Clinical trial results:
Antihemophilic Factor (Recombinant) Plasma/Albumin-Free Method (rAHF PFM): A Phase 3/4, Prospective, Controlled, Randomized, Multi-Center Study to Compare the Efficacy and Safety of Continuous Infusion (CI) versus Intermittent Bolus Infusion (BI) in Subjects with Severe or Moderately Severe Hemophilia A Undergoing Major Orthopedic Surgery

Summary

EudraCT number	2005-005697-71
Trial protocol	AT SE BE PT ES HU NL GB IT PL
Global end of trial date	09 December 2015

Results information

Result version number	v1 (current)
This version publication date	23 December 2016
First version publication date	23 December 2016

Trial information

Trial identification

Sponsor protocol code	060402

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00357656
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxalta US Inc.
Sponsor organisation address	One Baxter Way, Westlake Village, United States, CA 91362
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com
Sponsor organisation name	Baxalta Innovations GmbH
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, 1221
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to compare the hemostatic efficacy of continuous infusion versus intermittent bolus infusion in the peri- and post-operative setting employing ADVATE (rAHF-PFM) in previously treated patients (PTPs) with severe or
moderately severe hemophilia A (baseline FVIII level less or equal to 2% of normal) undergoing elective unilateral major orthopedic surgery that requires drain placement by assessing the cumulative packed red blood cell (PRBC) volume in the drainage fluid during the first 24 hours following surgery.

Protection of trial subjects:

This study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2006
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	United States: 4
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Poland: 13
Worldwide total number of subjects	72
EEA total number of subjects	41

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)	72
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment was conducted at 22 clinical sites in 12 countries (Austria, France, Hungary, Italy, Norway, Poland, Portugal, Romania, Russia, Spain, The Netherlands, USA). Of 85 subjects enrolled, 72 subjects participated in a PK study in the preoperative period; 63 subjects were then randomized to treatment by continuous or bolus infusion.

Pre-assignment

Screening details:

Of 85 subjects enrolled, 15 were screen failures, 4 were discontinued on the basis of the PK study in the preoperative period, 1 subject died, 1 was discontinued by physician decision (imprisonment), and 1 was discontinued per sponsor decision. Eventually, 63 subjects were randomized to treatment by continuous (n=32) or bolus infusion (n=31).

Pre-assignment period milestones

Number of subjects started	72
Intermediate milestone: Number of subjects	PK infusion: 72
Number of subjects completed	63

Pre-assignment subject non-completion reasons

Reason: Number of subjects	PK results: 4
Reason: Number of subjects	Physician decision (imprisonment): 1
Reason: Number of subjects	Sponsor decision: 1
Reason: Number of subjects	Death: 1
Reason: Number of subjects	Screen failure: 2

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	Treatment by Continuous infusion

Arm description:

This reporting group comprises all 32 subjects in the Full Analysis Set who were randomized to receive ADVATE (rAHF-PFM) by continuous infusion (CI).

Arm type	Experimental
Investigational medicinal product name	Advate
Investigational medicinal product code	
Other name	rAHF-PFM (Antihemophilic Factor (Recombinant) - Plasma/Albumin Free Method)
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects initially underwent a pharmacokinetic (PK) evaluation with ADVATE (dose: 50 IU ± 5 IU/kg). Prior to surgery, subjects received a loading dose with ADVATE (based on subject´s PK profile), to maintain a minimum target FVIII level of at least 80% of normal. After the loading dose(s), subjects received ADVATE either as intermittent bolus infusion (BI) or as continuous infusion (CI). The dose

recommendations were provided by the sponsor and were based on the subject´s PK profile. For safety reasons, all subjects were to receive a rebolus in the recovery room to compensate for perioperative blood loss and increased FVIII consumption. The following minimum FVIII levels were to be targeted for both CI and BI treatment: at least 80% of normal for the first 72 hours after the initial loading dose, then at least 50% of normal until postoperative Day 7. For CI, ADVATE was to be administered with a syringe pump (infusion rate according to dosing regimen).

Arm title	Treatment by Bolus infusion

Arm description:

This reporting group comprises all 31 subjects in the Full Analysis Set who were randomized to receive ADVATE (rAHF-PFM) by intermittent bolus infusion (BI).

Arm type	Experimental
Investigational medicinal product name	Advate
Investigational medicinal product code	
Other name	rAHF-PFM (Antihemophilic Factor (Recombinant) - Plasma/Albumin Free Method)
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects initially underwent a pharmacokinetic (PK) evaluation with ADVATE (dose: 50 IU ± 5 IU/kg). Prior to surgery, subjects received a loading dose with ADVATE (based on subject´s PK profile), to maintain a minimum target FVIII level of at least 80% of normal. After the loading dose(s), subjects received ADVATE either as intermittent bolus infusion (BI) or as continuous infusion (CI). The dose recommendations were provided by the sponsor and were based on the subject´s PK profile. For safety reasons, all subjects were to receive a rebolus in the recovery room to compensate for perioperative blood loss and increased FVIII consumption. The following minimum FVIII levels were to be targeted for both CI and BI treatment: at least 80% of normal for the first 72 hours after the initial loading dose, then at least 50% of normal until postoperative Day 7. For CI, ADVATE was to be administered with a syringe pump (infusion rate according to dosing regimen).

Number of subjects in period 1[1]	Treatment by Continuous infusion	Treatment by Bolus infusion
Started	32	31
Completed	29	31
Not completed	3	0
No surgery performed	3	-

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: Of 85 subjects enrolled, 72 subjects participated in a PK evaluation in the preoperative period; 63 subjects were then randomized to treatment by continuous or bolus infusion.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment by Continuous infusion
Reporting group description:	
This reporting group comprises all 32 subjects in the Full Analysis Set who were randomized to receive ADVATE (rAHF-PFM) by continuous infusion (CI).	
Reporting group title	Treatment by Bolus infusion
Reporting group description:	
This reporting group comprises all 31 subjects in the Full Analysis Set who were randomized to receive ADVATE (rAHF-PFM) by intermittent bolus infusion (BI).	

Reporting group values	Treatment by Continuous infusion	Treatment by Bolus infusion	Total
Number of subjects	32	31	63
Age categorical Units: Subjects			
Adults (18-64 years)	32	31	63
Age continuous Units: years			
log mean	39	38.6	
standard deviation	± 11.52	± 9.76	-
Gender categorical Units:			
Male	32	31	63
Female	0	0	0

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) comprises all subjects who were randomized to receive bolus infusion (BI) or continuous infusion (CI) of ADVATE (rAHF-PFM).	
Subject analysis set title	Full Analysis Set - Continuous Infusion (CI)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set comprises all subjects in the Full Analysis Set (FAS) who were randomized to receive continuous infusion (CI) of ADVATE (rAHF-PFM). This analysis set is identical to Reporting Group 1 (Treatment by Continuous Infusion).	
Subject analysis set title	Full Analysis Set - Bolus Infusion (BI)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set comprises all subjects in the FAS who were randomized to receive bolus infusion (BI) of ADVATE (rAHF-PFM). This analysis set is identical to Reporting Group 2 (Treatment by Bolus Infusion).	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set (SAS) comprises all subjects treated with at least one ADVATE (rAHF-PFM) dose. All safety analyses were performed on the SAS.	
Subject analysis set title	Per Protocol Analysis Set

Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Analysis Set (PPAS) comprises all subjects who were randomized to receive BI or CI of ADVATE (rAHF-PFM) and have observed drainage volumes up to 24 hours including hematocrit results for these drainage fluids.

Subject analysis set title	Per Protocol Analysis Set - CI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set comprises all subjects in the PPAS who were randomized to receive CI of ADVATE (rAHF-PFM) and have observed drainage volumes up to 24 hours including hematocrit results for these drainage fluids.

Subject analysis set title	Per Protocol Analysis Set - BI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set comprises all subjects in the PPAS who were randomized to receive BI of ADVATE (rAHF-PFM) and have observed drainage volumes up to 24 hours including hematocrit results for these drainage fluids.

Subject analysis set title	Pharmacokinetic (PK) Full Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK Full Analysis Set (PKFAS) consists of all subjects who had a PK evaluation. If a subject had a repeat PK, the PK parameters of all evaluations were to be listed, but only the last value was to be used for summary statistics. This analysis set is identical to the Full Analysis Set (FAS).

Subject analysis set title	PKFAS - CI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set comprises all subjects in the PKFAS who had a PK evaluation and were randomized to CI. This analysis set is identical to the FAS - CI.

Subject analysis set title	PKFAS - BI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set comprises all subjects in the PKFAS who had a PK evaluation and were randomized to BI. This analysis set is identical to the FAS - BI.

Subject analysis set title	Stratum A - CI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum A (CI) includes subjects in the per-protocol analysis set who underwent unilateral knee replacement and were treated by continuous infusion.

Subject analysis set title	Stratum B - CI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum B (CI) includes subjects in the per-protocol analysis set who underwent hip surgery and were treated by continuous infusion.

Subject analysis set title	Stratum C - CI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum C (CI) includes subjects in the per-protocol analysis set who underwent shoulder/elbow/ankle/knee (except knee replacement) surgery and were treated by continuous infusion.

Subject analysis set title	Stratum A - BI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum A (BI) includes subjects in the per-protocol analysis set who underwent unilateral knee replacement and were treated by bolus infusion.

Subject analysis set title	Stratum B - BI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum B (BI) includes subjects in the per-protocol analysis set who underwent hip surgery and were treated by bolus infusion.

Subject analysis set title	Stratum C - BI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum C (BI) includes subjects in the per-protocol analysis set who underwent shoulder/elbow/ankle/knee (except knee replacement) surgery and were treated by bolus infusion.

Reporting group values	Full Analysis Set	Full Analysis Set - Continuous Infusion (CI)	Full Analysis Set - Bolus Infusion (BI)
Number of subjects	63	32	31
Age categorical Units: Subjects			
Adults (18-64 years)	63	32	31
Age continuous Units: years			
log mean	38.8	39	38.6
standard deviation	± 10.61	± 11.52	± 9.76
Gender categorical Units:			
Male	63	32	31
Female	0	0	0

Reporting group values	Safety Analysis Set	Per Protocol Analysis Set	Per Protocol Analysis Set - CI
Number of subjects	72	60	29
Age categorical Units: Subjects			
Adults (18-64 years)	72	60	29
Age continuous Units: years			
log mean	38.6	38.7	38.8
standard deviation	± 10.49	± 10.69	± 11.77
Gender categorical Units:			
Male	72	60	29
Female	0	0	0

Reporting group values	Per Protocol Analysis Set - BI	Pharmacokinetic (PK) Full Analysis Set	PKFAS - CI
Number of subjects	31	63	32
Age categorical Units: Subjects			
Adults (18-64 years)	31	63	32
Age continuous Units: years			
log mean	38.6	38.8	39
standard deviation	± 9.76	± 10.61	± 11.52
Gender categorical Units:			
Male	31	63	32

Female	0	0	0

Reporting group values	PKFAS - BI	Stratum A - CI	Stratum B - CI
Number of subjects	31	24	2
Age categorical Units: Subjects			
Adults (18-64 years)	31	24	2
Age continuous Units: years log mean standard deviation	 38.6 ± 9.76	 38.4 ± 10.95	 47 ± 14.14
Gender categorical Units:			
Male	31	24	2
Female	0	0	0

Reporting group values	Stratum C - CI	Stratum A - BI	Stratum B - BI
Number of subjects	3	24	2
Age categorical Units: Subjects			
Adults (18-64 years)	3	24	2
Age continuous Units: years log mean standard deviation	 36.3 ± 19.6	 37.5 ± 9.06	 55.5 ± 3.54
Gender categorical Units:			
Male	3	24	2
Female	0	0	0

Reporting group values	Stratum C - BI		
Number of subjects	5		
Age categorical Units: Subjects			
Adults (18-64 years)	5		
Age continuous Units: years log mean standard deviation	 37.2 ± 9.34		
Gender categorical Units:			
Male	5		
Female	0		

End points

End points reporting groups

Reporting group title	Treatment by Continuous infusion
Reporting group description:	
This reporting group comprises all 32 subjects in the Full Analysis Set who were randomized to receive ADVATE (rAHF-PFM) by continuous infusion (CI).	
Reporting group title	Treatment by Bolus infusion
Reporting group description:	
This reporting group comprises all 31 subjects in the Full Analysis Set who were randomized to receive ADVATE (rAHF-PFM) by intermittent bolus infusion (BI).	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) comprises all subjects who were randomized to receive bolus infusion (BI) or continuous infusion (CI) of ADVATE (rAHF-PFM).	
Subject analysis set title	Full Analysis Set - Continuous Infusion (CI)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set comprises all subjects in the Full Analysis Set (FAS) who were randomized to receive continuous infusion (CI) of ADVATE (rAHF-PFM). This analysis set is identical to Reporting Group 1 (Treatment by Continuous Infusion).	
Subject analysis set title	Full Analysis Set - Bolus Infusion (BI)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set comprises all subjects in the FAS who were randomized to receive bolus infusion (BI) of ADVATE (rAHF-PFM). This analysis set is identical to Reporting Group 2 (Treatment by Bolus Infusion).	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set (SAS) comprises all subjects treated with at least one ADVATE (rAHF-PFM) dose. All safety analyses were performed on the SAS.	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Analysis Set (PPAS) comprises all subjects who were randomized to receive BI or CI of ADVATE (rAHF-PFM) and have observed drainage volumes up to 24 hours including hematocrit results for these drainage fluids.	
Subject analysis set title	Per Protocol Analysis Set - CI
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set comprises all subjects in the PPAS who were randomized to receive CI of ADVATE (rAHF-PFM) and have observed drainage volumes up to 24 hours including hematocrit results for these drainage fluids.	
Subject analysis set title	Per Protocol Analysis Set - BI
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This analysis set comprises all subjects in the PPAS who were randomized to receive BI of ADVATE (rAHF-PFM) and have observed drainage volumes up to 24 hours including hematocrit results for these drainage fluids.	
Subject analysis set title	Pharmacokinetic (PK) Full Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PK Full Analysis Set (PKFAS) consists of all subjects who had a PK evaluation. If a subject had a repeat PK, the PK parameters of all evaluations were to be listed, but only the last value was to be used	

for summary statistics. This analysis set is identical to the Full Analysis Set (FAS).

Subject analysis set title	PKFAS - CI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set comprises all subjects in the PKFAS who had a PK evaluation and were randomized to CI. This analysis set is identical to the FAS - CI.

Subject analysis set title	PKFAS - BI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set comprises all subjects in the PKFAS who had a PK evaluation and were randomized to BI. This analysis set is identical to the FAS - BI.

Subject analysis set title	Stratum A - CI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum A (CI) includes subjects in the per-protocol analysis set who underwent unilateral knee replacement and were treated by continuous infusion.

Subject analysis set title	Stratum B - CI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum B (CI) includes subjects in the per-protocol analysis set who underwent hip surgery and were treated by continuous infusion.

Subject analysis set title	Stratum C - CI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum C (CI) includes subjects in the per-protocol analysis set who underwent shoulder/elbow/ankle/knee (except knee replacement) surgery and were treated by continuous infusion.

Subject analysis set title	Stratum A - BI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum A (BI) includes subjects in the per-protocol analysis set who underwent unilateral knee replacement and were treated by bolus infusion.

Subject analysis set title	Stratum B - BI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum B (BI) includes subjects in the per-protocol analysis set who underwent hip surgery and were treated by bolus infusion.

Subject analysis set title	Stratum C - BI
Subject analysis set type	Per protocol

Subject analysis set description:

Stratum C (BI) includes subjects in the per-protocol analysis set who underwent shoulder/elbow/ankle/knee (except knee replacement) surgery and were treated by bolus infusion.

Primary: Cumulative packed red blood cell (PRBC) volume in the drainage fluid during the first 24 hours following surgery in subjects receiving ADVATE (rAHF-PFM) by bolus (BI) or continuous infusion (CI)

End point title	Cumulative packed red blood cell (PRBC) volume in the drainage fluid during the first 24 hours following surgery in subjects receiving ADVATE (rAHF-PFM) by bolus (BI) or continuous infusion (CI)

End point description:

Drainage fluid volume was to be measured cumulatively and recorded every 8 hours +/- 30 minutes during the first 24 hours following surgery.

End point type	Primary

End point timeframe:

During the first 24 postoperative hours

End point values	Treatment by Continuous infusion	Treatment by Bolus infusion	Per Protocol Analysis Set - CI	Per Protocol Analysis Set - BI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	26	28	26	28
Units: T/L				
arithmetic mean (standard deviation)	3.383 (± 0.632)	3.632 (± 0.971)	3.383 (± 0.632)	3.632 (± 0.971)

End point values	Stratum A - CI	Stratum B - CI	Stratum C - CI	Stratum A - BI
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	1	2	22
Units: T/L				
arithmetic mean (standard deviation)	3.345 (± 0.616)	3.4 (± 0)	3.82 (± 1.103)	3.718 (± 0.978)

End point values	Stratum B - BI	Stratum C - BI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	4		
Units: T/L				
arithmetic mean (standard deviation)	2.855 (± 1.732)	3.548 (± 0.577)		

Statistical analyses

Statistical analysis title	Non-inferiority of CI to BI

Statistical analysis description:

The main analysis used a point estimate and a two-sided 95% confidence interval for ratio of the primary outcome measure of CI over BI combined over the three strata: stratum A: unilateral knee replacement,
stratum B: hip surgery, stratum C: shoulder/elbow/ankle/knee (except knee replacement) surgery. Non-inferiority by the 200% margin of non-inferiority was demonstrated if the upper confidence limit of a 95% 2-sided confidence interval for the ratio of means did not exceed 200%.

Comparison groups	Treatment by Bolus infusion v Treatment by Continuous infusion
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [1]
Method	Hypothesis test
Parameter estimate	Mean ratio CI/BI
Point estimate	0.924

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.816
upper limit	1.046

Notes:

[1] - one-sided p-value against the null hypothesis of ratio >=200%

Secondary: Actual postoperative blood loss during the first 24 hours compared with the average blood loss as predicted preoperatively by the operating surgeon

End point title	Actual postoperative blood loss during the first 24 hours compared with the average blood loss as predicted preoperatively by the operating surgeon

End point description:

Drainage fluid volume was to be measured cumulatively and recorded every 8 hours +/- 30 minutes during the first 24 hours following surgery.
Prior to surgery, the operating surgeon was to predict the estimated duration of surgery and the volume (mL) of the estimated expected blood loss for the surgery in a hemostatically normal individual of the same sex, age, and stature as the study subject 1) for the intraoperative procedure (defined as the time period from incision to application of compressive dressing and release of tourniquet, if applicable), 2) for the first 24 hours postoperatively, and 3) for the postoperative period until drain removal, if drainage continued beyond 24 hours.

End point type	Secondary

End point timeframe:

During the first 24 postoperative hours

End point values	Treatment by Continuous infusion	Treatment by Bolus infusion	Per Protocol Analysis Set - CI	Per Protocol Analysis Set - BI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29	31	29	31
Units: millilitre (mL)				
arithmetic mean (standard deviation)	811.11 (± 79.511)	709.28 (± 150.103)	811.11 (± 79.511)	709.28 (± 150.103)

End point values	Stratum A - CI	Stratum B - CI	Stratum C - CI	Stratum A - BI
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	2	3	24
Units: millilitre (mL)				
arithmetic mean (standard deviation)	819.22 (± 66.992)	713.49 (± 0)	811.25 (± 163.027)	724.48 (± 66.367)

End point values	Stratum B - BI	Stratum C - BI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	5		
Units: millilitre (mL)				

arithmetic mean (standard deviation)	265 (± 49.497)	814.03 (± 171.019)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual postoperative blood loss compared to the expected average blood loss until drain removal as predicted preoperatively by the surgeon

End point title	Actual postoperative blood loss compared to the expected average blood loss until drain removal as predicted preoperatively by the surgeon

End point description:

If drainage continued beyond 24 hours, the PRBC volume and hemoglobin was to be measured cumulatively every 24 hours or whenever the drainage bottle was emptied and at the time of drain removal.
Prior to surgery, the operating surgeon was to predict the estimated duration of surgery and the volume (mL) of the estimated expected blood loss for the surgery in a hemostatically normal individual of the same sex, age, and stature as the study subject 1) for the intraoperative procedure (defined as the time period from incision to application of compressive dressing and release of tourniquet, if applicable), 2) for the first 24 hours postoperatively, and 3) for the postoperative period until drain removal, if drainage continued beyond 24 hours.

End point type	Secondary

End point timeframe:

Postoperatively until drain removal

End point values	Treatment by Continuous infusion	Treatment by Bolus infusion	Per Protocol Analysis Set - CI	Per Protocol Analysis Set - BI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	28	30	28	30
Units: mL				
arithmetic mean (standard deviation)	929.49 (± 167.662)	766.73 (± 182.463)	929.49 (± 167.662)	766.73 (± 182.463)

End point values	Stratum A - CI	Stratum B - CI	Stratum C - CI	Stratum A - BI
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	2	3	23
Units: mL				
arithmetic mean (standard deviation)	899.83 (± 45.459)	921.1 (± 42.906)	1162.48 (± 514.033)	752.91 (± 42.343)

End point values	Stratum B - BI	Stratum C - BI		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	5		
Units: mL				
arithmetic mean (standard deviation)	341.5 (± 135.075)	1000.37 (± 259.239)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of bleeding episodes during treatment with continuous or bolus infusion (through postoperative Day 7)

End point title	Number of bleeding episodes during treatment with continuous or bolus infusion (through postoperative Day 7)

End point description:

To simplify the results below: Bleeding episodes were reported for 4 subjects (3 subjects on bolus infusion: 2 in Stratum A and 1 in Stratum B, and 1 subject on continuous infusion/Stratum B). The 4 subjects had 1 bleeding episode each. No bleeding episodes were reported for Stratum C.

End point type	Secondary

End point timeframe:

Postoperative Day 7

End point values	Treatment by Continuous infusion	Treatment by Bolus infusion	Per Protocol Analysis Set - CI	Per Protocol Analysis Set - BI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29	31	29	31
Units: Bleeding episodes				
arithmetic mean (standard deviation)	0.03 (± 0.186)	0.1 (± 0.301)	0.03 (± 0.186)	0.1 (± 0.301)

End point values	Stratum A - CI	Stratum B - CI	Stratum C - CI	Stratum A - BI
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	2	3	24
Units: Bleeding episodes				
arithmetic mean (standard deviation)	0 (± 0)	0.5 (± 0.707)	0 (± 0)	0.08 (± 0.282)

End point values	Stratum B - BI	Stratum C - BI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	5		
Units: Bleeding episodes				
arithmetic mean (standard deviation)	0.5 (± 0.707)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of units of packed red blood cells (PRBC) transfused

End point title	Number of units of packed red blood cells (PRBC) transfused

End point description:

End point type	Secondary

End point timeframe:

During the first postoperative 24 hours

End point values	Treatment by Continuous infusion	Treatment by Bolus infusion	Per Protocol Analysis Set - CI	Per Protocol Analysis Set - BI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29	31	29	31
Units: PRBC units				
arithmetic mean (standard deviation)	1.3 (± 1.4)	0.9 (± 1.2)	1.3 (± 1.4)	0.9 (± 1.2)

End point values	Stratum A - CI	Stratum B - CI	Stratum C - CI	Stratum A - BI
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	2	3	24
Units: PRBC units				
arithmetic mean (standard deviation)	1.2 (± 1.3)	3.5 (± 2.1)	0.7 (± 1.2)	1 (± 1.3)

End point values	Stratum B - BI	Stratum C - BI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	5		
Units: PRBC units				
arithmetic mean (standard deviation)	1.5 (± 2.1)	0.2 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events (AEs) related to the administration of the study product

End point title	Number of adverse events (AEs) related to the administration of the study product

End point description:

All AEs from the first study drug exposure until the study completion/ discontinuation date were to be recorded. Each AE was to be evaluated by the investigator for "seriousness", "severity" and "causal relationship to the investigational product exposure or study procedure".

End point type	Secondary

End point timeframe:

From first study drug exposure until study completion/discontinuation (approx. 9-26 weeks per subject)

End point values	Treatment by Continuous infusion	Treatment by Bolus infusion	Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	5	5	10	
Units: adverse events (AEs)	8	6	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Factor VIII inhibitory antibody (≥0.4 Bethesda Units using the Nijmegen modification of the Bethesda assay) formation

End point title	Incidence of Factor VIII inhibitory antibody (≥0.4 Bethesda Units using the Nijmegen modification of the Bethesda assay) formation

End point description:

End point type	Secondary

End point timeframe:

Until study completion (approx. 9-26 weeks per subject)

End point values	Treatment by Continuous infusion	Treatment by Bolus infusion	Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2	2	4	
Units: subjects	2	2	4	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall: 9 years and 6 months
Per subject: 9-26 weeks

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Safety Analysis Set (n=72)

Reporting group description:

The Safety Analysis Set (SAS) comprises all 72 subjects treated with at least one ADVATE (rAHF-PFM) dose. A total of 72 subjects received ADVATE (rAHF-PFM) for the pharmacokinetic evaluation in the preoperative period. Of these, 32 subjects were subsequently randomized to treatment with continous infusion, and 31 subjects were randomized to treatment with intermittent bolus infusion.

Serious adverse events	Safety Analysis Set (n=72)		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 72 (13.89%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Hemarthrosis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint swelling			

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle hemorrhage			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Febrile infection			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomembranous colitis			
subjects affected / exposed	1 / 72 (1.39%)		
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	Safety Analysis Set (n=72)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 72 (59.72%)		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	26 / 72 (36.11%)		
occurrences (all)	32		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	5		
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	18 / 72 (25.00%)		
occurrences (all)	21		
Thrombocytosis			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	15 / 72 (20.83%)		
occurrences (all)	21		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 72 (9.72%)		
occurrences (all)	30		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2007	Amendment 4: - Maximum subject age was raised from previously 65 to 70 years to allow the inclusion of subjects older than 65 years provided that their health status corresponds to NYHA classification less than or equal to II as defined by the New York Heart Association (NYHA) - The exclusion threshold for history of FVIII inhibitors in the Bethesda assay was raised from equal to or greater than 0.4 BU to equal to or greater than 0.5 BU.
02 September 2011	Amendment 5: Prior to Protocol Amendment 5 (version 02Sep2011), the study was performed in subjects undergoing unilateral primary total knee replacement. In Protocol Amendment 5, the surgeries were expanded to major orthopedic surgeries to increase the enrollment rate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported