Clinical trial results:
Pharmacokinetic Comparison of Advate (rAHF-PFM) With Recombinate (rAHF) in Patients With Severe Hemophilia A: A Phase 4, Prospective, Randomized, Controlled, Cross-over, Single Center Study

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2007-004834-18
Trial protocol	DE
Global end of trial date	18 February 2009

Results information

Result version number	v1 (current)
This version publication date	13 February 2016
First version publication date	13 February 2016

Trial information

Trial identification

Sponsor protocol code	060601

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00666406
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	No

1901/2006 apply to this trial?	
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	23 March 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 February 2009
Global end of trial reached?	Yes
Global end of trial date	18 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to further evaluate observations of decreased efficacy in subjects who had been switched to Advate (rAHF-PFM) from Recombinate (rAHF) by comparing the pharmacokinetic (PK) parameters of the two products in PTPs with severe hemophilia A (factor VIII level < 1%) in whom decreased efficacy with Advate (rAHF-PFM) compared to Recombinate (rAHF) had been observed clinically. Speicifically, the following PK parameters were compared: Area under the plasma concentration vs. time curve from 0 to 48 hours (AUC 0-48h), total area under the plasma concentration vs. time curve (AUC 0-inf), plasma half-life, maximum concentration (Cmax), minimal time to reach maximum concentration (Tmax), incremental recovery (IR), clearance (Cl), mean residence time (MRT), volume of distribution at steady state (Vss).

Protection of trial subjects:

This study was conducted in accordance with the clinical protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

Background therapy: -

Evidence for comparator:

The purpose of this study was to compare the pharmacokinetic parameters of Advate (rAHF-PFM) versus Recombinate (rAHF) in previously treated patients (PTPs) with severe hemophilia A (factor VIII level < 1%) in whom decreased efficacy with Advate (rAHF-PFM) compared to Recombinate (rAHF) was observed clinically after they had been switched to Advate (rAHF-PFM) from Recombinate (rAHF).

Actual start date of recruitment	31 March 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	Germany: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

9 unique participants were enrolled and treated at a single study site in Germany.

Pre-assignment

Screening details:

Participants required a factor VIII (FVIII) washout period ≥48 hours before receiving any pharmacokinetic (PK) infusions and could not be actively bleeding at the time of the infusion.

Pre-assignment period milestones

Number of subjects started	9
Number of subjects completed	9

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PK Infusion with Advate rAHF-PFM and then Recombinate rAHF

Arm description:

All 9 treated subjects received a PK infusion with ADVATE and a PK infusion with Recombinate. The order of the PK infusions was determined by randomization. Infusion 2 was to be administered 7-28 days after first PK infusion.

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:

Dose of 50 +/-5 IU/kg for PK infusion

Investigational medicinal product name	Recombinate
Investigational medicinal product code	
Other name	rAHF (Antihemophilic Factor (Recombinant))
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 50 +/-5 IU/kg for PK infusion

Arm title	PK Infusion with Recombinate rAHF and then Advate rAHF-PFM

Arm description:

All 9 treated subjects received a PK infusion with ADVATE and a PK infusion with Recombinate. The order of the PK infusions was determined by randomization. Infusion 2 was to be administered 7-28 days after first PK infusion.

Arm type	Active comparator

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:

Dose of 50 +/-5 IU/kg for PK infusion

Investigational medicinal product name	Recombinate
Investigational medicinal product code	
Other name	rAHF (Antihemophilic Factor (Recombinant))
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 50 +/-5 IU/kg for PK infusion

Number of subjects in period 1	PK Infusion with Advate rAHF-PFM and then Recombinate rAHF	PK Infusion with Recombinate rAHF and then Advate rAHF-PFM
Started	6	3
Completed	6	3

Baseline characteristics

Reporting groups

Reporting group title	PK Infusion with Advate rAHF-PFM and then Recombinate rAHF
Reporting group description:	
All 9 treated subjects received a PK infusion with ADVATE and a PK infusion with Recombinate. The order of the PK infusions was determined by randomization. Infusion 2 was to be administered 7-28 days after first PK infusion.	
Reporting group title	PK Infusion with Recombinate rAHF and then Advate rAHF-PFM
Reporting group description:	
All 9 treated subjects received a PK infusion with ADVATE and a PK infusion with Recombinate. The order of the PK infusions was determined by randomization. Infusion 2 was to be administered 7-28 days after first PK infusion.	

Reporting group values	PK Infusion with Advate rAHF-PFM and then Recombinate rAHF	PK Infusion with Recombinate rAHF and then Advate rAHF-PFM	Total
Number of subjects	6	3	9
Age categorical Units: Subjects			
85 years and over	0	0	0
From 65-84 years	0	0	0
Adults (18-64 years)	5	3	8
Adolescents (12-17 years)	1	0	1
Children (2-11 years)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Newborns (0-27 days)	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
In utero	0	0	0
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	0	0	
standard deviation	± 0	± 0	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	0
Male	6	3	9
Region of Enrollment Units: Subjects			
Germany	6	3	9

Subject analysis sets

Subject analysis set title	Advate rAHF-PFM
Subject analysis set type	Full analysis

Subject analysis set description:
PK infusion with ADVATE.

Subject analysis set title	Recombinate rAHF
Subject analysis set type	Full analysis

Subject analysis set description:
PK infusion with Recombinate.

Reporting group values	Advate rAHF-PFM	Recombinate rAHF	
Number of subjects	9	9	
Age categorical Units: Subjects			
85 years and over	0	0	
From 65-84 years	0	0	
Adults (18-64 years)	8	8	
Adolescents (12-17 years)	1	1	
Children (2-11 years)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Newborns (0-27 days)	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
In utero	0	0	
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	37.3	37.3	
standard deviation	± 14.9	± 14.9	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	
Male	9	9	
Region of Enrollment Units: Subjects			
Germany	9	9	

End points

End points reporting groups

Reporting group title	PK Infusion with Advate rAHF-PFM and then Recombinate rAHF
Reporting group description:	
All 9 treated subjects received a PK infusion with ADVATE and a PK infusion with Recombinate. The order of the PK infusions was determined by randomization. Infusion 2 was to be administered 7-28 days after first PK infusion.	
Reporting group title	PK Infusion with Recombinate rAHF and then Advate rAHF-PFM
Reporting group description:	
All 9 treated subjects received a PK infusion with ADVATE and a PK infusion with Recombinate. The order of the PK infusions was determined by randomization. Infusion 2 was to be administered 7-28 days after first PK infusion.	
Subject analysis set title	Advate rAHF-PFM
Subject analysis set type	Full analysis
Subject analysis set description:	
PK infusion with ADVATE.	
Subject analysis set title	Recombinate rAHF
Subject analysis set type	Full analysis
Subject analysis set description:	
PK infusion with Recombinate.	

Primary: Area under the plasma concentration versus time curve (AUC) from 0 to 48 hours. One-Stage Activated Partial Thromboplastin Time (aPTT) -Based Assay Performed at Central Laboratory (Medical University Vienna)

End point title	Area under the plasma concentration versus time curve (AUC) from 0 to 48 hours. One-Stage Activated Partial Thromboplastin Time (aPTT) -Based Assay Performed at Central Laboratory (Medical University Vienna)
End point description:	
AUC estimated by linear trapezoidal method. The linear trapezoidal method is a numerical method used to approximate the area under a curve.	
End point type	Primary
End point timeframe:	
0-30 minutes before infusion up to 48 hours post-infusion	

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU*h/dL				
geometric mean (confidence interval 90%)	1104 (950 to 1328)	1294 (1149 to 1536)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of the geometric means
Point estimate	1.173
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.089
upper limit	1.262

Primary: Area under the plasma concentration versus time curve (AUC) from 0 to 48 hours. Chromogenic Assay Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Area under the plasma concentration versus time curve (AUC) from 0 to 48 hours. Chromogenic Assay Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

AUC estimated by linear trapezoidal method. The linear trapezoidal method is a numerical method used to approximate the area under a curve.

End point type	Primary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU*h/dL				
geometric mean (confidence interval 90%)	1180 (999 to 1497)	1358 (1146 to 1547)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.139
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.043
upper limit	1.243

Primary: Area under the plasma concentration versus time curve (AUC) from 0 to 48 hours. FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Area under the plasma concentration versus time curve (AUC) from 0 to 48 hours. FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

AUC estimated by linear trapezoidal method. The linear trapezoidal method is a numerical method used to approximate the area under a curve.

End point type	Primary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU*h/dL				
geometric mean (confidence interval 90%)	833 (697 to 970)	901 (629 to 1070)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.866
upper limit	1.297

Primary: Area under the plasma concentration versus time curve (AUC) from 0 to 48 hours. FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Area under the plasma concentration versus time curve (AUC) from 0 to 48 hours. FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

AUC estimated by linear trapezoidal method. The linear trapezoidal method is a numerical method used to approximate the area under a curve.

End point type	Primary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU*h/dL				
geometric mean (confidence interval 90%)	1505 (1215 to 1741)	1664 (1340 to 1911)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.071
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.972
upper limit	1.179

Secondary: Area under the plasma concentration versus time curve (AUC) from 0 to Infinity. One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point title	Area under the plasma concentration versus time curve (AUC) from 0 to Infinity. One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point description:

AUC estimated by linear trapezoidal method. The linear trapezoidal method is a numerical method used to approximate the area under a curve. FVIII activity measurement

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU*h/dL				
geometric mean (confidence interval 90%)	1190 (1031 to 1360)	1393 (1232 to 1574)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.171
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.099
upper limit	1.247

Secondary: Area under the plasma concentration versus time curve (AUC) from 0 to infinity. Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Area under the plasma concentration versus time curve (AUC) from 0 to infinity. Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

AUC estimated by linear trapezoidal method. The linear trapezoidal method is a numerical method used to approximate the area under a curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU*h/dL				
geometric mean (confidence interval 90%)	1282 (1037 to 1626)	1452 (1137 to 1696)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.135
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.092
upper limit	1.18

Secondary: Area under the plasma concentration versus time curve (AUC) from 0 to infinity. FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Area under the plasma concentration versus time curve (AUC) from 0 to infinity. FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

AUC estimated by linear trapezoidal method. The linear trapezoidal method is a numerical method used to approximate the area under a curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU*h/dL				
geometric mean (confidence interval 90%)	874 (734 to 1031)	926 (655 to 1152)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.036
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.857
upper limit	1.253

Secondary: Area under the plasma concentration versus time curve (AUC) from 0 to infinity. FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Area under the plasma concentration versus time curve (AUC) from 0 to infinity. FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

AUC estimated by linear trapezoidal method. The linear trapezoidal method is a numerical method used to approximate the area under a curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU*h/dL				
geometric mean (confidence interval 90%)	1598 (1340 to 1923)	1731 (1453 to 2162)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.093
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.007
upper limit	1.186

Secondary: Systemic clearance (Cl). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point title	Systemic clearance (Cl). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point description:

Systemic clearance in mL/kg/h will be calculated as the dose in IU/kg divided by the total area under the curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: mL/h/kg				
geometric mean (confidence interval 90%)	4.31 (3.92 to 4.85)	3.68 (3.41 to 4.19)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.854
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.798
upper limit	0.913

Secondary: Systemic clearance (Cl). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Systemic clearance (Cl). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Systemic clearance in mL/kg/h will be calculated as the dose in IU/kg divided by the total area under the curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: mL/h/kg				
geometric mean (confidence interval 90%)	4 (3.28 to 4.88)	3.53 (3.03 to 4.43)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.881
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.847
upper limit	0.916

Secondary: Systemic clearance (Cl). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Systemic clearance (Cl). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Systemic clearance in mL/kg/h will be calculated as the dose in IU/kg divided by the total area under the curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: mL/h/kg				
geometric mean (confidence interval 90%)	5.87 (4.4 to 7.35)	5.53 (4.28 to 8.19)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.964
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.799
upper limit	1.164

Secondary: Systemic clearance (Cl). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Systemic clearance (Cl). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Systemic clearance in mL/kg/h will be calculated as the dose in IU/kg divided by the total area under the curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: mL/h/kg				
geometric mean (confidence interval 90%)	3.21 (2.63 to 3.85)	2.96 (2.35 to 3.79)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.915
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.841
upper limit	0.995

Secondary: Maximum plasma concentration (C-max). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point title	Maximum plasma concentration (C-max). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point description:

C-max will be calculated as the maximum concentration following infusion of either Advate or Recombinate.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU/dL				
geometric mean (confidence interval 90%)	93 (74 to 112)	108 (91 to 130)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.177

Confidence interval	
level	90 %
sides	2-sided
lower limit	1.104
upper limit	1.256

Secondary: Maximum Plasma Concentration (C-max). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Maximum Plasma Concentration (C-max). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

C-max will be calculated as the maximum concentration following infusion of either Advate or Recombinate.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU/dL				
geometric mean (confidence interval 90%)	104 (79 to 148)	119 (104 to 144)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.152
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.039
upper limit	1.277

Secondary: Maximum Plasma Concentration (C-max). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the

study site)	
End point title	Maximum Plasma Concentration (C-max). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

C-max will be calculated as the maximum concentration following infusion of either Advate or Recombinate.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU/dL				
geometric mean (confidence interval 90%)	78 (66 to 100)	94 (72 to 149)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.182
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.029
upper limit	1.359

Secondary: Maximum Plasma Concentration (C-max). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)	
End point title	Maximum Plasma Concentration (C-max). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

C-max will be calculated as the maximum concentration following infusion of either Advate or Recombinate.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU/dL				
geometric mean (confidence interval 90%)	100 (72 to 121)	112 (92 to 137)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.133
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.01
upper limit	1.27

Secondary: Terminal Half-life. One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point title	Terminal Half-life. One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point description:

Computed from the terminal or disposition rate constant obtained from log-linear fitting using the least squares deviation to the last five quantifiable concentrations (9 to 48 hours).

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: hours				
geometric mean (confidence interval 90%)	10.7 (8.3 to 12.8)	10.9 (9.1 to 13.1)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.008
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.969
upper limit	1.05

Secondary: Terminal Half-life. Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Terminal Half-life. Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Computed from the terminal or disposition rate constant obtained from log-linear fitting using the least squares deviation to the last five quantifiable concentrations.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: hours				
geometric mean (confidence interval 90%)	11.7 (8.5 to 13.5)	10.8 (8.2 to 12.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.964
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.843
upper limit	1.102

Secondary: Terminal Half-life. FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Terminal Half-life. FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Computed from the terminal or disposition rate constant obtained from log-linear fitting using the least squares deviation to the last five quantifiable concentrations.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: hours				
geometric mean (confidence interval 90%)	9.5 (7.5 to 12.8)	9.9 (7.6 to 11.5)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.038
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.926
upper limit	1.163

Secondary: Terminal Half-life. FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Terminal Half-life. FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Computed from the terminal or disposition rate constant obtained from log-linear fitting using the least squares deviation to the last five quantifiable concentrations.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: hours				
geometric mean (confidence interval 90%)	12.4 (9.3 to 14.2)	12.1 (8.9 to 13.9)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.015
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.901
upper limit	1.144

Secondary: Incremental recovery. One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point title	Incremental recovery. One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point description:

Increase in factor VIII concentration from pre- to post-infusion.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: (IU/dL)/(IU/kg)				
geometric mean (confidence interval 90%)	1.81 (1.52 to 2.1)	2.11 (1.89 to 2.42)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.178
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.106
upper limit	1.254

Secondary: Incremental recovery. Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Incremental recovery. Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Computed from the terminal or disposition rate constant obtained from log_e -linear fitting using the least squares deviation to the last five quantifiable concentrations.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: (IU/dL)/(IU/kg)				
geometric mean (confidence interval 90%)	2.04 (1.53 to 2.7)	2.33 (2.02 to 2.69)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.152
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.038
upper limit	1.279

Secondary: Incremental recovery. FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Incremental recovery. FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)
End point description:	
Increase in factor VIII concentration from pre- to post-infusion	
End point type	Secondary
End point timeframe:	
0-30 minutes before infusion up to 48 hours post-infusion	

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: (IU/dL)/(IU/kg)				
geometric mean (confidence interval 90%)	1.53 (1.24 to 1.82)	1.84 (1.49 to 2.82)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.183
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.027
upper limit	1.362

Secondary: Incremental recovery. FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Incremental recovery. FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)
End point description:	
Increase in factor VIII concentration from pre- to post-infusion	
End point type	Secondary
End point timeframe:	
0-30 minutes before infusion up to 48 hours post-infusion	

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: (IU/dL)/(IU/kg)				
geometric mean (confidence interval 90%)	1.94 (1.44 to 2.27)	2.19 (1.74 to 2.64)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.133
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.012
upper limit	1.27

Secondary: Mean Residence Time (MRT). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point title	Mean Residence Time (MRT). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point description:

The MRT in hours will be calculated as total area under the moment curve divided by the total area under the curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Hours				
geometric mean (confidence interval 90%)	14.1 (11 to 17.5)	14.4 (12.1 to 17.6)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.009
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.964
upper limit	1.056

Secondary: Mean Residence Time (MRT). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Mean Residence Time (MRT). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

The MRT in hours will be calculated as total area under the moment curve divided by the total area under the curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Hours				
geometric mean (confidence interval 90%)	15.1 (10.9 to 18.6)	14.2 (10.3 to 16.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.971
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.849
upper limit	1.112

Secondary: Mean Residence Time (MRT). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Mean Residence Time (MRT). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

The MRT in hours will be calculated as total area under the moment curve divided by the total area under the curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Hours				
geometric mean (confidence interval 90%)	12.5 (9.1 to 16.7)	12.8 (10.1 to 16.4)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.938
upper limit	1.109

Secondary: Mean Residence Time (MRT). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Mean Residence Time (MRT). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

The MRT in hours will be calculated as total area under the moment curve divided by the total area under the curve.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Hours				
geometric mean (confidence interval 90%)	17.3 (12.4 to 19.6)	16.9 (13.2 to 19.6)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.996
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.894
upper limit	1.111

Secondary: Time to reach the maximum plasma concentration (Tmax). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point title	Time to reach the maximum plasma concentration (Tmax). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point description:

Tmax in hours was defined as the minimum time to reach Maximum plasma concentration (Cmax).

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Hours				
geometric mean (confidence interval 90%)	0.25 (0.25 to 0.25)	0.25 (0.25 to 0.25)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1

Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1

Secondary: Time to reach the maximum plasma concentration (Tmax). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Time to reach the maximum plasma concentration (Tmax). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Tmax in hours was defined as the minimum time to reach Maximum plasma concentration (Cmax).

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Hours				
geometric mean (confidence interval 90%)	0.31 (0.25 to 0.5)	0.42 (0.25 to 1)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.303
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.841
upper limit	2.02

Secondary: Time to reach the maximum plasma concentration (Tmax). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Time to reach the maximum plasma concentration (Tmax). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Tmax in hours was defined as the minimum time to reach Maximum plasma concentration (Cmax).

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Hours				
geometric mean (confidence interval 90%)	0.45 (0.25 to 1)	0.31 (0.25 to 0.5)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.724
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.304
upper limit	1.728

Secondary: Time to reach the maximum plasma concentration (Tmax). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Time to reach the maximum plasma concentration (Tmax). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point description:

Tmax in hours was defined as the minimum time to reach Maximum plasma concentration (Cmax).

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 48 hours post-infusion

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Hours				
geometric mean (confidence interval 90%)	0.38 (0.25 to 1)	0.51 (0.25 to 3)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	1.059
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.442
upper limit	2.539

Secondary: Volume of Distribution at Steady State (Vss). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)

End point title	Volume of Distribution at Steady State (Vss). One-Stage aPTT-Based Assay Performed at Central Laboratory (Medical University Vienna)
End point description:	
Computed as weight-adjusted Clearance * Mean Residence Time	
End point type	Secondary
End point timeframe:	
0-30 minutes before infusion up to 48 hours post-infusion	

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: mL/kg				
geometric mean (confidence interval 90%)	60.8 (48.2 to 75.7)	52.9 (43.9 to 62)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.862
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.807
upper limit	0.92

Secondary: Volume of Distribution at Steady State (Vss). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Volume of Distribution at Steady State (Vss). Chromogenic Assay performed at Local Laboratory (i.e., University of Bonn, the study site)
End point description:	
Computed as weight-adjusted Clearance (CL) * Mean Residence Time	
End point type	Secondary
End point timeframe:	
0-30 minutes before infusion up to 48 hours post-infusion	

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: mL/kg				
geometric mean (confidence interval 90%)	60.4 (45.5 to 76.6)	50.2 (45.4 to 58.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.855
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.73
upper limit	1.002

Secondary: Volume of Distribution at Steady State (Vss). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)

End point title	Volume of Distribution at Steady State (Vss). FVIII One-Stage Clotting Assay (Bonn Method) Performed at Local Laboratory (i.e., University of Bonn, the study site)
End point description:	
Computed as weight-adjusted CL * Mean Residence Time	
End point type	Secondary
End point timeframe:	
0-30 minutes before infusion up to 48 hours post-infusion	

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: mL/kg				
geometric mean (confidence interval 90%)	73.2 (54.6 to 87.5)	70.9 (67.5 to 89.5)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.984
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.788
upper limit	1.228

Secondary: Volume of Distribution at Steady State (Vss). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)	
End point title	Volume of Distribution at Steady State (Vss). FVIII Clotting Assay. Performed at Local Laboratory (i.e., University of Bonn, the study site)
End point description:	
Computed as weight-adjusted CL * Mean Residence Time	
End point type	Secondary
End point timeframe:	
0-30 minutes before infusion up to 48 hours post-infusion	

End point values	Advate rAHF-PFM	Recombinate rAHF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: mL/kg				
geometric mean (confidence interval 90%)	55.6 (40.4 to 69.1)	50 (39.8 to 63.8)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advate rAHF-PFM v Recombinate rAHF
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of the geometric means
Point estimate	0.911
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	1.039

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
Slightly less than 1 year (31Mar2008 - 18Feb2009)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	N/A

Reporting groups	
Reporting group title	All Study Participants

Reporting group description:

Includes all 9 treated subjects (ie, all subjects who received a PK infusion with Advate rAHF-PFM and a PK infusion with Recombinate rAHF).

Serious adverse events	All Study Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (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	All Study Participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No AEs were reported for any of the 9 subjects enrolled and treated in this study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2008	- Original target enrollment of 15-20 previously treated patients (PTPs) reduced to 15 PTPs - Exclusion criterion of detectable factor VIII inhibitor titer ≥ 0.4 BU not limited to central laboratory measurements any more but also applicable when measured at the local laboratory - More flexibility allowed in the choice of butterfly gauge catheter to be used for infusion of the study product or for blood draws: change from previously allowed 23-gauge butterfly catheter to 21- or 23-gauge butterfly catheter

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported