 years	18	20	38
85 years and over	3	6	9
Gender categorical Units: Subjects			
Female	10	7	17
Male	19	23	42

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS) - Octaplex 25 IU/kg
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised patients who received at least one infusion of study medication.

Subject analysis set title	Full Analysis Set (FAS) - Octaplex 40 IU/kg
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised patients who received at least one infusion of study medication.

Reporting group values	Full Analysis Set (FAS) - Octaplex 25 IU/kg	Full Analysis Set (FAS) - Octaplex 40 IU/kg	
Number of subjects	29	30	
Age categorical Units: Subjects			
Adults (18-64 years)	8	4	
From 65-84 years	18	20	

85 years and over	3	6	

Gender categorical Units: Subjects			
Female	10	7	
Male	19	23	

End points

End points reporting groups

Reporting group title	Octaplex 25 IU/kg

Reporting group description:

Octaplex was administered as a single dose by intravenous infusion (at the standard dose) in accordance with the randomisation. All patients were also given 5 mg vitamin K.
Throughout the stay in the hospital, efficacy and safety assessments were performed at precise time points calculated from the end of Octaplex infusion: The medical part of the study ended on Day 30 (or the last day of hospitalisation if the patient was discharged earlier) after the Octaplex infusion. Three months after the Octaplex infusion, patients had to complete a quality of life (SF-36) and a pharmaco-economic self-questionnaire.

Reporting group title	Octaplex 40 IU/kg

Reporting group description:

Octaplex was administered as a single dose by intravenous infusion (at the high dose) in accordance with the randomisation. All patients were also given 5 mg vitamin K. Throughout the stay in the hospital, efficacy and safety assessments were performed at precise time points calculated from the end of Octaplex infusion: The medical part of the study ended on Day 30 (or the last day of hospitalisation if the patient was discharged earlier) after the Octaplex infusion. Three months after the Octaplex infusion, patients had to complete a quality of life (SF-36) and a pharmaco-economic self-questionnaire. less

Subject analysis set title	Full Analysis Set (FAS) - Octaplex 25 IU/kg
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised patients who received at least one infusion of study medication.

Subject analysis set title	Full Analysis Set (FAS) - Octaplex 40 IU/kg
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised patients who received at least one infusion of study medication.

Primary: INR at 10 +/- 5 minutes

End point title	INR at 10 +/- 5 minutes[1]

End point description:

The primary study objective was to compare the efficacy of two dose regimens of Octaplex on the INR (International normalised ratio) at 10 ± 5 minutes after the end of injection in patients with intracranial haemorrhage related to oral anticoagulant therapy.

End point type	Primary

End point timeframe:

after the end of injection

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: No inferential statistical analysis was pre-planned for this study, but the endpoint was to be presented descriptively only.

End point values	Full Analysis Set (FAS) - Octaplex 25 IU/kg	Full Analysis Set (FAS) - Octaplex 40 IU/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27[2]	29[3]		
Units: INR at 10 +/- 5 min				
arithmetic mean (standard deviation)	1.26 (± 0.13)	1.16 (± 0.1)		

Notes:
[2] - there were missing values for primary endpoint data in 3 patients, which were not replaced.
[3] - there were missing values for primary endpoint data in 3 patient, which were not replaced.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed throughout the whole study.

Adverse event reporting additional description:

All SAEs, whether suspected to be related to study treatment or not, are reported by telephone, fax or e-mail immediately to the responsible Clinical Project Manager, study monitor, or to the responsible local CRO.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Octaplex 25 IU/kg

Reporting group description:

Octaplex was administered as a single dose by intravenous infusion (at the standard dose) in accordance with the randomisation. All patients were also given 5 mg vitamin K.
Throughout the stay in the hospital, efficacy and safety assessments were performed at precise time points calculated from the end of Octaplex infusion: The medical part of the study ended on Day 30 (or the last day of hospitalisation if the patient was discharged earlier) after the Octaplex infusion. Three months after the Octaplex infusion, patients had to complete a quality of life (SF-36) and a pharmaco-economic self-questionnaire.

