Clinical trial results:
Phase 4, Multicenter, Prospective, Interventional, Post-Marketing Study in Hemophilia A Patients in India Receiving ADVATE as On-Demand or Prophylaxis Under Standard Clinical Practice

Summary

EudraCT number	2022-004149-11
Trial protocol	Outside EU/EEA
Global end of trial date	10 February 2023

Results information

Result version number	v1 (current)
This version publication date	23 August 2023
First version publication date	23 August 2023

Trial information

Trial identification

Sponsor protocol code	TAK-761-4009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04985682
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 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	10 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to assess the safety of ADVATE based on serious adverse events (SAEs) [including factor VIII (FVIII) inhibitors].

Protection of trial subjects:

All study participants or legally authorised representative (in case of study participants <18 years of age) were required to read and sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 2022
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	India: 50
Worldwide total number of subjects	50
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)	14
Adolescents (12-17 years)	10
Adults (18-64 years)	26
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 4 investigative sites in India from 14 January 2022 to 10 February 2023.

Pre-assignment

Screening details:

Participants previously treated for hemophilia A who met eligibility criteria were enrolled to receive ADVATE according to a dosing regimen determined by the treating physician and in accordance with the national product label.

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	Hemophilia A Group

Arm description:

Participants with hemophilia A were treated with ADVATE according to a regimen determined by the treating physician at the study site and in accordance with the national product label under standard clinical practice for 6.7 months.

Arm type	Experimental
Investigational medicinal product name	ADVATE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Antihemophilic factor (AHF) activity expressed in international units (IU) per vial.

Number of subjects in period 1	Hemophilia A Group
Started	50
Completed	49
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Hemophilia A Group
Reporting group description:	
Participants with hemophilia A were treated with ADVATE according to a regimen determined by the treating physician at the study site and in accordance with the national product label under standard clinical practice for 6.7 months.	

Reporting group values	Hemophilia A Group	Total	
Number of subjects	50	50	
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	19.5		
standard deviation	± 13.01	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	50	50	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	50	50	
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	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	50	50	
Unknown or Not Reported	0	0	
Region of Enrollment Units: Subjects			
India India	50	50	
Weight Units: kilograms (kg)			
arithmetic mean	48.5		
standard deviation	± 20.95	-	
Height Units: centimetres (cm)			
arithmetic mean	152.0		
standard deviation	± 22.68	-	
Body Mass Index (BMI)			

BMI = Weight (kg)/Height (m)^2			
Units: kilograms per meter square (kg/m^2)			
arithmetic mean	19.9		
standard deviation	± 5.42	-	

End points

End points reporting groups

Reporting group title	Hemophilia A Group

Reporting group description:

Participants with hemophilia A were treated with ADVATE according to a regimen determined by the treating physician at the study site and in accordance with the national product label under standard clinical practice for 6.7 months.

Primary: Number of Participants With Serious Adverse Events (SAE) at Least Possibly Related to ADVATE

End point title	Number of Participants With Serious Adverse Events (SAE) at Least Possibly Related to ADVATE[1]

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. An SAE was defined as any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalization or prolongation of present hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect or was a medically important event. Number of participants with SAEs (including FVIII inhibitor formation) that were at least possibly related to ADVATE were reported. Safety Analysis Set (SAS) included all participants who received ADVATE at any time during the study.

End point type	Primary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

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 statistics were planned to be analysed for this endpoint.

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Non-serious Adverse Events (AEs) at Least Possibly Related to ADVATE

End point title	Number of Participants With Non-serious Adverse Events (AEs) at Least Possibly Related to ADVATE

End point description:

An AE was any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. Number of participants with non-serious AEs that were at least possibly related to ADVATE were reported. SAS included all participants who received ADVATE at any time during the study.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Annualized Bleeding Rate (ABR) With Prophylactic Treatment of ADVATE

End point title	Total Annualized Bleeding Rate (ABR) With Prophylactic Treatment of ADVATE

End point description:

ABR was defined as number of bleeding episodes during the study period divided by total number of study period days multiplied by 365.25. The mean ABR and standard error was estimated using a generalized linear model (GLM). The total ABR is reported in this outcome measure. EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: bleeds per year				
arithmetic mean (standard error)				
Total ABR	2.65 (± 0.195)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes in Clinical Laboratory Parameters

End point title	Number of Participants With Clinically Significant Changes in Clinical Laboratory Parameters

End point description:

Clinical laboratory parameters included hematology, clinical chemistry, viral serology, factor VIII (FVIII) antigen, FVIII activity, incremental recovery, and FVIII inhibitor. Clinical significance was judged as per Investigator's assessment. SAS included all participants who received ADVATE at any time during the study.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR With Prophylactic Treatment of ADVATE Categorized Based on Location of Bleed

End point title	ABR With Prophylactic Treatment of ADVATE Categorized Based on Location of Bleed

End point description:

ABR was defined as number of bleeding episodes during the study period divided by total number of study period days multiplied by 365.25. The mean ABR and standard error were estimated using a GLM. The ABR by bleed sites (example, joint, soft tissue, muscle, other [mouth, gums or nose] are reported in this outcome measure. EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: bleeds per year				
arithmetic mean (standard error)				
Bleed Location: Joint	2.33 (± 0.203)			
Bleed Location: Soft Tissue	0.04 (± 1.000)			
Bleed Location: Muscle	0.16 (± 0.628)			
Bleed Location: Other (Mouth, Gums or Nose)	0.12 (± 0.813)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Number of ADVATE Infusions Required per Week During Prophylactic Treatment

End point title	Average Number of ADVATE Infusions Required per Week During Prophylactic Treatment

End point description:

EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: infusions per week				
arithmetic mean (standard deviation)				
Per Week	2.5 (± 0.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of ADVATE Infusions Required During Prophylactic Treatment

End point title	Total Number of ADVATE Infusions Required During Prophylactic Treatment

End point description:

EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: infusions				
arithmetic mean (standard deviation)	65.8 (± 22.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: ABR With Prophylactic Treatment of ADVATE Categorized Based on Type of Bleed

End point title	ABR With Prophylactic Treatment of ADVATE Categorized Based on Type of Bleed

End point description:

ABR was defined as number of bleeding episodes during the study period divided by total number of study period days multiplied by 365.25. The mean ABR and standard error were estimated using a GLM. The ABR by bleed cause (example, spontaneous, injury, and unknown) are reported in this outcome measure. EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: bleeds per year				
arithmetic mean (standard error)				
Bleed Type: Spontaneous	1.86 (± 0.211)			
Bleed Type: Injury	0.20 (± 0.692)			
Bleed Type: Unknown	0.59 (± 0.541)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Body Mass Adjusted Consumption of ADVATE per Week During Prophylactic Treatment

End point title	Average Body Mass Adjusted Consumption of ADVATE per Week During Prophylactic Treatment

End point description:

Body mass adjusted consumption (IU/kg) was derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion. EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: IU/kg per week				
arithmetic mean (standard deviation)				
Per Week	67.1 (± 24.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Mass Adjusted Consumption of ADVATE During Prophylactic Treatment

End point title	Total Body Mass Adjusted Consumption of ADVATE During Prophylactic Treatment

End point description:

Body mass adjusted consumption international units per kilograms (IU/kg) was derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion. EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: IU/kg				
arithmetic mean (standard deviation)	1739.7 (± 621.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Number of ADVATE Infusions Required per Month During Prophylactic Treatment of Bleeding Episode

End point title	Average Number of ADVATE Infusions Required per Month During Prophylactic Treatment of Bleeding Episode

End point description:

EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: infusions per month				
arithmetic mean (standard deviation)	11.0 (± 3.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Hemostatic Efficacy Rating of ADVATE for Treatment of Bleeding Episodes

End point title	Overall Hemostatic Efficacy Rating of ADVATE for Treatment of Bleeding Episodes

End point description:

Overall hemostatic efficacy for bleeding episodes treatment 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;moderate=probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion,required multiple infusions for complete resolution;none=no improvement of signs/symptoms/conditions worsen.EFAS=all participants for whom all inclusion and none of the exclusion criteria were met.Number of subjects analysed=participants with bleeds who required ADVATE infusion for management of bleeding episode.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: bleeding episodes				
Excellent	21			
Good	26			
Moderate	4			
None	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of ADVATE Infusions Required to Achieve Resolution of Bleeding Episodes

End point title	Number of ADVATE Infusions Required to Achieve Resolution of Bleeding Episodes

End point description:

EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met. Number of subjects analysed are the number of participants with bleeds who required ADVATE infusion for management of the bleeding episode.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: infusions				
arithmetic mean (standard deviation)	1.2 (± 0.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Body Mass Adjusted Consumption of ADVATE per Month During Prophylactic Treatment

End point title	Average Body Mass Adjusted Consumption of ADVATE per Month During Prophylactic Treatment

End point description:

Body mass adjusted consumption (IU/kg) was derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion. EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: IU/kg per month				
arithmetic mean (standard deviation)	291.7 (± 104.80)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Mass Adjusted Consumption of ADVATE per Bleeding Episode

End point title	Total Body Mass Adjusted Consumption of ADVATE per Bleeding Episode

End point description:

Body mass adjusted consumption (IU/kg) was derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion. EFAS comprised of all participants for whom all inclusion and none of the exclusion criteria were met. Number of subjects analysed are the number of participants with bleeds who required ADVATE infusion for management of the bleeding episode.

End point type	Secondary

End point timeframe:

Baseline (Day 0) up to end of study (up to 12.9 months)

End point values	Hemophilia A Group			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: IU/kg				
arithmetic mean (standard deviation)	34.8 (± 19.79)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline (Day 0) up to end of study (up to 12.9 months)	
Adverse event reporting additional description:	
SAS included all participants who received ADVATE at any time during the study.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Hemophilia A Group
Reporting group description:	
Participants with hemophilia A were treated with ADVATE according to a regimen determined by the treating physician at the study site and in accordance with the national product label under standard clinical practice for 6.7 months.	

Serious adverse events	Hemophilia A Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Hemophilia A Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 50 (12.00%)		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	3		
Skin laceration			

subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 2 / 50 (4.00%) 2		
Infections and infestations Varicella subjects affected / exposed occurrences (all)	 1 / 50 (2.00%) 1		

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