Clinical Study Protocol

NCT Number: NCT04985682

Title: 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

Study Number: TAK-761-4009

Document Version and Date: Version 1.0 (02-December-2022)

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PROTOCOL AMENDMENT 1: TAK-761-4009

TITLE:	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
SHORT TITLE:	ADVATE INDIA PMC Study
STUDY PHASE:	Phase 4 (post-marketing)
DRUG:	ADVATE (Coagulation Factor VIII (Recombinant) rFVIII, Plasma/Albumin Free Method; Octocog Alfa)
IND NUMBER:	Non-IND
EUDRACT NUMBER:	Non-EUDRACT
SPONSOR:	Takeda Biopharmaceuticals India Pvt. Ltd. 6th Floor, Building 8, Tower C, DLF Cyber City, Gurgaon 122002, Haryana, India
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter study
PROTOCOL HISTORY:	Original Protocol: 31 JUL 2019

PROTOCOL AMENDMENT 1 SIGNATURE PAGE

Sponsor's (Takeda) Approval

Signature:	Date: 02-Dec-2022 | 13:49:35 JST
[redacted], MD [redacted], Takeda Biopharmaceuticals India Pvt. Ltd.	DocuSigned by: [redacted]

Investigator's Acknowledgement

I have read this protocol for ADVATE Study TAK-761-4009.

Title: Phase 4, Multicenter, Prospective, Interventional, Post-Marketing Study in Hemophilia A Patients in India Receiving ADVATE as On-demand or Prophylaxis Under Standard Clinical PracticeI have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

PROTOCOL AMENDMENT 1 SIGNATURE PAGE

Sponsor's (Takeda) Approval

Signature:	Date:
[redacted], MD [redacted], Takeda Biopharmaceuticals India Pvt. Ltd.	

Investigator's Acknowledgement

I have read this protocol for ADVATE Study TAK-761-4009.

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Investigator Name and Address: (please handprint or type)	

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Takeda Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" within 24 hours to the Takeda Global Drug Safety Department. The fax number and e-mail address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Takeda medical monitor using the details below.

Takeda India medical monitor:
[redacted]
Tel: [redacted]
Email: [redacted]

CRO local medical monitor:
Contact details will be provided separately prior to first site initiation.

For protocol- or safety-related questions or concerns, the investigator must contact the medical monitor:

Takeda India medical monitor (during business hours 9:00 AM through 5:00 PM IST [India]):
[redacted]
Tel: [redacted]
Email: [redacted]

CRO local medical monitor:
Contact details will be provided separately prior to first site initiation.

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Takeda within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

This includes any instances wherein the quality or performance of a Takeda product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination); or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products); or a product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE, which include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg, reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

For instructions on reporting AEs related to product complaints, see Appendix 3.4.

Please use the information below as applicable to report the Product Quality Complaint or Non-Medical Complaint:

Origin of Product Quality Complaint	**E-mail Address**
North and South America	PQC@Takeda.com
European Union and Rest of World	PQCROW@Takeda.com

Telephone number (provided for reference if needed):

Takeda, Lexington, MA (USA)
1-800-828-2088

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: TAK-761-4009	**Drug:** ADVATE (Coagulation Factor VIII (Recombinant) rFVIII, Plasma/Albumin Free Method; Octocog Alfa)
Title of the study: 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	
Short title: ADVATE INDIA PMC Study	
Study phase: Phase 4 (post-marketing)	
Number of subjects (total and per treatment arm): Total: 50 subjects (single-group assignment)	
Investigator(s): Multicenter study	
Site(s) and Region(s): India (multicenter)	
Study period (planned): Q2/Q3 2021 to Q1 2023	**Clinical phase:** 4 (post-marketing)

Objectives:

Primary:

- To assess the safety of ADVATE based on serious adverse events (SAEs) (including FVIII inhibitors)

Secondary:

- To assess the safety of ADVATE based on adverse events (AEs) and changes in laboratory parameters
- To assess the efficacy of prophylactic treatment with ADVATE
- To assess the efficacy of on-demand treatment with ADVATE in the control of bleeding episodes

Rationale:

The purpose of this study is to evaluate the safety and efficacy of ADVATE when used under standard clinical practice in previously treated hemophilia A patients (PTPs) in India.

Investigational product, dose, and mode of administration:

ADVATE (Coagulation Factor VIII (Recombinant) rFVIII, Plasma/Albumin Free Method; Octocog Alfa)

Refer to the ADVATE India Product Label for further information.

Methodology:

This is a Phase 4, multicenter, prospective, interventional, post-marketing study in previously treated hemophilia A patients (PTPs) in India receiving ADVATE under standard clinical practice.

All enrolled subjects who have met the inclusion and exclusion criteria will be treated with ADVATE according to a regimen determined by the treating physician and in accordance with the national product label. The individual subject´s duration of participation is expected to be approximately 7-8 months. The period of observation for each subject will be 6 months; another 10 to 15 days are anticipated for the study completion visit ("End-of-Treatment

Visit"). The starting point of the observation will be an infusion of ADVATE at baseline to determine incremental recovery (IR).

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. The subject or legally authorized representative (in case of study participants <18 years of age) gave written informed consent to participate in the study.
2. Subject of any age with hemophilia A.
3. Subject is defined as previously treated patient (PTP):
   - Subject aged ≥ 6 years that has been previously treated with plasma-derived and/or recombinant FVIII concentrate(s) for a minimum of 150 exposure days (EDs).
   - Subject aged < 6 years that has been previously treated with plasma-derived and/or recombinant FVIII concentrate(s) for a minimum of 50 EDs.
4. Subject has negative history of FVIII inhibitors and negative inhibitor at screening defined as less than 0.6 Bethesda units (BU)/mL (Nijmegen-modified Bethesda assay).
5. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm^3, as confirmed by central laboratory at screening.
6. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
7. The subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria:

1. Subject has known hypersensitivity to mouse or hamster proteins or to any of the excipients of FVIII concentrates.
2. Subject has been diagnosed with bleeding disorder(s) other than congenital hemophilia A, such as acquired hemophilia A, von Willebrand´s disease or thrombocytopenia (platelet count<100,000/mL).
3. Subject has received treatment for hemophilia A with non-FVIII products/concentrates (eg, emicizumab [Hemlibra®]) in the 6 months prior to screening.
4. Subject has severe chronic hepatic dysfunction [eg, ≥ 5 times upper limit of normal alanine aminotransferase (ALT), aspartate aminotransferase (AST) or INR > 1.5 as confirmed by central laboratory at screening].
5. Subject has planned, or is likely to have, surgery during the study period.
6. Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance.
7. Subject is currently receiving or is scheduled to receive during the course of the study, an immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than antiretroviral chemotherapy.
8. Subject has participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.

9. Subject is a family member or employee of the investigator.

Maximum duration of subject participation in the study: Approximately 7-8 months

- Planned duration of screening period: up to 45 days (until Day 0/Baseline Visit)
- Planned duration of treatment period: 6 months
- Time allocated for End-of-Treatment Visit: 10-15 days
- Planned duration of follow-up: Not applicable. There will be no follow-up.

Sample size calculation:

According to the WFH Report on the Annual Global Survey 2017[i], there were a total of 15,920 cases of hemophilia A in India in 2017. Due to the low prevalence of hemophilia A and the difficulty in switching patients from their current therapy, the planned sample size is 50 subjects.

Statistical analysis:

The statistical analysis for this study will be descriptive in nature. Descriptive statistics will include specifically, but not exclusively, arithmetic mean, standard deviation, medians, quartiles and interquartile range, minimum, maximum, proportions, frequency counts, and 95% confidence intervals of point estimates.

Statistical Analysis for Primary Outcome Measure:

Frequency counts and percentages for possibly or probably related SAEs (including FVIII inhibitor formation) as well as for subjects with possibly or probably related SAEs (including FVIII inhibitor formation) that occurred during or after first ADVATE infusion will be summarized. The incidence of FVIII inhibitor development will also be summarized by high-titer (>5 BU) and low-titer (0.6-5 BU).

Statistical Analysis for Secondary Outcome Measures:

Safety:

See statistical analysis for primary outcome measure.

All AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term. A listing of all AEs will be presented by subject identifier, age, sex, preferred term and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment by investigator, onset date, stop date and medication or non-drug therapy to treat the AE.

Shift tables will be presented for the results of clinical laboratory data.

Efficacy:

The annualized bleeding rate (ABR) during the prophylactic treatment will be assumed to have a negative binomial distribution, and the mean ABR (95% CI) will be estimated using a generalized linear model (GLM). The total ABR and ABR by bleed cause/ site, i.e. joint, non-joint, target joints, spontaneous, traumatic, will be summarized descriptively as well.

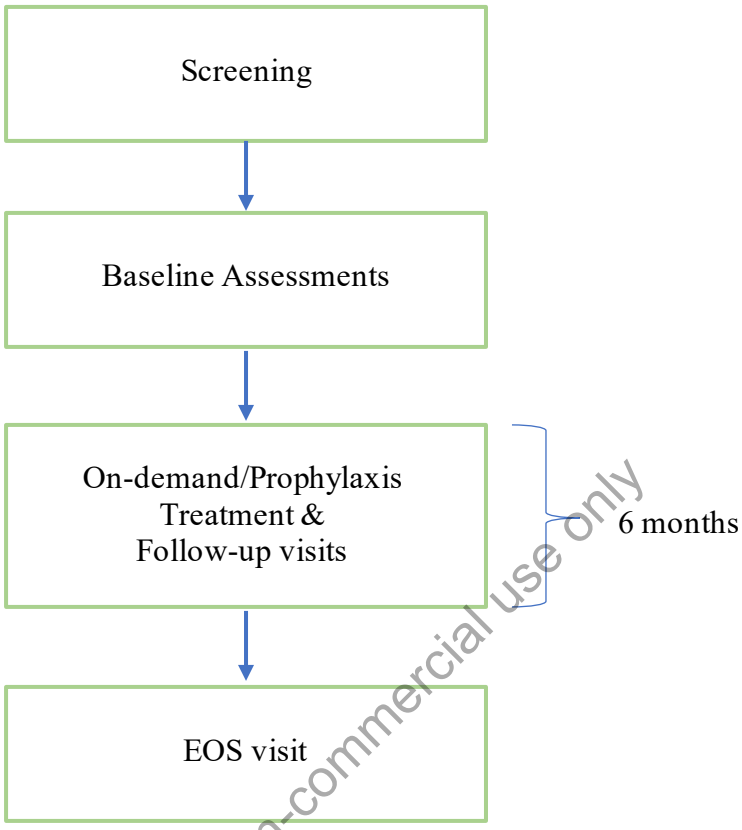
[i] World Federation of Hemophilia report on the annual global survey 2017. Published by the World Federation of Hemophilia. Montréal, Québec, Canada. October 2018.

Summary statistics for the total number of infusions, as well as the average number of prophylactic infusions per week and per month of prophylaxis will be provided. Similarly, the total body mass adjusted consumption and the average consumption of ADVATE per week and per month during prophylactic treatment will be provided.

For the overall hemostatic efficacy rating at resolution of bleed, for the number of infusions of ADVATE to control a bleeding episode, as well as for the body mass adjusted consumption of ADVATE per bleeding event, summary statistics will be presented. These tables will be also presented by bleeding site, cause and severity.

1.2 Schema

Figure 1. Study Design and Visit Schedule



1.3 Schedule of Activities

Table 1. Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening Visit	Baseline Visit	Visit 1	Visit 2	Unscheduled Visit(s)[a]	End of Treatment Visit	Study Termination Visit[b]
Time point	**Up to 45 days prior to Day 0**	**Day 0**	**1 month ± 1 week**	**3 month ± 1 week**		**6 month ± 1 week**	
Informed Consent[c]	X						
Eligibility Criteria	X	X[d]					
Medical History	X						
Hemophilia A Disease History, Bleeding History and FVIII Treatment History	X						
Medications History (other than Hemophilia A)	X						
Physical Exam	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Concomitant Medications and Non-drug Therapies	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Laboratory assessments	See Table 2						
Bleeding Episodes and Treatment[e]	X	X	X	X	X	X	X
Review of Subject Diary		X	X	X	X	X	X
IP Use		X	X	X	X	X	X
IP Dispense[f]		X	X	X	X		

[a] Unscheduled visits could be performed for any reason (bleed management, safety event, etc.) as per Investigators' discretion.
[b] Study Termination Visit will be performed only if subject is discontinuing the study or withdrawing from the study without completing the End of Treatment Visit.
[c] Occurs prior to any study-specific procedure.
[d] Same eligibility criteria to be used as at Screening.
[e] To collect information on the type of bleeding episodes (site, severity, duration) and the treatment used for the bleeding episodes (drug, dose, frequency, duration).
[f] ADVATE should be dispensed to provide sufficient treatment until at least the next scheduled visit, or as appropriate.

Table 2. Schedule of Clinical Laboratory Assessments

Procedures/ Assessments	Screening Visit	Baseline Visit	Visit 1	Visit 2	Unscheduled Visit(s)[a]	End of Treatment Visit	Study Termination Visit[b]
Time point	**Up to 45 days prior to Day 0**	**Day 0**	**1 month ± 1 week**	**3 month ± 1 week**		**6 month ± 1 week**	
Hematology[c]	X				X (optional)	X	X
Clinical chemistry[d]	X				X (optional)	X	X
Viral serology[e]	X					X	X
FVIII Antigen	X						
FVIII Activity	X				X (optional)		
Incremental Recovery (IR)[f]		X		X (optional)		X	X
FVIII Inhibitor[g]	X	X	X	X	X	X	X

[a] Unscheduled visits could be performed for any reason (bleed management, safety event, etc.) as per Investigators' discretion

[b] Study Termination Visit will be performed only if subject is discontinuing the study or withdrawing from the study without completing the End of Treatment Visit.

[c] Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count.

[d] Clinical chemistry assessments include: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose.

[e] Viral serology includes: HIV-1 Ab, HIV-2 Ab, HBcAb, HBsAb, HBsAg, and HCV Ab. Any HIV or HCV positive sample will be tested by PCR for viral titer, HIV positive subjects will have CD4 counts monitored every 3 months during the course of the study.

[f] For assessment of IR: samples will be taken within 0.5 h before the start of the infusion, and at 15-30 minutes after the infusion. Prior to the pre-infusion blood draw for IR determination, subjects should have a washout period from previous plasma-derived and/or recombinant FVIII concentrate(s) treatment. The washout period will depend on the type of product the subject receives, ie, at least 48 hours for products with standard half-life and 84-96 hours for extended half-life products.

[g] If an inhibitory titer ≥ 0.6 BU by Nijmegen, the test will be confirmed in the central laboratory within 2 weeks of study site notification.

2. INTRODUCTION

2.1 Indication and Current Treatment Options

FVIII is the blood clotting factor deficient or absent in individuals with hemophilia A. Hemophilia A is an X-linked chromosomal recessive disorder that results from defective or deficient plasma FVIII and consequently insufficient coagulant activity. Approximately 1 in 5,000 live male births worldwide has hemophilia A, resulting in over 400,000 affected individuals (Bolton-Maggs and Pasi, 2003, Soucie et al., 1998). Disease severity is dictated by plasma FVIII levels with approximately 60% of patients having severe disease, defined by FVIII levels < 1% of normal, and the remaining patients have moderate (FVIII levels 1-5%) or mild disease (FVIII levels 5-40%). Patients with severe disease are at risk of spontaneous bleeding into joints, muscles, and internal organs as well as trauma-induced bleeding following injury and surgery. Repeated bleeding into joints, which may occur as frequently as 20 to 30 times per year, is a major cause of morbidity and leads to hemophilic arthropathy (Lee, 2007). Bleeding episodes in young children also contribute to school absenteeism, interfere with physical function, and prevent them from participating in normal childhood activities (Shapiro et al., 2001).

At present, FVIII replacement is the only symptomatic therapy (in terms of bleed treatment) available for the treatment of hemophilia A. FVIII administration temporarily increases FVIII levels and has been shown to temporarily correct the bleeding tendency. FVIII can be administered in response to a bleeding episode or as prophylactic replacement.

ADVATE contains recombinant coagulation factor VIII (FVIII), a glycoprotein that has an amino acid sequence comparable to human FVIII, and posttranslational modifications that are similar to those of the plasma-derived molecule. Activated FVIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin and a fibrin clot is formed.

ADVATE is a third-generation recombinant FVIII concentrate, produced by a genetically engineered Chinese hamster ovary (CHO) cell line and without the addition of any human or animal-derived protein in the cell-culture process, purification or final formulation. This production process virtually eliminates the risk of pathogen transmission (see Section 2.2).

ADVATE is indicated for use in adults and children with hemophilia A for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

2.2 Product Background and Clinical Information

Baxalta US Inc., now part of Takeda, has developed a third-generation recombinant FVIII concentrate (Antihemophilic Factor [Recombinant], Plasma/Albumin-Free Method [rAHF-PFM]) by the name of ADVATE[ii], produced by a genetically engineered Chinese hamster ovary (CHO) cell line. The plasma/albumin-free method does not employ any exogenously added proteins of human or animal origin in the cell culture, purification or formulation of the final product. Other than factor VIII, the only proteins present in the final container product are trace quantities of murine immunoglobulin G (IgG) (from the immunoaffinity purification), CHO cell protein, and recombinant human von Willebrand factor (VWF). This process virtually eliminates any risk of transmission of human blood-borne viruses or other adventitious agents that could, in theory, be introduced by the use of animal-derived raw materials.

The CHO cell line employed in the production of ADVATE is derived from that used in the biosynthesis of RECOMBINATE, Takeda´s first-generation recombinant antihemophilic factor (rAHF, RECOMBINATE[iii]), which has been licensed since 1988.

Comprehensive physicochemical characterization studies have shown that ADVATE is virtually identical to RECOMBINATE. Consistent with this observation, nonclinical studies have demonstrated that ADVATE is comparable to RECOMBINATE with respect to hemostatic efficacy and pharmacokinetic (PK) parameters, as well as acute and repeat-dose toxicity.

Extensive experience from over 30 completed clinical studies in the ADVATE clinical development program has shown ADVATE to be well tolerated and efficacious for hemostatic control, including for perioperative management, in previously treated pediatric, adolescent and adult patients (PTPs) and in previously untreated pediatric patients (PUPs) with severe or moderately-severe hemophilia A.

ADVATE was first approved in the United States (US) on 25 July 2003 (= international birth date) for treatment of hemophilia A. In India, ADVATE was licensed in July 2015. ADVATE is currently licensed in 71 countries worldwide (as of 31 July 2018) for the prevention and control of bleeding episodes and for perioperative management in patients with hemophilia A (congenital FVIII deficiency). ADVATE is not indicated for the treatment of von Willebrand's disease.

[ii] ADVATE is a registered trademark of Baxalta Incorporated, a wholly owned, indirect subsidiary of Takeda plc.
[iii] RECOMBINATE is a registered trademark of Baxalta Incorporated, a wholly owned, indirect subsidiary of Takeda plc.

2.3 Study Rationale

The results derived from the ADVATE clinical development program have shown ADVATE to be well tolerated and efficacious for hemostatic control, including for perioperative management, in previously treated pediatric, adolescent and adult patients (PTPs) and in previously untreated pediatric patients (PUPs) with severe or moderately severe hemophilia A.

This study will collect data on ADVATE administered to previously treated patients (PTPs) with hemophilia A in standard clinical practice and as per Product Label in India.

The purpose of this study is to evaluate the safety and efficacy of ADVATE when used under standard clinical practice in previously treated hemophilia A patients (PTPs) in India.

2.4 Benefit/Risk Assessment

At present, FVIII replacement is the only symptomatic therapy available for the treatment of hemophilia A. ADVATE has structural and functional characteristics similar to those of endogenous FVIII. The development of a production process that virtually eliminates the risk of pathogen transmission represents a significant technical advance for hemophilia A patients who rely on chronic FVIII replacement therapy for their health and well-being, as it reduces the potential safety concerns associated with the use of FVIII concentrates.

Data from ADVATE studies demonstrated that the annualized bleeding rates (ABRs) could be reduced to as low as one event with prophylactic treatment. In PTPs, most bleeding episodes can be managed with a single infusion. The PK-driven prophylactic regimens should be more effective in maintaining FVIII trough levels above a threshold for bleeding and may reduce the number of required weekly infusions, which may in turn, improve treatment adherence. Furthermore, the PK-driven dosing regimen based on patient's clinical response, offers some patients the option of fewer infusions over one year of treatment than the standard prophylaxis regimen. Thus, ADVATE PK-driven regimens have the potential to be more cost effective and thereby may expand access to prophylactic therapy. The efficacy of ADVATE for ITI has been demonstrated in subjects with inhibitors to FVIII. Data show that ADVATE has been used to induce immune tolerance. In patients where immune tolerance was achieved, the bleedings could be prevented or controlled with ADVATE again, and the patient could continue prophylactic treatment with ADVATE as maintenance therapy.

The available safety data confirm that ADVATE is safe and well-tolerated in the treatment of moderately severe to severe hemophilia A. Review of spontaneous post-marketing AE reporting sources did not result in the detection of previously unrecognized risks or new safety concerns.

Potential risks are listed in the Package Insert, Section 4.4 Specials warnings and precautions for use (see Appendix 4.1).

2.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; E6 R2, 2017), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of this study is to assess the safety of ADVATE based on serious adverse events (SAEs) (including FVIII inhibitors).

3.1.2 Secondary Objectives

- To assess the safety of ADVATE based on adverse events (AEs) and changes in laboratory parameters
- To assess the efficacy of prophylactic treatment with ADVATE
- To assess the efficacy of on-demand treatment with ADVATE in the control of bleeding episodes

3.2 Study Endpoints

See Table 3. Each endpoint is mapped to the objective it supports.

Table 3. Objectives and Endpoints

Objective	Endpoint(s)
Primary	
• To assess the safety of ADVATE based on SAEs (including FVIII inhibitors)	• Incidence of SAEs (including FVIII inhibitor formation) that are at least possibly related to ADVATE
Secondary	
• To assess the safety of ADVATE based on AEs and changes in laboratory parameters	• Incidence of non-serious AEs that are at least possibly related to ADVATE • Clinically significant changes in clinical laboratory parameters (hematology and clinical chemistry)
• To assess the efficacy of prophylactic treatment with ADVATE	• Annualized bleeding rate (ABR) with prophylactic use of ADVATE • Total number of infusions and the average number of infusions per week per month during prophylactic treatment • Total and average body mass adjusted consumption of ADVATE per week per month during prophylactic treatment
• To assess the efficacy of bleed treatment with ADVATE	• Overall hemostatic efficacy rating for treatment of bleeding episodes • Number of ADVATE infusions required to achieve bleed resolution • Body mass adjusted consumption of ADVATE per bleeding episode

Abbreviations: ABR = annualized bleeding rate; AE = adverse event; FVIII = Factor VIII;
SAE = serious adverse event

4. STUDY DESIGN

4.1 Overall Design

This is a Phase 4, multicenter, prospective, interventional, post-marketing study in previously treated hemophilia A patients (PTPs) in India receiving ADVATE under standard clinical practice.

All enrolled subjects who have met the inclusion and exclusion criteria will be treated with ADVATE according to a regimen determined by the treating physician and in accordance with the national product label. The period of observation for each subject will be 6 months. For all subjects (regardless of prophylactic or on-demand treatment), the starting point of the observation will be an infusion of ADVATE at baseline (dose: 50±5 IU/kg) to determine incremental recovery (IR). See study design flowchart in Figure 1.

According to the WFH Report on the Annual Global Survey 2017 (World Federation of Hemophilia, 2018) there were a total of 15,920 cases of hemophilia A in India in 2017. Due to the low prevalence of hemophilia A and the difficulty in switching patients from their current therapy, the planned sample size is 50 subjects.

4.2 Scientific Rationale for Study Design

This phase 4 study is designed to evaluate the safety and efficacy of ADVATE when used under standard clinical practice (ie, per Product Label) in previously treated hemophilia A patients (PTPs) in India.

4.3 Justification for Dose

Subjects will be treated according to a regimen determined by the treating physician and in accordance with the national product label. Guidance on dosing for prophylactic and on-demand treatment can be found in the ADVATE Package Insert for India (see Appendix 4.1).

For the ADVATE infusion to determine IR, a dose of 50±5 IU/kg of ADVATE shall be given, as in previous ADVATE clinical studies.

4.4 Duration of Subject Participation and Study Completion Definition

Any subject who provides informed consent (ie, signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study (see Section 8.1 and Appendix 1.5).

The subject's maximum duration of participation is expected to be approximately 7-8 months. The period of observation for each subject will be 6 months; another 10 to 15 days are anticipated for the study completion visit ("End-of-Treatment Visit"). The study will be completed in approximately 2 years´ time.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). This includes the follow-up visit or contact, whichever is later (refer to Section 8.3.3 for the defined follow-up period for this protocol).

4.5 Sites and Regions

The study will be a multicenter study in India.

5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. The subject or legally authorized representative (in case of study participants <18 years of age) gave written informed consent to participate in the study.
2. Subject of any age with hemophilia A.
3. Subject is defined as a previously treated patient (PTP):
   - Subject aged ≥ 6 years that has been previously treated with plasma-derived and/or recombinant FVIII concentrate(s) for a minimum of 150 EDs.
   - Subject aged < 6 years that has been previously treated with plasma-derived and/or recombinant FVIII concentrate(s) for a minimum of 50 EDs.
4. Subject has negative history of FVIII inhibitors and negative inhibitor at screening defined as less than 0.6 Bethesda units (BU)/mL (Nijmegen-modified Bethesda assay).
5. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm^3, as confirmed by central laboratory at screening.
6. Subject is hepatitis C virus negative (HCV-) by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
7. The subject is willing and able to comply with the requirements of the protocol.

5.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. Subject has known hypersensitivity to mouse or hamster proteins or to any of the excipients of FVIII concentrates.
2. Subject has been diagnosed with bleeding disorder(s) other than congenital hemophilia A, such as acquired hemophilia A, von Willebrand´s disease (VWD) or thrombocytopenia (platelet count<100,000/mL).
3. Subject has received treatment for hemophilia A with non-FVIII products/concentrates (eg, emicizumab [Hemlibra®]) in the 6 months prior to screening.

4. Subject has severe chronic hepatic dysfunction [eg, ≥ 5 times upper limit of normal alanine aminotransferase (ALT), aspartate aminotransferase (AST) or INR > 1.5 as confirmed by central laboratory at screening].
5. Subject has planned, or is likely to have, surgery during the study period.
6. Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance.
7. Subject is currently receiving or is scheduled to receive during the course of the study, an immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than antiretroviral chemotherapy.
8. Subject has participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
9. Subject is a family member or employee of the investigator.

5.3 Restrictions

No dietary or activity restrictions are associated with this study.

5.4 Reproductive Potential

5.4.1 Female Contraception

Not applicable for this post-marketing study.

5.4.2 Male Contraception

Not applicable for this post-marketing study.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

ADVATE is formulated as a sterile, nonpyrogenic, lyophilized powder or friable solid of concentrated FVIII of white to off-white color and is provided in single-dose vials. Each vial of ADVATE is labeled with the antihemophilic factor (AHF) activity expressed in international units (IU) per vial.

The ADVATE powder vial is provided together with the diluent vial (containing Sterile Water for Injections [SWFI]) and a needleless transfer device for reconstitution (BAXJECT II).

ADVATE has a shelf life of 2 years when stored unopened under refrigeration (ie, 2°C- 8°C). Alternatively, ADVATE may be stored at room temperature (up to 25°C) for a period up to 6 months, not to exceed the expiration date. Freezing should be avoided to prevent damage to the diluent vial.

ADVATE will be provided by the sponsor and will be labeled as investigational product (IP).

6.1.2 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

ADVATE is to be administered intravenously after reconstitution. For reconstitution instructions, please refer to the ADVATE Package Insert for India (see Appendix 4.1).

The prepared solution should be inspected for particulate matter and discoloration prior to administration. The solution should be clear and colorless and free from foreign particles. If not, do not use the solution and notify the sponsor immediately.

ADVATE should be administered by bolus injection over a period of ≤5 minutes. The rate of administration should be at a rate that ensures the comfort of the patient, up to a maximum of 10 ml/min. ADVATE should be administered at room temperature within 3 hours of reconstitution. Plastic syringes must be used with this product, since proteins such as ADVATE tend to stick to the surface of glass syringes.

6.2.1 Allocation of Subjects to Treatment

This is an open-label, uncontrolled, single-group, post-marketing study. Subjects will receive either prophylactic or on-demand treatment. The actual treatment given to individual subjects will be according to a regimen determined by the treating physician and in accordance with standard clinical practice and the national product label.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

6.2.2 Dosing

The dosage and duration of treatment depend on the severity of FVIII deficiency, the location and extent of the bleeding, and the patient´s clinical condition.

Dosing details are provided in the ADVATE Product Label for India.

6.2.3 Unblinding the Treatment Assignment

Not applicable.

6.2.4 Dose Modification

Not applicable.

6.3 Labeling, Packaging, Storage, and Handling of Investigational Product

6.3.1 Labeling

Each vial will be labeled with the actual potency in International Units and a Product Label. The Product Label will meet country-specific regulatory label requirements.

6.3.2 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Details are provided in Section 6.1.1. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range.

The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer/dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered/dispensed medication will be documented in the subject's source and/or other investigational product record. The investigator is responsible for ensuring the retrieval of all study supplies from subjects. The investigator must request that subjects keep the empty investigational product packaging after use and return it to the site for drug accountability purposes.

No investigational product stock or returned inventory from a Takeda-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, IRT) do not require a shipment form. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

6.6 Prior and Concomitant Therapy

All non-study treatment received within 3 months prior to the screening visit and through the final study contact must be recorded in the subject's source document.

The physician is expected to follow standard clinical practice and all kinds of medications and/or non-drug therapies are allowed.

If any subject develops FVIII inhibitors during the study, they will be withdrawn from the study and treated as per standard of care (SoC) at the discretion of the Investigator (Note: ADVATE will not be used for ITI).

6.6.1 Prior Treatment

Prior treatment includes all treatment received within 6 months from the date of first dose of investigational product. Prior treatment information must be recorded in the subject's source document. In addition, the history of any hemophilia product usage for 6 months prior to screening must be recorded in the medical history. Please note that the use of non-FVIII products/concentrates (eg, Hemlibra) in the 6 months prior to screening represents an exclusion criterion (see Section 5.2).

6.6.2 Concomitant Treatment

All medications taken and non-drug therapies received within 3 months before providing informed consent until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

6.6.3 Permitted Treatment

The physician is expected to follow standard clinical practice and all kinds of medications and/or non-drug therapies are allowed.

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding during the study or during a surgical or other invasive procedure (Please note that subjects will be withdrawn from the study if they need emergency surgery during the study.)
  - Any medications deemed necessary by the subject's physician to treat or prevent any medical condition
  - Any over-the-counter medication used by the subject to treat symptoms or signs
  - Supplemental vitamins, minerals
  - **Immunization:**

- The concurrent administration of a vaccine and ADVATE at site visits should be avoided.
- If possible, intramuscular vaccination should be replaced by subcutaneous administration.
- Vaccinations 1 month prior to and during the study should be recorded as concomitant medications

- Non-drug therapies:
  - Any non-drug therapy (eg, physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

Note: If any subject develops FVIII inhibitors during the study, they will be withdrawn from the study and treated as per standard of care (SoC) at the discretion of the Investigator (Note: ADVATE will not be used for ITI).

6.6.4 Prohibited Treatment

- The use of a FVIII concentrate other than ADVATE (eg, any other plasma derived or recombinant FVIII product) will disqualify the subject from further participation in the study.
- Immunomodulating drugs are also not allowed as concomitant medication (see also exclusion criteria, Section 5.2).

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection.

If investigational product is discontinued, regardless of the reason, the evaluations listed for the Study Termination Visit will be performed as completely as possible. The assessments to be performed at the Study Termination Visit are described in Section 1.3 (Table 1, Table 2). Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the investigational product, and the total amount of investigational product administered must be recorded in the source documents.

7.2 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's source document. If a subject is discontinued for more than 1 reason, each reason should be documented in the source and the most clinically relevant reason should be indicated.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Use of a FVIII concentrate other than ADVATE (see also Section 6.6.4 and Section 8.4.2.1)
- Development of FVIII inhibitors
- Other (if "Other" is selected, the investigator must specify on the CRF)

Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Note: If any subject develops FVIII inhibitors during the study, they will be withdrawn from the study and treated as per standard of care (SoC) at the discretion of the investigator (Note: ADVATE will not be used for ITI.)

Note: Subjects will also be withdrawn from the study if they need emergency surgery during the study.

7.3 Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

7.4 Subjects "Lost to Follow-up" Prior to the Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that the subject return to the site for final safety evaluations and return any unused investigational product.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Informed Consent and Enrollment

Investigators will choose patients for participation considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

Prior to performing any trial assessments that are not part of routine medical care for the subject, all patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. An assent form may be provided and should be signed by patients less than 18 years of age. Any patient who provides informed consent (ie, signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study.

More detailed information on the informed consent procedure can be found in Appendix 1.5.

8.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (eg, TAK-761-4009) to be provided by the sponsor, 2- or 3-digit number study site number (eg, 02) to be provided by the sponsor, and 3-digit subject number (eg, 003) reflecting the order of providing informed consent. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject TAK-761-4009-02003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

8.3 Study Periods

The overall study periods are shown in Figure 1. Refer to Table 1 for the schedule of study activities and to Table 2 for an overview of the clinical laboratory assessments to be performed at each study visit, including screening. Study assessments are detailed in Section 8.4.

8.3.1 Screening Period

8.3.1.1 Screening Visit

The screening visit will take place within 45 days prior to the Baseline Visit on Day 0 (see Table 1 and Table 2).

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome.

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been administered investigational product(s). Subjects who are considered as screen failures can be rescreened at a later date if there is reason to believe that they may then meet all eligibility criteria.

8.3.1.2 Baseline Visit (Day 0)

Refer to Table 1 and Table 2 for the procedures and assessments to be performed at the Baseline Visit.

8.3.2 Treatment Period

The treatment period will be 6 months, starting with the Baseline Visit (Day 0) and ending with the End-of-Treatment Visit (Month 6 ± 1 week). The starting point of the treatment/observation period will be an infusion of ADVATE at the Baseline Visit to determine IR.

8.3.2.1 Visit 1 and Visit 2

Two scheduled study visits are to be performed during the treatment period: Visit 1 at Month 1 (± 1 week) and Visit 2 at Month 3 (± 1 week). Additional unscheduled visits are also possible. For the individual assessments to be performed at each study visit, see Table 1 and Table 2.

In addition, ADVATE will be dispensed to the subjects at the study visits (Baseline, Visit 1, Visit 2, unscheduled visits) to provide sufficient treatment until the next scheduled visit, or as appropriate (see Table 1).

8.3.2.2 Final Visit (End-of-Treatment Visit / Study Termination Visit)

After subjects have completed 6 months of treatment on the study, the End-of-Treatment Visit will take place. Refer to Table 1 and Table 2 for the individual assessments and procedures to be performed at this visit.

If subjects discontinue the study early or withdraw from the study, a Study Termination Visit will be performed instead of the End-of-Treatment Visit. The assessments and procedures for the Termination Visit will be the same as for the End-of-Treatment Visit.

8.3.3 Follow-up Period

There is no follow-up period.

8.3.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

8.4 Study Assessments

8.4.1 Demographic and Other Baseline Characteristics

Subject demographic information including gender, age, and race will be collected prior to the subject receiving the first dose of investigational product.

8.4.1.1 Height and Weight

Height and weight will be measured and recorded in the subject's source documents.

8.4.1.2 Medical and Medication History

Medical and medication history will be collected and recorded in the subject's source documents.

8.4.2 Efficacy

8.4.2.1 Effectiveness of ADVATE as On-demand and Prophylactic Treatment

In all cases, the treatment with ADVATE will be at the discretion of the investigator and will consist of either a prophylactic or on-demand treatment as per the ADVATE Product Label for India. The following information will be recorded by the subject, the subject's legal representative (for home treatment) or by authorized, qualified personnel at the participating site (for hospital-based treatment in case of a bleeding episode):

- Location of bleed, ie, joint, soft tissue, muscle, body cavity, intracranial, other
- Type of bleed, ie, spontaneous, injury, unknown
- Severity of bleed, ie, minor, moderate, major, life/limb threatening
- Date and time of onset of bleed
- Date and time of each infusion of ADVATE required to achieve adequate hemostasis
- Date and time of resolution of bleeding episode
- Type and number of analgesics required
- Overall effectiveness assessment for on-demand or prophylactic treatment as described in Section 8.4.2.1.1.

If a bleed occurs following resolution of the bleed, it will be considered a "new" bleed and will be recorded accordingly.

Subjects will resume their prophylactic treatment regimen the next scheduled day after the last therapeutic infusion for the treatment of a bleeding episode.

Details pertaining to all home treatments for each bleed, including response to treatment, will be recorded by study subjects or the subject's legal representative in subject diaries provided by the study sponsor. At each study visit the investigator will review together with the subject the response to treatment and evaluate the hemostatic efficacy rating. Any inconsistency between the efficacy rating and the number of infusions required to treat a bleeding episode, or a response to treatment rated as "none" must be immediately clarified. If 2 or more responses to treatment are rated with "fair", the investigator may re-evaluate the dosing regimen, and the time from bleeding onset to start of treatment. In case more than one infusion was given to treat a bleeding episode, but the treatment was rated with "excellent", information should be provided about the severity of the bleeding episode and/or whether additional infusions were given to maintain hemostasis. If infusions were given to maintain hemostasis after resolution of bleed, this should be recorded accordingly in the CRF. It may become necessary to re-discuss the rating with the subject to ensure that the Rating Scale is fully understood. In case of bleeding episodes requiring only one infusion but the response to treatment is rated with "fair", this should also be evaluated.

Note: The investigator must confirm all the efficacy ratings entered in the subject diary. If the investigator identifies any inconsistency/error in the efficacy rating, the investigator will make his/her own assessment in conjunction with the subject (or the subject's legal representative) and enter it into the CRF. In cases where there are discrepancies between assessments made by subjects (or the subject's legal representative) and the investigator, assessment made by the investigator shall supersede and be considered the final assessment.

If, at any time during the study a subject's bleeding episode does not adequately respond to ADVATE therapy, he/she will be evaluated for the presence of inhibitory or total binding antibodies to FVIII and clinically managed at the discretion of the investigator. In addition, AEs and the details of concomitant medication use coincident with the treatment of all acute bleeds will be recorded. Note that bleeding episodes are not to be reported as AEs (Appendix 3.1 Adverse Event Definition [subheading: symptoms of the disease under study]).

Any non-study FVIII therapy or hemostatic product use administered for a bleeding event will be recorded on the appropriate section of the subject's diary and the CRF. The use of a FVIII concentrate other than ADVATE will disqualify the subject from further participation in the study.

8.4.2.1.1 Assessment of Effectiveness

Total number (%) of treated bleeds and their corresponding hemostatic effectiveness ratings using an "excellent-to-none" 4-point Likert scale by the subjects/care-giver (subjects <12 years: care-giver, subjects ≥ 12 years: self-assessment) for treatments given at home, or by the investigator for treatments given in the hospital/clinic.

Table 4. Overall Effectiveness Assessment for Bleed Treatment

Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) within approximately 6 hours to 12 hours and after 1 or 2 infusions. No additional infusion is required for the control of bleeding. Any additional infusion for treatment of bleeding will preclude this rating. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding within approximately 6 hours to 24 hours requiring more than 2 infusions for complete resolution. Administration of further infusions to maintain hemostasis would not affect this scoring.
Moderate	Probable and/or slight relief of pain and slight improvement in signs of bleeding within approximately 6 hours to 24 hours. Requires multiple infusions for complete resolution.
None[iv]	No improvement of signs or symptoms or conditions worsen.

Table 5. Overall Effectiveness Assessment for Prophylactic Treatment

Excellent	Definitely low bleeding rate with improvement in daily activities and quality of life. Very satisfied with the treatment and worth being continued
Good	Relatively low bleeding rate with some improvement in daily activities and quality of life. Satisfied with the treatment and worth being continued
Moderate	Relative increase in breakthrough bleeding episodes with only partial benefit in terms of activity level and quality of life. Partially satisfied with the treatment. Not sure if it is worth continuing treatment
None[iv]	Frequent breakthrough bleeding episodes interfering with activity level and quality of life. Not satisfied with the treatment.

8.4.2.2 Determination of Incremental Recovery

The assessment of FVIII levels to determine IR will be mandatory at the Baseline Visit and at the End of Treatment Visit / Study Termination Visit (see Table 2). For a more detailed description of the IR assessment, see Appendix 2.5.

8.4.2.3 Blood Sampling for Determination of Factor VIII Level

See Appendix 2.4.

[iv] If checked, the investigator should determine whether it is considered as "lack of effect" and, if yes, it should be considered as an AE.

8.4.3 Safety

8.4.3.1 Physical Examination

At screening and all subsequent study visits (as shown in Section 1.3, Table 1), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal preexisting condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Appendix 3.1), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

8.4.3.2 Adverse Events

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed.[v] Refer to Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures.

8.4.3.3 Vital Signs

Vital signs will include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Blood pressure will be measured when subjects are in the supine position.

Vitals signs will be measured at all study visits (see Table 1) and will be recorded on the CRF. Vital signs should always be assessed before any blood sampling is done at a particular timepoint.

The investigator will assess whether a change from baseline in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

8.4.3.4 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE.

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[v] Please note that AEs are only considered treatment-emergent AEs (TEAEs) if they emerge or manifest at or after initiation of treatment with IP.

The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed (see also Table 2):

- Hematology assessments: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count
- Clinical chemistry assessments: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose
- Viral serology: HIV-1Ab, HIV-2 Ab, HBcAb, HBsAb, HBsAg, and HCVAb.
  Any HIV or HCV positive sample will be tested by PCR for viral titer, HIV positive subjects will have CD4 counts monitored every 3 months during the course of the study.
- FVIII antigen
- FVIII activity
- Incremental recovery
- FVIII inhibitor

More detailed descriptions of the clinical laboratory tests to be performed are provided in Appendix 2.

8.4.3.5 Clinical Pharmacology

Incremental recovery will be determined at baseline and at study completion (see Table 2 and Appendix 2.5).

8.4.4 Volume of Blood to Be Drawn from Each Subject

The volume of blood to be drawn from each subject for laboratory assessments will be specified in the laboratory manual.

8.4.5 Backup Samples and Biobanking

Backup samples taken and stored short-term may be used for example for re-testing, follow-up of an AE(s) or other test results, and/or assay development. After study testing is completed, the remaining samples may be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

For subjects < 6 years of age, back-up samples are optional; for subjects < 12 years of age, back-up samples for serum are optional.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® 9.4 or later (SAS Institute, Cary, NC 27513).

The statistical analysis for this study will be descriptive in nature. Descriptive statistics will include specifically, but not exclusively, arithmetic mean, standard deviation, medians, quartiles and interquartile range, minimum, maximum, proportions, frequency counts, and 95% confidence intervals of point estimates.

9.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

No interim analysis, adaptive design, or data monitoring committee (DMC) is planned for this study.

9.3 Sample Size and Power Considerations

According to the WFH Report on the Annual Global Survey 2017 (World Federation of Hemophilia, 2018) there were a total of 15,920 cases of hemophilia A in India in 2017. Due to the low prevalence of hemophilia A and the difficulty in switching patients from their current therapy, the planned sample size is 50 subjects.

9.4 Statistical Analysis Set(s)

9.4.1 Effectiveness Full Analysis Set (EFAS)

The EFAS will be comprised of all subjects for whom all inclusion and none of the exclusion criteria are met. This dataset will be used for the efficacy analyses.

9.4.2 Safety Analysis Set (SAS)

All subjects having received ADVATE at any time during the study will be included in the SAS.

9.5 Efficacy Analyses

9.5.1 Primary Efficacy Endpoint

Not applicable. There is no primary efficacy endpoint.

9.5.2 Secondary Efficacy Endpoints

The annualized bleeding rate (ABR) during the prophylactic treatment will be assumed to have a negative binomial distribution, and the mean ABR (95% CI) will be estimated using a generalized linear model (GLM). The total ABR and ABR by bleed cause/ site, i.e. joint, non-joint, target joints, spontaneous, traumatic, will be summarized descriptively as well.

Summary statistics for the total number of infusions, as well as the average number of prophylactic infusions per week and per month of prophylaxis will be provided. Similarly, the total body mass adjusted consumption and the average consumption of ADVATE per week and per month during prophylactic treatment will be provided.

For the overall hemostatic efficacy rating at resolution of bleed, for the number of infusions of ADVATE to control a bleeding episode, as well as for the body mass adjusted consumption of ADVATE per bleeding event, summary statistics will be presented. These tables will be also presented by bleeding site, cause and severity.

9.5.3 Multiplicity Adjustment

As the analyses will be descriptive in nature, no adjustments for multiplicity will be applied.

9.6 Safety Analyses

Frequency counts and percentages for possibly or probably related SAEs (including FVIII inhibitor formation) as well as for subjects with possibly or probably related SAEs (including FVIII inhibitor formation) that occurred during or after first ADVATE infusion will be summarized. The incidence of FVIII inhibitor development will also be summarized by high-titer (>5 BU) and low-titer (0.6-5 BU).

All AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term. A listing of all AEs will be presented by subject identifier, age, sex, preferred term and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment by investigator, onset date, stop date and medication or non-drug therapy to treat the AE.

Shift tables will be presented for the results of clinical laboratory data.

9.7 Other Analyses

No other analyses are planned at this time.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix 1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Appendix 1.1 Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

Appendix 1.2 Sponsor's Responsibilities

Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the investigator as necessary.

Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

Appendix 1.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide

documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

Documentation and Retention of Records

Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

The CRFs should be approved by the investigator per study specifications and the sponsor's data delivery requirements.

Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diary cards, and original clinical laboratory reports.

All key data must be recorded in the subject's source documents.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

Appendix 1.4 Data Management Considerations

Data Collection

The investigators' authorized site personnel must enter the information required by the study CRF Completion Guidelines or similar for all data requiring transcription of the source. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

Data Management

Data are to be entered into a clinical database as specified in the CRO´s data management plan or similar. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

Data Handling

Not applicable to this study, as this study is not blinded.

Appendix 1.5 Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. An assent form may be provided and should be signed by subjects less than 18 years of age. All consent and assent documentation must be in accordance with applicable regulations and GCP. Subjects or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. By signing the informed consent form, subjects or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason. A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, that have been approved by the applicable Ethics Committee and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement. Investigational product supplies will not be released until the sponsor has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the sponsor or investigator for sites within the EU; or for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

Privacy and Confidentiality

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market ADVATE; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities. Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

Study Results/Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

Takeda is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from Takeda-supported research. Therefore, after January 1, 2018, Takeda will require the submission of all Takeda-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

Appendix 2 CLINICAL LABORATORY TESTS

The following clinical laboratory assessments will be performed (see also Table 2):

- Hematology assessments: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count
- Clinical chemistry assessments: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose
- Viral serology: HIV-1 Ab, HIV-2 Ab, HBcAb, HBsAb, HBsAg, and HCVAb.
  Any HIV or HCV positive sample will be tested by PCR for viral titer, HIV positive subjects will have CD4 counts monitored every 3 months during the course of the study.
- FVIII antigen
- FVIII activity
- Incremental recovery
- FVIII inhibitor

Appendix 2.1 Hematology and Clinical Chemistry

Blood will be obtained for assessment of hematology and clinical chemistry parameters at the timepoints indicated in Table 2. In addition, assessments may be performed whenever clinically indicated. Hematology and clinical chemistry assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at the central laboratory.

Appendix 2.2 Viral Serology

Viral serology assessments will be performed at Screening and at the End-of-Treatment / Study Termination Visit (see Table 2).

The following viral serology tests will be performed: HIV-1 Ab, HIV-2 Ab, HBcAb, HBsAb, HBsAg, and HCVAb. Any HIV or HCV positive sample will be tested by PCR for viral titer, HIV positive subjects will have CD4 counts monitored every 3 months during the course of the study.

Appendix 2.3 FVIII Antigen

FVIII antigen will be measured at the screening visit using a commercially available ELISA kit (Table 2). The samples will be prepared as described in Section Appendix 2.4.

Appendix 2.4 Blood Sampling for Determination of FVIII Activity

At each blood sampling time point whole blood will be collected in S-Monovette® tubes (Sarstedt, Nümbrecht, Germany) containing 3.2% trisodium citrate, or equivalent blood drawing equipment (eg, Vacutainer tubes), and immediately mixed. **The citrated whole blood samples will be capped and transported at room temperature (ie, 20-25°C) to the local clinical laboratory for centrifugation, processing, and storage.** Monovettes must be kept in an upright position at all times to avoid leakage.

For all clotting assays, citrated whole blood will be spun in **a refrigerated centrifuge (2 to 8°C)** at ≥ 2000 x gravity for approximately 20 minutes in capped tubes **within 2 hours of collection**. The plasma supernatant will be re-centrifuged at the same rate and duration to ensure removal of platelets and other particulate matter.

At least three aliquots of 0.6 mL of the centrifuged, citrated plasma will be pipetted into appropriate storage tubes, capped, labeled, and **stored in a freezer at ≤ -70°C, ideally within 15 minutes, but no later than 30 minutes after processing.**

All citrated plasma samples will be stored and shipped to the central laboratory at ≤ -70°C for testing. All samples will be maintained capped to the greatest extent possible. All citrated plasma samples will be assayed for FVIII activity using the one-stage aPTT-based assay method.

Appendix 2.5 Incremental recovery (IR)

The assessment of FVIII levels to determine IR will be mandatory at the Baseline Visit and at the End of Treatment Visit (at 6 months) / Study Termination Visit. IR determination is optional at Visit 2 (at 3 months) (see Table 2).

Prior to the pre-infusion blood draw for IR determination, subjects should have a washout period from previous plasma-derived and/or recombinant FVIII concentrate(s) treatment. The washout period will depend on the type of product the subject receives, ie, 48-72 hours for products with standard half-life and 84-96 hours for extended half-life products (consistent with clinical studies with ADYNOVATE).

Subjects will be infused with a dose of 50±5 IU/kg of ADVATE. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 ml of saline solution. The procedures for blood sampling are described in Section Appendix 2.4.

Table 6. Time Points for FVIII Activity Assessment for IR Determination

Assessment of recovery	Pre-infusion	0-30 minutes prior to infusion
	Infusion of ADVATE	
	Post-infusion	15-30 minutes post infusion

The sample for measurement of FVIII activity will be obtained from an extremity different from that used for the infusion of IP.

Appendix 2.6 FVIII Inhibitor

If an inhibitory antibody with a titer ≥ 0.6 BU is detected, the inhibitor will be confirmed in the central laboratory within 2 weeks of study site notification of the original central laboratory result. Subjects who develop an inhibitor that changes from a low to a high titer inhibitor or from a high titer to a low titer upon a second evaluation should return to the study site for a third inhibitor test with a suggested minimum washout phase of 72 hours within 2 weeks of the second inhibitor assessment. Once a low (0.6 to 5 BU) or a high titer (> 5 BU) inhibitor is confirmed, the subject will be withdrawn from the study. Any inhibitor confirmed by the central laboratory must be recorded as an SAE (Section Appendix 3.1).

All tests will be performed at a defined central laboratory.

Appendix 3 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Appendix 3.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not causality is suspected (ICH Guidance E2A 1995).

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the investigational product or medicinal product.

Serious Adverse Event

A serious adverse event (SAE) is any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to investigational product or not and at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of hospitalization. Note: Hospitalizations that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs.
- For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality/birth defect

- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include:
- Bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.
- Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
- Further examples of important medical events that are specific to this study include, but are not limited to:
  - Thromboembolism/DIC/Fibinolysis
  - FVIII inhibitor development (≥ 0.6 BU/mL)

For this protocol, elective and planned surgeries, when these surgeries relate to a preexisting disease that has not worsened during study participation will not be considered as (S)AEs.

Unexpected Adverse Event

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the prescribing information (Product Label) as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the prescribing information (Product Label) as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or product labeling; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Symptoms of the Disease under Study

Bleeding episodes are part of the underlying disease and are therefore not AEs; they will be assessed as part of the efficacy assessments. However, the investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances. If a bleeding episode was caused by an injury, the injury will be reported as an AE. Bleeding events will not be considered as AEs if they do not qualify as an SAE. All bleeding episodes must be entered in the bleeding event CRF.

Preexisting conditions prior to randomization or initiation of study medication are described in the medical history, and those that manifest with the same severity, frequency, or duration after drug exposure, are not be recorded as AEs. However, when there is an increase in the severity, duration or frequency of a preexisting condition, the event must be described on the AE CRF.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

Appendix 3.2 Collection of Adverse Events

All AEs/SAEs are collected from the time the informed consent document is signed until the final visit (End-of-Treatment / Study Termination Visit) stated in Section 8.3.2. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered.

All AEs/SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Appendix 3.3 Assessment of Adverse Events

Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity is captured as a new event. Worsening medical conditions, signs or symptoms present prior to initiation of investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, and the dyspepsia becomes severe and more frequent after first dose a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

The medical assessment of severity is determined by using the following definitions:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

Table 7. Adverse Event Relationship Categorization

Related	The temporal relationship between the event and the administration of the investigational product is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

Outcome Categorization

The outcome of AEs must be documented in the source during the course of the study. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

If applicable, action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF

Appendix 3.4 Safety Reporting

Reference Safety Information

The RSI for this study is the product package insert which the sponsor has provided under separate cover to all investigators (see also Appendix 4.1).

Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Takeda Global Drug Safety Department and the CRO/Takeda medical monitor within 24 hours of becoming aware of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section Appendix 3.9) unless they result in an SAE.

The investigator must complete, sign, and date the Takeda "Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol", verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and fax or e-mail the form to the Takeda Global Drug Safety Department. A copy of the Takeda Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol.

Medical Device Safety Reporting

The IP kit contains the BAXJECT II device. All serious injuries and UADEs must be reported to the sponsor as an SAE in the same process as described above. Serious injury (SI) is defined as:

- Led to death;
- Led to a serious deterioration in health of a patient, user, or others that
- Results in a life-threatening illness or injury
- Results in a permanent impairment/ damage of a body function or body structure
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in medical or surgical intervention to prevent permanent impairment/ damage to body function/ structure.
- Led to fetal distress, fetal death or a congenital abnormality/birth defect

Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the final visit (End-of-Treatment / Study Termination Visit) stated in Section 8.3.2 and must be reported to the Takeda Global Drug Safety Department and the CRO/Takeda medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Takeda Global Drug Safety Department within 24 hours of the reported first becoming aware of the event.

Appendix 3.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms reported by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

Appendix 3.7 Fatal Outcome

Any SAE that results in the subject's death (eg, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

Appendix 3.8 Pregnancy

All pregnancies are reported from the time informed consent is signed until the final visit (End-of-Treatment / Study Termination Visit) stated in Section 8.3.2

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Takeda Global Drug Safety Department using the Takeda Investigational and Marketed Products Pregnancy Report Form.

A copy of the Takeda Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days and 1 year post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the Takeda Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Takeda Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Takeda Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG

test or ultrasound result will determine the pregnancy onset date.

Appendix 3.9 Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section Appendix 3.1.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- Overdose – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

Appendix 3.10 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, and within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

Appendix 3.11 Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

The sponsor and the local CRO are responsible for notifying the relevant regulatory authorities and ethics committees of related, unexpected SAEs.[vi]

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the ADVATE clinical program.

The investigator is responsible for notifying the local IRB/EC of SAEs or significant safety findings that occur at his or her site as required by IRB/EC procedures (see Appendix 1.5).

[vi] The sponsor is responsible for notifying the relevant regulatory authorities, and the local CRO is responsible for notifying the ethics committees.

Appendix 4 COUNTRY-SPECIFIC REQUIREMENTS

Appendix 4.1 Package Insert

Please see enclosed an example of the ADVATE Package Insert for the dose strength 500 IU. Other dose strengths will also be used in the study.

ADVATE® 500 IU

LE74583

ADVATE®

[R]-Coagulation Factor VIII (Recombinant) rFVIII – I.P.
(Advate®) 500 I.U.
(Plasma/Albumin Free Method)

1. NAME OF THE MEDICINAL PRODUCT

[R]-Coagulation Factor VIII (Recombinant) r FVIII I.P.
ADVATE® 500 IU powder and solvent for solution for injection.
(Plasma/Albumin Free Method)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 500 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE® contains approximately 250 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution.

Target Composition of the Final Drug Product (Reconstituted with 2 mL sWFI)

Name of constituent	Qty/Vial	Ref to Standard
rFVIII (Octocog Alfa)	500 IU/Vial	I.P./ Baxalta Specification
α,α-Trehalose	2% (w/v)	EP
L-histidine	25 mM	EP
Tris (hydroxymethyl) aminomethane	25 mM	EP
Sodium Chloride	225 mM	EP
Calcium Chloride	4.2 mM	EP
Glutathione (Reduced)	0.2 mg/mL	EP
Polysorbate 80 (Vegetable-derived)	0.025% (w/v)	EP
Mannitol	8 % (w/v)	EP
Sterilized Water for Injection	2 ml	EP

The potency (International Units) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of ADVATE® is approximately 4,000-10,000 IU/mg protein.
Octocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 2332 amino acids. It is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. It is prepared without the addition of any (exogenous) human- or animal-derived protein in the cell culture process, purification or final formulation.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: White to off-white friable powder.
Solvent: Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). ADVATE® is indicated in all age groups.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and with resuscitation support immediately available in case of anaphylaxis.

Posology
The dose and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor VIII is expressed in International Units (IU), which are related to the WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IUs (relative to the international standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

On demand treatment
The calculation of the required dose of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl. The required dose is determined using the following formula:

Required units (IU) = body weight (kg) x desired factor VIII rise (%) x 0.5

In case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table 1 can be used to guide dosing in bleeding episodes and surgery:

Table 1 Guide for dosing in bleeding episodes and surgery

Degree of haemorrhage/ type of surgical procedure	Factor VIII level required (% or IU/dl)	Frequency of doses (hours)/ duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding.	20 – 40	Repeat injections every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for at least 1 day, until the bleeding episode, as indicated by pain, is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma.	30 – 60	Repeat injections every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for 3 – 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages.	60 – 100	Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.

Table 1 Guide for dosing in bleeding episodes and surgery

Degree of haemorrhage/ type of surgical procedure	Factor VIII level required (% or IU/dl)	Frequency of doses (hours)/ duration of therapy (days)
Surgery		
Minor Including tooth extraction.	30 – 60	Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.
Major	80 – 100 (pre- and postoperative)	Repeat injections every 8 to 24 hours (6 to 24 hours for patients under the age of 6) until adequate wound healing, then continue therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).

The dose and frequency of administration should be adapted to the clinical response in the individual case. Under certain circumstances (e.g. presence of a low-titre inhibitor), doses larger than those calculated using the formula may be necessary.

During the course of treatment, appropriate determination of plasma factor VIII levels is advised to guide the dose to be administered and the frequency of repeated injections. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of plasma factor VIII activity assay is indispensable. Individual patients may vary in their response to factor VIII, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

Prophylaxis
For long-term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days.

Paediatric population
For on demand treatment dosing in paediatric patients (0 to 18 years of age) does not differ from adult patients. In patients under the age of 6, doses of 20 to 50 IU of factor VIII per kg body weight 3 to 4 times weekly are recommended for prophylactic therapy.
Use of 2 ml presentations has not been documented for paediatric subjects < 2 years of age.

Method of administration
ADVATE® should be administered via the intravenous route. In case of administration by a non health care professional appropriate training is needed.

The rate of administration should be determined to ensure the comfort of the patient up to a maximum of 10 ml/min.

After reconstitution, the solution is clear, colourless, free from foreign particles and has a pH of 6.7 to 7.3.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to mouse or hamster proteins.

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE®. The product contains traces of mouse and hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

Due to the decrease in injection volume for ADVATE® reconstituted in 2 ml sterilised water for injections, if hypersensitivity reactions occur there is less time to react by stopping the injection. Therefore, caution is advised during injection of ADVATE® reconstituted in 2 ml sterilised water for injections, especially in children.

Inhibitors
The formation of neutralising antibodies (inhibitors) against factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. In patients who develop inhibitors to factor VIII, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. The risk of developing inhibitors is correlated to the extent of exposure to factor VIII, the risk being highest within the first 20 exposure days, and to other genetic and environmental factors. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII substitution therapy may not be effective and other therapeutic options should be considered. The management of such patients should be directed by physicians with experience in the care of patients with haemophilia and factor VIII inhibitors.

Misapplication of ADVATE®
For ADVATE® reconstituted with 2 ml sterilised water for injections, misapplication (intra-arterially or paravenously) may lead to mild, short term injection site reactions, such as bruising and erythema.

Catheter-related complications in treatment
If central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.

Excipient related considerations
After reconstitution this medicinal product contains 0.45 mmol sodium (10 mg) per vial. To be taken into consideration by patients on a controlled sodium diet.

It is strongly recommended that every time ADVATE® is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Paediatric population:
The listed warnings and precautions apply to both adults and children.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with ADVATE®.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and breast-feeding only if clearly indicated.

4.7 Effects on ability to drive and use machines

ADVATE® has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Clinical studies with ADVATE® included 418 subjects with at least one exposure to ADVATE® reporting in total 93 adverse drug reactions (ADRs). The ADRs that occurred in the highest frequency were development of neutralising antibodies to factor VIII (inhibitors), headache and fever. Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock).

Development of antibodies to mouse and/or hamster protein with related hypersensitivity reactions may be observed.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated summary of adverse reactions
The following table 2 provides the frequency of adverse drug reactions in clinical trials and from spontaneous reporting. The table is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Frequency of adverse drug reactions (ADRs) in clinical trials and from spontaneous reports

MedDRA Standard System Organ Class	Adverse reaction	Frequency[a]
Infections and infestations	Influenza	Uncommon
	Laryngitis	Uncommon
Blood and lymphatic system disorders	Factor VIII inhibition[b]	Common
	Lymphangitis	Uncommon
Immune system disorders	Anaphylactic reaction	Not known
	Hypersensitivity[c]	Not known
Nervous system disorders	Headache	Common
	Dizziness	Uncommon
	Memory impairment	Uncommon
	Syncope	Uncommon
	Tremor	Uncommon
	Migraine	Uncommon
	Dysgeusia	Uncommon
Eye disorders	Eye inflammation	Uncommon
Cardiac disorders	Palpitations	Uncommon
Vascular disorders	Haematoma	Uncommon
	Hot flush	Uncommon
	Pallor	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Uncommon
Gastrointestinal disorders	Diarrhoea	Uncommon
	Abdominal pain upper	Uncommon
	Nausea	Uncommon
	Vomiting	Uncommon
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Uncommon
	Hyperhidrosis	Uncommon
	Urticaria	Uncommon
General disorders and administration site conditions	Pyrexia	Common
	Peripheral oedema	Uncommon
	Chest pain	Uncommon
	Chest discomfort	Uncommon
	Chills	Uncommon
	Feeling abnormal	Uncommon
	Vessel puncture site haematoma	Uncommon
	Fatigue	Not known
	Injection site reaction	Not known
	Malaise	Not known
Investigations	Monocyte Count increased	Uncommon
	Coagulation factor VIII level decreased[b]	Uncommon
	Haematocrit decreased	Uncommon
	Laboratory test abnormal	Uncommon
Injury, poisoning and procedural complications	Post procedural complication	Uncommon
	Post procedural haemorrhage	Uncommon
	Procedural site reaction	Uncommon

a) Calculated based on total number of patients who received ADVATE® (418).
b) The unexpected decrease in coagulation factor VIII levels occurred in one patient during continuous infusion of ADVATE® following surgery (postoperative days 10-14). Haemostasis was maintained at all times during this period and both plasma factor VIII levels and clearance rates returned to appropriate levels by postoperative day 15. Factor VIII inhibitor assays performed after completion of continuous infusion and at study termination were negative.
c) ADR explained in the section below.

Description of selected adverse reactions
Inhibitor Development
Inhibitor development in previously treated patients (PTPs) and in previously untreated patients (PUPs) has been reported. For details refer to sections 5.1 (Pharmacological properties) and 4.4 (Special warnings and precautions for use).

ADRs specific to residues from the manufacturing process

Of the 229 treated patients who were assessed for antibodies to Chinese hamster ovary (CHO) cell protein, 3 showed a statistically significant upward trend in titres, 4 displayed sustained peaks or transient spikes and one patient had both but no clinical symptoms. Of the 229 treated patients who were assessed for antibodies to murine IgG, 10 showed a statistically significant upward trend, 2 displayed a sustained peak or transient spike and one patient had both. Four of these patients reported isolated events of urticaria, pruritus, rash, and slightly elevated eosinophil counts amongst repeated exposures to the study product.

Hypersensitivity

Allergic type reactions include anaphylaxis and have been manifested by dizziness, paresthesias, rash, flushing, face swelling, urticaria, and pruritus.

Paediatric population

Other than the development of inhibitors in previously untreated paediatric patients (PUPs), and catheter-related complications, no age-specific differences in ADRs were noted in the clinical studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No symptoms of overdose with recombinant coagulation factor VIII have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII. ATC code: B02BD02.

The factor VIII/von Willebrand Factor complex consists of two molecules (factor VIII and von Willebrand Factor) with different physiological functions. ADVATE® contains recombinant coagulation factor VIII (octocog alfa), a glycoprotein that is biologically equivalent to the factor VIII glycoprotein found in human plasma.

Octocog alfa is a glycoprotein consisting of 2332 amino acids with an approximate molecular mass of 280 kD. When infused into a haemophilia patient, octocog alfa binds to endogenous von Willebrand Factor in the patient's circulation. Activated factor VIII acts as a Cofactor for activated Factor IX, accelerating the conversion of Factor X to activated Factor X. Activated Factor X converts prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII activity and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. The plasma levels of factor VIII are increased by replacement therapy, thereby enabling a temporary correction of the factor VIII deficiency and correction of the bleeding tendency.

Inhibitor Development

The immunogenicity of ADVATE® was evaluated in previously treated patients. During clinical trials with ADVATE® in 233 paediatric and adult patients [paediatric patients (age 0 –16 years) and adult patients (age over 16 years)] diagnosed with severe haemophilia A (factor VIII < 1%), with previous exposure to factor VIII concentrates ≥ 150 days for adults and older children and ≥ 50 days for children < 6 years of age, one patient developed a low-titre inhibitor (2.4 BU in the modified Bethesda assay) after 26 exposure days to ADVATE®. Follow-up inhibitor tests in this patient after withdrawal from the study were negative. Across all studies, median exposure to ADVATE® was 97.0 exposure days per subject (range 1 to 709) for previously treated patients. The overall incidence of any factor VIII inhibitor development (low or high) was 0.4% (1 of 233).

In the completed uncontrolled study 060103, 16 out of 45 (35.6%) of previously untreated patients with severe haemophilia A (FVIII < 1%) and at least 25 EDs to FVIII developed FVIII inhibitors: 7 (15.6%) subjects developed high-titre inhibitors and 9 (20%) subjects developed low-titre inhibitors, 1 of which was also classified as a transient inhibitor.

Risk factors related to inhibitor development in this study included non-Caucasian ethnicity, family history of inhibitors and intensive treatment at high dose within the first 20 EDs. In the 20 subjects who had none of these risk factors there was no inhibitor development.

Data on Immune Tolerance Induction (ITI) in patients with inhibitors have been collected. Within a sub-study of PUP-study 060103, ITI-treatments in 11 PUPs were documented. Retrospective chart review was done for 30 subjects on ITI (study 060703) and collection of Registry data is on-going.

In study 060201 two long-term prophylaxis treatment schemes have been compared in 53 PTPs: an individualized pharmacokinetic guided dosing regimen (within a range of 20 to 80 IU of factor VIII per kg body weight at intervals of 72 ± 6 hours, n=23) with a standard prophylactic dosing regimen (20 to 40 IU/kg every 48 ±6 hours, n=30). The pharmacokinetic guided dosing regimen (according to a specific formula) was targeted to maintain factor VIII trough levels ≥ 1% at the inter-dosing interval of 72 hours. The data from this study demonstrate that the two prophylactic dosing regimens are comparable in terms of reduction of bleeding rate.

The European Medicines Agency has waived the obligation to submit the results of studies with ADVATE® in all subsets of the paediatric population in haemophilia A (congenital factor VIII deficiency) in "Immune Tolerance Induction (ITI) in patients with haemophilia A (congenital factor VIII deficiency) who have developed inhibitors to factor VIII" and "treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)".
(see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

All pharmacokinetic studies with ADVATE® were conducted in previously treated patients with severe to moderately severe haemophilia A (baseline factor VIII ≤ 2%). The analysis of plasma samples was conducted in a central laboratory using a one-stage clotting assay.

A total of 195 subjects with severe haemophilia A (baseline factor VIII < 1%) provided PK parameters that were included in the Per-Protocol PK analysis set. Categories of these analyses for infants (1 month to <2 years of age), children (2 to <5 years of age), older children (5 to <12 years of age), adolescents (12 to <18 years of age), and adults (18 years of age and older) were used to summarize PK parameters, where age was defined as age at time of PK infusion.

Table 3 Summary of Pharmacokinetic Parameters of ADVATE® per Age Group with severe haemophilia A (baseline factor VIII < 1%)

Parameter (mean ± standard deviation)	Infants (n=5)	Children (n=30)	Older Children (n=18)	Adolescents (n=33)	Adults (n=109)
Total AUC (IU*h/dl)	1362.1 ± 311.8	1180.0 ± 432.7	1506.6 ± 530.0	1317.1 ± 438.6	1538.5 ± 519.1
Adjusted Incremental Recovery at Cmax (IU/dL per IU/kg)[a]	2.2 ± 0.6	1.8 ± 0.4	2.0 ± 0.5	2.1 ± 0.6	2.2 ± 0.6
Half-life (h)	9.0 ± 1.5	9.6 ± 1.7	11.8 ± 3.8	12.1 ± 3.2	12.9 ± 4.3
Maximum Plasma Concentration Post Infusion (IU/dl)	110.5 ± 30.2	90.8 ± 19.1	100.5 ± 25.6	107.6 ± 27.6	111.3 ± 27.1
Mean Residence Time (h)	11.0 ± 2.8	12.0 ± 2.7	15.1 ± 4.7	15.0 ± 5.0	16.2 ± 6.1
Volume of Distribution at Steady State (dl/kg)	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.2
Clearance (ml/kg*h)	3.9 ± 0.9	4.8 ± 1.5	3.8 ± 1.5	4.1 ± 1.0	3.6 ± 1.2

[a] Calculated as (Cmax - baseline Factor VIII) divided by the dose in IU/kg, where Cmax is the maximal post-infusion Factor VIII measurement.

The safety and haemostatic efficacy of ADVATE® in the paediatric population are similar to that of adult patients. Adjusted recovery and terminal half-life ($t_{1/2}$) was approximately 20% lower in young children (less than 6 years of age) than in adults, which may be due in part to the known higher plasma volume per kilogram body weight in younger patients.

Pharmacokinetic data with ADVATE® on previously untreated patients are currently not available.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, acute toxicology, repeated dose toxicity, local toxicity and genotoxicity.

A local tolerance study in rabbits showed that ADVATE® reconstituted with 2 ml of sterilised water for injections is well tolerated after intravenous administration. Slight transient reddening at the administration site was observed after intraarterial application and after paravenous administration. However, no correlating adverse histopathological changes could be observed indicating a transient nature of this finding.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

α,α-Trehalose	2% (w/v)	EP
L-histidine	25 mM	EP
Tris (hydroxymethyl) aminomethane	25 mM	EP
Sodium Chloride	225 mM	EP
Calcium Chloride	4.2 mM	EP
Glutathione (Reduced)	0.2 mg/mL	EP
Polysorbate 80 (Vegetable-derived)	0.025% (w/v)	EP
Mannitol	8 % (w/v)	EP
Sterilized Water for Injection	2 ml	EP

Solvent
Sterilised water for injections- 2ml

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or solvents.

6.3 Shelf life

2 years.

After reconstitution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at 25 °C.

During the shelf life, the product may be kept at room temperature (up to 25 °C) for a single period not exceeding 6 months. The end of the 6 months storage at room temperature should be recorded on the product carton. The product may not be returned to refrigerated storage again.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
ADVATE® with BAXJECT II device: Keep the product vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Both the powder vial and the vial containing 2 ml solvent are of type I glass closed with chlorobutyl rubber stoppers. The product is provided in the following configuration:

- ADVATE® with BAXJECT II device: Each pack contains a powder vial, a vial containing 2 ml solvent and a device for reconstitution (BAXJECT II).

6.6 Special precautions for disposal and other handling

ADVATE® is to be administered intravenously after reconstitution of the product. The reconstituted solution should be inspected visually for any foreign particulate matter and/or discoloration.
After reconstitution the solution should be clear, colourless and free from foreign particles.
Do not use solutions that are cloudy or have deposits.

- For administration the use of a luer-lock syringe is required.
- Use within three hours after reconstitution.
- Do not refrigerate the preparation after reconstitution.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Reconstitution with the BAXJECT II device

- For reconstitution use only the sterilised water for injections and the reconstitution device provided in the pack.
- Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
- Aseptic Technique should be used

1. If the product is still stored in a refrigerator, take both the ADVATE® powder and solvent vials from the refrigerator and let them reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.
5. Open the package of BAXJECT II device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the device from the package. Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
6. Turn the package over and insert the clear plastic spike through the solvent stopper. Grip the package at its edge and pull the package off BAXJECT II (Fig. b). Do not remove the blue cap from the BAXJECT II device.
7. For reconstitution only the sterilised water for injections and the reconstitution device provided in the pack should be used. With BAXJECT II attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the white plastic spike through the ADVATE® powder stopper. The vacuum will draw the solvent into the ADVATE® powder vial (Fig. c).
8. Swirl gently until all material is dissolved. Be sure that the ADVATE® powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

Fig. a Fig. b Fig. c

Administration

Use Aseptic Technique

Parenteral medicinal products should be inspected for particulate matter prior to administration, whenever solution and container permit. Only a clear and colourless solution should be used.

1. Remove the blue cap from BAXJECT II. **Do not draw air into the syringe**. Connect the syringe to BAXJECT II
2. Invert the system (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly.
3. Disconnect the syringe.
4. Attach a butterfly needle to the syringe. Inject intravenously. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute. The pulse rate should be determined before and during administration of ADVATE®. Should a significant increase occur, reducing the rate of administration or temporarily interrupting the injection usually allows the symptoms to disappear promptly (see sections 4.4 and 4.8).

7. MANUFACTURER:

Baxalta Belgium Manufacturing S.A.,
Boulevard Rene Branquart 80,
7860 Lessines,
Belgium.

8. IMPORTER:

Baxalta Bioscience India Pvt. Ltd.,
Ist Floor of Plot No. 70/A-26,
Rama Road Industrial Area,
New Delhi

Import License No.: FF-94-194

Consumer Care No.: 0080 0050 4087

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: July 1, 2015
Date of latest renewal: Dec 18, 2015

10. DATE OF REVISION OF THE TEXT

24 July 2014.

Warning: "To be sold by retail on the prescription of a Registered Medical Practitioner Only"

Appendix 4.2 Undertaking by the Investigator

The following is a commitment/agreement from the investigator participating in the study and is based on the New Drugs and Clinical Trial Rules set forth by the Central Drugs Standard Control Organization in India (The Gazette of India et al., 2019):

UNDERTAKING BY THE INVESTIGATOR

1. Full name, address and title of the Principal Investigator (or Investigators when there is no Principal Investigator).
2. Name and address of the medical college, hospital or other facility where the clinical trial will be conducted: Education, training & experience that qualify the Investigator for the clinical trial (Attach details including Medical Council registration number, or any other statements of qualifications)
3. Name and address of all clinical laboratory facilities to be used in the study.
4. Name and address of the Ethics Committee that is responsible for approval and continuing review of the study.
5. Names of the other members of the research team (Co-or sub-Investigators) who will be assisting the Investigator in the conduct of the investigations.
6. Protocol Title and Study number (if any) of the clinical trial to be conducted by the Investigator.
7. Commitments:

   (i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary ethics committee and regulatory approvals have been obtained.

   (ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval or favourable opinion from the ethics committee of the amendment, except where necessary to eliminate an immediate hazard to the trial subject or when the changes involved are only logistical or administrative in nature.

   (iii) I agree to personally conduct or supervise the clinical trial at my site.

   (iv) I agree to inform all trial subject, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and

ethics committee review and approval specified in the New Drugs and Clinical Trials Rules, 2019 and Good Clinical Practices guidelines are met.

(v) I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory requirements and Good Clinical Practices guidelines.

(vi) I have read and understood the information in the Investigator's brochure, including the potential risks and side effects of the drug.

(vii) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the trial.

(viii) I agree to maintain adequate and accurate records and to make those records available for audit or inspection by the Sponsor, ethics committee, Central Licencing Authority or their authorised representatives, in accordance with regulatory provisions and the Good Clinical Practices guidelines. I will fully cooperate with any study related audit conducted by regulatory officials or authorised representatives of the Sponsor.

(ix) I agree to promptly report to the ethics committee all changes in the clinical trial activities and all unanticipated problems involving risks to human subjects or others.

(x) I agree to inform all serious adverse events to the Central Licencing Authority, sponsor as well as the ethics committee within twenty-four hours of their occurrence. In case, of failure to do so, I shall furnish the reason for the delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event.

(xi) The report of the serious adverse event, after due analysis, shall also be forwarded by me to the Central Licencing Authority, the Chairperson of the ethics committee and the Head of the institution where the trial has been conducted within fourteen days in accordance with the regulatory requirements.

(xii) I will maintain confidentiality of the identification of all participating subjects and assure security and confidentiality of study data.

(xiii) I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical trials.

8. Signature of Investigator with date.

Appendix 5 ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
AE	adverse event
AHF	antihemophilic factor
ALT	alanine aminotransferase (synonymous with SGPT)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (synonymous with SGOT)
AUC	area under the curve
AUC0-∞	area under the curve from time 0 to infinity
AUC0-tlast	area under the curve from time 0 to the time of last concentration measured
AUMC	area under the moment curve
BI	bolus infusion
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
C_{max}	maximum concentration
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
ED	exposure day
EDC	electronic data capture/collection
EFAS	effectiveness full analysis set
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union

Abbreviation	Definition
EUDRA	European Union Drug Regulatory Authorities
EUDRACT	European Union clinical trials database
FVIII	factor VIII
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLM	generalized linear model
h	hour(s)
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
INR	international normalized ratio
IP	investigational product
IR	incremental recovery
IRB	institutional review board
ISTH	International Society for Thrombosis and Haemostasis
IU	international unit(s)
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeter(s) of mercury
NA	not applicable
PCR	polymerase chain reaction
PFM	plasma/albumin free method
PK	pharmacokinetic(s)
PTP	previously treated patient
PUP	previously untreated patient
rAHF	antihemophilic factor (recombinant)
rAHF-PFM	Antihemophilic Factor (Recombinant) - Plasma/Albumin Free Method
rFVIII	recombinant FVIII
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SAS	safety analysis set
SAS	statistical analysis system
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SOC	system organ class
SoC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SWFI	sterile water for injections
$t_{1/2}$	half-life
TBD	to be determined
T_{max}	time to maximum concentration
US	United States
VWD	von Willebrand´s disease
VWF	von Willebrand factor
WHO	World Health Organization

Appendix 6 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	31 JUL 2019	India
Amendment 1.0	01 DEC 2022	India
Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1.0	Amendment Date 01 DEC 2022	Global/Country/Site Specific Global
Description of Change		Section(s) Affected by Change
Sponsor name changed from Baxalta to Takeda and Sponsor contact information updated **Rationale: Sponsor name changed from Baxalta/Shire to Takeda to reflect the current company name.**		Throughout
Takeda approver updated **Rationale: Change made to reflect a change in the Takeda approver.**		Protocol Amendment 1 Signature page
Takeda medical monitor was updated **Rationale: Change made to reflect a change in the Takeda medical monitor.**		Emergency Contact Information
Study period (planned) updated **Rationale: Study period was updated based on the actual First Patient In date however overall study period remains the same**		Protocol Summary

11. REFERENCES

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