Reporting group title	Octaplex 40 IU/kg

Reporting group description:

Octaplex was administered as a single dose by intravenous infusion (at the high dose) in accordance with the randomisation. All patients were also given 5 mg vitamin K. Throughout the stay in the hospital, efficacy and safety assessments were performed at precise time points calculated from the end of Octaplex infusion: The medical part of the study ended on Day 30 (or the last day of hospitalisation if the patient was discharged earlier) after the Octaplex infusion. Three months after the Octaplex infusion, patients had to complete a quality of life (SF-36) and a pharmaco-economic self-questionnaire. less

Serious adverse events	Octaplex 25 IU/kg	Octaplex 40 IU/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 29 (37.93%)	12 / 30 (40.00%)	
number of deaths (all causes)	4	6	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			

subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem ischaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral Haematoma			
subjects affected / exposed	3 / 29 (10.34%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hydorcephalus			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial haematoma			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intracranial pressure increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic Stroke			

subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hypercoagulation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Brain death			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			

subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Endocarditis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Octaplex 25 IU/kg	Octaplex 40 IU/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 29 (82.76%)	25 / 30 (83.33%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 29 (10.34%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	3 / 29 (10.34%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Pain			

subjects affected / exposed	4 / 29 (13.79%)	3 / 30 (10.00%)	
occurrences (all)	4	3	
Pyrexia			
subjects affected / exposed	2 / 29 (6.90%)	4 / 30 (13.33%)	
occurrences (all)	2	4	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Pneumonia aspiration			
subjects affected / exposed	1 / 29 (3.45%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Pulmonary congestion			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	3 / 29 (10.34%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Anxiety			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Confusional state			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	3	
Depression			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Insomnia			
subjects affected / exposed	1 / 29 (3.45%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Nervous system disorders			

Cerebral haematoma			
subjects affected / exposed	3 / 29 (10.34%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Cerebral haemorrhage			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Ischaemic stroke			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Nervous system disorder			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Somnolence			
subjects affected / exposed	2 / 29 (6.90%)	3 / 30 (10.00%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Leukocytosis			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
ABdominal pain			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	11 / 29 (37.93%)	4 / 30 (13.33%)	
occurrences (all)	11	4	
Diarrhoea			
subjects affected / exposed	3 / 29 (10.34%)	4 / 30 (13.33%)	
occurrences (all)	3	5	
Vomiting			
subjects affected / exposed	3 / 29 (10.34%)	6 / 30 (20.00%)	
occurrences (all)	3	7	
Skin and subcutaneous tissue disorders			

Decubitus ulcer			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Erythema			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Renal failure acute			
subjects affected / exposed	1 / 29 (3.45%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Urinary retention			
subjects affected / exposed	3 / 29 (10.34%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Fungal skin infection			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Urinary tract infection			
subjects affected / exposed	5 / 29 (17.24%)	3 / 30 (10.00%)	
occurrences (all)	5	3	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	6 / 29 (20.69%)	3 / 30 (10.00%)	
occurrences (all)	6	3	
Hypokalaemia			
subjects affected / exposed	2 / 29 (6.90%)	4 / 30 (13.33%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2008	Amendment No. 1 • The CT scan imaging technique only was allowed at inclusion to confirm diagnosis and at 48 hours to evaluate the haematoma volume. The same technique had to be used at inclusion and 48 hours. If CT scan and MRI are commonly used to confirm diagnosis, CT scan is preferred at 48 hours for control imaging. • Modification of the exclusion criteria: Some exclusion criteria needed an explanation for a better understanding. General seizure has been deleted as they are frequently associated with intracranial haemorrhage. • Modification of Octaplex administration: According to Scientific Committee members request (Pr P. Coriat, principal investigator and Pr B. Riou, investigator, Dr B. Vigué and Pr. C Négrier), an additional Octaplex dose could be administered at 10 ± 5 minutes and at 6 hours after the first Octaplex infusion, following precise recommendation and not at the discretion of the investigator. The recommendation was 1.5 as target INR for the first rescue dose. The table has been simplified to facilitate the additional dose calculation by the investigators. • Modification of Octaplex infusion rate: The context of very high emergency implies to shorten all the delays in patient care including treatment administration. • Update of information on Octaplex storage (new Octaplex variation approved by reference member state via Mutual Recognition Procedure in 30-Nov-2007). • New laboratory parameters: Digital glucose was performed instead of being analysed in the laboratory. Additional laboratory tests were done (liver function, haematology) in order to follow the overall safety data.
30 June 2008	Amendment No. 2 • Modification of the informed consent procedure: The previous procedure was not adapted to the emergency situation. According to the law, in emergency situations, if prior informed consent of the patient is not possible and the patient's legally acceptable representative is not available, the patient can be enrolled without prior informed consent. The informed consent procedure was modified in consequence: if the patient's legally acceptable representative was not available, the patient could be included by the investigator in presence of a witness independent from the investigator and the Sponsor. • Because of the change of the informed consent procedure, the patient concomitant disability could not be assessed by the physician if the patient's legally acceptable representative was absent. This exclusion criterion was thus suppressed. • Population of the study better defined: The type of intracranial haemorrhage has been precisely defined for a better understanding.

22 August 2008	Amendment No. 3 • Modification of biological analyses: Some of the centralised analyses (fibrin degradation products and thrombin-prothrombin complexes) have been cancelled with the agreement of the central laboratory, in order to lighten plasma tubes preparation for local laboratories. Moreover, central laboratory analyses were only to be performed in the centres that possessed laboratory facilities (adequate devices and personnel during night and day) to prepare plasma tubes. The laboratory parameters analysis was performed locally or centrally upon local laboratory facilities. • ECG surveillance: ECG is monitored continuously during the whole stay in the investigator's ward, thus the surveillance at 48 hours was added. • Modification of the determination of sample size based on the results obtained from previous studies with Octaplex. • Precision of the anticoagulant therapy: The type of anticoagulant therapy has been added. Only patients under vitamin K antagonist therapy were admitted. • Precision of the type of subdural haematoma: Only patients with acute subdural haematoma were admitted. This criterion was assessed by CT scan.
17 December 2008	Amendment No. 5 • Change of Sponsor: Octapharma France SAS (Boulogne-Billancourt, France) replaced Octapharma AG (Lachen, Switzerland). • Modification of the sample labels for investigational medicinal products: Addition of FIX content in Octaplex and change of Sponsor. • Modification of the study duration: Due to the late clinical study start, the study duration was prolonged accordingly.
03 August 2009	Amendment No. 6 • In the entire text, thrombin generation assay (TGA) analysis was suppressed. The results of TGA analysis in the first patients included in the study were not interpretable due to a bad plasma preparation. As this test was still experimental, it was decided to stop this analysis in agreement with Pr Negrier (Head of Central Laboratory). • In the entire text, a time window of 15 minutes before and 15 minutes after the fixed time points 1 hour, 3 hours, 6 hours and 24 hours was added. As this study was carried out in a context of emergency, it appeared that greater flexibility in the times of blood sample collection was appropriate to avoid protocol deviations and give more comfort to the investigator during the care of patient. • In the entire text, the National Institute of Health (NIH) stroke scale was suppressed. As the NIH stroke scale was not usually used by most study investigators and requires a specific training, it was decided to not perform this scale anymore. Alternatively, the neurological worsening was assessed by a routine neurological examination. • An English translation, certified by a sworn translator, of the Informed consent and the Patient information approved by the IEC on 01-Jul-2008 was added to Appendix 2 of the protocol. This translation was supplied, for information, to two patients speaking English.
18 November 2009	Amendment No. 7 • Modification of the study duration: Due to a recruitment rate below what was expected, the duration of the study had to be extended accordingly.
15 September 2010	Amendment No. 8 • Modification of the study duration: Due to a recruitment rate below what was expected, the duration of the study had to be extended accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported