Clinical trial results:
A Phase 2/3, multicenter, open-label clinical study to assess the safety and efficacy of BAY86-6150 in subjects with hemophilia A or B with inhibitors, composed of 2 Parts (A & B). Part A: Sequential cohorts of four dose levels of the modified rFVIIa BAY86-6150 assessed in a non-controlled dose response design in acutely bleeding subjects and for PK/ PD in an intra-individual crossover design compared with one fixed dose of eptacog alfa (activated) in non-bleeding subjects. Part B: Confirmatory study to further investigate the efficacy and safety of BAY86-6150.

Summary

EudraCT number	2011-000323-33
Trial protocol	DE HU PL DK IT
Global end of trial date	24 March 2014

Results information

Result version number	v2 (current)
This version publication date	08 September 2016
First version publication date	26 July 2015
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY86-6150/15534

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01625390
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	24 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Part A:
- To identify the recommended dose by conducting a risk-benefit assessment of four different dose levels of BAY86-6150 based on safety and dose response assessments in acutely bleeding subjects with hemophilia A or B with inhibitors.
Part B:
- To further investigate the safety and efficacy of the recommended dose of BAY86-6150 in acutely bleeding subjects with hemophilia A or B with inhibitors.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 June 2012
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	Bulgaria: 3
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	South Africa: 5
Worldwide total number of subjects	10
EEA total number of subjects	3

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)	1
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 8 study centers in Bulgaria, Korea, Poland, Singapore, Turkey, Ukraine, and South Africa. Overall, subjects enrolled in 3 countries (Bulgaria, Singapore and South Africa) were assigned to treatment. The study was conducted between 21 June 2012 (first subject first visit) and 24 March 2014 (last subject last visit).

Pre-assignment

Screening details:

Study was composed of
Part A: 4 dose levels were to be evaluated sequentially,
Part B: subjects were to be treated with the recommended dose level of BAY86-6150.
However, the study was prematurely discontinued due to safety reasons and only 10 out of 20 enrolled subjects were treated with an initial dose of 6.5 microgram per kilogram.

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	Experimental, modified rFVIIa (BAY86-6150)

Arm description:

Subjects received targeted intravenous injection of modified recombinant human Factor VIIa (rFVIIa) (BAY86-6150) at an initial dose of 6.5 microgram per kilogram. Dose was escalated as per investigator's discretion or until the highest dose level was completed.

Arm type	Experimental
Investigational medicinal product name	Modified recombinant human Factor VIIa (rFVIIa)
Investigational medicinal product code	BAY86-6150
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received targeted intravenous injection of modified rFVIIa (BAY86-6150) at an initial dose of 6.5 microgram per kilogram. Dose was escalated as per investigator's discretion or until the highest dose level was completed.

Number of subjects in period 1	Experimental, modified rFVIIa (BAY86-6150)
Started	10
Completed	0
Not completed	10
Consent withdrawn by subject	1
Study terminated by sponsor	9

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Subjects received targeted intravenous injection of modified recombinant human Factor VIIa (rFVIIa) (BAY86-6150) at an initial dose of 6.5 microgram per kilogram. Dose was escalated as per investigator's discretion or until the highest dose level was completed.

Reporting group values	Overall Study	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	27.4		
standard deviation	± 8.2	-	
Gender categorical Units: Subjects			
Male	10	10	

End points

End points reporting groups

Reporting group title	Experimental, modified rFVIIa (BAY86-6150)

Reporting group description:

Subjects received targeted intravenous injection of modified recombinant human Factor VIIa (rFVIIa) (BAY86-6150) at an initial dose of 6.5 microgram per kilogram. Dose was escalated as per investigator's discretion or until the highest dose level was completed.

Primary: Number of Subjects with Successful Treatments of Bleeding Episodes

End point title	Number of Subjects with Successful Treatments of Bleeding Episodes[1]

End point description:

The successful treatment was defined by "No rescue medication administered".

End point type	Primary

End point timeframe:

Baseline up to the last injection of BAY86-6150

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: Data was not analysed as the study was terminated due to safety reasons and hence, statistical analysis was not performed.

End point values	Experimental, modified rFVIIa (BAY86-6150)			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: subjects				

Notes:

[2] - Data was not analysed as the study was terminated due to safety reasons.

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of Successful Treatments of Bleeding Episodes on Subject Level

End point title	Proportion of Successful Treatments of Bleeding Episodes on Subject Level[3]

End point description:

The individual success rate was calculated as the number of bleeding episodes treated successfully (without rescue medication) divided by the total number of bleeding episodes experienced on a dose level. A responder was defined as at least 70% of bleeding episodes treated without rescue medication.

End point type	Primary

End point timeframe:

Baseline up to the last injection of BAY86-6150

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: Data was not analysed as the study was terminated due to safety reasons and hence, statistical analysis was not performed.

End point values	Experimental, modified rFVIIa (BAY86-6150)			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: percentage of successful treatment				
number (not applicable)				

Notes:

[4] - Data was not analysed as the study was terminated due to safety reasons.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Needed to Stop the Bleeding Episode

End point title	Number of Injections Needed to Stop the Bleeding Episode

End point description:

The number of injections needed to stop the bleeding episodes were calculated as total number of injections given divided by the total number of bleeds. In case rescue medication was given, the number of injections was set to 3, regardless of how many applications of rescue medication were applied.

End point type	Secondary

End point timeframe:

Baseline up to the last injection of BAY86-6150

End point values	Experimental, modified rFVIIa (BAY86-6150)			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: injections				

Notes:

[5] - Data was not analysed as the study was terminated due to safety reasons.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Stop the Bleed

End point title	Time to Stop the Bleed

End point description:

The time to stop a bleeding episode was assessed as the period between the onset of bleeding and the complete cessation of the bleeding episode as assessed by the subject. Analyses were decided to perform using life table methods.
Subjects assessed the cessation of a bleeding episode based on their long-term experiences coping with bleeds since childhood.

End point type	Secondary

End point timeframe:

Baseline up to the last injection of BAY86-6150

End point values	Experimental, modified rFVIIa (BAY86-6150)			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: hours				
arithmetic mean (standard deviation)	()			

Notes:

[6] - Data was not analysed as the study was terminated due to safety reasons.

Statistical analyses

No statistical analyses for this end point

Secondary: Subject’s Efficacy Assessment

End point title	Subject’s Efficacy Assessment

End point description:

The effective response to treatment as rated by the subject’s assessment was determined according to: “Please rate the effectiveness (for example, cessation of bleed, pain, tenderness, size of hemorrhage, swelling and joint mobility) of the treatment as per your assessment: Very effective; Effective; Partially effective; Not effective".

End point type	Secondary

End point timeframe:

After every acute bleeding episode or every other week up to 14 days after last exposure to BAY 86-6150

End point values	Experimental, modified rFVIIa (BAY86-6150)			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: units on a scale				
number (not applicable)				

Notes:

[7] - Data was not analysed as the study was terminated due to safety reasons.

Statistical analyses

No statistical analyses for this end point

Secondary: Euro Quality of Life-5 Dimension (EQ-5D)

End point title	Euro Quality of Life-5 Dimension (EQ-5D)

End point description:

Health related quality of life (HRQoL) was assessed using the self administered Euro-QoL (EQ-5D). EQ-5D is a participant answered questionnaire scoring 5 dimensions - mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D is a validated, generic preference based measure of health widely used in health economic calculations. Subjects rated their general health using the EQ-5D.

The EQ-5D total score ranges from 0 (worst imaginable health state) to 100 (best imaginable health state which is also the best possible outcome).

End point type	Secondary

End point timeframe:

Baseline up to 14 days after last exposure to BAY86-6150

End point values	Experimental, modified rFVIIa (BAY86-6150)			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: units on a scale				
number (not applicable)				

Notes:

[8] - Data was not analysed as the study was terminated due to safety reasons.

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Pain Inventory (BPI) Score

End point title	Brief Pain Inventory (BPI) Score

End point description:

Brief Pain Inventory - Short Form (BPI-SF) allows subjects to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function (e.g., general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). BPI-SF was a 15-item, self-administered, clinically valid, reliable and responsive measure developed to assess pain. BPI-SF was typically scored by averaging the pain severity score and overall pain interference score. Scores range from 0-10 and a higher score indicates a higher level of pain/interference.

End point type	Secondary

End point timeframe:

Baseline up to 14 days after last exposure to BAY86-6150

End point values	Experimental, modified rFVIIa (BAY86-6150)			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: units on a scale				
number (not applicable)				

Notes:

[9] - Data was not analysed as the study was terminated due to safety reasons.

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Pain Inventory (BPI) Score: Item 3 and 6

End point title	Brief Pain Inventory (BPI) Score: Item 3 and 6

End point description:

The effectiveness of BAY 86-6150 in alleviating the subject's pain through bleed resolution was assessed by the subjects using Items 3 and 6 of the BPI-SF measure.
Item 3: "Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours." Score range from 0-10 and a higher score indicates a higher level of pain. It was completed by the subject in an e-diary prior to the first injection of BAY 86-6150 and every night for 7 days following the start of the bleed that was treated with BAY 86-6150.
Item 6: "Please rate your pain by circling the one number that tells how much pain you have right now." Score range from 0-10 and a higher score indicates a higher level of pain. It was completed by the subject in an e-diary prior to the first injection of BAY 86-6150. Item 6 was then completed at every hour for 6 hours following an injection of BAY 86-6150 but before the use of rescue medication (that is, if rescue medication was required).

End point type	Secondary

End point timeframe:

Pre-injection, every night for a week after any BAY86-6150 injection for Item 3
Pre-injection, 1, 2, 3, and 4 hours after administration of BAY86-6150 for Item 6

End point values	Experimental, modified rFVIIa (BAY86-6150)			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: units on a scale				
number (not applicable)				

Notes:

[10] - Data was not analysed as the study was terminated due to safety reasons.

Statistical analyses

No statistical analyses for this end point

Secondary: Work Productivity and Activity Impairment (WPAI) Questionnaire

End point title	Work Productivity and Activity Impairment (WPAI) Questionnaire

End point description:

The effect of hemophilia on the subject's ability to work and perform regular activities was evaluated by determination of a WPAI in adult subjects only.
Six-items that assess impairment in work productivity and daily activity during the 7 days before the assessment. It measures the percentage of overall impairment in work productivity and daily activity due to hemophilia. A WPAI score of 0% = no impairment and a score of 100% = total loss of work productivity or activity.

End point type	Secondary

End point timeframe:

Baseline, within 24 to 48 hours after the 2nd treatment with BAY86-6150, after every 5th exposure day to BAY86-6150, 14 days after last exposure to BAY86-6150

End point values	Experimental, modified rFVIIa (BAY86-6150)			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: percent total impairment				
number (not applicable)				

Notes:

[11] - Data was not analysed as the study was terminated due to safety reasons.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 14 days after last exposure to BAY86-6150

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Experimental, modified rFVIIa (BAY86-6150)

Reporting group description:

Subjects received targeted intravenous injection of modified recombinant human Factor VIIa (rFVIIa)(BAY86-6150) at an initial dose of 6.5 microgram per kilogram. Dose was escalated as per investigator'sdiscretion or until the highest dose level was completed.

Serious adverse events	Experimental, modified rFVIIa (BAY86-6150)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Anti factor VII antibody positive			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemophilic arthropathy			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acute hepatitis B			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral candidiasis			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Experimental, modified rFVIIa (BAY86-6150)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Eye injury			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia paroxysmal			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastritis			

subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Renal and urinary disorders Urine abnormality subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Infections and infestations Acute tonsillitis alternative assessment type: Systematic subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2012	The amendment was prepared in response to the comments by the Medical and Healthcare Products Regualtory Agency (MHRA) in the United Kingdom. The required changes led to modifications of the stopping rules for subjects in the study who experienced drug related adverse events. - The Common Terminology Criteria for Adverse Events (CTCAE) grading has been removed and replaced with more specific description of relevant clinical conditions. - Exclusion criterion was modified to clarify that besides activated Prothrombin Complex Concentrates (“aPCC”) also non-activated Prothrombin Complex Concentrates (“PCC”) were allowed to be administered during the study period. - The text was added as, hypersensitivity adverse events that could occur with any injected protein under definition of serious adverse event. - The dose of study medication for a subject would be de-escalated to the next lower level or withdrawn from the study if two or more drug-related severe adverse events or or a single drug-related serious adverse event occurred in a subject.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 April 2013	The recruitment and sequential cohorts of four dose levels in an intra-individual crossover design of Part A and Part B of the study were prematurely terminated due to development of neutralizing and cross-reacting antibodies to eptacog alfa (activated) which was a pre-specified withdrawal criterion in the study protocol.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Results for primary or secondary endpoints were not able to be reported as the study was prematurely terminated due to safety reasons.

Notes: