Clinical trial results:
A Phase 3b clinical study to assess whether regular administration of ADVATE in the absence of immunological danger signals reduces the incidence rate of inhibitors in previously untreated patients with hemophilia A

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	2011-000410-18
Trial protocol	AT DE SK LT GB HU CZ SE BE BG ES NL GR PL PT
Global end of trial date	16 November 2012

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	061002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01376700
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 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2012
Global end of trial reached?	Yes
Global end of trial date	16 November 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to determine the incidence rate of inhibitor formation in previously untreated patients (PUPs) with severe and moderately severe hemophilia A during the first 50 exposure days of treatment with ADVATE, starting with a once weekly prophylactic regimen together with the minimization of immunological danger signals

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:

The inhibitor incidence rate observed during the early prophylaxis regimen in this study was to be compared to the rate previously observed in historical cohorts, including the ADVATE PUP Study (Baxalta study number 060103; historical control).

Evidence for comparator: -

Actual start date of recruitment	26 August 2011
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: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 2

Worldwide total number of subjects	19
EEA total number of subjects	12

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)	19
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment was conducted in Europe and North America at 19 clinical sites.

Pre-assignment

Screening details:

22 subjects were enrolled. One was a screen failure; one did not have screening laboratory assessments performed prior to study termination; and one met screening criteria, but was not exposed to investigational product prior to study termination. Therefore, 19 participants were treated.

Pre-assignment period milestones

Number of subjects started	19
Number of subjects completed	19

Period 1

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

Arms

Arm title	ADVATE - Prophylactic Regimen

Arm description:

The initial dosing regimen of 25 +/-5 IU/kg once weekly was to continue throughout the first 20 exposure days and for as long as possible beyond this early prophylaxis period. If required by the clinical situation, the frequency of infusions could be increased to twice or three times per week by the investigator in accordance with the instructions given in the study protocol. The maximum dose for any once weekly infusion was 50 IU/kg.

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:

25 +/-5 IU/kg once weekly

Number of subjects in period 1	ADVATE - Prophylactic Regimen
Started	19
Completed	3
Not completed	16
Sponsor terminated study early	8
Low or high titer inhibitor	8

Baseline characteristics

Reporting groups

Reporting group title	ADVATE - Prophylactic Regimen

Reporting group description:

The initial dosing regimen of 25 +/-5 IU/kg once weekly was to continue throughout the first 20 exposure days and for as long as possible beyond this early prophylaxis period. If required by the clinical situation, the frequency of infusions could be increased to twice or three times per week by the investigator in accordance with the instructions given in the study protocol. The maximum dose for any once weekly infusion was 50 IU/kg.

Reporting group values	ADVATE - Prophylactic Regimen	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: weeks			
arithmetic mean	43.3		
standard deviation	± 10.2	-	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	
Male	19	19	
Region of Enrollment Units: Subjects			
Serbia	1	1	
United States	2	2	
Czech Republic	2	2	
Canada	1	1	
Spain	1	1	
Poland	4	4	
Austria	1	1	
Russian Federation	3	3	
Bulgaria	1	1	
Netherlands	1	1	
Germany	2	2	

Subject analysis sets

Subject analysis set title	ADVATE - Prophylactic Regimen
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (= Safety Analysis Set) comprises 19 subjects who received at least 1 infusion of Advate.

Subject analysis set title	Previously untreated patients (PUPs)

Austria	1	1	0
Russian Federation	3	3	0
Bulgaria	1	0	1
Netherlands	1	0	1
Germany	2	0	2

Reporting group values	Subjects with confirmed FVIII inhibitor	Subjects with confirmed low-titer FVIII inhibitor	Subjects with confirmed high-titer FVIII inhibitor
Number of subjects	8	5	3
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: weeks arithmetic mean standard deviation	±	±	±
Gender categorical			
Gender categorical description			
Units: Subjects			
Female Male			
Region of Enrollment Units: Subjects			
Serbia United States Czech Republic Canada Spain Poland Austria Russian Federation Bulgaria Netherlands Germany			

End points

End points reporting groups

Reporting group title	ADVATE - Prophylactic Regimen

Reporting group description:

The initial dosing regimen of 25 +/-5 IU/kg once weekly was to continue throughout the first 20 exposure days and for as long as possible beyond this early prophylaxis period. If required by the clinical situation, the frequency of infusions could be increased to twice or three times per week by the investigator in accordance with the instructions given in the study protocol. The maximum dose for any once weekly infusion was 50 IU/kg.

Subject analysis set title	ADVATE - Prophylactic Regimen
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (= Safety Analysis Set) comprises 19 subjects who received at least 1 infusion of Advate.

Subject analysis set title	Previously untreated patients (PUPs)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PUPs have had no prior exposure to any FVIII containing product before the start of the early low dose prophylactic regimen in this study.

Subject analysis set title	Minimally treated patients (MTPs)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

MTPs have had up to 4 exposures to any FVIII product before the start of the early low dose prophylactic regimen in this study.

Subject analysis set title	Subjects with confirmed FVIII inhibitor
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Confirmed inhibitor is defined as any FVIII inhibitor assay result equal or greater than 0.6 BU/mL confirmed by the central laboratory on 2 consecutive samples, i.e. at least 2 positive inhibitor results (including the first positive inhibitor test, in accordance with the study protocol) assessed as either: i. High FVIII inhibitor titer (> 5 BU/mL) or ii. Low FVIII inhibitor titer (≥0.6 - ≤5.0 BU/mL).

Subject analysis set title	Subjects with confirmed low-titer FVIII inhibitor
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Low FVIII inhibitor titer (≥0.6 - ≤5.0 BU/mL) confirmed by the central laboratory on 2 consecutive samples, i.e. at least 2 positive inhibitor results (including the first positive inhibitor test, in accordance with the study protocol)

Subject analysis set title	Subjects with confirmed high-titer FVIII inhibitor
Subject analysis set type	Sub-group analysis

Subject analysis set description:

High FVIII inhibitor titer (> 5 BU/mL) confirmed by the central laboratory on 2 consecutive samples, i.e. at least 2 positive inhibitor results (including the first positive inhibitor test, in accordance with the study protocol)

Primary: Number of subjects with severe and moderately severe hemophilia A (FVIII ≤ 2%) with Factor VIII (FVIII) inhibitor formation within the first 50 exposure days to ADVATE

End point title	Number of subjects with severe and moderately severe hemophilia A (FVIII ≤ 2%) with Factor VIII (FVIII) inhibitor formation within the first 50 exposure days to ADVATE[1]

End point description:

Inhibitor testing will be performed in the central laboratory and a non-zero result must be confirmed in the central laboratory as soon as possible, preferably 1 week after inhibitor testing. Confirmed FVIII inhibitor is defined as any FVIII inhibitor assay result equal or greater than 0.6 Bethesda Units (BU)/mL confirmed by the central laboratory on 2 consecutive samples, i.e. at least 2 positive inhibitor results (including the first positive inhibitor test, in accordance with the study protocol) assessed as either: - i.

High FVIII inhibitor titer (> 5 BU/mL) or - ii. Low FVIII inhibitor titer (≥0.6 - ≤5.0 BU/mL).

End point type	Primary

End point timeframe:

50 exposure days to ADVATE

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol, descriptive statistics were collected for this endpoint.

End point values	ADVATE - Prophylactic Regimen	Previously untreated patients (PUPs)	Minimally treated patients (MTPs)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	19	11	8	
Units: subjects	8	4	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with severe hemophilia A (FVIII ≤ 1%) with Factor VIII (FVIII) inhibitor formation within the first 50 exposure days to ADVATE

End point title	Number of subjects with severe hemophilia A (FVIII ≤ 1%) with Factor VIII (FVIII) inhibitor formation within the first 50 exposure days to ADVATE

End point description:

Inhibitor testing will be performed in the central laboratory and a non-zero result must be confirmed in the central laboratory as soon as possible, preferably 1 week after inhibitor testing. Confirmed FVIII inhibitor is defined as any FVIII inhibitor assay result equal or greater than 0.6 Bethesda Units (BU)/mL confirmed by the central laboratory on 2 consecutive samples, i.e. at least 2 positive inhibitor results (including the first positive inhibitor test, in accordance with the study protocol) assessed as either: - i. High FVIII inhibitor titer (> 5 BU/mL) or - ii. Low FVIII inhibitor titer (≥0.6 - ≤5.0 BU/mL).

End point type	Secondary

End point timeframe:

50 exposure days to ADVATE

End point values	ADVATE - Prophylactic Regimen	Previously untreated patients (PUPs)	Minimally treated patients (MTPs)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	19	11	8	
Units: subjects	8	4	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Exposure Days of Treatment with Advate Prior to First Positive Factor VIII (FVIII) Confirmed Inhibitor Assessment

End point title	Number of Exposure Days of Treatment with Advate Prior to First Positive Factor VIII (FVIII) Confirmed Inhibitor Assessment

End point description:

Confirmed inhibitor is defined as any FVIII inhibitor assay result equal or greater than 0.6 BU/mL confirmed by the central laboratory on 2 consecutive samples, i.e. at least 2 positive inhibitor results (including the first positive inhibitor test, in accordance with the study protocol) assessed as either: - i. High FVIII inhibitor titer (> 5 BU/mL) or - ii. Low FVIII inhibitor titer (≥0.6 - ≤5.0 BU/mL).

End point type	Secondary

End point timeframe:

50 exposure days to ADVATE

End point values	Subjects with confirmed FVIII inhibitor	Subjects with confirmed low-titer FVIII inhibitor	Subjects with confirmed high-titer FVIII inhibitor	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	5	3	
Units: days				
median (inter-quartile range (Q1-Q3))	14.5 (7 to 21)	15 (14 to 23)	9 (2 to 19)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with low-titer, high-titer, transient, and all Factor VIII (FVIII) inhibitors

End point title	Number of subjects with low-titer, high-titer, transient, and all Factor VIII (FVIII) inhibitors

End point description:

- High FVIII inhibitor titer (> 5 Bethesda Unit (BU)/mL) - Low FVIII inhibitor titer (≥0.6 - ≤5.0 BU/mL)

End point type	Secondary

End point timeframe:

50 exposure days to ADVATE

End point values	ADVATE - Prophylactic Regimen			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: participants				
Low FVIII inhibitor titer	5			
High FVIII inhibitor titer	3			
Transient FVIII inhibitors	0			
All FVIII inhibitors	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Number, type, and severity of all bleeds experienced when different prophylactic dosing frequencies are used (once or twice per week and unknown frequency)

End point title	Number, type, and severity of all bleeds experienced when different prophylactic dosing frequencies are used (once or twice per week and unknown frequency)

End point description:

Nominal Dosing Frequency: 1 time per week, 2 times per week, Unknown dosing frequency (UK).
Bleeding Type (BT): Skin, Muscle and Soft Tissue, Mucosal, Joint, Other, Multiple, Total.
Bleeding severity: Minor, Moderate, Severe, Total.

End point type	Secondary

End point timeframe:

50 exposure days to ADVATE

End point values	ADVATE - Prophylactic Regimen			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Bleeds				
number (not applicable)				
Dose: 1/week; skin; minor bleed	130			
Dose: 1/week; skin; moderate bleed	2			
Dose: 1/week; skin; severe bleed	0			
Dose: 1/week; skin; total bleeds	132			
Dose: 1/week; muscle & soft tissue; minor bleed	8			
Dose: 1/week; muscle & soft tissue; moderate bleed	10			
Dose: 1/week; muscle & soft tissue; severe bleed	0			
Dose: 1/week; muscle & soft tissue; total bleeds	18			
Dose: 1/week; mucosal; minor bleed	9			
Dose: 1/week; mucosal; moderate bleed	3			
Dose: 1/week; mucosal; severe bleed	0			
Dose: 1/week; mucosal; total bleeds	12			
Dose: 1/week; joint; minor bleed	0			
Dose: 1/week; joint; moderate bleed	0			
Dose: 1/week; joint; severe bleed	0			
Dose: 1/week; joint; total bleeds	0			

Dose: 1/week; other BT; minor bleed	3			
Dose: 1/week; other BT; moderate bleed	3			
Dose: 1/week; other BT; severe bleed	1			
Dose: 1/week; other BT; total bleeds	7			
Dose: 1/week; multiple BT; minor bleed	2			
Dose: 1/week; multiple BT; moderate bleed	1			
Dose: 1/week; multiple BT; severe bleed	0			
Dose: 1/week; multiple BT; total bleeds	3			
Dose: 1/week; total BT; minor bleed	152			
Dose: 1/week; total BT; moderate bleed	19			
Dose: 1/week; total BT; severe bleed	1			
Dose: 1/week; total BT; total bleeds	172			
Dose: 2/week; skin; minor bleed	9			
Dose: 2/week; skin; moderate bleed	0			
Dose: 2/week; skin; severe bleed	0			
Dose: 2/week; skin; total bleeds	9			
Dose: 2/week; muscle & soft tissue; minor bleed	0			
Dose: 2/week; muscle & soft tissue; moderate bleed	1			
Dose: 2/week; muscle & soft tissue; severe bleed	0			
Dose: 2/week; muscle & soft tissue; total bleeds	1			
Dose: 2/week; mucosal; minor bleed	3			
Dose: 2/week; mucosal; moderate bleed	1			
Dose: 2/week; mucosal; severe bleed	0			
Dose: 2/week; mucosal; total bleeds	4			
Dose: 2/week; joint; minor bleed	0			
Dose: 2/week; joint; moderate bleed	0			
Dose: 2/week; joint; severe bleed	0			
Dose: 2/week; joint; total bleeds	0			
Dose: 2/week; other BT; minor bleed	0			
Dose: 2/week; other BT; moderate bleed	0			
Dose: 2/week; other BT; severe bleed	0			
Dose: 2/week; other BT; total bleeds	0			
Dose: 2/week; multiple BT; minor bleed	0			
Dose: 2/week; multiple BT; moderate bleed	0			
Dose: 2/week; multiple BT; severe bleed	0			
Dose: 2/week; multiple BT; total bleeds	0			
Dose: 2/week; total BT; minor bleed	12			
Dose: 2/week; total BT; moderate bleed	2			
Dose: 2/week; total BT; severe bleed	0			
Dose: 2/week; total BT; total bleeds	14			
Dose: UK/week; skin; minor bleed	4			
Dose: UK/week; skin; moderate bleed	1			
Dose: UK/week; skin; severe bleed	0			
Dose: UK/week; skin; total bleeds	5			

Dose: UK/week; muscle & soft tissue; minor bleed	0			
Dose: UK/week; muscle & soft tissue;moderate bleed	1			
Dose: UK/week; muscle & soft tissue; severe bleed	0			
Dose: UK/week; muscle & soft tissue; total bleeds	1			
Dose: UK/week; mucosal; minor bleed	0			
Dose: UK/week; mucosal; moderate bleed	0			
Dose: UK/week; mucosal; severe bleed	0			
Dose: UK/week; mucosal; total bleeds	0			
Dose: UK/week; joint; minor bleed	0			
Dose: UK/week; joint; moderate bleed	1			
Dose: UK/week; joint; severe bleed	0			
Dose: UK/week; joint; total bleeds	1			
Dose: UK/week; other BT; minor bleed	0			
Dose: UK/week; other BT; moderate bleed	0			
Dose: UK/week; other BT; severe bleed	0			
Dose: UK/week; other BT; total bleeds	0			
Dose: UK/week; multiple BT; minor bleed	0			
Dose: UK/week; multiple BT; moderate bleed	0			
Dose: UK/week; multiple BT; severe bleed	0			
Dose: UK/week; multiple BT; total bleeds	0			
Dose: UK/week; total BT; minor bleed	4			
Dose: UK/week; total BT; moderate bleed	3			
Dose: UK/week; total BT; severe bleed	0			
Dose: UK/week; total BT; total bleeds	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Number and type of surgeries

End point title	Number and type of surgeries

End point description:

- Elective surgery is not allowed during period of first 20 exposure days (EDs).
- Abbreviation PICC = Peripherally inserted central catheter

End point type	Secondary

End point timeframe:

50 exposure days to ADVATE

End point values	ADVATE - Prophylactic Regimen			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: surgeries				
Surgery: Cimino Shunt Surgery: PICC Line Insertion in right arm	1 1			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of known risk factors to Factor VIII (FVIII) inhibitor formation

End point title	Correlation of known risk factors to Factor VIII (FVIII) inhibitor formation

End point description:

Known genetic risk factors to inhibitor formation include FVIII gene mutation type, FVIII haplotype, human leukocyte antigen (HLA) haplotypes, severity of hemophilia, family history of inhibitors and immunomodulatory gene polymorphisms. Due to the low number of subjects available for evaluation, no statistical tests were performed to assess associations between known risk factors to inhibitor formation.

End point type	Secondary

End point timeframe:

50 exposure days to ADVATE

End point values	ADVATE - Prophylactic Regimen			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: subjects				

Notes:

[2] - No statistical tests performed due to low number of subjects (see endpoint description)

Statistical analyses

No statistical analyses for this end point

Secondary: Total Factor VIII (FVIII) consumption by subject

End point title	Total Factor VIII (FVIII) consumption by subject

End point description:

Due to the low number of subjects available for evaluation, no statistical tests were performed to assess the total FVIII consumption by subject.

End point type	Secondary

End point timeframe:

50 exposure days to ADVATE

End point values	ADVATE - Prophylactic Regimen			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: International Units (IU)				

Notes:

[3] - No statistical tests performed due to low number of subjects (see endpoint description)

Statistical analyses

No statistical analyses for this end point

Secondary: FVIII-Specific Antibody Isotype for All Subjects at Study Entry and Every 10 Exposure Days (EDs)

End point title	FVIII-Specific Antibody Isotype for All Subjects at Study Entry and Every 10 Exposure Days (EDs)

End point description:

Summary statistics of FVIII-specific antibody isotypes were not performed due to the early termination of the study.

End point type	Secondary

End point timeframe:

50 exposure days to ADVATE

End point values	ADVATE - Prophylactic Regimen			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: subjects				

Notes:

[4] - Summary statistics of FVIII-specific antibody isotypes not performed due to early study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Number of serious adverse events (SAEs) and non-serious adverse events (non-SAEs) at least possibly related to ADVATE

End point title	Number of serious adverse events (SAEs) and non-serious adverse events (non-SAEs) at least possibly related to ADVATE

End point description:

Possibly or probably related adverse events

End point type	Secondary

End point timeframe:

50 exposure days to ADVATE

End point values	ADVATE - Prophylactic Regimen			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: adverse events				
SAEs	9			
non-SAEs	1			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of subjects with Factor VIII (FVIII) Inhibitors by Inhibitor Type (Only 'true' inhibitors)

End point title	Number of subjects with Factor VIII (FVIII) Inhibitors by Inhibitor Type (Only 'true' inhibitors)

End point description:

'True' positive inhibitor (PI) defined as any FVIII inhibitor assay result ≥0.6 Bethesda Units (BU)/mL confirmed by central lab on 2 consecutive samples, ie ≥2 PI results (including first PI test, in accordance with study protocol) assessed as either: i. High FVIII inhibitor titer (> 5 BU/mL) ii. Low FVIII inhibitor titer (≥0.6 - ≤5.0 BU/mL). In addition, to be classified as 'true' positive low FVIII inhibitors titer (≥0.6 - ≤5.0 BU/mL), one of following criteria must be met: - a) Lower or absent therapeutic response at infusion of standard replacement doses ("clinically relevant") as deemed by the clinician in charge. - b) Any lab result of binding FVIII antibodies (IgM, IgA, IgG, IgG1, IgG2, IgG3, or IgG4) must be positive. Classification based on first positive FVIII inhibitor assessment. Inhibitor test result is: - > 5 BU/mL, then categorized as a high-titer inhibitor - ≥0.6 BU/mL but ≤5 BU/mL, then categorized as a low-titer.

End point type	Post-hoc

End point timeframe:

50 exposure days to ADVATE

End point values	ADVATE - Prophylactic Regimen			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: subjects				
Inhibitor Type: Low-Titer	3			
Inhibitor Type: High-Titer	3			
Inhibitor Type: All Inhibitors	6			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of Inhibitors in Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs) - (Only 'true' inhibitors)

End point title	Number of Inhibitors in Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs) - (Only 'true' inhibitors)

End point description:

PUPs = no previous FVIII exposure; MTPs ≤4 previous FVIII exposures 'True' positive inhibitor (PI) = any FVIII inhibitor assay result ≥0.6 Bethesda Units (BU)/mL confirmed by central lab on 2 consecutive samples, ie ≥2 PI results (including first PI test, per study protocol) assessed as either: i. High FVIII inhibitor titer (>5 BU/mL) ii. Low FVIII inhibitor titer (≥0.6 - ≤5.0 BU/mL). In addition, to be classified as 'true' positive low FVIII inhibitors titer (≥0.6 - ≤5.0 BU/mL), one of following criteria must be met: - a) Lower or absent therapeutic response at infusion of standard replacement doses ("clinically relevant") as deemed by clinician in charge. - b) Any lab result of binding FVIII antibodies (IgM, IgA, IgG, IgG1, IgG2, IgG3, or IgG4) must be positive. Classification based on first positive FVIII inhibitor assessment. Inhibitor test result is: - > 5 BU/mL, categorized as high-titer inhibitor - ≥0.6 BU/mL but ≤5 BU/mL, categorized as low-titer

End point type	Post-hoc

End point timeframe:

50 exposure days to ADVATE

End point values	Previously untreated patients (PUPs)	Minimally treated patients (MTPs)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11			

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1 year and 3 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	N/A

Reporting groups

Reporting group title	ADVATE - Prophylactic Regimen

Reporting group description:

Weekly infusions of ADVATE. Study visits (physical examination, lab tests including FVIII inhibitor tests) every week during the first 10 exposure days (EDs), every 5 weeks during the next 10 EDs and every 10 weeks thereafter.

Recombinant antihemophilic factor, plasma/albumin-free method (rAHF-PFM): Intravenous infusion at a dose of 25 ± 5 IU/kg once per week. After 20 exposure days, the weekly infusions should be continued for as long as possible following the early prophylaxis period. If required by the clinical situation, dosing may be increased to twice weekly or even three times weekly after 20 exposure days, while keeping the low dose.

Serious adverse events	ADVATE - Prophylactic Regimen		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 19 (57.89%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
HEAD INJURY			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
TRAUMATIC HAEMATOMA			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
HAEMORRHAGE			

subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
ARTERIOVENOUS FISTULA OPERATION			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
FACTOR VIII INHIBITION			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
SOFT TISSUE HAEMORRHAGE			
subjects affected / exposed	1 / 19 (5.26%)		
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	ADVATE - Prophylactic Regimen		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
VASCULAR RUPTURE			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
General disorders and administration site conditions			

PYREXIA			
subjects affected / exposed	10 / 19 (52.63%)		
occurrences (all)	13		
Immune system disorders			
FOOD ALLERGY			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	6		
NASAL CONGESTION			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
NASAL DRYNESS			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
RHINORRHOEA			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
FACE INJURY			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
FALL			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
LIP INJURY			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
TONGUE INJURY			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

VACCINATION COMPLICATION			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
WRONG DRUG ADMINISTERED			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
FACTOR VIII INHIBITION (UNCONFIRMED)			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
LYMPHADENOPATHY			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ear and labyrinth disorders			
MIDDLE EAR EFFUSION			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eye disorders			
EYE DISCHARGE			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
LACRIMATION INCREASED			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
DIARRHOEA			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
TEETHING			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	10		
VOMITING			

subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
DERMATITIS			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
DERMATITIS ALLERGIC			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
DERMATITIS DIAPER			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	5		
ECZEMA			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
ERYTHEMA			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
RASH			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
JOINT RANGE OF MOTION DECREASED			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
ACUTE TONSILLITIS			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
CANDIDIASIS			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
COXSACKIE VIRAL INFECTION			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
EAR INFECTION			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
GASTROENTERITIS			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
GASTROENTERITIS VIRAL			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
HORDEOLUM			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
NASOPHARYNGITIS			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	7		
RHINITIS			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	13		
TONSILLITIS			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	7		
VIRAL INFECTION			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
VITAMIN D DEFICIENCY			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Early termination led to:
-) No statistical tests done on risk factors & inhibitor formation
-) FVIII consumption by subject not calculated due to large variation in # of exposure days
-) FVIII-specific antibody isotypes summary statistics not done

Notes: