Clinical trial results:
A Phase 3, Prospective, Multicenter, Open-label Study of Efficacy, Safety, and Pharmacokinetics of PEGylated Recombinant Factor VIII (ADYNOVATE) Administered for Prophylaxis and Treatment of Bleeding in Chinese Previously Treated Patients with Severe Hemophilia A (FVIII <1%).

Summary

EudraCT number	2023-000502-26
Trial protocol	Outside EU/EEA
Global end of trial date	05 September 2024

Results information

Result version number	v1 (current)
This version publication date	21 March 2025
First version publication date	21 March 2025

Trial information

Trial identification

Sponsor protocol code	TAK-660-3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05707351
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Ave, Lexington, MA, United States, 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.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	05 September 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the safety, efficacy, and pharmacokinetics of adynovate in chinese participants with severe Hemophilia A.

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study. For participants <18 years old, participants gave assent and their parents/legally authorized representative signed the ICF accordingly.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2023
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 37
Worldwide total number of subjects	37
EEA total number of subjects	0

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)	10
Adults (18-64 years)	27
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at various investigative sites in China from 27 March 2023 to 05 September 2024.

Pre-assignment

Screening details:

Participants with a diagnosis of severe hemophilia A were enrolled in this study to receive Adynovate (45 [±5] international units per kilogram [IU/kg]), infusion, intravenously (IV).

Period 1

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

Arms

Arm title	Adynovate

Arm description:

Participants received prophylactic treatment with Adynovate (45 [±5] IU/kg), infusion, IV, twice weekly, for at least 50 EDs or approximately 28 weeks.

Arm type	Experimental
Investigational medicinal product name	Adynovate
Investigational medicinal product code	TAK-660
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Adynovate 45±5 IU/kg, twice-weekly, for at least 50 exposure days (EDs), or approximately 28 weeks.

Number of subjects in period 1	Adynovate
Started	37
Completed	34
Not completed	3
Consent withdrawn by subject	2
Reason Not Specified	1

Baseline characteristics

Reporting groups	
Reporting group title	Adynovate
Reporting group description:	
Participants received prophylactic treatment with Adynovate (45 [±5] IU/kg), infusion, IV, twice weekly, for at least 50 EDs or approximately 28 weeks.	

Reporting group values	Adynovate	Total	
Number of subjects	37	37	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	24.1		
standard deviation	± 8.15	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	37	37	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	37	37	
Unknown or Not Reported	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	37	37	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	0	0	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Adynovate

Reporting group description:

Participants received prophylactic treatment with Adynovate (45 [±5] IU/kg), infusion, IV, twice weekly, for at least 50 EDs or approximately 28 weeks.

Subject analysis set title	Adynovate
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received prophylactic treatment with Adynovate (45 [±5] IU/kg), infusion, IV, twice weekly, for at least 50 EDs, or approximately 28 weeks.

Primary: Total Annualized Bleeding Rates (ABR)

End point title	Total Annualized Bleeding Rates (ABR)[1]

End point description:

Total ABR was defined as the number of treated and non-treated bleeding episodes (BEs) that occurred during the treatment period, calculated as, ABR= number of unique bleeds during treatment period/(length of treatment period [days]/365.25). Total ABR for all BEs, spontaneous or traumatic, recorded in the participant's electronic diary and/or recorded in the physician/nurse/study site notes were reported. The FAS included all participants who were assigned to receive a treatment regimen of

End point type	Primary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

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: Only descriptive analysis was planned for this endpoint.

End point values	Adynovate			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: bleeds per year				
arithmetic mean (standard deviation)	4.1 (± 13.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR Based on Bleeding Site

End point title	ABR Based on Bleeding Site

End point description:

ABR= number of unique bleeds during treatment period/(length of treatment period [days]/365.25). ABR for BEs based on bleeding site: joint or non-joint, recorded in the participant's electronic diary and/or recorded in the physician/nurse/study site notes were reported. The FAS included all participants who were assigned to receive a treatment regimen of Adynovate.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: bleeds per year				
arithmetic mean (standard deviation)				
Bleeding Site: Joint	2.7 (± 8.35)			
Bleeding Site: Non-Joint	1.4 (± 5.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Adynovate Infusions per Week During the Prophylactic Treatment Period

End point title	Number of Adynovate Infusions per Week During the Prophylactic Treatment Period

End point description:

The FAS included all participants who were assigned to receive a treatment regimen of Adynovate.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: infusions per week				
arithmetic mean (standard deviation)	2.003 (± 0.0563)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR Based on Bleeding Cause

End point title	ABR Based on Bleeding Cause

End point description:

ABR= number of unique bleeds during treatment period/(length of treatment period [days]/365.25). ABR for BEs based on bleeding cause: spontaneous/unknown or injury, recorded in the participant's electronic diary and/or recorded in the physician/nurse/study site notes were reported. The FAS included all participants who were assigned to receive a treatment regimen of Adynovate.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: bleeds per year				
arithmetic mean (standard deviation)				
Bleeding Cause: Spontaneous/Unknown	3.8 (± 13.65)			
Bleeding Cause: Injury	0.3 (± 0.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Adynovate Infusions per Month During the Prophylactic Treatment Period

End point title	Number of Adynovate Infusions per Month During the Prophylactic Treatment Period

End point description:

The FAS included all participants who were assigned to receive a treatment regimen of Adynovate.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: infusions per month				
arithmetic mean (standard deviation)	8.711 (± 0.2447)			

Statistical analyses

No statistical analyses for this end point

Secondary: Weight-adjusted Consumption of Adynovate per Week During the Prophylactic Treatment Period

End point title	Weight-adjusted Consumption of Adynovate per Week During the Prophylactic Treatment Period

End point description:

Weight-adjusted consumption (IU/kg) was derived as the total units infused (IU) divided by the last

available body weight (kg) prior to the infusion. The FAS included all participants who were assigned to receive a treatment regimen of Adynovate.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: IU/kg				
arithmetic mean (standard deviation)	89.637 (± 3.6807)			

Statistical analyses

No statistical analyses for this end point

Secondary: Weight-adjusted Consumption of Adynovate per Month During the Prophylactic Treatment Period

End point title	Weight-adjusted Consumption of Adynovate per Month During the Prophylactic Treatment Period

End point description:

Weight-adjusted consumption (IU/kg) was derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion. The SAS included all participants treated with at least 1 Adynovate dose. Subjects analysed is the number of participants with treated bleeding episodes.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: IU/kg				
arithmetic mean (standard deviation)	389.760 (± 16.0045)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeding Events in Each Category of Hemostatic Efficacy Rating at Resolution of Breakthrough Bleeding Episode

End point title	Number of Bleeding Events in Each Category of Hemostatic

	Efficacy Rating at Resolution of Breakthrough Bleeding Episode

End point description:

Hemostatic efficacy for treatment of BEs was rated on 4-point Likert scale as: excellent=full relief of pain & cessation of objective signs of bleeding after single infusion, no additional infusion is required for control of bleeding & administration of further infusion to maintain hemostasis would not affect scoring; good=definite pain relief and/or improvement in signs of bleeding after single infusion, possibly requires more than 2 infusions for complete resolution & administration of further infusion to maintain hemostasis would not affect scoring; fair=probable and/or slight relief of pain & slight improvement in signs of bleeding after single infusion, required multiple infusions for complete resolution; none=no improvement of signs/symptoms/conditions worsen. Missing indicates number of unique bleeding episodes without any overall hemostatic efficacy rating at resolution of breakthrough bleeding episode. FAS included all participants treated with at least 1 Adynovate dose.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: bleeding events				
number (not applicable)				
Excellent	7			
Good	14			
Fair	4			
None	0			
Missing	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Time Interval Between Bleeding Episodes (BEs)

End point title	Average Time Interval Between Bleeding Episodes (BEs)

End point description:

Average time interval between bleeding episodes (days)= Length of treatment period (days)/ Number of unique bleeds during treatment period. Average time interval was computed for participants with more than 1 unique BEs. The FAS included all participants who were assigned to receive a treatment regimen of Adynovate. Subjects analysed is the number of participants with more than 1 unique BEs.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: days				
arithmetic mean (standard deviation)	61.869 (± 30.9437)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Zero Bleeding Episodes During the Study

End point title	Percentage of Participants With Zero Bleeding Episodes During the Study

End point description:

Percentages were rounded off to the nearest single decimal place. The FAS included all participants who were assigned to receive a treatment regimen of Adynovate.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: percentage of participants				
number (not applicable)	54.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Weight-adjusted Consumption of Adynovate per Bleeding Episode

End point title	Weight-adjusted Consumption of Adynovate per Bleeding Episode

End point description:

Weight-adjusted consumption (IU/kg) was derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion. The SAS included all participants treated with at least 1 Adynovate dose. Subjects analysed is the number of participants with treated bleeding episodes.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: IU/kg				
arithmetic mean (standard deviation)	77.766 (± 81.7538)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Minor Surgeries With Hemostatic Efficacy Based on Global Hemostatic Efficacy Assessment (GHEA) Score as Assessed by the Operating Surgeon/Investigator

End point title	Number of Minor Surgeries With Hemostatic Efficacy Based on Global Hemostatic Efficacy Assessment (GHEA) Score as Assessed by the Operating Surgeon/Investigator

End point description:

GHEA score consisted of 3 individual rating scales: (1) Intra-operative Efficacy Assessment Scale, (2) Post-operative Efficacy Assessment Scale, and (3) Peri-operative Efficacy Assessment Scale. Each rating scale is based on 4 points scale ranging from: 3 (Excellent), 2 (Good), 1 (Fair), and 0 (None). The scores of 3 individual ratings scales were added together to form a GHEA score. Total score ranged from 0 to 9, where scores evaluate as: excellent (7 to 9), good (5 to 7), fair (3 to 4), and none (0 to 2). For a GHEA score of 7 to be rated "excellent" no individual assessment scores could be less than (<) 2 and at least 1 assessment score had to be equal to (=) 3; otherwise a score of 7 was rated "good". The FAS included all participants treated with at least 1 Adynovate dose. Only participants with hemostatic efficacy were to be assessed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: score on a scale				
number (not applicable)				

Notes:

[2] - Subjects analysed is zero as no participant reported blood loss for minor surgeries.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Actual and Predicted Intra-operative and Post-operative Blood Loss After the Surgery as Assessed by the Operating Surgeon/Investigator

End point title	Volume of Actual and Predicted Intra-operative and Post-operative Blood Loss After the Surgery as Assessed by the Operating Surgeon/Investigator

End point description:

The FAS included all participants treated with at least 1 Adynovate dose. Only subjects with blood loss for minor surgeries were to be assessed for this endpoint.

End point type	Secondary

End point timeframe:

Post-operative: Day 1 and at discharge Week 26

End point values	Adynovate			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: Liters				
arithmetic mean (standard deviation)	()			

Notes:

[3] - Subjects analysed is zero as no participant reported blood loss for minor surgeries.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Adynovate Infusions per Bleeding Episode

End point title	Number of Adynovate Infusions per Bleeding Episode

End point description:

The Safety Analysis Set (SAS) included all subjects treated with at least 1 Adynovate dose. Subjects analysed is the number of participants with treated bleeding episodes.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: infusions/bleeding episode				
arithmetic mean (standard deviation)	2.839 (± 2.9337)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Required Perioperative Transfusion of Blood, Red blood Cells, Platelets, and Other Blood Products

End point title	Number of Participants who Required Perioperative Transfusion of Blood, Red blood Cells, Platelets, and Other Blood Products

End point description:

The FAS included all participants treated with at least 1 Adynovate dose.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: FVIII Activity Level in Plasma Assessed by a 1-stage Clotting Assay

End point title	FVIII Activity Level in Plasma Assessed by a 1-stage Clotting Assay

End point description:

As per planned analysis, data for this outcome measure was collected and reported for initial pharmacokinetic (PK) assessment and second PK assessment. The initial PK assessment was performed prior to the baseline visit at Day -1. The second PK assessment was performed during the Week 20 visit. FVIII activity level reported was corrected for pre-infusion measurement. The Pharmacokinetic Full Analysis Set (PK FAS) included all participants who consented to PK evaluation, were treated with at least 1 Adynovate dose, and had at least 1 evaluable PK concentration post dose. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Day -1 and Week 20: pre-infusion, post-infusion at multiple time-points up to 96 hours

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: International units per deciliter(IU/dL)				
arithmetic mean (standard deviation)				
Initial PK Assessment: Pre-Infusion	0.00 (± 0.000)			
Initial PK Assessment:Post-Infusion:30 Mins(n=14)	112.02 (± 26.739)			
Initial PK Assessment:Post-Infusion:1 Hour(n=14)	106.67 (± 22.066)			
Initial PK Assessment:Post-Infusion:2 Hours	94.64 (± 32.185)			
Initial PK Assessment:Post-Infusion:4 Hours	87.67 (± 21.186)			

Initial PK Assessment:Post-Infusion:8 Hours	71.87 (± 16.929)			
Initial PK Assessment:Post-Infusion:12 Hours	58.96 (± 14.378)			
Initial PK Assessment:Post-Infusion:24 Hours	37.24 (± 11.573)			
Initial PK Assessment:Post-Infusion:48 Hours	14.60 (± 7.616)			
Initial PK Assessment:Post-Infusion:72 Hours	5.17 (± 3.876)			
Initial PK Assessment:Post-Infusion:96 Hours	2.06 (± 2.040)			
Second PK Assessment:Pre-Infusion(n=14)	0.00 (± 0.000)			
Second PK Assessment:Post-Infusion:30 Mins(n=13)	109.75 (± 18.192)			
Second PK Assessment:Post-Infusion:1 Hour(n=14)	109.51 (± 20.705)			
Second PK Assessment:Post-Infusion:2 Hours(n=14)	98.82 (± 20.196)			
Second PK Assessment:Post-Infusion:4 Hours(n=13)	86.41 (± 9.587)			
Second PK Assessment:Post-Infusion:8 Hours(n=14)	73.57 (± 15.750)			
Second PK Assessment:Post-Infusion:12 Hours(n=13)	62.31 (± 14.766)			
Second PK Assessment:Post-Infusion:24 Hours(n=14)	40.53 (± 11.918)			
Second PK Assessment:Post-Infusion:48 Hours(n=14)	16.13 (± 8.275)			
Second PK Assessment:Post-Infusion:72 Hours(n=14)	7.20 (± 4.754)			
Second PK Assessment:Post-Infusion:96 Hours(n=13)	3.25 (± 2.811)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Confirmed Inhibitory Antibodies to Factor VIII (FVIII), Binding Immunoglobulin G (IgG) and Immunoglobulin M (IgM) Antibodies to Adynovate and Chinese Hamster Ovary (CHO) Protein

End point title	Number of Participants With Confirmed Inhibitory Antibodies to Factor VIII (FVIII), Binding Immunoglobulin G (IgG) and Immunoglobulin M (IgM) Antibodies to Adynovate and Chinese Hamster Ovary (CHO) Protein

End point description:

The SAS included all participants treated with at least 1 Adynovate dose.

End point type	Secondary

End point timeframe:

Up to approximately 28 weeks

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: participants				
Inhibitory Antibodies to FVIII	0			
Binding IgG Antibodies to Adynovate (n=31)	0			
Binding IgM Antibodies to Adynovate (n=31)	0			
Binding Antibodies to CHO Proteins	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious Treatment-emergent Adverse Events (Serious TEAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious Treatment-emergent Adverse Events (Serious TEAEs)

End point description:

Adverse event(AE): any untoward medical occurrence in participant administered pharmaceutical product; untoward medical occurrence does not necessarily have causal relationship with this treatment. AE can therefore be any unfavorable & unintended sign (including an abnormal laboratory finding), symptom/disease temporally associated with use of medicinal (investigational) product whether or not it is related to medicinal product. TEAE: any AE either reported for first time or worsening of pre-existing event after first dose of study drug & within 30 days of last administration of study drug. Serious TEAEs: any untoward medical occurrence that: results in death, is life-threatening, requires inpatient hospitalization/prolongation of existing hospitalization, results in persistent or significant disability/incapacity, leads to congenital anomaly/birth defect in offspring of participant or is medically important. The SAS included all participants treated with at least 1 Adynovate dose.

End point type	Secondary

End point timeframe:

Up to approximately 28 weeks

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: participants				
TEAEs	16			
Serious TEAEs	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Daily Intra-Operative and Post-Operative Weight-Adjusted Consumption

Dose of Adynovate

End point title	Daily Intra-Operative and Post-Operative Weight-Adjusted Consumption Dose of Adynovate

End point description:

The FAS included all participants treated with at least 1 Adynovate dose. Only participants who were administered Adynovate for minor surgeries were to be assessed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline through study completion or ≥50 EDs whichever occurred last (approximately 28 weeks)

End point values	Adynovate			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: participants				

Notes:

[4] - Subjects analysed is zero as no participants were administered Adynovate for minor surgeries.

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery Over Time During Adynovate Prophylactic Treatment

End point title	Incremental Recovery Over Time During Adynovate Prophylactic Treatment

End point description:

Incremental recovery (IR) was calculated as IR (international units per deciliter)/(international units per kilogram [(IU/dL)/(IU/kg)] = [PostFVIII (IU/dL)-PreFVIII (IU/dL)]/Weight Adjusted Dose (IU/kg). The SAS included all participants treated with at least 1 Adynovate dose. Subjects analysed is the number of participants with data available for analyses. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Baseline, Week 6, and Study Completion (approximately Week 28)

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)				
Baseline	2.4777 (± 0.67876)			
Week 6 (n=31)	2.5147 (± 0.64379)			
Study Completion (n=31)	2.4083 (± 0.50714)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Level of FVIII Activity in Plasma

End point title	Pre-dose Level of FVIII Activity in Plasma

End point description:

The SAS included all participants treated with at least 1 Adynovate dose. Subjects analysed is the number of participants with data available for analyses. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 6, 12, and Study Completion (approximately Week 28): Within 30 minutes pre-infusion

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: IU/dL				
arithmetic mean (standard deviation)				
Baseline	0.06 (± 0.232)			
Week 2 (n=29)	3.28 (± 4.999)			
Week 6 (n=31)	2.91 (± 2.802)			
Week 12 (n=31)	3.61 (± 3.994)			
Study Completion	7.06 (± 16.365)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Level of FVIII Antigen in Plasma

End point title	Pre-dose Level of FVIII Antigen in Plasma

End point description:

IU/mL stands for international units per milliliter. The SAS included all participants treated with at least 1 Adynovate dose. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 6, 12, and Study Completion (approximately Week 28): Within 30 minutes pre-infusion

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: IU/mL				
arithmetic mean (standard deviation)				
Baseline	0.0276 (± 0.06577)			
Week 2 (n=36)	0.0782 (± 0.07888)			
Week 6 (n=35)	0.0689 (± 0.04518)			
Week 12 (n=34)	0.0649 (± 0.04286)			
Week 20 (n=14)	0.0856 (± 0.05404)			
Study Completion	0.1011 (± 0.11326)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Level of Von Willebrand Factor (VWF) Antigen in Plasma

End point title	Pre-dose Level of Von Willebrand Factor (VWF) Antigen in Plasma

End point description:

The SAS included all participants treated with at least 1 Adynovate dose. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 6, 12, and Study Completion (approximately Week 28): Within 30 minutes pre-infusion

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: percent (%)				
arithmetic mean (standard deviation)				
Baseline	83.69 (± 35.967)			
Week 2 (n=36)	84.46 (± 30.811)			
Week 6 (n=35)	84.99 (± 34.216)			
Week 12 (n=34)	86.57 (± 30.024)			

Week 20 (n=14) Study Completion	91.26 (± 34.240) 90.26 (± 31.714)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point title	Clearance (CL) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point description:

Clearance reported was calculated based on pre-infusion corrected concentration data. As per planned analysis, data for this outcome measure was collected and reported for initial PK assessment and second PK assessment. The initial PK assessment was performed prior to the baseline visit at Day -1. The second PK assessment was performed during the Week 20 visit. [(dL/h)/kg] stands for deciliters per hour per kilogram. The PK FAS included all participants who consented to PK evaluation, were treated with at least 1 Adynovate dose, and had at least 1 evaluable PK concentration post dose. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Day -1 and Week 20: pre-infusion, post-infusion at multiple timepoints up to 96 hours

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: (dL/h)/kg				
arithmetic mean (standard deviation)				
Initial PK Assessment Second PK Assessment (n=14)	0.0206 (± 0.00629) 0.0192 (± 0.00594)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point title	Volume of Distribution for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point description:

Volume of distribution was calculated based on pre-infusion corrected concentration data. As per planned analysis, data for this outcome measure was collected and reported for initial PK assessment and second PK assessment. The initial PK assessment was performed prior to the baseline visit at Day -1. The second PK assessment was performed during the Week 20 visit.'n' denotes the number of participants with data available for analysis at the specified time-point. The PK FAS included all

participants who consented to PK evaluation, were treated with at least 1 Adynovate dose, and had at least 1 evaluable PK concentration post dose. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Day -1 and Week 20: pre-infusion, post-infusion at multiple timepoints up to 96 hours

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: deciliters per kilogram (dL/kg)				
arithmetic mean (standard deviation)				
Initial PK Assessment	0.458 (± 0.107)			
Second PK Assessment (n=14)	0.480 (± 0.0953)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Versus Time Curve From 0 to 96 Hours (AUC0-96) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point title	Area Under the Concentration Versus Time Curve From 0 to 96 Hours (AUC0-96) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point description:

AUC0-96 was calculated based on pre-infusion corrected concentration data. As per planned analysis, data for this outcome measure was collected and reported for initial PK assessment and second PK assessment. The initial PK assessment was performed prior to the baseline visit at Day -1. The second PK assessment was performed during the Week 20 visit. h*IU/dL stands for hour*international units per deciliter. The PK FAS included all participants who consented to PK evaluation, were treated with at least 1 Adynovate dose, and had at least 1 evaluable PK concentration post dose. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Day -1 and Week 20: pre-infusion, post-infusion at multiple timepoints up to 96 hours

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: h*IU/dL				
arithmetic mean (standard deviation)				
Initial PK Assessment	2348 (± 737)			
Second PK Assessment (n=14)	2582 (± 736)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point title	Maximum Concentration (Cmax) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point description:

Cmax was calculated based on pre-infusion corrected concentration data. As per planned analysis, data for this outcome measure was collected and reported for initial PK assessment and second PK assessment. The initial PK assessment was performed prior to the baseline visit at Day -1. The second PK assessment was performed during the Week 20 visit. The PK FAS included all participants who consented to PK evaluation, were treated with at least 1 Adynovate dose, and had at least 1 evaluable PK concentration post dose. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Day -1 and Week 20: pre-infusion, post-infusion at multiple timepoints up to 96 hours

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: IU/dL				
arithmetic mean (standard deviation)				
Initial PK Assessment	113 (± 26.1)			
Second PK Assessment (n=14)	115 (± 20.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Concentration (Cpredose) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point title	Pre-dose Concentration (Cpredose) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point description:

Cpredose was calculated based on pre-infusion corrected concentration data. As per planned analysis, data for this outcome measure was collected and reported for initial PK assessment and second PK assessment. The initial PK assessment was performed prior to the baseline visit at Day -1. The second PK assessment was performed during the Week 20 visit. The PK FAS included all participants who consented to PK evaluation, were treated with at least 1 Adynovate dose, and had at least 1 evaluable PK concentration post dose. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Day -1 and Week 20: pre-infusion, post-infusion at multiple timepoints up to 96 hours

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: IU/dL				
arithmetic mean (standard deviation)				
Initial PK Assessment	0 (± 0)			
Second PK Assessment (n=14)	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Phase Elimination Half-life (T1/2) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point title	Terminal Phase Elimination Half-life (T1/2) for FVIII Activity Following an Initial Single Dose and Steady-state Dose of Adynovate

End point description:

T1/2 was calculated based on pre-infusion corrected concentration data. As per planned analysis, data for this outcome measure was collected and reported for initial PK assessment and second PK assessment. The initial PK assessment was performed prior to the baseline visit at Day -1. The second PK assessment was performed during the Week 20 visit. The PK FAS included all participants who consented to PK evaluation, were treated with at least 1 Adynovate dose, and had at least 1 evaluable PK concentration post dose. 'n' denotes the number of participants with data available for analysis at the specified time-point.

End point type	Secondary

End point timeframe:

Day -1 and Week 20: pre-infusion, post-infusion at multiple timepoints up to 96 hours

End point values	Adynovate			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: hour				
arithmetic mean (standard deviation)				
Initial PK Assessment	16.0 (± 3.27)			
Second PK Assessment (n=14)	18.5 (± 4.61)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 28 weeks	
Adverse event reporting additional description:	
The SAS included all participants treated with at least 1 Adynovate dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Adynovate
Reporting group description:	
Participants received prophylactic treatment with Adynovate (45 [±5] IU/kg), infusion, IV, twice weekly, for at least 50 EDs or approximately 28 weeks.	

Serious adverse events	Adynovate		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 37 (2.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Adynovate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 37 (21.62%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	 3 / 37 (8.11%) 3		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 2 / 37 (5.41%) 2 3 / 37 (8.11%) 7		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	 2 / 37 (5.41%) 2		
Metabolism and nutrition disorders Hyperlipidaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia subjects affected / exposed occurrences (all)	 2 / 37 (5.41%) 2 2 / 37 (5.41%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported