Clinical Study Protocol

NCT Number: NCT05707351

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

Study Number: TAK-660-3001

Document Version and Date: Amendment 1.0, 16 April 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

Protocol:	TAK-660-3001
Title:	A Phase 3, Prospective, Multicenter, Open-label Study of Efficacy, Safety, and Pharmacokinetics of PEGylated Recombinant Factor VIII (ADYNOVATE) Administered for Prophylaxis and Treatment of Bleeding in Chinese Previously Treated Patients With Severe Hemophilia A (FVIII <1%)
Short Title:	China ADYNOVATE PTP Study in Hemophilia A
Study Phase:	Phase 3
Drug:	ADYNOVATE (antihemophilic factor [recombinant] PEGylated, rurioctocog alfa pegol)
IND Number:	Non-IND
EUDRACT Number:	2023-000502-26
Sponsor:	Baxalta US Inc.* * NOTE: Takeda Development Center Americas, Inc. with its legal registered address at 95 Hayden Avenue, Lexington, MA 02421 USA, has been authorized by Baxalta US Inc. to conduct this Study in the People's Republic of China. Both companies are wholly owned subsidiaries of Takeda Pharmaceutical Company Limited.
Principal / Coordinating Investigator:	[redacted], MD

Protocol History:

Date	Amendment Number	Amendment Type	Region
16 Apr 2023	Amendment 1	Non-substantial	China
21 Jun 2022	Original protocol	Not applicable	China

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

DocuSigned by: [redacted]

Sponsor's (Takeda) Approval

20-Apr-2023 | 10:28:23 JST

Signature: *Date:*

[redacted] MD, [redacted]

Investigator's Acknowledgement

I have read this protocol for Study TAK-660-3001.

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

I 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:*

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

Noteworthy changes to the protocol are captured in the table below. The primary reason for this amendment is to remove the Haemo-SYM questionnaire for patient-reported outcome assessment.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only and are not described in this table.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Description of Each Change and Rationale			**Section(s) Affected by Change**
Change Number	**Description of change(s)**	**Rationale for change(s)**	**Section**
1	Removed the Haemo-SYM questionnaire from patient-reported outcome assessments	Failed to obtain the questionnaire license in China	Section 1.1 Synopsis Table 1 Schedules of Activities Table 4 Objectives and Endpoints Section 4.1 Overall Design Section 8.2.7.1 Patient-reported Outcomes Section 9.8.1 Patient-reported Outcomes Appendix 4 Scales and Assessments
2	Removed the exploratory biomarker assessments for joint health	Followed the recommendation written in the NMPA approval letter for Study TAK-660-3001 Clinical Trial Application (CTA)	Section 1.1 Synopsis Table 1 Schedule of Activities Section 3.1.3 Exploratory Objectives Table 4 Objectives and Endpoints previous Section 8.2.7.3 (removed)
3	Added the study stopping rules	Specified the criteria of study stopping	Section 4.6 Study Stopping Rules Section 7.2 Reasons for Withdrawal/Discontinuation from Study
4	Specified that dose adjustment for prophylactic treatment may be increased gradually by 10 IU/kg increments	Clarification	Section 6.2.2.2 Prophylactic Treatment (Dose Adjustment for Prophylactic Treatment)

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Description of Each Change and Rationale			**Section(s) Affected by Change**
Change Number	**Description of change(s)**	**Rationale for change(s)**	**Section**
5	Added the blood urea nitrogen (BUN) as an alternative test of the urea	Allow for use of an alternative local practice	Table 2 Clinical Laboratory Assessments Section 8.2.5.4.2 Hematology and Clinical Chemistry Appendix 2 Clinical Laboratory Tests
6	A new criterion was added for serious adverse event (SAE): severe hypersensitivity/allergic reactions to ADYNOVATE	Consistency with the ADYNOVATE global pivotal study protocols	Appendix 3.1 Adverse Event Definitions (Serious Adverse Event)
7	Amended the text regarding the report of changes in the severity of adverse events (AEs)	Only the highest severity rating will be reported during the course of an AE. Reporting every change in the severity of an ongoing AE may cause confusion and lead to repeated counts of the same event	Appendix 3.3 Assessment of Adverse Events (Severity Categorization)
8	Modified language to clarify that the doses for the pharmacokinetic (PK) and incremental recovery (IR) assessments are required to use the same lot	Clarification	Section 6.2 Administration of Investigational Product
9	Removed Study 261202 as a reference for the study design	Correction	Section 4.2 Scientific Rationale for Study Design
10	Amended the description of PK analyses	Clarification	Section 1.1 Synopsis Section 9.7 Pharmacokinetic Analyses
11	Updated the text regarding the commercial availability of extended half-life FVIII product	Per the up-to-date market status	Section 2.1 Indication and Current Treatment Options

Protocol Amendment 1			
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Description of Each Change and Rationale			**Section(s) Affected by Change**
Change Number	**Description of change(s)**	**Rationale for change(s)**	**Section**
12	Removed the time point restriction: patient-reported outcome (PRO) assessments/eDiaries should be completed ~~the night~~ prior to each specified study visit.	Completion of the PRO assessments/eDiaries just prior to each specified study visit is acceptable	Section 1.1 Synopsis Table 1 Schedule of Activities Section 4.1 Overall Design Section 8.2.3 Subject Electronic Diary Section 8.2.7.1 Patient-reported Outcome
13	Removed the collection and analysis of the duration of emergency room visits	Correction	Section 1.1 Synopsis Table 1 Schedule of Activities Section 8.2.7.2 Healthcare Resource Utilization Section 9.8.2 Healthcare Resource Utilization Analyses (Section 9 Statistical Considerations)
14	Changed the schedule of anti-CHO Ab analysis to only screening visit, Week 12, and completion/termination visit.	To reduce unnecessary blood draws while meeting safety monitoring requirements	Table 2 Clinical Laboratory Assessments
15	Modified the language regarding the informed consent for additional PK sampling	PK sampling item has been included in the ICF and no separate informed consent for PK sampling will be obtained	Appendix 1.5 Ethical Considerations (Additional Pharmacokinetic Sampling Consent Procedure)

CONTACTS

Contacts

Certain events and study-related activities will require the investigator and/or patient to have appropriate contact information. The sponsor or contract research organization (CRO) will provide investigators with emergency medical contact information cards to be carried by each subject.

SAE Reporting

If a subject experiences a serious adverse event (SAE) or a non-serious adverse event (AE) requiring expedited reporting per the protocol, the investigator must report the event to the sponsor or CRO ***within 24 hours*** of becoming aware of the event on the electronic case report form (eCRF). If the eCRF is not available, then the event must be reported on the Takeda Safety Report Form and faxed or emailed to the sponsor or CRO to meet the 24-hour timeline requirement. The fax number and e-mail address are provided in the Form Completion Instructions.

Protocol and Safety-related Questions or Concerns

For protocol- or safety-related questions or concerns, a separate contact information list will be provided.

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product (IP) quality complaints or non-medical complaints to Takeda within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Takeda licensed or IPs, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that the product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of IP quality complaints include, but are not limited to, the following:

Unit issues	• Capsule fill empty or overage • Bottle/vial fill shortage or overage • Capsule/tablet damaged/broken • Syringe/vial cracked/broken	• Syringe leakage • Missing components • Product discoloration • Device malfunction
Labeling	• Label missing • Leaflet or Instructions For Use missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (eg, secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial • Particulate in packaging	

Please report the product quality complaint using the Clinical Trial Material Complaint Form via the email address:
ctmcomplaint@takeda.com

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

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: TAK-660-3001	**Drug:** ADYNOVATE
Title of the study: A Phase 3, Prospective, Multicenter, Open-label Study of Efficacy, Safety, and Pharmacokinetics of PEGylated Recombinant Factor VIII (ADYNOVATE) Administered for Prophylaxis and Treatment of Bleeding in Chinese Previously Treated Patients With Severe Hemophilia A (FVIII <1%)	
Short title: China ADYNOVATE PTP Study in Hemophilia A	
Number of subjects (total): At least 30 evaluable subjects aged 12 to 65 years	
Investigator(s): Multicenter study	
Site(s) and Region(s): The study will be conducted at approximately 12 sites in China.	
Study period (planned): 2023 to 2025	**Clinical phase**: 3
Objectives: Primary: • To assess the efficacy of ADYNOVATE® for prophylactic treatment in previously treated Chinese subjects with severe hemophilia A based on the total annualized bleeding rate (ABR) Secondary: • To assess the efficacy of ADYNOVATE for prophylactic treatment based on ABR by bleeding site and cause • To assess the overall hemostatic efficacy rating of ADYNOVATE for treatment of nonsurgical breakthrough bleeding episodes during the study period • To assess the efficacy of ADYNOVATE for perioperative bleeding management if minor surgery is performed during the study period • To evaluate the safety of ADYNOVATE as assessed by adverse events (AEs) and serious AEs (SAEs) as well as clinically significant findings in vital signs and clinical laboratory parameters • To evaluate the safety and the immunogenicity of ADYNOVATE based on the incidence of factor VIII (FVIII) inhibitory antibodies and binding antibodies to ADYNOVATE • To evaluate the pharmacokinetics (PK) of ADYNOVATE in Chinese subjects Exploratory: • To assess the effect of ADYNOVATE on health-related quality of life (QoL) and healthcare resource utilization	
Rationale: The study will evaluate the efficacy and safety of ADYNOVATE for prophylaxis and treatment of bleeding episodes in previously treated patients with severe hemophilia A (FVIII <1%) in the Chinese population. The study will also provide ADYNOVATE PK data in Chinese patients with severe hemophilia A.	
Investigational product, dose, and mode of administration: The investigational product (IP) is ADYNOVATE (antihemophilic factor [recombinant] PEGylated, rurioctocog alfa pegol). ADYNOVATE, following reconstitution, is injected intravenously using an appropriately sized syringe as a bolus infusion in ≤5 minutes (maximum infusion rate: 10 mL/min). The doses for ADYNOVATE are as follows: • **PK Evaluation:** 45±5 international units (IU)/kg as a single-dose infusion for the initial PK assessment before receiving the first prophylactic dose. The second PK assessment will be performed during the	

Week 20 (±1 week) visit following the scheduled prophylactic treatment dose. The dose for incremental recovery (IR) assessments is the same as that for prophylactic treatment at the scheduled visits.

- **Prophylactic Treatment:** 45±5 IU/kg twice weekly. The subject will be treated for a minimum of 50 exposure days (EDs) to ADYNOVATE or approximately 26 weeks (+2 weeks), whichever occurs last.
- **Treatment of Bleeding Episodes:** ADYNOVATE at an individualized dose of 10 to 60 IU/kg.
- **Perioperative Bleeding Management:** The dose and frequency will be individualized based on the subject's IR to obtain the target level required for the minor surgical, dental, or other invasive procedures being performed.

Methodology:

All subjects and/or legal representatives are required to provide signed informed consent prior to any study procedure. For screening, subjects need to undergo a minimum washout period of at least 72 to 96 hours following their last FVIII therapy (on-demand or prophylactic), if applicable. The study screening procedures (Table 1) will be performed for eligibility determination and will be completed within 30 days prior to the initial PK assessment (if applicable) or baseline visit. Screening procedures will include demographics, medical/medication history, concomitant medications, AEs, physical examination, vital signs, and clinical laboratory assessments (Table 2). Medical history (including immunization history) will include surgery history, hemophilia history, bleeding episode history, and history of FVIII usage over the last year. Target joints and subject's ABR based on the previous 9 to 12 months will also be recorded. Medication history will include the name of the medication, dose, dosing interval, and regimen start and end date.

All enrolled subjects will receive twice-weekly prophylactic treatment with ADYNOVATE (45±5 IU/kg) over a period of 26 weeks (+2 weeks), or at least 50 EDs, whichever occurs last.

Pharmacokinetic evaluation is planned to be performed in at least 12 evaluable subjects. For subjects participating in the PK portion of the study, the initial PK assessment will be performed after a washout period of at least 72 to 96 hours following their last FVIII therapy (if applicable) and prior to the baseline visit. The second PK assessment will be performed during the Week 20 (±1 week) visit of the prophylactic treatment phase. The PK samples will be collected at specified time points listed in Table 3 and measured for FVIII activity by a 1-stage clotting assay. For subjects not participating in the PK portion, the baseline visit may be initiated immediately upon eligibility confirmation.

Following the baseline visit, subjects will return to the study site at the below timepoints for the efficacy and safety assessments:

- Week 2 (±1 week)
- Week 6 (±1 week)
- Week 12 (±1 week)
- Week 20 (±1 week) (only for subjects undergoing PK assessment)
- Study Completion/Termination Visit: Week 26 (+2 weeks) or at least 50 EDs (whichever occurs last)

All other study treatments may be administered either at a clinic/hospital/study site or at home by self-administration/administration by a parent/caregiver. The investigator will determine the setting of treatment administration. Unscheduled visits may occur between scheduled site visits as required. Assessments may be performed as clinically indicated at the discretion of the investigator.

Factor VIII (activity and antigen) and von Willebrand factor (VWF) antigen levels will be measured at specified study visits, preinfusion, in both PK and non-PK subjects. During the baseline visit, Week 6, and the study completion/termination visit, peak levels of FVIII activity will also be assessed at 30±10 minutes post the bolus infusion of ADYNOVATE for the determination of IR. The IR determination at the baseline visit will only be performed in subjects who have not undergone the initial PK assessment.

The subject electronic diary (eDiary) and electronic PRO (ePRO) devices will be dispensed after subject eligibility is confirmed and before first dose. The eDiary will be completed before each site visit and reviewed by the investigator during the visit. The investigator will check the eDiary for prophylactic treatment compliance, bleeding episodes and treatment, AEs, concomitant medications, and nondrug therapies. It is crucial that the investigator evaluates and discusses with the subject at each study visit whether the subject/legal representative

has adhered to the prescribed treatment regimen for prophylaxis, treatment of bleeding episodes (if applicable), and whether the subject/legal representative has correctly entered all necessary information.

The PRO assessment, using the European Quality of Life Questionnaire in 5 Dimensions 5-level version (EQ-5D-5L), will be captured via an ePRO device. Subjects should complete the EQ-5D-5L prior to the baseline visit (or initial PK assessment for subjects participating in the PK portion of the study) and study completion/termination visit. Healthcare resource utilization will be gathered by sites via questionnaire as part of the electronic case report form. Upon completion of prophylactic treatment (at least 50 EDs or 26 weeks [+2 weeks], whichever occurs last), the study site will follow up via phone call with each subject after 3 to 5 days to determine the occurrence of AEs.

During the study period, subjects will also be treated for breakthrough bleeding episodes with ADYNOVATE. The dose and frequency of ADYNOVATE administration will be individualized based on the subject's weight, type and severity of bleeding episode, and monitoring of appropriate clinical and laboratory measures per the investigator's judgment.

If a subject requires minor elective or emergency surgical, dental, or other invasive procedures during the study after enrollment (ie, a surgery that was not planned before study enrollment), perioperative bleeding will be managed with ADYNOVATE. The dose and frequency of ADYNOVATE administration will be individualized based on the subject's IR to obtain the FVIII target level required for the procedure being performed. Major surgeries are not in the scope of this study; any required major surgery will result in the withdrawal of the subject.

Primary Outcome Measure:

Total ABR

Secondary Outcome Measures:

Efficacy:

- Annualized bleeding rates based on bleeding site and cause
- Number of infusions and weight-adjusted consumption of ADYNOVATE per week and month during the prophylactic treatment period
- Proportion of subjects with zero bleeding episodes during the study
- Time intervals between bleeding episodes
- Overall hemostatic efficacy rating at bleed resolution for treatment of breakthrough bleeding episodes
- Number of infusions and weight-adjusted consumption of ADYNOVATE per bleeding episode
- Overall assessment of hemostatic efficacy based on the Global Hemostatic Efficacy Assessment score as assessed by the operating surgeon/investigator
- Intra- and postoperative actual versus predicted blood loss after the surgery, at postoperative day 1, and at discharge, as assessed by the operating surgeon/investigator
- Perioperative transfusion requirement of blood, red blood cells, platelets, and other blood products
- Daily intra- and postoperative weight-adjusted consumption dose of ADYNOVATE

Safety:

- Occurrence of AEs and SAEs, total incidence, by severity, and by causality
- Occurrence of thromboembolic events and hypersensitivity reactions
- Clinically significant changes in vital signs and clinical laboratory parameters

Immunogenicity:

- Development of confirmed inhibitory antibodies (≥0.6 Bethesda units (BU)/mL using the Nijmegen modification of the Bethesda assay) to FVIII
- Binding antibodies to ADYNOVATE
- Binding antibodies to Chinese hamster ovary (CHO) proteins

Pharmacokinetics:

- Factor VIII activity (1-stage clotting assay) in PK samples collected following single-dose and steady-state dose for PK assessments
- Incremental recovery over time during prophylactic treatment at ED1, Week 6 (approximately ED10 to ED15), and ED50
- Predose FVIII (activity and antigen) and VWF (antigen) at scheduled visits
- Pharmacokinetic parameters including, not limited to, CL (clearance), V (volume of distribution), AUC (area under the concentration versus time curve between defined timepoints), C_{max} (maximum concentration), $C_{predose}$ (predose concentration), and elimination phase $T_{1/2}$ (half-life), following a single dose and steady-state dose, using noncompartmental analysis (NCA) methodology, subject to data availability

Exploratory Outcome Measures:

Patient-reported Outcome and Healthcare Resource Utilization Endpoints:

- Health-related quality of life as assessed using the EQ-5D-5L
- Healthcare resource utilization endpoints, including number and duration of hospitalizations, number of emergency room visits, number of acute care visits, and number of days missed from school/work

Inclusion and Exclusion Criteria:

Inclusion Criteria:

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

1. Subject and/or legally authorized representative must voluntarily sign a written informed consent form (ICF) after all relevant aspects of the study have been explained and discussed with the subject. For the subjects <18 years old, subjects will give assent AND their parents/legally authorized representative should sign the ICF accordingly.
2. Subject and/or legally authorized representative understands and is willing and able to comply with all requirements of the study protocol.
3. Subject should be ethnic Chinese.
4. Subject is 12 to 65 years of age at screening and male.
5. Subject has severe hemophilia A (FVIII clotting activity <1%) as confirmed by the central laboratory at screening after a washout period of at least 72 to 96 hours.
6. The last on-demand or prophylactic treatment received is within 3 months before screening.
7. Subject has documented previous treatment with plasma-derived FVIII concentrates or recombinant FVIII for >150 EDs.
8. Subject is human immunodeficiency virus (HIV) negative, or HIV-positive with stable disease and $CD4^+$ count ≥200 cells/mm^3.
9. Subject is hepatitis C virus (HCV) negative by antibody testing (if positive, additional polymerase chain reaction testing will be performed to confirm), as confirmed at screening; or HCV-positive with chronic stable hepatitis as assessed by the investigator.

Exclusion Criteria:

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

1. Subject has detectable FVIII inhibitory antibodies (≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay) as confirmed by the central laboratory at screening.
2. Subject has a confirmed history of FVIII inhibitory antibodies (≥0.6 BU using the Nijmegen modification of the Bethesda assay or ≥0.6 BU using the Bethesda assay) at any time prior to screening.
3. Subject has a known hypersensitivity to ADYNOVATE or ADVATE or any of the components of the study drugs, such as mouse or hamster proteins, or other FVIII products.
4. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease).
5. Subject has severe hepatic dysfunction (eg, ≥5 times the upper limit of normal [ULN] for alanine aminotransferase or aspartate aminotransferase, a recent or persistent international normalized ratio >1.5, as confirmed by the local laboratory at screening).
6. Subject has severe renal impairment (serum creatinine >1.5 times the ULN) as confirmed by the local laboratory at screening.
7. Subject is planned or likely to undergo major surgery during the study period.
8. Subject has current or recent (<30 days) use of other PEGylated drugs before study participation or scheduled use of such drugs during study participation.
9. Subject has received emicizumab therapy within 6 months of screening.
10. Subject is currently receiving, or scheduled to receive during the study, an immunomodulating drug (eg, systemic corticosteroid agent at a dose equivalent to hydrocortisone >10 mg/day, or α-interferon) other than antiretroviral chemotherapy.
11. Subject has participated in another clinical study involving the use of an IP other than ADYNOVATE or an investigational device within 30 days before the screening visit or is scheduled to participate in another clinical study involving an IP or investigational device during this study.
12. Subject has a medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
13. Subject, in the opinion of the investigator, is unable or unwilling to comply with the study protocol.

The maximum duration of subject participation in the study:

The subject's duration of participation is expected to be approximately 8 months unless prematurely discontinued.

Statistical analysis:

Sample Size Determination:

At least 30 evaluable adult and adolescent subjects (aged 12 to 65 years) will be enrolled. The sample size was not based on statistical consideration. The evaluable subjects are defined as all subjects who are treated with Adynovate for a minimum of 50 EDs or approximately 26 weeks (+2 weeks), whichever occurs last. Subjects who withdraw or discontinue before study completion may be replaced.

Analysis Sets:

The safety analysis set (SA set) will comprise all subjects treated with at least 1 Adynovate dose. All safety analyses will be performed on the SA set.

The full analysis set (FAS) will comprise all subjects who were assigned to receive a treatment regimen of Adynovate. All efficacy analyses will be performed on the FAS.

The per protocol analysis set (PPAS) will comprise all subjects who were treated with the prophylaxis Adynovate treatment regimen and comply with their originally assigned dose for the duration of study participation. The PPAS will be the supportive analysis set.

The PK full analysis set (PK FAS) will comprise all subjects who consented to PK evaluation, were treated with at least 1 Adynovate dose, and have at least 1 evaluable PK concentration post dose. All PK analyses will be performed on the PK FAS.

The PK analysis set (PK AS), a subset of the PK FAS, will comprise all PK subjects who received at least 1 Adynovate PK dose with a sufficient number of evaluable PK concentrations post dose for the estimation of PK parameters using an NCA.

Efficacy Analyses:

Primary Efficacy Outcome Measure (Total ABR):

The primary efficacy endpoint is the total ABR for all bleeding episodes that occurred during the study (after the first dose of the study drug). The ABR during the study is to be analyzed in the FAS. Point estimates with 95% confidence intervals (CIs) of ABRs will be presented.

Safety Analyses:

For this study, any untoward medical occurrence occurring from the time the ICF is signed will be considered an AE. A treatment-emergent AE (TEAE) is any event emerging or manifesting at or after the initiation of treatment with an IP or any existing event that worsens in either intensity or frequency following exposure to the IP.

Adverse events will be coded with the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of TEAEs, SAEs, treatment-related AEs, and TEAEs leading to discontinuation of the study will be summarized overall and by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be further summarized by severity and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Occurrence of hypersensitivity reactions and thromboembolic events will be monitored throughout the study and summarized by SOC and PT.

For immunogenicity analysis, the incidence of confirmed inhibitory antibodies (≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay) to FVIII will be summarized by frequency table. The proportion of subjects, including a 95% CI using an exact Clopper-Pearson interval, who developed inhibitory antibodies to FVIII at any time during the study (after the first dose of the study drug) will be summarized. Histograms will be used to show the number and proportion of subjects with binding antibodies to Adynovate and binding antibodies to CHO proteins.

Clinical laboratory parameters and vital signs will be summarized for baseline and postbaseline scheduled visits (including the termination visit), as well as their changes from baseline. Number and percent of subjects with clinically significant abnormal results for vital signs and clinical laboratory parameters will be summarized for any postbaseline assessment. Shift tables will be used to assess the frequency of changes for clinically significant vital signs and clinical laboratory parameters (hematology and clinical chemistry) to note clinically significant changes, or vice versa, after first exposure to Adynovate.

Pharmacokinetics Analyses:

Pharmacokinetic parameters will be estimated for FVIII activity measured by the 1-stage clotting assay following an initial single dose and steady-state dose of Adynovate. Pharmacokinetic parameters, as appropriate but not limited to, will include CL, V, AUC, Cmax, Cpredose, and elimination phase T1/2. For PK subjects, subject to availability of FVIII activity, NCA methodology will be used. For all subjects, the population PK modeling and simulation method will be used, as appropriate, and reported separately.

Factor VIII activity (1-stage clotting assay) in PK samples collected following single-dose and steady-state dose for PK assessments, predose FVIII levels (activity and antigen), FVIII activity and VWF antigen will be tabulated and summarized descriptively. Incremental recovery over the prophylactic treatments will be calculated and summarized descriptively.

Other Analyses:

Patient-reported Outcome Analysis:

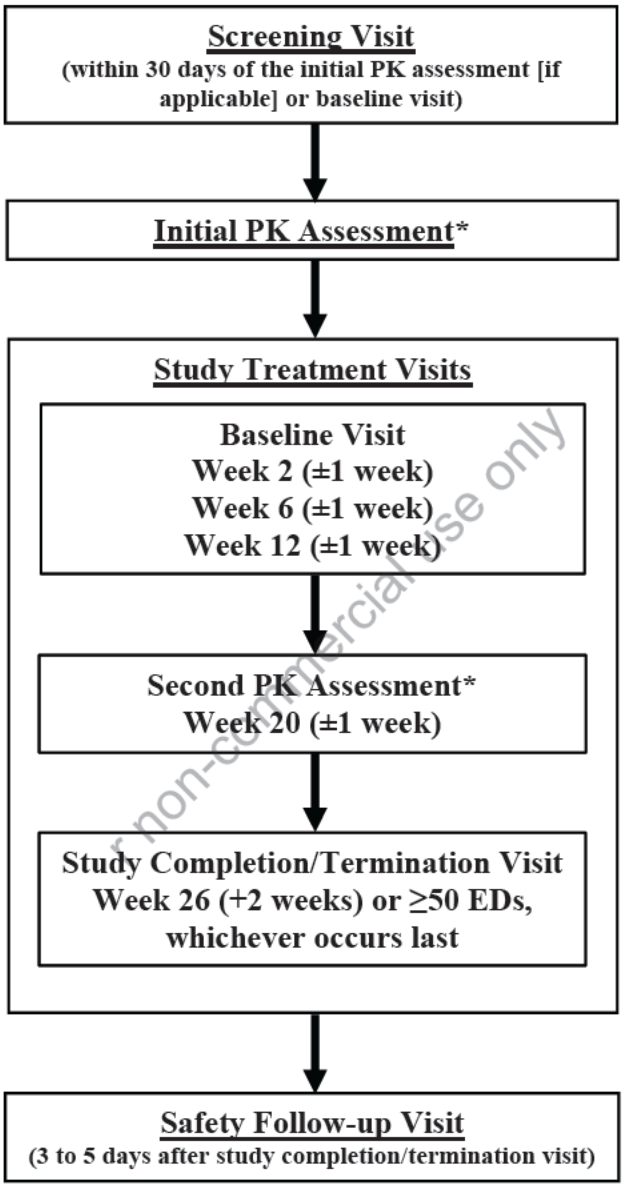
Health-related quality of life results as assessed using the EQ-5D-5L will be summarized using descriptive statistics in accordance with the questionnaire user guide. Changes from baseline/preinfusion to study completion in this PRO will be estimated using the Hodges-Lehmann estimator.

Healthcare Resource Utilization Analyses:

Healthcare resource utilization endpoints, including number and duration of hospitalizations, number of emergency room visits, number of acute care visits, and number of days missed from school/work, will be summarized descriptively. Additional analyses may include mean hospitalizations per subject, mean length of stay, and mean days missed from school/work.

1.2 Schema

Figure 1. Study Schematic Diagram



ED=exposure day; PK=pharmacokinetic

* Only for subjects who undergo the PK assessments

1.3 Schedules of Activities

Table 1. Schedule of Activities

Procedures/ Assessments	Screening Visit [a]	Initial PK Assessment [b]			Study Treatment Visits								Safety Follow-up Visit [d]
									Second PK Assessment [b]			Study Completion/ Termination Visit	
	Within 30 days	Preinfusion	Infusion	Postinfusion	Baseline Visit	Week 2 (±1 week)	Week 6 (±1 week)	Week 12 (±1 week)	Week 20 (±1 week)			Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last	
									Preinfusion	Infusion	Postinfusion		
Informed Consent/ Assent[e]	X												
Demographics	X												
Eligibility Criteria	X												
Medical/ Medication History [f]	X												
Concomitant Medication [g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment [g]	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Schedule of Activities

Procedures/ Assessments	Screening Visit [a]	Initial PK Assessment [b]			Study Treatment Visits								Safety Follow-up Visit [d]
									Second PK Assessment [b]			Study Completion/ Termination Visit	
	Within 30 days	Preinfusion	Infusion	Postinfusion	Baseline Visit	Week 2 (±1 week)	Week 6 (±1 week)	Week 12 (±1 week)	Week 20 (±1 week)			Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last	
									Preinfusion	Infusion	Postinfusion		
Physical Examination [h]	X	X			X	X	X	X	X			X	
Vital Signs [i]	X	X		X	X	X	X	X	X		X	X	
Clinical Laboratory Assessments [j]	X	X		X	X	X	X	X	X		X	X	
Subject eDiary [k]		X [l]			X [l]	X	X	X	X			X	
ePRO Assessment [m]		X [l]			X [l]							X	
Healthcare Resource Utilization [n]					X	X	X	X	X			X	
IP Treatment [o]			X		X	X	X	X		X		X	
IP Dispensation					X	X	X	X			X		

Table 1. Schedule of Activities

Procedures/ Assessments	Screening Visit [a]	Initial PK Assessment [b]			Study Treatment Visits							Study Completion/ Termination Visit	Safety Follow-up Visit [d]
									Second PK Assessment [b]				
	Within 30 days	Preinfusion	Infusion	Postinfusion	Baseline Visit	Week 2 (±1 week)	Week 6 (±1 week)	Week 12 (±1 week)	Week 20 (±1 week)			Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last	
									Preinfusion	Infusion	Postinfusion		
Investigator Assessment of Hemostatic Efficacy [p]					X	X	X	X				X	
IR Assessments [q]					X		X [r]					X	

ABR=annualized bleeding rate; AE=adverse event; EC=ethics committee; eCRF=electronic case report form; ED=exposure day; eDiary=electronic diary; ePRO=electronic patient-reported outcome; FVIII=factor VIII; IP=investigational product; IR=incremental recovery; PK=pharmacokinetic(s); PRO=patient reported outcome

[a] The screening visit procedures, including laboratory evaluations, are to be completed within 30 days prior to the initial PK assessment procedures (if applicable) or baseline visit. At least 72 to 96 hours must have elapsed since the subject's last FVIII therapy (on-demand or prophylactic), if applicable, and the subject must not be actively bleeding.

[b] For subjects participating in the PK portion of the study, the initial PK assessment will be conducted after a washout period of at least 72 to 96 hours following their last FVIII therapy (if applicable) and prior to baseline visit. The second PK assessment will be performed following the scheduled prophylactic treatment dose. The PK samplings for both the initial and second PK assessments should be taken following the time points listed in Table 3. The PK blood samples collected for PK assessments will be measured for FVIII activity (1-stage clotting assay). Subjects undergoing PK evaluation will enter the prophylactic treatment phase 96 hours (±4 hours) after the initial PK infusion.

[c] Exposure day calculation starts from the first PK infusion or baseline visit and completes at study completion/termination visit.

[d] The study site will follow up via phone call with each subject 3 to 5 days after the last ADYNOVATE infusion for the occurrence of AEs.

Table 1. Schedule of Activities

Procedures/ Assessments	Screening Visit [a]	Initial PK Assessment [b]			Study Treatment Visits							Safety Follow-up Visit [d]
									Second PK Assessment [b]		Study Completion/ Termination Visit	
	Within 30 days	Preinfusion	Infusion	Postinfusion	Baseline Visit	Week 2 (±1 week)	Week 6 (±1 week)	Week 12 (±1 week)	Week 20 (±1 week)		Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last	
									Preinfusion	Infusion / Postinfusion		

[e] Written informed consent/assent must be obtained prior to any study-specific procedure.

[f] Medical history will include immunization history, surgery history, hemophilia history, bleeding episode history, and history of FVIII usage over the last year. Target joints and subject's ABR based on the previous 9 to 12 months will also be recorded. Medication history will include the name of the product, dose, dosing interval, and regimen start and end date.

[g] Concomitant medications, nondrug therapies, AEs, bleeding episodes, and their treatment will be continuously monitored by the study site and reviewed and discussed with the subject at study visits.

[h] Physical examination will include, at a minimum, assessments of the general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.

[i] Vital signs include height (only at screening), weight, body temperature, respiratory rate, pulse rate, and blood pressure taken following 15 minutes of rest. The time points for pre- and postinfusion measurements are: within 30 minutes before infusion start (prior to blood sample collection) and 30±15 minutes post infusion. Weight is measured preinfusion only.

[j] At all laboratory assessments, subjects must not be actively bleeding. Assessments should only be performed after a washout period of at least 72 to 96 hours following the last infusion of any other nonmodified FVIII concentrate and 84 to 96 hours following the last infusion of ADYNOVATE. In addition to the assessments shown, clinical laboratory assessments should be performed whenever clinically indicated. For more detailed information, please see Table 2.

[k] The eDiary will be dispensed after subject eligibility is confirmed and before first dose. eDiaries will be completed before each site visit and reviewed by the investigator during the visit. The investigator will check the eDiary for completeness and request missing information periodically, at a minimum at each subject visit, and in a timely manner.

Table 1. Schedule of Activities

Procedures/ Assessments	Screening Visit [a]	Initial PK Assessment [b]			Study Treatment Visits							Safety Follow-up Visit [d]
									Second PK Assessment [b]		Study Completion/ Termination Visit	
	Within 30 days	Preinfusion	Infusion	Postinfusion	Baseline Visit	Week 2 (±1 week)	Week 6 (±1 week)	Week 12 (±1 week)	Week 20 (±1 week)		Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last	
									Preinfusion	Infusion / Postinfusion		

[l] For subjects participating in the PK portion of the study, the first eDiary/PRO assessment should be completed prior to the initial PK assessment. For subjects not undergoing PK assessment, the first eDiary/PRO assessment should be completed prior to baseline visit.

[m] The PRO assessment, using the EQ-5D-5L, will be captured via an ePRO device dispensed after subject eligibility is confirmed and before the first dose. The EQ-5D-5L is to be completed before specified study visits and reviewed by the investigator during the visit.

[n] Healthcare resource utilization evaluation, including number and duration of hospitalizations, number of emergency room visits, number of acute care visits, and number of days missed from school/work will be gathered by the sites via questionnaire as part of the eCRF.

[o] ADYNOVATE is administered at the study site for all study-required visits. Whenever possible, the IP treatment at the study site shall be in accordance with the subject's twice-weekly ADYNOVATE prophylactic treatment regimen. All other study treatments may be administered either at a clinic/hospital/study site or at home by self-administration/administration by a parent/caregiver. The investigator will determine the setting of treatment administration.

[p] Efficacy of ADYNOVATE treatment will be assessed using a 4-point efficacy rating scale (Table 7).

[q] Incremental recovery will be calculated by the investigator. Blood samples should be taken within 30 minutes before ADYNOVATE administration and 30±10 minutes post ADYNOVATE infusion. The IR determination at baseline visit will only be performed in subjects who have not undergone the initial PK assessment.

[r] Incremental recovery over time during prophylactic treatment will be evaluated at ED1, Week 6, and ED50. If possible, the Week 6 visit should evaluate ED10 to ED15.

Table 2. Clinical Laboratory Assessments

Procedures/ Assessments	Screening Visit [a]	Initial PK Assessment [b]			Study Treatment Visits							
									Second PK Assessment [b]			Study Completion/ Termination Visit
	Within 30 days	Preinfusion	Infusion	Postinfusion	Baseline Visit	Week 2 (±1 week)	Week 6 (±1 week)	Week 12 (±1 week)	Week 20 (±1 week) Preinfusion	Week 20 (±1 week) Infusion	Week 20 (±1 week) Postinfusion	Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last
Immunology [d]	X											
Blood Type [e]	X											
Hematology [f]	X				X			X				X
Clinical Chemistry [g]	X				X			X				X
Immunogenicity [h]	X				X	X	X	X				X
FVIII Activity [i]	X	X [j]			X [k]	X	X [k]	X	X			X [k]
FVIII/VWF Antigen [i]	X	X [j]			X	X	X	X	X			X
Coagulation Function [l]	X											
Pharmacokinetic Test [m]		X		X					X		X	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BU=Bethesda unit(s); BUN=blood urea nitrogen; CHO=Chinese hamster ovary; eCRF=electronic case report form; ED=exposure day; FVIII=factor VIII; GGT=gamma-glutamyl transferase; HbcAb=hepatitis B core antibody; HbsAb=hepatitis B surface antibody; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR= international normalized ratio; IR=incremental recovery; PK=pharmacokinetic(s); VWF=von Willebrand factor.

[a] The screening visit procedures, including laboratory evaluations, are to be completed within 30 days prior to the initial PK assessment procedures (if applicable) or baseline visit.

[b] For subjects participating in the PK portion of the study, the initial PK assessment will be conducted after a washout period of at least 72 to 96 hours following their last FVIII therapy (if applicable) and prior to baseline visit. The second PK assessment will be performed following the scheduled prophylactic treatment dose. The PK samplings for both initial and second PK assessments should be taken following the time points listed in Table 3. The PK blood samples will be measured for FVIII activity (1-stage clotting assay).

[c] Exposure day calculation starts from the first PK infusion or baseline visit and completes at study completion/termination visit.

Table 2. Clinical Laboratory Assessments

Procedures/ Assessments	Screening Visit [a]	Initial PK Assessment [b]			Study Treatment Visits							Study Completion/ Termination Visit
									Second PK Assessment [b]			
									Week 20 (±1 week)			Week 26 (+2 weeks) or ≥50 EDs [c], whichever occurs last
	Within 30 days	Preinfusion	Infusion	Postinfusion	Baseline Visit	Week 2 (±1 week)	Week 6 (±1 week)	Week 12 (±1 week)	Preinfusion	Infusion	Postinfusion	

[d] Immunology assessments will include HIV-1/HIV-2 antibody, HbsAg, HbsAb, HbcAb, and HCV antibodies. The HCV titer will be confirmed by polymerase chain reaction for all subjects reported as HCV-positive. If a subject is HIV-positive, CD4 count is measured to determine the subject's eligibility.

[e] If historical data on blood group type are available, this may be recorded in the eCRF and blood type does not need to be determined. For subjects who do not have documentation of their blood type in their medical record, ABO blood type will be measured locally at screening.

[f] The hematology panel will consist of complete blood count: hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), leukocytes (ie, white blood cell count) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), and platelet count.

[g] Clinical chemistry assessments will include sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, AST, GGT, bilirubin, ALP, urea/BUN, creatinine, glucose, cholesterol, very low-density lipoprotein, low-density lipoprotein, high-density lipoprotein, and triglycerides.

[h] Immunogenicity assessments will include the measurement of inhibitory antibodies to FVIII and binding antibodies to ADYNOVATE. A minimum washout of 72 to 96 hours is required following the last infusion of any other nonmodified FVIII therapy and 84 to 96 hours following the last infusion of ADYNOVATE. Binding antibodies to CHO protein will be included in immunogenicity assessment only at the screening visit, Week 12, and the completion/termination visit.

[i] The blood sample for FVIII activity and FVIII/VWF antigen tests should be collected preinfusion.

[j] For PK subjects, preinfusion blood draws are performed within 30 minutes prior to infusion, meaning no additional blood draw is needed at the baseline visit for these assessments.

[k] For IR determination: blood samples should be taken within 30 minutes before ADYNOVATE administration and 30±10 minutes post ADYNOVATE infusion. The IR determination at the baseline visit will only be performed in subjects who have not undergone PK assessment.

[l] Coagulation function will be assessed via INR at screening and aPTT, as needed, for surgery.

[m] The samples collected for PK assessments following single- and multiple-dose administrations should be taken following the time points listed in Table 3.

Note: At all laboratory assessments, subjects must not be actively bleeding. Assessments should only be performed after a washout period of at least 72 to 96 hours following the last infusion of any other nonmodified FVIII concentrate and 84 to 96 hours following the last infusion of ADYNOVATE.

Table 3. Pharmacokinetic Sampling Time Points

	Preinfusion	Postinfusion									
	Within 30 min	**30 min (±10 min)**	**1 hour (±30 min)**	**2 hours (±30 min)**	**4 hours (±30 min)**	**8 hours (±1 hour)**	**12 hours (±1 hour)**	**24 hours (±2 hours)**	**48 hours (±4 hours)**	**72 hours (±4 hours)**	**96 hours (±4 hours)**
Initial PK Assessment	X	X	X	X	X	X	X	X	X	X	X
Second PK Assessment Week 20 (±1 week)	X	X	X	X	X	X	X	X	X	X	X [a]

PK=pharmacokinetic

[a] Performance of 96-hour sampling is dependent on subject's prophylaxis dosing schedule (ie, subject must be on a 3- to 4-day dosing regimen with 4 days until the next infusion at the time of the second PK assessment).

2. INTRODUCTION

ADYNOVATE (antihemophilic factor [recombinant] PEGylated, rurioctocog alfa pegol) is an extended half-life ($T_{1/2}$) recombinant human coagulation factor VIII (rFVIII) modified with polyethylene glycol (PEG). It was developed by Baxalta (a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, referred to as "Takeda" throughout this document) and was first approved in the United States (US) on 13 Nov 2015. As of 12 Nov 2021, ADYNOVATE is approved to treat hemophilia A (congenital FVIII deficiency) in 28 countries. The indications for use of ADYNOVATE may vary in different countries.

The therapeutic activity of ADYNOVATE is derived from its parent drug substance, ADVATE (antihemophilic factor [recombinant]; international nonproprietary name: octocog alfa), which was also developed by Baxalta and was approved in China on 16 May 2012.

This study will evaluate the efficacy and safety of ADYNOVATE for prophylaxis and treatment of bleeding episodes in previously treated patients (PTPs) with severe hemophilia A (factor VIII [FVIII] <1%) in the Chinese population. The study will also provide ADYNOVATE pharmacokinetic (PK) data in Chinese patients with severe hemophilia A.

2.1 Indication and Current Treatment Options

Factor VIII is a critical component of the intrinsic coagulation pathway. Hemophilia A is an X-linked recessive, congenital bleeding disorder caused by deficient or defective coagulation FVIII leading to bleeding episodes in joints and tissues. The incidence of hemophilia A is approximately 1/5000 in males, and based on Chinese survey data, the prevalence of hemophilia is 2.73/100,000 (Chinese Medical Association; Hematology Branch Thrombosis and Hemostasis Group 2017) The total number of Chinese patients with hemophilia A is 17,779 based on registry data collected between 2007 and 2019 by the Hemophilia Treatment Center Collaboration Network of China (HTCCNC); of those, 6,519 (49.7%) had severe hemophilia A (Song et al. 2021).

Factor VIII concentrates (either plasma derived or recombinant) are used in hemophilia A patients to provide a hemostatic FVIII level sufficient to treat and prevent bleeding episodes. Current management of severe hemophilia A includes on-demand treatment for bleeding episodes and prophylaxis to prevent bleeding episodes (National Hemophilia Foundation 2007; National Hemophilia Foundation. 2006). The Medical and Scientific Advisory Council of the National Hemophilia Foundation considers prophylactic therapy with FVIII to be the optimal treatment for hemophilia A patients without inhibitors (National Hemophilia Foundation 2007). A number of clinical studies have investigated the effects of prophylactic regimens in patients diagnosed with severe hemophilia A (Aledort et al. 1994; Berntorp et al. 2014; Fischer et al.

2002; Gouw et al. 2007; Hoots and Nugent 2006; Lee 2007; Löfqvist et al. 1997; Mahlangu et al. 2014; Manco-Johnson 2007; Manco-Johnson et al. 1994; Morado et al. 2005; Roosendaal and Lafeber 2007; Royal et al. 2002). These studies have demonstrated that when begun at a young age, prophylaxis reduces the number of bleeding episodes and prevents hemophilic arthropathy (Löfqvist et al. 1997), thereby decreasing the rate of disability and resulting in lower long-term health care costs for patients (Manco-Johnson et al. 1994; Roosendaal and Lafeber 2007). The discontinuation of prophylactic therapy and suboptimal adherence to the prophylactic regimen compromise the clinical outcome, leading to further arthropathy (Berntorp 2009; Hoots and Nugent 2006). In addition, the early initiation of prophylaxis may have a protective effect against inhibitor development, the most serious complication associated with FVIII treatment (Gouw et al. 2007; Morado et al. 2005).

The average $T_{1/2}$ of current FVIII products is in the range of 10 to 14 hours for adults and is lower in children (Björkman 2003; Björkman and Berntorp 2001; Björkman et al. 2009; Manco-Johnson et al. 2007; White et al. 1997). Thus, current prophylactic regimens require infusion of FVIII every other day, or every 2 to 3 days when based on each patient's individual PK profile (Valentino et al. 2012). Recombinant FVIII products with an extended $T_{1/2}$ may prolong the efficacy of replacement therapy. Recombinant FVIII concentrates or plasma-derived FVIII product are still the first choice for the replacement therapy of hemophilia A.

Non–factor replacement therapy differs from clotting factor replacement therapy in that it provides hemostasis through a different mechanism than FVIII/factor IX (FIX) replacement. Emicizumab was approved in China in 2018 for patients with hemophilia A who develop inhibitors. Emicizumab represents a much-needed alternative approach to managing FVIII deficiency, especially for those with inhibitors or limited ability to perform self-infusion (Langer et al. 2018). In China, the first rFVIII product was launched after 2000, but no extended half-life (EHL) FVIII product is available on the market as of February 2023.

2.2 Product Background and Clinical Information

The investigational product (IP), ADYNOVATE, is composed of full-length rFVIII protein identical to the albumin/plasma-free manufactured octocog alfa known as ADVATE. Polyethylene glycol chains are covalently bound to the protein using a stable linker. The ADYNOVATE product is reconstituted with sterile water for injection (SWFI) and delivered as a solution by bolus infusion. The same stabilizing agents (mannitol, trehalose dehydrate, histidine, and glutathione) are used as the parent rFVIII product (octocog alfa, ADVATE). ADYNOVATE is intended for use as an FVIII replacement therapy with an extended $T_{1/2}$ in prophylaxis and treatment of bleeding events in subjects with severe hemophilia A.

Nonclinical in vivo studies demonstrated that ADYNOVATE and ADVATE have similar safety and efficacy profiles. In vitro safety studies have shown that ADYNOVATE and ADVATE have similar effects on cytokine release and complement activation. The functional characterization of ADYNOVATE revealed similar characteristics of ADYNOVATE and ADVATE in terms of FIXa cofactor activity, time course of thrombin-mediated activation and inactivation, thrombin generation assay, activated protein C-mediated inactivation of FVIII and FVIIIa, binding to von Willebrand factor (VWF), and synthetic phospholipids. Interaction with the low-density lipoprotein receptor–related protein 1 was reduced by PEGylation of rFVIII. Nonclinical study results demonstrated that ADYNOVATE has prolonged efficacy and improved PK compared with ADVATE and a similar safety profile, including FVIII immunogenicity profile.

The clinical development program for ADYNOVATE follows the European Medicines Agency (EMA) guidance outlined in EMA/CHMP/BPWP/144533/2009 and consists of 6 completed studies in PTPs and 1 ongoing study in previously untreated patients (PUPs).

A first-in-human prospective, open-label, crossover, dose-escalation study to evaluate safety and PK parameters of single doses of ADYNOVATE compared to single doses of ADVATE was conducted in 19 adult PTPs with severe hemophilia A (FVIII <1%) (Study 261101). The mean $T_{1/2}$ was 1.4- and 1.5-fold higher for ADYNOVATE compared to ADVATE in Cohorts 1 (30 international units [IU]/kg) and 2 (60 IU/kg), respectively, demonstrating an extended $T_{1/2}$ for ADYNOVATE compared to ADVATE. No subjects developed inhibitory antibodies to FVIII or binding antibodies to FVIII, PEG-FVIII, or PEG after a single ADYNOVATE infusion. There were no notable differences in the type or rate of adverse events (AEs) experienced by subjects after single infusions of ADVATE versus ADYNOVATE. Based on these data, ADYNOVATE was shown to be safe and well tolerated after single-dose administration.

Based on the results of the Phase 1 study, the pivotal, Phase 2/3, multicenter, nonrandomized open-label study (Study 261201) in adult and adolescent male PTPs with severe hemophilia A was performed to evaluate efficacy, safety, and PK parameters of ADYNOVATE and to assess health-related quality of life (HRQoL) in subjects using a prophylactic dosing regimen or an on-demand treatment regimen. The study included 138 evaluable subjects and confirmed the results of Study 261101, demonstrating that ADYNOVATE extends the mean $T_{1/2}$ by approximately 1.4-fold and mean residence time (MRT) by approximately 1.5-fold as compared to ADVATE. Twice-weekly prophylactic infusions at the intended dose of 45±5 IU/kg ADYNOVATE resulted in an annualized bleeding rate (ABR) that was significantly lower than that observed with on-demand treatment, with a prophylaxis/on-demand ABR ratio of 0.10. Approximately 40% of subjects treated on prophylaxis did not experience any bleeding episodes, while all subjects treated on-demand experienced bleeding episodes. ADYNOVATE was efficacious in the treatment of bleeding episodes, with 96.1% rated “excellent” or “good” and

95.9% treated with 1 or 2 infusions. No FVIII inhibitory antibodies or persistent binding antibodies against FVIII, PEG-FVIII, PEG, or Chinese hamster ovary (CHO) proteins were reported, and no safety signals were identified. This study demonstrated that ADYNOVATE is safe and efficacious in treating bleeding episodes and in prophylaxis administered twice weekly in adults and adolescents ≥12 years of age with severe hemophilia A (Konkle et al. 2015).

A study in pediatric PTPs <12 years of age (Study 261202) commenced only after the data of 20 PTPs ≥12 years of age who had been treated for ≥50 exposure days (EDs) and the PK data of at least 12 PTPs ≥12 years of age had become available in pivotal Study 261201, had been reviewed by an independent data monitoring committee, and had received a go decision. This Phase 3, prospective, uncontrolled, multicenter study was performed to evaluate PK, hemostatic efficacy, safety, immunogenicity, and HRQoL of ADYNOVATE and included 66 pediatric subjects who received prophylactic treatment. The study showed an extended $T_{1/2}$ of ADYNOVATE also in children (N=31). Depending on the assay (1-stage clotting or chromogenic) and PK model (nonlinear mixed effects model or noncompartmental estimation approach) used, $T_{1/2}$ and MRT were 1.3 to 1.5 times longer for ADYNOVATE than for ADVATE. Twice-weekly prophylactic infusions at the intended dose of 50±10 IU/kg resulted in a point estimate for the mean ABR of 3.04 (95% confidence interval [CI]: 2.208; 4.186). Approximately 38% of subjects did not experience any bleeding episodes. ADYNOVATE was efficacious in the treatment of bleeding episodes: 90.0% had an efficacy rating of "excellent" or "good" and 91.5% were treated with 1 or 2 infusions. No FVIII inhibitory antibodies or persistent binding antibodies against FVIII, PEG-FVIII, PEG, or CHO proteins influencing safety or PK parameters were reported. Twice-weekly administration of ADYNOVATE at a dose of 50±10 IU/kg was safe and efficacious for prophylaxis and control of bleeding in pediatric subjects <12 years of age with severe hemophilia A (Mullins et al. 2017).

A Phase 3, prospective, open-label, single-group, uncontrolled, multicenter study to evaluate the efficacy and safety of ADYNOVATE in male PTPs, 2 to 75 years of age, with severe hemophilia A who were to undergo major or minor elective or minor emergency surgical, dental, or other invasive procedures (Study 261204) included 22 subjects who received at least 1 dose of ADYNOVATE. The subjects either completed another ADYNOVATE study or were newly recruited. Twenty-six surgical procedures (21 major and 5 minor) were performed in 21 unique subjects. Of these, 24 surgeries (21 major and 3 minor) with available scores were rated "excellent" and therefore considered a treatment success. For major orthopedic surgeries, the median intraoperative blood loss was substantially less than the average volume predicted preoperatively by the investigator/surgeon. Actual median postoperative blood loss for major orthopedic surgeries was higher than the average volume predicted preoperatively but lower than the maximum predicted blood loss for the specific procedures. Median intra- and postoperative blood loss for nonorthopedic major surgeries and minor surgeries was similar to the average

volume predicted. None of the subjects who received ADYNOVATE for surgery required an additional surgical intervention. No FVIII inhibitors were detected in this study. ADYNOVATE was safe and well tolerated for perioperative management of subjects with severe hemophilia A.

A Phase 3b, prospective, open-label, multicenter continuation study (Study 261302) was completed. This study evaluated long-term safety and efficacy of ADYNOVATE for prophylactic use and the control of bleeding episodes. The study included 216 pediatric and adult PTPs ≤75 years of age with severe hemophilia A who received a fixed-dose prophylactic regimen or opted to receive a regimen based on the subject's individual PK, tailored to maintain FVIII trough levels of ≥3%. Subjects from other ADYNOVATE studies and ADYNOVATE-naïve subjects were included in this study. Efficacy outcomes after long-term exposure demonstrated that ADYNOVATE was efficacious for prophylaxis in children, adolescents, and adults when administered using a fixed or a PK-tailored dose regimen. Efficacy was demonstrated also for the treatment of breakthrough bleeding episodes in these patient populations. No subject developed confirmed inhibitory antibodies to ADYNOVATE during the study. Safety outcomes demonstrated that ADYNOVATE remained safe and well tolerated during long-term administration for prophylaxis and treatment of bleeding episodes in children, adolescents, and adults.

Study 261303 was a Phase 3, prospective, randomized, open-label, multicenter study to compare the safety and efficacy of a PK-guided ADYNOVATE treatment regimen targeting 2 different FVIII trough levels of 1% to 3% and approximately 10% (8% to 12%) in adolescent and adult PTPs with severe hemophilia A (<1% FVIII). A total of 121 subjects received at least 1 infusion of ADYNOVATE. Among them, 57 were assigned to the 1% to 3% trough arm and 58 to the 10% trough arm; 6 were not randomized. The study results showed that targeting a prophylactic FVIII trough level of 8% to 12% in patients with severe hemophilia A leads to lower bleeding rates than targeting a trough of 1% to 3%. The effect size for the proportion of subjects with an ABR of 0 during the second 6-month study period of 0.421 in the 1% to 3% trough arm versus 0.621 in the 8% to 12% trough arm is large and relevant in a clinical scenario. Achieving a prophylactic trough target of 8% to 12% was shown to be as safe as targeting a lower trough of 1% to 3%. There was only 1 case of a transient low-titer FVIII inhibitor. None of the AEs that occurred during or after ADYNOVATE administration led to death or to discontinuation of ADYNOVATE or discontinuation of the subject from the study. There were also no severe allergic reaction AEs.

There is 1 currently ongoing Phase 3 study (Study 261203) to evaluate safety and immunogenicity in PUPs <6 years of age.

Clinical evidence from these studies supported ADYNOVATE's approval in countries worldwide indicated in children and adults with hemophilia A (congenital FVIII deficiency) for on-demand

treatment and control of bleeding episodes, perioperative management, and routine prophylaxis to reduce the frequency of bleeding episodes.

2.3 Study Rationale

Although the importance of adherence to prophylactic regimens for hemophilia A treatment has long been established, the frequency of infusions still poses a challenge to patient compliance. Clinical studies showed an association between poor adherence and self-reported bleeding episodes among adult hemophilia patients and more days of work/school missed and lower physical health status scores among pediatric patients (Hacker et al. 2001; Krishnan et al. 2015). This highlights the need for reducing the treatment burden associated with frequent prophylactic dosing and the potential for improved outcomes if patients are able to be more compliant with less frequent dosing regimens.

Clinical studies in pediatric and adult PTPs with severe hemophilia A demonstrated that the $T_{1/2}$ of ADYNOVATE is 1.3 to 1.5 times longer compared to nonextended $T_{1/2}$ FVIII products, allowing an increase of the prophylactic dosing interval from every other day with conventional FVIII products to twice weekly (Konkle et al. 2015; Mullins et al. 2017). The PK results from completed clinical studies showed comparable PK parameters across different ethnicities, suggesting ethnic insensitivity of ADYNOVATE PK.

Multicenter international clinical studies demonstrated that ADYNOVATE is well tolerated, has an acceptable safety profile, and is effective in the prevention and treatment of bleeding, including surgical hemostasis, in PTPs with severe hemophilia A. Efficacy was demonstrated across age groups and ethnicities, indicating that ADYNOVATE is a non–ethnically sensitive extended $T_{1/2}$ rFVIII, from which children, adults, and adolescents may equally benefit.

Based on the above, this study is designed to evaluate the efficacy and safety of ADYNOVATE for prophylaxis and treatment of bleeding episodes in PTPs with severe hemophilia A (FVIII <1%) in the Chinese population. The study will also provide ADYNOVATE PK data in Chinese patients with severe hemophilia A.

2.4 Benefit/Risk Assessment

The chemical modification of Takeda's well-established rFVIII product ADVATE with PEG (PEGylation) resulted in an FVIII product, ADYNOVATE, that combines the safety and efficacy profile of ADVATE with a 1.3- to 1.5-fold increase in $T_{1/2}$ for subjects <12 years age and a 1.4- to 1.5-fold increase in $T_{1/2}$ for subjects ≥12 years of age, depending on the assay and the PK calculation used. A twice-weekly regimen of ADYNOVATE was demonstrated to be efficacious in the prophylaxis of bleeding across age groups, and although administered at a longer interval

(twice weekly), compared favorably with data obtained with the parent product ADVATE and other unmodified FVIII preparations administered every other day or 3 times/week. ADYNOVATE was also efficacious in the treatment of bleeding episodes in pediatric, adolescent, and adult PTPs with severe hemophilia A and in perioperative hemostasis. ADYNOVATE was well tolerated with a safety profile comparable to its parent molecule.

Please refer to the latest version of the ADYNOVATE investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of ADYNOVATE.

2.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6 (ICH GCP, 1996; ICH E6 R2, 2016), 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 efficacy of ADYNOVATE for prophylactic treatment in previously treated Chinese subjects with severe hemophilia A based on the total ABR.

3.1.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the efficacy of ADYNOVATE for prophylactic treatment based on ABR by bleeding site and cause
- To assess the overall hemostatic efficacy rating of ADYNOVATE for treatment of nonsurgical breakthrough bleeding episodes during the study period
- To assess the efficacy of ADYNOVATE for perioperative bleeding management if minor surgery is performed during the study period
- To evaluate the safety of ADYNOVATE as assessed by AEs and serious AEs (SAEs) as well as clinically significant findings in vital signs and clinical laboratory parameters
- To evaluate the safety and the immunogenicity of ADYNOVATE based on the incidence of FVIII inhibitory antibodies and binding antibodies to ADYNOVATE
- To evaluate the PK of ADYNOVATE in Chinese subjects

3.1.3 Exploratory Objective

- To assess the effect of Adynovate on health-related quality of life and healthcare resource utilization

3.2 Study Endpoints

Table 4. Objectives and Endpoints

Objective	Endpoint(s)
Primary	
• To assess the efficacy of ADYNOVATE for prophylactic treatment in previously treated Chinese subjects with severe hemophilia A based on the total ABR	• Total ABR
Secondary	
• To assess the efficacy of ADYNOVATE for prophylactic treatment based on ABR by bleeding site and cause	• Annualized bleeding rates based on bleeding site and cause • Number of infusions and weight-adjusted consumption of ADYNOVATE per week and month during the prophylactic treatment period • Proportion of subjects with zero bleeding episodes during the study • Time intervals between bleeding episodes
• To assess the overall hemostatic efficacy rating of ADYNOVATE for treatment of nonsurgical breakthrough bleeding episodes during the study period	• Overall hemostatic efficacy rating at bleed resolution for treatment of breakthrough bleeding episodes • Number of infusions and weight-adjusted consumption of ADYNOVATE per bleeding episode
• To assess the efficacy of ADYNOVATE for perioperative bleeding management if minor surgery is performed during the study period	• Overall assessment of hemostatic efficacy based on the GHEA score as assessed by the operating surgeon/investigator • Intra- and postoperative actual versus predicted blood loss after the surgery, at postoperative day 1, and at discharge as assessed by the operating surgeon/investigator • Perioperative transfusion requirement of blood, red blood cells, platelets, and other blood products • Daily intra- and postoperative weight-adjusted consumption dose of ADYNOVATE
• To evaluate the safety of ADYNOVATE as assessed by AEs and SAEs as well as clinically significant findings in vital signs and clinical laboratory parameters	• Occurrence of AEs and SAEs, total incidence, by severity, and by causality • Occurrence of thromboembolic events and hypersensitivity reactions • Clinically significant changes in vital signs and clinical laboratory parameters

Table 4. Objectives and Endpoints

Objective	Endpoint(s)

• To evaluate the safety and the immunogenicity of ADYNOVATE based on the incidence of FVIII inhibitory antibodies and binding antibodies to ADYNOVATE	• Immunogenicity:
	  • Development of confirmed inhibitory antibodies (≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay) to FVIII
	  • Binding antibodies to ADYNOVATE
	  • Binding antibodies to CHO proteins

• To evaluate the PK of ADYNOVATE in Chinese subjects	• Factor VIII activity (1-stage clotting assay) in PK samples collected for single-dose and steady-state PK assessments • Incremental recovery over time during prophylactic treatment at ED1, Week 6 (approximately ED10 to ED15), and ED50 • Predose FVIII (activity and antigen) and VWF (antigen) at scheduled visits • Pharmacokinetic parameters including CL, V, AUC, C_{max}, $C_{predose}$, and elimination phase $T_{1/2}$, following a single dose and steady-state dosing, using NCA methodology, subject to data availability
Exploratory	
• To assess the effect of ADYNOVATE on health-related quality of life and healthcare resource utilization	• Health-related quality of life as assessed using the European Quality of Life Questionnaire in 5 Dimensions 5-level version (EQ-5D-5L) • Healthcare resource utilization endpoints, including number and duration of hospitalizations, number of emergency room visits, number of acute care visits, and number of days missed from school/work

ABR=annualized bleeding rate; AE=adverse event; AUC=area under the concentration versus time curve between defined timepoints; BU=Bethesda unit(s); CHO=Chinese hamster ovary; CL=clearance; C_{max}=maximum concentration; $C_{predose}$=predose concentration; ED=exposure day; FVIII=factor VIII; GHEA=Global Hemostatic Efficacy Assessment; NCA=noncompartmental analysis; PK=pharmacokinetic(s); PRO=patient-reported outcome; SAE=serious adverse event; $T_{1/2}$=half-life; V=volume of distribution; VWF=von Willebrand factor

4. STUDY DESIGN

4.1 Overall Design

This Phase 3, prospective, multicenter, open-label study will evaluate the efficacy and safety of ADYNOVATE for prophylaxis and treatment of bleeding episodes in PTPs with severe hemophilia A (FVIII <1%) in the Chinese population. The study will also provide ADYNOVATE PK data in Chinese patients with severe hemophilia A. The overall study flow chart is illustrated in Figure 1.

It is planned to enroll at least 30 evaluable Chinese subjects aged 12 to 65 years. All subjects and/or legal representatives are required to provide signed informed consent. For screening, subjects need to undergo a minimum washout period of at least 72 to 96 hours following their last FVIII therapy (on-demand or prophylactic), if applicable. Thereafter, the study screening procedures (Table 1) will be performed for eligibility determination and will be completed within 30 days prior to the initial PK assessment (if applicable) or baseline visit. Screening procedures will include demographics, medical/medication history, concomitant medications, AEs, physical examination, vital signs, and clinical laboratory assessments (Table 2). Medical history (including immunization history) will include surgery history, hemophilia history, bleeding episode history, and history of FVIII usage over the last year. Target joints and subject's ABR based on the previous 9 to 12 months will also be recorded. Medication history will include the name of the product, dose, dosing interval, and regimen start and end date.

All enrolled subjects will receive twice-weekly prophylactic treatment with ADYNOVATE (45±5 IU/kg) over a period of 26 weeks (+2 weeks) or at least 50 EDs, whichever occurs last.

Pharmacokinetic evaluation is planned to be performed in at least 12 evaluable subjects. For subjects participating in the PK portion of the study, the initial PK assessment will be performed after a washout period of at least 72 to 96 hours following their last FVIII therapy (if applicable) and prior to the baseline visit. The second PK assessment will be performed during the Week 20 (±1 week) visit following the scheduled prophylactic treatment dose. The PK samples will be collected at specified time points and measured for FVIII activity by a 1-stage clotting assay. For subjects not participating in the PK portion, the baseline visit will be initiated immediately upon eligibility confirmation.

Following the baseline visit, subjects will return to the study site for study treatment visits at the below timepoints for the efficacy and safety assessments:

- Week 2 (±1 week)
- Week 6 (±1 week)

- Week 12 (±1 week)
- Week 20 (±1 week) (only for subjects undergoing PK assessment)
- Study Completion/Termination Visit: Week 26 (+2 weeks) or at least 50 EDs (whichever occurs last)

All other study treatments may be administered either at a clinic/hospital/study site or at home by self-administration/administration by a parent/caregiver. The investigator will determine the setting of treatment administration. Unscheduled visits may occur between scheduled site visits as required. Assessments may be performed as clinically indicated at the discretion of the investigator.

Factor VIII (activity and antigen) and VWF antigen levels will be measured at specified study visits, preinfusion, in both PK and non-PK subjects. During the baseline visit, Week 6 visit, and the study completion/termination visit, peak levels of FVIII activity will also be assessed within 30 minutes before ADYNOVATE administration and 30±10 minutes post ADYNOVATE infusion for the determination of incremental recovery (IR). The IR determination at the baseline visit will only be performed in subjects who have not undergone initial PK assessment. All PK samples collected in this part will be used, along with the samples collected in the PK assessments, to characterize PK properties in PTPs across age groups.

At each study visit, investigators will review subject electronic diaries (eDiaries) for prophylactic treatment compliance, bleeding episodes and treatment, AEs, concomitant medications, and nondrug therapies. The PRO assessment, using the EQ-5D-5L, will be captured via an electronic PRO (ePRO) device. Subjects should complete the EQ-5D-5L prior to baseline visit (or initial PK assessment for subjects participating in the PK portion of the study) and study completion/termination visit. Healthcare resource utilization will be gathered by sites via questionnaire as part of the electronic case report form (eCRF). Upon completion of prophylactic treatment (at least 50 EDs or 26 weeks [+2 weeks], whichever occurs last), the study site will follow up via phone call with each subject after 3 to 5 days to determine the occurrence of AEs.

During the study period, subjects will also be treated for breakthrough bleeding episodes with ADYNOVATE. The dose and frequency of ADYNOVATE administration will be individualized based on the subject's weight, type and severity of bleeding episode, and monitoring of appropriate clinical and laboratory measures per the investigator's judgment (as described in Section 6.2.2.3).

If a subject requires minor elective or emergency surgical, dental, or other invasive procedures during the study after enrollment (ie, a surgery that was not planned before study enrollment), perioperative bleeding will be managed with ADYNOVATE. The dose and frequency of

ADYNOVATE administration will be individualized based on the subject's IR to obtain the FVIII target level required for the procedure being performed (as described in Section 6.2.2.4). Major surgeries are not in the scope of this study; any required major surgery will result in the withdrawal of the subject.

The primary objective of this study is to assess the efficacy of ADYNOVATE for prophylactic treatment in previously treated Chinese subjects with severe hemophilia A based on the total ABR.

4.2 Scientific Rationale for Study Design

The design of this study is based on a previously completed multinational confirmatory study (Study 261201). The study design, including endpoints, study population, and inclusion/exclusion criteria, are all supported by the results of previous global studies in this program (refer to Section 2.2).

4.3 Justification for Dose

Pharmacokinetic results from global studies with ADYNOVATE showed similar results between the Chinese/Asian subjects and the overall study populations, suggesting ethnic insensitivity of ADYNOVATE PK. Further, efficacy was demonstrated across age groups and ethnicities, indicating that ADYNOVATE is a non–ethnically sensitive EHL rFVIII from which Chinese adult and adolescent subjects may benefit. Thus, the doses and regimen of the current study are considered to be appropriate.

4.4 Duration of Subject Participation and Study Completion Definition

All enrolled subjects will receive twice-weekly prophylactic treatment with ADYNOVATE over a period of 26 weeks (+2 weeks) or at least 50 EDs, whichever occurs last. Each subject's maximum duration of participation is expected to be approximately 8 months unless prematurely discontinued.

Study completion is defined as the date on which the last subject in the study completes the final protocol-defined assessments and includes the safety follow-up conducted via phone 3 to 5 days following prophylactic treatment completion (refer to Section 8.1.4 for the defined follow-up period for this protocol). The total study duration will be approximately 3 years.

4.5 Sites and Regions

The study will be conducted at approximately 12 sites in China.

4.6 Study Stopping Rules

The study will be halted (enrollment and treatment temporarily suspended), or stopped (enrollment and treatment permanently discontinued), pending further review by sponsor, if one or more of the following criteria are met:

1. If 2 or more subjects develop a high responder inhibitory antibody (>5 BU), confirmed by 2 separate measurements within 2 weeks at the central laboratory, after ADYNOVATE administration
2. If 2 or more subjects develop anaphylaxis caused by the exposure to ADYNOVATE

The study may be terminated if one or more of the following criteria are met:

1. The sponsor decides to terminate the study based upon its assessment of safety
2. The sponsor decides to terminate the study for administrative reasons

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. Subject and/or legally authorized representative must voluntarily sign a written informed consent form (ICF) after all relevant aspects of the study have been explained and discussed with the subject. For the subjects <18 years old, subjects will give assent AND their parents/legally authorized representative should sign the ICF accordingly.
2. Subject and/or legally authorized representative understands and is willing and able to comply with all requirements of the study protocol.
3. Subject should be ethnic Chinese.
4. Subject is 12 to 65 years of age at screening and male.
5. Subject has severe hemophilia A (FVIII clotting activity <1%) as confirmed by the central laboratory at screening after a washout period of at least 72 to 96 hours.
6. The last on-demand or prophylactic treatment received is within 3 months before screening.
7. Subject has documented previous treatment with plasma-derived FVIII concentrates or recombinant FVIII for >150 EDs.
8. Subject is human immunodeficiency virus (HIV)-negative, or HIV-positive with stable disease and CD4+ count ≥200 cells/mm^3.
9. Subject is hepatitis C virus (HCV) negative by antibody testing (if positive, additional polymerase chain reaction testing will be performed to confirm), as confirmed at screening; or HCV-positive with chronic stable hepatitis, as assessed by the investigator.

5.2 Exclusion Criteria

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

1. Subject has detectable FVIII inhibitory antibodies (≥0.6 Bethesda units (BU)/mL using the Nijmegen modification of the Bethesda assay) as confirmed by the central laboratory at screening.
2. Subject has a confirmed history of FVIII inhibitory antibodies (≥0.6 BU using the Nijmegen modification of the Bethesda assay or ≥0.6 BU using the Bethesda assay) at any time prior to screening.

3. Subject has a known hypersensitivity to ADYNOVATE or ADVATE or any of the components of the study drugs, such as mouse or hamster proteins, or other FVIII products.
4. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease).
5. Subject has severe hepatic dysfunction (eg, ≥5 times the upper limit of normal [ULN] for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), a recent or persistent international normalized ratio [INR] >1.5, as confirmed by the local laboratory at screening).
6. Subject has severe renal impairment (serum creatinine >1.5 times the ULN) as confirmed by the local laboratory at screening.
7. Subject is planned or likely to undergo major surgery during the study period.
8. Subject has current or recent (<30 days) use of other PEGylated drugs before study participation or scheduled use of such drugs during study participation.
9. Subject has received emicizumab therapy within 6 months of screening.
10. Subject is currently receiving, or scheduled to receive during the study, an immunomodulating drug (eg, systemic corticosteroid agent at a dose equivalent to hydrocortisone >10 mg/day, or α-interferon) other than antiretroviral chemotherapy.
11. Subject has participated in another clinical study involving the use of an IP other than ADYNOVATE or an investigational device within 30 days before the screening visit or is scheduled to participate in another clinical study involving an IP or investigational device during this study.
12. Subject has a medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
13. Subject, in the opinion of the investigator, is unable or unwilling to comply with the study protocol.

5.3 Restrictions

Not applicable.

5.4 Reproductive Potential

Males, including males who are surgically sterile (vasectomy), with female partners of childbearing potential must agree to be abstinent or use a medically acceptable form of contraception from screening through at least 30 days or 5 elimination half-lives after the last dose of IP.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The IP, ADYNOVATE (antihemophilic factor [recombinant] PEGylated, rurioctocog alfa pegol), is formulated as a sterile, highly purified protein preparation in lyophilized form for intravenous infusion and is provided in single-use vials, which may contain nominally 250, 500, 1000, 2000, and 3000 IU PEGylated rFVIII/vials, along with a vial of diluent (2 or 5 mL SWFI). It is filled in a colorless neutral Type I (US Pharmacopeia, European Pharmacopoeia) glass vial, sealed with a chlorobutyl rubber stopper with inert coating. Additional information is provided in the ADYNOVATE IB.

6.1.2 Blinding the Treatment Assignment

Not applicable; this is an open-label clinical study. There is no randomized allocation to study treatment; all subjects will receive the same prophylaxis dosing schedule of ADYNOVATE.

6.2 Administration of Investigational Product

Following reconstitution, ADYNOVATE should be administered using plastic syringes provided by the sponsor since proteins such as ADYNOVATE may adhere to the surface of glass syringes. ADYNOVATE is injected intravenously using an appropriately sized syringe as a bolus infusion over a period of less than or equal to 5 minutes (maximum infusion rate, 10 mL/min). The reconstituted ADYNOVATE must be administered at room temperature and as soon as possible, but no later than 3 hours after the reconstitution.

ADYNOVATE dose calculation will be based on the stated actual potency on vials in respective lots.

For an individual subject, study product from only 1 lot/infusion and only vials with a nominal potency of 500 IU may normally be used for the PK portions of the study and the determination of IRs. However, if due to a subject's weight, the PK or IR infusion volume will exceed 30 mL, 1000 IU vials should preferably be used to reduce the volume administered.

In case of infusions for PK or IR determination, the exact amount of IUs has to be administered (eg, 1.5 vials) and should not be rounded up or down to the nearest whole vial. In case of prophylactic infusions or infusions to control bleeding episodes or manage perioperative bleeding, the dose can be rounded up or down to the nearest whole vial (eg, 2 vials).

Subjects will return to the study sites to receive study treatment at the scheduled visits. All other study treatments may be administered either at a clinic/hospital/study site or at home by

self-administration/administration by a parent/caregiver. The investigator will determine the setting of treatment administration. If the subject/caregiver will self-administer ADYNOVATE, the investigator should ensure that the subject and/or subject's caregiver has been adequately trained. Investigational product can be shipped directly from the site or local depot to the subject's home.

For complete details on preparation, reconstitution, and administration of ADYNOVATE, please refer to the ADYNOVATE pharmacy manual.

6.2.1 Allocation of Subjects to Treatment

This is an open-label clinical study. There is no randomized allocation to study treatment; all subjects will receive the same prophylaxis dosing schedule of ADYNOVATE.

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.

Once a unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a unique identifier is allocated incorrectly, the clinical research associate/study monitor must be notified as soon as the error is discovered.

Investigational product packaging identification numbers will be assigned to subjects. The same IP packing identification number will only be assigned once.

6.2.2 Dosing

6.2.2.1 Dosing for PK Characterization

The dose to be used for PK determination is 45±5 IU/kg as a single-dose infusion for the initial PK assessment before the subject receives the first prophylactic dose. The second PK assessment will be performed during the Week 20 (±1 week) visit following the scheduled prophylactic treatment dose. The dose for IR assessments is the same as that for prophylactic treatment at the scheduled visits. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution.

For subjects who have a bleeding episode requiring treatment with FVIII concentrates, if the bleed occurs after the start of the PK period, only ADYNOVATE should be used to treat the bleeding episode.

If a bleed occurs <7 hours after the start of the PK period and requires treatment with ADYNOVATE, the subject will undergo an 84- to 96-hour washout, followed by reinfusion of ADYNOVATE, and all PK time points will be repeated. If a bleed occurs ≥7 hours from the start of the PK period, then no further PK samples will be taken in that specific PK assessment period

and the PK assessment does not have to be repeated. Subjects will resume participation in the PK subgroup once they recover, per the study protocol, and are eligible to proceed to the following PK period as part of the PK subgroup.

See Section 8.2.6 for additional details about PK assessments.

6.2.2.2 Prophylactic Treatment

For prophylactic treatment, subjects will be treated with 45±5 IU/kg of ADYNOVATE administered twice weekly. Subjects will be treated with prophylactic infusions for a minimum of 50 EDs to ADYNOVATE or approximately 26 weeks (+2 weeks), whichever occurs last.

Subjects must adhere as closely as possible to the dosing regimen. The days of the week on which treatment is administered may be selected by the subject and/or subject's physician and should be selected to provide maximum coverage for vigorous activities. Dosing must be administered twice weekly (see Table 5), at 3- and 4-day intervals (Option X) or at 3.5-day intervals (Option Y with AM and PM dosing), and should be maintained during the study. If a dose is missed, it must be documented and the next dose will be taken as soon as possible. After this dose, the regularly scheduled regimen will be resumed. For example, in Option X, if twice-weekly dosing is scheduled for every Monday and Thursday and the subject misses the Thursday dose, they should infuse the next dose on Friday and then resume their schedule with subsequent dose on Monday. For Option Y, if dosing is scheduled for the morning on Monday and the evening dose on Thursday and the subject misses the Thursday dose, they should infuse the next dose on Friday morning and then resume their schedule with a subsequent dose on Monday morning.

Table 5. ADYNOVATE Example Dosing Frequency

Day	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
Morning	X or Y			X			
Evening				Y			

Subjects requiring treatment for a breakthrough bleeding episode should resume prophylaxis as soon as the bleeding episode is resolved. They should return to the same schedule of dosing as if prophylactic dosing were not interrupted. For example, if the subject is typically dosed every Monday and Thursday and is treated for a bleeding episode on Wednesday and the bleeding episode is resolved on Thursday, they would resume prophylaxis on Thursday; if the bleeding episode is not resolved until Friday, their next prophylactic dose would be on Monday (ie, subjects will resume their prophylactic treatment regimen the next scheduled day after the last therapeutic infusion for the treatment of a bleeding episode).

In order to ensure the required washout periods of 84 to 96 hours prior to study visits, the scheduled regimen may be interrupted for this period but should be resumed once the study visit is completed.

Dose Adjustment for Prophylactic Treatment

Based on the investigator's clinical evaluation, the dose may be increased gradually by 10 IU/kg increments up to a maximum of 80 IU/kg but not exceeding plasmatic FVIII peak levels of 200% for subjects receiving prophylactic treatment at any time to ensure patient safety is adequately managed.

Subjects meeting any of the following criteria during prophylaxis may have their ADYNOVATE dose increased up to a maximum of 80 IU/kg:

- Two or more spontaneous (not related to trauma) bleeding episodes in the same target joint within any 2-month period, or
- One or more spontaneous (not related to trauma) bleeding episodes in a nontarget joint within any 2-month period, or
- Factor VIII trough level <1% and the investigator assesses the study subject is at increased risk of bleeding

A target joint is defined as a single joint (ankles, knees, hips, or elbows) with ≥3 spontaneous bleeding episodes in any consecutive 6-month period.

In order not to exceed plasmatic FVIII peak levels of 200%, the increase in frequency may be considered. Prior approval of the sponsor should be obtained.

In subjects with severe hemophilic arthropathy and/or target joints who continue to experience recurrent bleeding episodes despite adjustments to the prophylactic dose and/or dosing frequency, an ultrasound of the affected joint(s) should be performed to verify the presence of a bleed.

6.2.2.3 On-demand Treatment of Bleeding Episodes

ADYNOVATE will be used for the treatment of bleeding episodes (ie, breakthrough bleeding episodes during prophylaxis) according to the guidelines outlined in Table 6. These guidelines may be adjusted by the investigator based upon his or her clinical judgment. If a breakthrough bleed occurs, the subject will be advised to contact the investigator to discuss dose and bleed severity.

The dose must be individualized based on the subject's weight, type and severity of bleeding episode, and monitoring of appropriate clinical and laboratory measures. The subject or their caregiver will rate the severity (mild, moderate, or severe) of the bleeding episode and will rate the overall treatment response at 24 hours (±2 hours) after initiating treatment. A 4-point efficacy rating scale (Table 7) will be used to assess the efficacy of ADYNOVATE treatment. Efficacy will be defined as a response of "good" or "excellent". An inadequate response to ADYNOVATE treatment is defined as a rating of "fair" or "none" 24 hours (±2 hours) after initiation of ADYNOVATE infusion. Since the efficacy rating is based to a large degree on cessation of pain, the investigator/subject shall, particularly in the case of injury-related bleeding into 1 or more than 1 location, take the injury-related symptoms into consideration when performing the efficacy rating at resolution of the bleed.

As per Table 6, multiple infusions of ADYNOVATE may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded.

It is critical that treatment of a bleed is initiated as soon as possible after occurrence of the bleeding episode.

When bleeding is controlled, additional infusions of ADYNOVATE to maintain hemostasis are permitted, if required. Infusions given to maintain hemostasis should be documented in the eDiary and eCRF.

Table 6. ADYNOVATE Treatment Guidelines for Bleeding Episodes

Severity and Type of Bleeding Episode	Factor VIII Level Required (%)	*Suggested Dose* Frequency of Dosing
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including epistaxis	20% to 40%	*10 to 20±5 IU/kg* Repeat infusions every 12 to 24 hours. Duration: at least 1 day, until the bleeding episode is resolved or healing is achieved.
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite/more extensive hemarthroses, and known trauma	30% to 60%	*15 to 30±5 IU/kg* Repeat infusions every 12 to 24 hours for 3 days or more until the pain and acute disability/incapacity are resolved.
Major/life-threatening Significant gastrointestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	60% to 100%	*30 to 60±5 IU/kg* *In case of life-threatening bleeds, a dose of 80±5 IU/kg may be considered.* Repeat infusions every 8 to 12 hours until the bleeding episode/threat is resolved.

The required units will be calculated according to the following formula:

body weight (kg) × desired FVIII rise (% or IU/dL) × {reciprocal of observed recovery}

Whenever possible, the subject's most recent individual IR should be used. In its absence, an average recovery of 2 [IU/dL]/[IU/kg] for FVIII products should be used, and the required units are calculated using the following formula:

body weight (kg) × desired FVIII rise (% or IU/dL) × 0.5 dL/kg

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

6.2.2.4 Perioperative Bleeding Management

Subjects with known plans or who are likely to undergo surgery during the study period are not eligible and will be excluded from study. However, eligible subjects who are later identified to require surgery during the study have the option to undergo **minor** elective or emergency surgical, dental, or other invasive procedures. Major elective or emergency surgeries are not in the scope of this study; any required major surgery will result in withdrawal of the subject. Subjects may undergo more than 1 surgery or 2 parallel surgeries; however, in these cases, prior approval by the sponsor is required.

Surgical procedures will be defined prospectively as major or minor by the investigator/surgeon and agreed with the sponsor, based on the protocol guidance and definitions and in consideration of each subject's characteristics. The main characteristics of minor and major surgeries are as follows:

- Minor surgeries comprise surgeries that can be safely and comfortably performed on a patient who has received local or topical anesthesia, without more than minimal preoperative medication or minimal intraoperative sedation. The likelihood of complications requiring hospitalization or prolonged hospitalization is remote. In addition, minor surgeries/interventions are expected to require clinical surveillance or hospital treatment ≤3 days after the surgery/intervention.
- Major surgeries involve surgeries that require moderate or deep sedation, general anesthesia, or major conduction blockade for patient comfort and comprise major orthopedic (eg, joint replacement), major abdominal, intracranial, cardiovascular, spinal, and any other surgery that has a significant risk of large volume blood loss or blood loss into a confined anatomical space. Extractions of several teeth or extraction of the third molar and adeno-tonsillectomy in children are also generally considered as major. In addition, major surgeries/interventions are expected to require clinical surveillance or hospital treatment >3 days after the surgery/intervention.

If the subject requires minor elective surgery, an FVIII substitution plan will be drawn up by the investigator outlining the target peak and trough levels covering the minor surgical, dental, or other invasive procedure until expected wound healing. The FVIII substitution plan will be provided to the sponsor to ensure that the recommendations regarding FVIII target levels as outlined in the protocol are followed. The dose and frequency adjustments during intra- and postoperative dosing should follow the substitution plan provided by the investigator prior to minor surgery. Slight deviations from the predefined substitution plan are allowed based on the investigator's clinical judgment and available laboratory FVIII data (must be based on regular FVIII activity measurements determined pre and post infusion of ADYNOVATE). Dosing should be guided by the dosing recommendations and continued until hemostasis.

If the subject requires major surgery, the subject will be withdrawn from the study. All EDs to ADYNOVATE accumulated as part of the minor surgery study will be factored into the overall number of EDs.

6.2.2.4.1 Preoperative Loading Dose for Minor Surgeries

The below procedures are required for minor elective surgery and are recommended for emergency minor surgery.

Prior to surgery

The following items must be completed prior to surgery and available, at the latest, 2 hours before surgery start:

- An accurate prediction of volume of expected blood loss intraoperatively (from completion of the procedure until approximately 24 hours post surgery) and for the overall perioperative time period (up to discharge/end of study)
- An outline of the expected FVIII substitution plan with target peak and trough levels provided to the sponsor

Loading Dose and Post-infusion Laboratory Assessment

Within 60 minutes before initiating surgery, subjects will receive a loading dose of ADYNOVATE to raise the preinfusion plasma level of FVIII. In general, for minor surgery, initial FVIII target levels in plasma should be 30% to 60% of the normal FVIII level.

The dose and frequency of ADYNOVATE administered will be individualized based on the subject's IR to obtain the target level required for the minor surgical, dental, or other invasive procedure being performed. Surgeries will be performed based on FVIII activity levels determined at the local laboratory. An additional blood sample needs to be drawn for testing at the central laboratory to confirm local laboratory results. Activated partial thromboplastin time (aPTT) will be tested at the local laboratory.

The formula for calculating the required number of units is as follows:

$$\textit{Required units (IU)} = \textit{body weight (kg)} \times \textit{desired FVIII rise (\% or IU/dL)} \times \{\textit{reciprocal of IR}\}\ \textit{(IU/kg)/(IU/dL)}$$

Subjects will undergo the following procedures:

Prior to initial ADYNOVATE loading dose:

- Record AEs, concomitant medications and nondrug therapy usage
- Physical examination, vital signs (pulse, respiratory rate, blood pressure, and body temperature), and weight

- Laboratory assessments, including:
  - Hematology (without differential but including platelets)
  - Clinical chemistry
  - Within 30 minutes before loading dose, blood draw for: FVIII activity and aPTT

Immediately followed by:

Loading dose of ADYNOVATE to raise the plasma level of FVIII to 30% to 60% for minor surgical, dental, or other invasive procedures. It will be administered within 60 minutes prior to surgery (prior to incision/intubation).

After infusion:

- Laboratory assessment of FVIII activity and aPTT: 15±5 minutes after infusion of the loading dose
- Vital signs (pulse, respiratory rate, blood pressure, and body temperature) will be recorded 15±5 minutes after infusion
- If aPTT is not normalized or desired FVIII level not obtained, rebolus of ADYNOVATE as necessary.

If the determination of the FVIII level is not feasible within a reasonable time period prior to the start of surgery, at least the postinfusion value of aPTT must be obtained. The FVIII level must be obtained within 4 hours after infusion of ADYNOVATE, and dose adjustments must be performed as needed.

The surgery can begin only if aPTT has normalized.

Intraoperative Procedures

During the surgical procedure:

- Record AEs, concomitant medications, and non-drug therapy usage
- Record blood product usage, including salvaged blood, packed red blood cells (pRBCs), platelets, and other blood products.
- Administer additional ADYNOVATE infusions according to the FVIII substitution plan
- Record intraoperative blood loss and transfusion requirements

If the subject has excessive or unexplained bleeding, perform blood draws for:

- Factor VIII activity
- Factor VIII inhibitory and binding antibodies

Treat by whatever means necessary until adequate hemostasis is achieved. If other FVIII concentrates become necessary, the subject will subsequently be withdrawn from this study.

After the surgical procedure:

- Record the volume of blood loss during surgery and total blood product usage, including salvaged blood, pRBCs, platelets, and other blood products
- Assess intraoperative hemostatic efficacy (Table 8) at the end of surgery

6.2.2.4.2 Postoperative Dose for Minor Surgeries

Subjects undergoing minor surgery can be re-dosed postoperatively with ADYNOVATE every 8 to 24 hours. Preinfusion trough levels of FVIII should be kept at 30% to 60% of normal for the first 24 hours, or longer as deemed necessary by the investigator. At least 1 postoperative dose should be given; the dose calculation should be based on the subject's most recent IR value.

In case subjects are hospitalized for more than 24 hours, subjects will have a preinfusion and 15-minute postinfusion FVIII level measurement assessed at a local laboratory at least once per day (preferably at the same time of the day), and the dose will be adjusted according to the most recent residual FVIII levels. The target FVIII levels should not exceed 180%. It is recommended to increase the frequency of dosing instead.

Once the subject is discharged from the hospital, the subject should resume prophylaxis treatment. They should return to the same schedule of dosing as if prophylactic dosing were not interrupted.

6.2.3 Unblinding the Treatment Assignment

Not applicable.

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

6.3.1 Labeling

Labels containing study information and pack identification are applied to the IP container.

All IP is labeled with a minimum of the following: protocol number, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date, batch number and/or packaging reference, and the statement "For clinical trial use only."

Space is allocated on the label so that the site representative can record a unique subject identifier.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the IP in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

ADYNOVATE is supplied in packages comprising a single-use vial. Actual FVIII activity in IU is stated on the label of each ADYNOVATE carton and vial.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The recommended storage condition for ADYNOVATE is +2°C to +8°C (see expiry date on the vial label). ADYNOVATE should be protected from light. The reconstituted product should ideally be used immediately but no longer than 3 hours after reconstitution.

The investigator has overall responsibility for ensuring that IP 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 product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the IP 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 IP 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 IP 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 IP to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the IP, documenting shipment content and condition. Accurate records of all IP received, dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing IP. 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 site may use an alternative method for dispensing. If permitted by country or local regulations and ethics committees (ECs), the IP can be shipped from the site or the depot directly to the subject's home address via courier. Subjects must be provided with instructions on how to receive, store, and ultimately return investigational/sponsor-supplied materials.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the IP only to subjects included in this study following the procedures set out in the study protocol. All administered medication will be documented in the subject's source and/or other IP record. The investigator is responsible for ensuring the retrieval of all study supplies from subjects.

No IP 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 and empty/used IP 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 contract research organization [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. Returned IP must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any IP prior to shipment. Shipment of all returned IP must comply with local, state, and national laws.

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

6.5 Subject Compliance

Subjects must be instructed how to have unused IP and empty/used IP packaging assessed for drug accountability. Drug accountability must be assessed at the container/packaging level for unused IP 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.

6.6 Concomitant, Permitted, and Prohibited Therapy

6.6.1 Concomitant Treatment

Concomitant treatment refers to all treatments taken from the time informed consent is signed until end of the safety follow-up period. Concomitant treatment information will be recorded on the eCRF and in the subject's eDiary.

6.6.2 Permitted Treatment

During the screening period (ie, between subject enrollment [signing of the ICF] up to the first prophylactic dose or the initial PK assessment), subjects will continue receiving their usual FVIII concentrate for prophylaxis and/or treatment of bleeding events.

The following medications and nondrug therapies are permitted before study entry and during the course of the study:

Medications:

- Hemostatic agents, such as tranexamic acid, as indicated by the subject's treating physician, to treat mucosal bleeding during the study

- Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of any PEGylated medication, any immunomodulating drug other than antiretroviral chemotherapy, any investigational drug or device, and any FVIII concentrate other than ADYNOVATE)
- Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition
- Supplemental vitamins and/or minerals

Nondrug therapies:

- Any nondrug therapy (eg, physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition.

6.6.3 Prohibited Treatment

The following medications are not permitted within 30 days before study entry and during the course of the study:

- Any PEGylated medication (eg, PEG-interferon)
- Any immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone >10 mg/day, or α-interferon) other than antiretroviral chemotherapy
- Any investigational drug or device
- Any FVIII concentrate other than ADYNOVATE following the first infusion of ADYNOVATE

A subject who has taken any of these medications will be withdrawn from further study participation.

Treatments not listed above that may influence study efficacy and safety results should be discussed with the sponsor.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

A subject is considered to have completed the study when they cease active participation because the subject has, or is presumed to have, completed all study procedures according to the protocol (with or without protocol deviations).

Every effort will be made to have discontinued subjects complete the assessments for the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the study termination visit, their last recorded assessments shall remain with their last visit in the eCRF.

In the event of subject discontinuation due to an AE or clinical and/or laboratory investigations that are beyond the scope of the required study, observations and assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

7.2 Reasons for Withdrawal/Discontinuation from Study

Any legal representative/subject may withdraw from the study at any time and for any reason without prejudice to their 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 sponsor when possible. The reason for withdrawal/discontinuation will be recorded on the eCRF. The data collected on withdrawn subjects will be used in the analysis and included in the clinical study report.

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.

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

Reasons for withdrawal/discontinuation include, but are not limited to:

- **Adverse event**

- Development of a confirmed inhibitory antibody based on a second blood draw to FVIII within 2 weeks of study site notification of an inhibitor determined at the central laboratory with an inhibitor level ≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay.
- The subject experiences a severe anaphylactic reaction to ADYNOVATE.

- **Protocol deviation**
  - The subject requires therapy with another PEGylated product (eg, PEG-interferon).
  - The subject frequently misses more than 30% of planned prophylactic doses within any 3-month period.
  - The subject uses an FVIII concentrate or treatment regimen other than ADYNOVATE or the treatment regimen prescribed.
  - The subject experiences a life-threatening bleeding episode (eg, any gastrointestinal hemorrhage or intracranial hemorrhage) requiring the use of another FVIII concentrate.
  - The subject requires a major emergency or major elective surgical procedure.
- **Withdrawal by subject**
- **Lost to follow-up**
- **Lack of efficacy**
- **Study termination by the sponsor**
  - See Section 4.6 for study stopping rules
- **Other**
  - The subject/legal representative is noncompliant with study procedures, in the opinion of the investigator.

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

A minimum of 3 documented attempts must be made to contact (by phone) any subject who is lost to follow-up at any time point prior to the last scheduled contact.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Periods

Refer to Table 1 for the schedule of study activities. Study assessments are detailed in Section 8.2.

The study period comprises a screening visit, initial PK assessment (for subjects participating in the PK portion of the study), a prophylactic treatment phase (includes the baseline, Week 2, Week 6, Week 12, second PK assessment [for subjects participating in the PK portion of the study], and study completion/termination visits), and a safety follow-up.

The prophylactic treatment phase consists of twice-weekly treatment that starts at the baseline visit and continues over a period of 26 weeks (+2 weeks) or at least 50 EDs (whichever occurs last). The treatment concludes at the study completion/termination visit.

8.1.1 Screening Visit

Written informed consent and, if appropriate, written assent must be obtained from each participant and/or their parent/legal guardian before any study-related procedures are performed. The investigational site is responsible for the consenting process. The requirements of informed consent are described in Appendix 1.5.

At least 72 to 96 hours must have elapsed since the subject's last FVIII therapy (on-demand or prophylactic), if applicable, and the subject must not be actively bleeding. The screening visit procedures (Table 1) will be performed for eligibility determination and completed within 30 days prior to the initial PK assessment (if applicable) or baseline visit. Screening procedures will include demographics, medical/medication history, concomitant medications, AEs, physical examination, vital signs, and clinical laboratory assessments (Table 2). Medical history (including immunization history) will include surgery history, hemophilia history, bleeding episode history, and history of FVIII usage over the last year. Target joints and subject's ABR based on the previous 9 to 12 months will also be recorded. Medication history will include the name of the product, dose, dosing interval, and regimen start and end date.

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 IP. Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the investigator. This includes a repeat of only the failed assessment (retesting) rather than a repeat of all screening assessments, which is allowed only once within 30 days of initial screening. If this screening time frame is exceeded, then all

screening assessments must be repeated and the subject assigned a new subject identification code. Exemptions may be provided if the time frame is exceeded due to administrative reasons.

Subjects with an inadequate interval between screening and prior PEGylated drug administration or prior participation in a drug or device study (ie, within 30 days), may be rescreened only once and only when the required interval is reached. Subjects who still do not meet eligibility criteria may not be rescreened a second time unless a justification can be provided.

Electronic devices (eDiary and ePRO device) will be handed out after subject eligibility is confirmed and before the first dose. Training will be provided to the subject and/or caregiver.

Treatment of Bleeding Episodes and Prophylaxis During Screening

During the screening period (ie, between subject enrollment [signing of the ICF] up to the first prophylactic dose or the initial PK assessment), subjects will continue receiving their usual FVIII concentrate for prophylaxis and/or treatment of bleeding events. Bleeding events and treatment information will be reviewed by the investigator before eligibility confirmation and will be recorded in the eCRF.

8.1.2 Initial Pharmacokinetic Assessment

For those subjects who will undergo PK assessments, and prior to PK infusion, the following 3 conditions must be met:

- The subject has not received an infusion of any FVIII-containing product for at least 72 to 96 hours prior to the PK infusion
- The subject is not actively bleeding at the time of the infusion
- The subject does not exhibit an FVIII inhibitor at levels ≥0.6 BU/mL, as tested at screening/enrollment in the central laboratory by the Nijmegen-modified Bethesda assay

Pre- and postinfusion activities and assessments will be carried out as presented in Table 1 and Table 2, respectively. Refer to Table 3 for PK sample collection timepoints.

8.1.3 Study Treatment Visits

8.1.3.1 Baseline Visit and Prophylaxis Visits (Weeks 2, 6, and 12)

The prophylactic treatment phase consists of twice-weekly treatment that starts at the baseline visit and continues over a period of 26 weeks (+2 weeks) or at least 50 EDs (whichever occurs last). The treatment concludes at the study completion/termination visit. Study procedures for assessment of efficacy and safety and review of subject eDiaries will be conducted as described in Table 1.

At all visits, blood will be drawn for the assessments presented in Table 2 only after a washout period of 72 to 96 hours following the last infusion of any other nonmodified FVIII concentrate and at least 84 to 96 hours following the last infusion of ADYNOVATE. Subjects must not be actively bleeding during visits.

For subjects not participating in the PK portion of the study, the baseline visit will be initiated immediately upon eligibility confirmation. Those subjects undergoing PK evaluation will enter the prophylactic treatment phase 96 hours (±4 hours) after the initial PK infusion.

Treatment administration will be done at the study site for all scheduled visits. All other study treatments may be administered either at a clinic/hospital/study site or at home by self-administration/administration by a parent/caregiver. The investigator will determine the setting of treatment administration. Unscheduled visits may occur between scheduled site visits as required. Assessments may be performed as clinically indicated at the discretion of the investigator.

A sufficient quantity of IP will be dispensed at the prophylactic treatment study visits to cover the period until the next scheduled visit.

8.1.3.2 Second Pharmacokinetic Assessment (Week 20)

A second PK assessment will be performed during the Week 20 (±1 week) visit following the scheduled prophylactic treatment dose. The PK samples will be collected at specified time points and measured for FVIII activity by a 1-stage clotting assay.

Pre- and postinfusion activities and assessments will be carried out as presented in Table 1 and Table 2, respectively. Refer to Table 3 for PK sample collection timepoints.

8.1.3.3 Study Completion/Termination Visit (Week 26 or ≥50 EDs)

Treatment administration will be done at the study site for the study completion visit. Study procedures for assessment of efficacy and safety and review of subject eDiaries will be conducted as described in Table 1. Blood will be drawn for the assessments presented in Table 2 only after a washout period of at least 84 to 96 hours following the last infusion of ADYNOVATE. Subjects must not be actively bleeding during the visit.

In case of early discontinuation, every effort will be made to have discontinued subjects complete the assessments for the study completion/termination visit.

8.1.4 Safety Follow-up

Upon completion of prophylactic treatment (at least 50 EDs or 26 weeks [+2 weeks], whichever occurs last), the study site will follow up via phone call with each subject after 3 to 5 days to determine the occurrence of AEs.

All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 3.2).

8.1.5 Additional Care of Subjects after the Study

No aftercare is planned for this study.

8.1.6 COVID-19–related Protocol Considerations

On a temporary basis, in order to maintain subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges presented by the coronavirus disease of 2019 (COVID-19) pandemic, subjects who may be impacted should contact study sites and investigators to determine the best course of action. Depending on the impact, in some cases it may be possible to arrange for alternative solutions as permitted by local regulations. Any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the sponsor, while maintaining subject safety and confidentiality as the priority.

Missing data, remote visits, changes to assessment approaches, and altered visit windows during the COVID-19 public health emergency may affect the study results. Thus, it is important to identify all protocol deviations and altered data collection or assessment methods. It is crucial that any deviations related to COVID-19 be clearly identified as such in the eCRF or tracked in the clinical trial management system of the participating CRO.

The following procedural changes may be considered:

- If necessary, informed consent from a potential or current trial participant may be obtained via electronic informed consent capabilities or an electronic face-to-face consent interview when potential participants are unable to travel to the site.
- Subjects who discontinued from screening due to COVID-19–related factors but were otherwise qualified to participate in the study may be rescreened if the sponsor agrees.
- Remote checks instead of site visits (if appropriate) may be performed as a safety check on subject well-being.
- Transfer to investigational sites away from risk zones to complete required visits.

8.2 Study Assessments

8.2.1 Demographic and Other Baseline Characteristics

Subject demographic information, including sex, age, and race, will be collected at screening prior to the subject receiving the first dose of ADYNOVATE.

8.2.2 Medical and Medication History

Medical and medication history will be collected at screening and recorded on the eCRF.

The subject's medical history (including immunization history) will be described and include surgery history, hemophilia history, bleeding episode history, and history of FVIII usage over the last year.

Target joints will be documented, whereby a target joint is defined as a single joint (ankles, knees, hips, or elbows) with ≥3 spontaneous bleeding episodes in any consecutive 6-month period. The joint is no longer considered a target joint when there have been ≤2 bleeds into the joint within a consecutive 12 month period (Blanchette et al. 2014).

The subject's ABR based on the previous 9 to 12 months will be recorded, based on the subject's own diary or recall.

Medication history will include the name of the product, dose, dosing interval, and regimen start and end date. All FVIII replacement therapies used within the previous 12 months will be documented, including:

- Factor VIII regimen (prophylaxis or on-demand)
- Product name (or IP name and manufacturer, if applicable)
- Dose (for prophylaxis, if applicable, and for treatment of bleeding episodes)
- Frequency of administration (for prophylaxis)
- Estimate of average number of infusions for each bleeding episode
- Usual response to treatment for bleeding episodes
- Total number of EDs

Any prior use of the following, at any time in the past, will also be recorded:

- Any PEGylated medication (name of drug, indication, and dates of use)
- Fresh frozen plasma, cryoprecipitate, and/or any type of FVIII concentrate

- Any kind of blood transfusion, such as pRBCs, platelets, or plasma

All nonstudy treatments (including but not limited to herbal treatments, vitamins, behavioral treatment, nonpharmacological treatment, such as psychotherapy) received within 30 days prior to the screening visit and through the final study contact (including protocol-defined follow-up period) must be recorded on the eCRF.

8.2.3 Subject Electronic Diary

After eligibility is confirmed (and before the first dose), an eDiary will be provided to each subject and/or subject's legally authorized representative to record the following information:

- Daily infusion record of ADYNOVATE, including:
  - Date and time of infusion
  - Number of units infused
  - Number of vials used
  - Reason for infusion (eg, bleeding episode, maintain hemostasis, prophylaxis)
  - Total volume
- Details of bleed episodes and response to treatment
- Untoward events
- Concomitant medications and nondrug therapies

For each bleeding episode, the following information will be recorded by the subject/subject's caregiver or by authorized, qualified personnel at the study site:

- Location of the bleed; eg, joint, soft tissue, muscle, body cavity, intracranial, other
- Type of bleed; ie, spontaneous (ie, not related to injury/trauma), injury (definitely due to injury/trauma)
- Severity of the bleed; eg, minor, moderate, major (see Table 6)
- Date and time of onset of the bleed
- Date and time of each infusion of ADYNOVATE required to achieve adequate hemostasis
- Date and time of resolution of bleeding episode
- Overall clinical efficacy rating according to the rating scale as described in Table 7 at 24 hours (±2 hours) after initiation of treatment and at a resolution of bleed

Subjects and/or their legally authorized representative will be trained on use of the eDiary at the time it is issued. The eDiary will be provided in electronic format and remain with the subject for the duration of the study. eDiaries will be completed before each site visit and reviewed by the investigator during the visit. The investigator will review the eDiary for completeness and request missing information periodically, at a minimum at each subject visit, and in a timely manner. Untoward events recorded in the eDiary will be reported as AEs according to the investigator's discretion and clinical judgment.

Subject entries in the eDiary will serve as source records. During study participation, the investigator has access to the database holding the subject eDiary data. After study closure, the investigator will receive the eDiary records for their subjects, including audit trail records. The eDiary records will be transmitted to the CRO.

Note: It is crucial that the investigator evaluates and discusses with the subject at each study visit whether the subject/legal representative has adhered to the prescribed treatment regimen for prophylaxis, treatment of bleeding episodes (if applicable), and whether the subject/legal representative has correctly entered all necessary information. The investigator will review the eDiary for completeness and ask for missing information. Any unclear or implausible information should be immediately clarified with the subject at each study visit, and instructions related to treatment and data entry should be reinforced. If necessary, an additional remote visit via phone or an unscheduled on-site visit can be conducted at the investigator's discretion.

8.2.4 Efficacy

This section details the efficacy assessments and procedures for prophylaxis treatment (Section 8.2.4.1), on-demand treatment of bleeding episodes (Section 8.2.4.2), and perioperative bleeding management (Section 8.2.4.3).

8.2.4.1 Prophylaxis Treatment Assessments

8.2.4.1.1 Annualized Bleeding Rates

The primary measure of hemostatic efficacy is the total ABR. The ABR will be assessed based upon each individual bleeding episode, spontaneous or traumatic, recorded in the subject's eDiary and/or recorded in the physician/nurse/study site notes. A bleed is defined as subjective (eg, pain consistent with a joint bleed) or objective evidence of bleeding that may or may not require treatment with FVIII. Bleeding episodes occurring at the same anatomical location (eg, right knee) with the same etiology (eg, spontaneous vs. injury) within 24 hours of onset of the first episode will be considered a single bleeding episode. If a bleed occurs following resolution of the bleed, it will be considered a "new" bleed and recorded accordingly. Bleeding occurring at multiple locations related to the same injury (eg, knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

The time intervals between bleeding episodes and proportion of subjects with zero bleeding episodes will also be determined based on the subject's eDiary and/or recorded in the physician/nurse/study site notes.

8.2.4.1.2 Consumption of ADYNOVATE for Prophylaxis Treatment

The total number of ADYNOVATE infusions and the average number of ADYNOVATE infusions per week and per month during prophylactic treatment will be measured.

The total and average weight-adjusted consumption of ADYNOVATE per week and per month during prophylactic treatment will be determined based upon the amount of ADYNOVATE infused, as recorded in the subject's eDiary or eCRF, and the subject's weight, as measured at the study site.

8.2.4.2 On-demand Treatment of Bleeding Episodes Assessments

8.2.4.2.1 Hemostatic Efficacy Rating

The subject or their caregiver will rate the severity (minor, moderate, or major) of the bleeding episode and will rate the overall treatment response at 24 hours (±2 hours) after the initiation of treatment and at the resolution of bleed using a 4-point efficacy rating scale (Table 7). Since the efficacy rating is based to a large degree on cessation of pain, the investigator/subject shall, in particular in case of injury-related bleeding into 1 or more than 1 location, consider the injury-related symptoms when performing the efficacy rating 24 hours (±2 hours) after initiating treatment and at resolution of bleed.

As per Table 7, multiple infusions of ADYNOVATE may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded at resolution of the bleed.

Table 7. Efficacy Rating Scale for Treatment of Bleeding Episodes

Excellent	Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

Details pertaining to all home treatments for each bleed, including response to treatment, will be recorded by study subjects (or their caregiver) in subject eDiaries provided by the sponsor or sponsor's representative (see Section 8.2.3). At each study visit, the investigator will review together with the subject (or their caregiver) the response to treatment and evaluate the hemostatic efficacy rating. If a breakthrough bleed occurs, the subject will be advised to contact the investigator to discuss dose and bleed severity. It may become necessary to rediscuss the rating with the subject (or their caregiver) to ensure the rating scale is fully understood:

- 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 of a unique bleeding episode are rated with "fair", the investigator may re-evaluate the dosing regimen and the time from bleeding onset to start of treatment. In case of bleeding episodes requiring only 1 infusion but response to treatment is rated as "fair", the rating scale should be evaluated and discussed with the subject (or their caregiver).
- In case more than 1 infusion was given to treat a bleeding episode but the treatment was rated as "excellent", information should be provided about the severity of the bleeding episode (see Table 6) 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 on the eCRF.

Adverse events and the details of concomitant medication use coincident with the treatment of all acute bleeding episodes will be recorded. Note that bleeding episodes are not to be reported as AEs (Appendix 3).

8.2.4.2.2 Consumption of ADYNOVATE per Bleeding Episode

The number of ADYNOVATE infusions to treat each bleeding episode is determined by the subject, subject's caregiver, and/or investigator and is based upon the subject's response to treatment, using the efficacy rating scale in Table 7. An infusion is defined as completion of administration of the calculated dose of ADYNOVATE. If an infusion is interrupted, eg, due to vascular access issues, and must be restarted, it will be recorded as 1 infusion. If an infusion is terminated for any reason prior to completion of infusion and not restarted, it will be recorded as an infusion; reasons for interruption and volume of the infusion will be recorded.

The weight-adjusted consumption of ADYNOVATE per bleeding episode will be determined based upon the amount of ADYNOVATE infused to treat the bleeding episode, as recorded in the subject's eDiary, and the subject's weight, as measured at the study site.

8.2.4.3 Perioperative Bleeding Management Assessments

8.2.4.3.1 Global Hemostatic Efficacy Assessment

The primary outcome measure for perioperative bleeding management is the Global Hemostatic Efficacy Assessment (GHEA) score, which is composed of 3 individual ratings (see Table 8, Table 9, and Table 10). Assessments are performed intraoperatively and postoperatively at 24 hours by the surgeon and at discharge by the investigator.

- Assessment of intraoperative hemostatic efficacy of ADYNOVATE is to be performed by the operating surgeon (Table 8).

Table 8. Intraoperative Efficacy Assessment Scale

Rating	Criteria	Score
Excellent	Intraoperative blood loss is less than or equal to that expected for the type of procedure performed in a non-hemophilic population (≤100%)	3
Good	Intraoperative blood loss is up to 50% more than expected for the type of procedure performed in a non-hemophilic population (101% to 150%)	2
Fair	Intraoperative blood loss is more than 50% of that expected for the type of procedure performed in a non-hemophilic population (>150%)	1
None	Uncontrolled hemorrhage that is the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

- Assessment of postoperative hemostatic efficacy of ADYNOVATE is to be performed on postoperative day 1 (ie, the day after surgery) by the operating surgeon (Table 9).

Table 9. Postoperative Efficacy Assessment Scale (Postoperative Day 1)

Rating	Criteria	Score
Excellent	Postoperative blood loss is less than or equal to (≤100%) that expected for the type of procedure performed in a non-hemophilic population	3
Good	Postoperative blood loss is up to 50% more (101% to 150%) than expected for the type of procedure performed in a non-hemophilic population	2
Fair	Postoperative blood loss is more than 50% (>150%) of that expected for the type of procedure performed in a non-hemophilic population	1
None	Significant postoperative bleeding that is the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

- Assessment of perioperative hemostatic efficacy of ADYNOVATE is to be performed by the investigator at discharge (Table 10).

Table 10. Perioperative Efficacy Assessment Scale (Discharge Visit)

Rating	Criteria	Score
Excellent	Perioperative blood loss is less than or equal to (≤100%) that expected for the type of procedure performed in a non-hemophilic population Required blood components for transfusions are less than or similar to that expected in non-hemophilic population	3
Good	Perioperative blood loss is up to 50% more (101% to 150%) than expected for the type of procedure performed in a non-hemophilic population Required blood components for transfusions are less than or similar to that expected in non-hemophilic population	2
Fair	Perioperative blood loss is more than 50% of that expected for the type of procedure performed in a non-hemophilic population (>150%) Required blood components transfusions are greater than that expected in non-hemophilic population	1
None	Significant perioperative bleeding that is the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy Required blood components for transfusions are substantially greater than that expected in non-hemophilic population	0

The scores of each of the 3 individual ratings described in Table 8, Table 9, and Table 10 are added together to form a GHEA score (Table 11). Treatment success is defined as a rating of "excellent" and/or "good". For a GHEA score of 7 to be rated "excellent", no individual assessment score is less than 2 (ie, an individual assessment score must be 3 and the other 2 individual assessment scores must be 2). The only other option to achieve a GHEA score of 7 is for 2 individual assessment scores of 3 and an individual assessment score of 1. Although this GHEA score will not qualify for a rating of "excellent", the GHEA score will satisfy the definition of "good" (with no individual assessment score less than 1).

Table 11. Global Hemostatic Efficacy Assessment

Assessment	Global Hemostatic Efficacy Assessment Score
Excellent	7 to 9 (with no category scored <2)
Good	5 to 7 (with no category scored <1)
Fair	3 to 4 (with no category scored <1)
None	0 to 2 (or at least 1 category scored 0)

8.2.4.3.2 Actual Versus Predicted Blood Loss

The observed versus predicted operative blood loss for all procedures will be described for the period from initiation of the intervention to discharge.

Prior to each surgery, the surgeon/investigator will predict the estimated volume (mL) of the expected average and maximum blood loss for the planned surgical intervention in a hemostatically normal individual of the same sex, age, and stature as the study subject for intraoperative, postoperative, and overall perioperative time periods. Every effort should be made to predict the volume as precisely as possible. The estimate will be for the intraoperative time period from completion of the procedure until approximately 24 hours after surgery and for the overall perioperative time period (assessed at discharge).

The intraoperative blood loss will be measured by determining the volume of blood and fluid removed through suction into the collection container (waste box and/or cell saver) and the estimated blood loss into swabs and towels during the procedure, per the anesthesiologist's record. Postoperatively, blood loss will be determined by the drainage volume collected, which will mainly consist of drainage fluid via vacuum or gravity drain, as applicable. In cases where no drain is present, blood loss will be determined by the surgeon's clinical judgment, as applicable, or entered as "not available".

8.2.4.3.3 Blood Transfusion Requirement

The volume of blood, pRBCs, platelets, and other blood products transfused to the subject to manage the intraoperative and postoperative bleeding until discharge will be recorded.

8.2.4.3.4 Consumption of ADYNOVATE for Perioperative Bleeding Management

The daily and total weight-adjusted consumption of ADYNOVATE for intraoperative and postoperative bleeding management until discharge will be determined based upon the amount of ADYNOVATE infused, as recorded in the subject's eDiary or eCRF, and the subject's weight, as measured at the study site.

8.2.5 Safety

8.2.5.1 Physical Examination

A physical examination will be performed by the investigator during each study visit. A complete physical examination will include, at a minimum, assessments of general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.

Abnormalities identified at the screening visit and at subsequent study visits will be recorded on the eCRF. The investigator will assess whether a change from baseline may be deemed clinically significant and therefore recorded as an AE. For each abnormal physical examination finding deemed to be an AE (see definition in Appendix 3.1), the medical diagnosis (preferably) or symptom will be recorded. Additional tests and other evaluations required to establish the significance or etiology of the abnormal value, or to monitor the course of the AE, should be obtained when clinically indicated. Any abnormal value that persists should be monitored at the discretion of the investigator.

8.2.5.2 Adverse Events

The occurrence of AEs and SAEs will be monitored, including the total incidence, by severity, and by causality. 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?"). Occurrence of thromboembolic events and hypersensitivity reactions will particularly be monitored. Adverse events are collected from the time the ICF is signed. Refer to Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures.

8.2.5.3 Vital Signs

Vital signs will include height (only at screening), weight (kg), body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg) taken following 15 minutes of rest. The time points for pre- and postinfusion measurements are within 30 minutes before infusion start (prior to blood sample collection) and 30±15 minutes after infusion. Vital signs will be measured at the study visits presented in Table 1. Weight is measured preinfusion only.

Blood pressure should be determined by cuff and measured while subjects are in a sitting position (the same method, same arm, and same position should be used throughout the study).

Vital sign values are to be recorded on the eCRF. The investigator will assess whether a change from baseline in vital signs may be deemed clinically significant and therefore recorded as an AE. For each abnormal vital sign value, if the investigator deems this to be an AE (see definition in Appendix 3), the medical diagnosis (preferably), symptom, or sign will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

8.2.5.4 Clinical Laboratory Tests

At all laboratory assessments, subjects must not be actively bleeding. Assessments should only be performed after a washout period of at least 72 to 96 hours following the last infusion of any other nonmodified FVIII concentrate and 84 to 96 hours following the last infusion of ADYNOVATE. In addition to the assessments shown, clinical laboratory assessments should be performed whenever clinically indicated.

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 that may be associated with, or constitute, an AE. 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.

A complete list of the clinical laboratory tests to be performed is provided in Appendix 2. The schedule of clinical laboratory assessments is presented in Table 2.

8.2.5.4.1 Immunology

Immunology assessments will include HIV-1/HIV-2 antibody, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody. The HCV titer will be confirmed by polymerase chain reaction for all subjects reported as HCV-positive.

If a subject is HIV-positive, CD4 count is measured using flow cytometry to determine the subject's eligibility.

All immunology assessments will be performed at screening only. Testing will be conducted at a local laboratory as the first choice and at a central laboratory as back-up.

8.2.5.4.2 Hematology and Clinical Chemistry

Blood will be obtained for assessment of hematology and clinical chemistry parameters at the study visits presented in Table 2. Hematology and clinical chemistry assessments will be performed on anticoagulated whole blood and serum, respectively, at a local laboratory.

The hematology panel will consist of complete blood count: hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), leukocytes (ie, white blood cell count) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), and platelet count.

If historical data on blood group type are available, this may be recorded in the eCRF and blood type does not need to be determined. For subjects who do not have documentation of their blood type in their medical record, ABO blood type will be measured locally at screening.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, AST, gamma-glutamyl transferase, bilirubin, alkaline phosphatase, urea/blood urea nitrogen (BUN), creatinine, glucose, cholesterol, very low-density lipoprotein, low-density lipoprotein, high-density lipoprotein, and triglycerides.

8.2.5.4.3 Coagulation Function

Coagulation function will be assessed at a local laboratory via INR at screening and aPTT, as needed, for surgery (see Section 6.2.2.4.1).

8.2.5.5 Immunogenicity

Blood samples for immunogenicity testing should only be collected after the required washout period and the subject is in a nonbleeding state. A minimum washout of 72 to 96 hours is required following the last infusion of FVIII therapy and 84 to 96 hours following the last infusion of ADYNOVATE.

Immunogenicity assessments will include the measurement of inhibitory antibodies to FVIII and binding antibodies to ADYNOVATE and CHO proteins.

- Inhibitory antibodies to FVIII will be measured using the Nijmegen modification of the Bethesda assay. A sample will be defined as positive for inhibitor development with a titer of ≥0.6 BU/mL. Any positive titers should be confirmed with a second repeat sample drawn within 2 weeks of study site notification of an inhibitor-positive result.
- Binding antibodies to ADYNOVATE will be measured via enzyme-linked immunosorbent assay (ELISA). A tiered approach will be used. All samples will be screened for anti-ADYNOVATE binding antibodies. Screen-positive samples will be tested by a confirmatory assay. Confirmed positive samples will be serially diluted to assess antibody titer.
- Binding antibodies to CHO proteins will be measured via ELISA. A tiered approach, as described above for anti-ADYNOVATE binding antibody, will be used.

Factor VIII inhibitory antibodies must be determined at the central laboratory. However, in order to ensure the timely availability of FVIII inhibitor results, the clinical management of the subject may be based on results generated at the local laboratory. An additional blood sample needs to

be drawn for testing at the central laboratory to confirm the result determined at the local laboratory. Blood will be obtained for these assessments at the visits shown in Table 2.

8.2.6 Pharmacokinetics

Pharmacokinetic activities, assessments, and sampling time points are listed in Table 1, Table 2, and Table 3, respectively.

8.2.6.1 Pharmacokinetic Sampling and Evaluation

The PK samples for both the initial and second PK assessments should be taken following the sampling time points listed in Table 3. Evaluation will be performed in the clinic to ensure a sufficient number of PK blood samples are available for participating subjects.

For subjects participating in the PK portion of the study, the initial PK assessment will be conducted after a washout period of at least 72 to 96 hours following their last FVIII therapy (if applicable) and prior to the baseline visit. The second PK assessment will be performed during the Week 20 (±1 week) visit following the scheduled prophylactic treatment dose.

8.2.6.2 Determination of Incremental Recovery

During the baseline visit (ED1), Week 6 visit (approximately ED10 to ED15), and the study completion visit (ED50), peak levels of FVIII activity will be assessed within 30 minutes before ADYNOVATE administration and 30±10 minutes post ADYNOVATE infusion for determination of IR. The IR determination at baseline visit will only be performed in subjects who have not undergone the initial PK assessment.

All PK samples collected in this part will be used, along with the samples collected in the PK assessments, to characterize PK properties in PTPs.

8.2.6.3 Factor VIII and von Willebrand Factor Measurements

In addition to PK and IR assessments, FVIII (activity and antigen) and VWF antigen levels will be measured at specified study visits, preinfusion, in both PK and non-PK subjects. For PK subjects, preinfusion blood draws are performed within 30 minutes prior to infusion, meaning no additional blood draw is needed at the baseline visit for these assessments.

Plasma FVIII levels will be measured using a 1-stage clotting assay for FVIII:C activity and ELISA for FVIII antigen concentrations. von Willebrand factor antigen will be measured via ELISA.

8.2.7 Other Assessments

8.2.7.1 Patient-reported Outcome

The PRO assessment, using the EQ-5D-5L, will be captured via an ePRO device dispensed after subject eligibility is confirmed and before the first dose. Subjects should complete the EQ-5D-5L prior to study visits listed in Table 1. Investigators should review subject responses during each scheduled visit.

For subjects participating in the PK portion of the study, the first PRO measurement should be completed prior to the initial PK assessment. For subjects not undergoing PK assessment, the first PRO measurement should be completed prior to the baseline visit.

Further information concerning the PRO assessment included in the study is provided in Appendix 4.

8.2.7.2 Healthcare Resource Utilization

Healthcare resource utilization endpoints will be gathered by the sites via questionnaire as part of the eCRF. This information is necessary to collect as input into a cost-effectiveness analysis that may be developed in the future. It assesses the following:

- Number and duration of hospitalizations
- Number of emergency room visits
- Number of acute care visits
- Number of days missed from school/work

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

The study will be analyzed by the sponsor and its designated agent.

Statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513) software package, Version 9.4 (or newer) on a suitably qualified environment.

The population PK analysis plan and statistical analysis plan (SAP) will be provided as separate documents.

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, IP 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.

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

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

9.3 Sample Size and Power Considerations

At least 30 evaluable adult and adolescent subjects (aged 12 to 65 years) will be enrolled. The sample size was not based on statistical consideration. The evaluable subjects are defined as all subjects who are treated with ADYNOVATE for a minimum of 50 EDs or approximately 26 weeks (+2 weeks), whichever occurs last. Subjects who withdraw or discontinue before study completion may be replaced.

9.4 Statistical Analysis Sets

9.4.1 Safety Analysis Set

The safety analysis set (SA set) will comprise all subjects treated with at least 1 ADYNOVATE dose. All safety analyses will be performed on the SA set.

9.4.2 Full Analysis Set

The full analysis set (FAS) will comprise all subjects who were assigned to receive a treatment regimen of ADYNOVATE. All efficacy analyses will be performed on the FAS.

9.4.3 Per Protocol Analysis Set

The per protocol analysis set (PPAS) will comprise all subjects who were treated with the prophylaxis ADYNOVATE treatment regimen and comply with their originally assigned dose for the duration of study participation. The PPAS will be the supportive analysis set.

9.4.4 Pharmacokinetic Full Analysis Set

The PK full analysis set (PK FAS) will comprise all subjects who consented to PK evaluation, were treated with at least 1 ADYNOVATE dose, and have at least 1 evaluable PK concentration post dose. All PK analyses will be performed on the PK FAS.

9.4.5 Pharmacokinetic Analysis Set

The PK analysis set (PK AS), a subset of the PK FAS, will comprise all PK subjects who received at least 1 ADYNOVATE PK dose with a sufficient number of evaluable PK concentrations post dose for the estimation of PK parameters using a noncompartmental analysis (NCA).

9.5 Efficacy Analyses

9.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the total ABR for all bleeding episodes that occurred during the study (after the first dose of the study drug). The ABR during the study is to be analyzed in the FAS. Point estimates with 95% CIs of ABRs will be presented.

9.5.2 Secondary Efficacy Endpoints

9.5.2.1 Bleeding Episodes and Annualized Bleeding Rate

The ABRs will be summarized using descriptive statistics (mean, standard deviation [SD], median, quartiles, and ranges) by bleed site and cause.

The number and percent of subjects with zero bleeding episodes during the study period will be summarized.

The time intervals between any 2 consecutive bleeding episodes will be summarized using descriptive statistics (mean, SD, median, quartiles, and ranges).

9.5.2.2 Consumption of ADYNOVATE

Drug consumption of ADYNOVATE will be summarized using descriptive statistics (mean, SD, median, quartiles, and ranges) as follows:

- Number of prophylactic infusions per week and per month

- Number of prophylactic units (IU) and weight-adjusted units (IU/kg) per week and per month
- Total number of infusions for prophylactic treatment during the study per subject
- Total number of prophylactic units (IU) and weight-adjusted units (IU/kg) during the study per subject
- Number of infusions per bleeding episode
- Number of units (IU) and weight-adjusted units (IU/kg) per bleeding episode
- Total number of infusions used to treat bleeding per subject
- Total number of units (IU) and weight-adjusted units (IU/kg) to treat bleeding per subject
- Total number of EDs per subject

9.5.2.3 Overall Hemostatic Efficacy Rating and Global Hemostatic Efficacy Assessment

The overall hemostatic efficacy at resolution of each bleeding episode will be summarized by frequency table and by severity (mild, moderate, or severe) of bleeding.

9.5.2.4 Efficacy for Surgeries

The overall assessment of hemostatic efficacy based on the GHEA score, as assessed by the operating surgeon/investigator, will be summarized by frequency table for minor surgeries.

Intra- and postoperative actual versus predicted blood loss after the surgery, at postoperative day 1, and at discharge as assessed by the operating surgeon/investigator will be summarized using descriptive statistics for minor surgeries.

Number and percent of subjects who have any surgeries and require perioperative transfusion of blood, red blood cells, platelets, and other blood products will be summarized by frequency table for minor surgeries. The volume of transfusions will be summarized using descriptive statistics for each surgery.

Daily intra- and postoperative weight-adjusted consumption dose of ADYNOVATE will be summarized using descriptive statistics for minor surgeries.

9.5.3 Multiplicity Adjustment

No multiplicity adjustment is planned in this single-arm study.

9.5.4 Control of Type I Error

No Type I error control will be applied for the study.

9.6 Safety Analyses

The analysis of the safety will be performed based on the SA set.

9.6.1 Adverse Events

For this study, any untoward medical occurrence occurring from the time the ICF is signed will be considered an AE. A treatment-emergent AE (TEAE) is any event emerging or manifesting at or after the initiation of treatment with an IP or any existing event that worsens in either intensity or frequency following exposure to the IP. Refer to Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events, incidence, and percentage of TEAEs, SAEs, treatment-related AEs, and TEAEs leading to discontinuation of the study will be summarized overall and by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be further summarized by severity and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Occurrence of hypersensitivity reactions and thromboembolic events will be monitored throughout the study and summarized by SOC and PT. Standardized MedDRA queries may be used, as applicable.

9.6.2 Immunogenicity

9.6.2.1 Factor VIII inhibitor development

The incidence of confirmed inhibitory antibodies (≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay) to FVIII will be summarized by frequency table. The proportion of subjects, including a 95% CI using an exact Clopper-Pearson interval, who developed inhibitory antibodies to FVIII at any time during the study (after the first dose of the study drug) will be summarized.

9.6.2.2 Binding Antibodies

Histograms will be used to show the number and proportion of subjects with binding antibodies to ADYNOVATE and binding antibodies to CHO proteins.

9.6.3 Vital Signs and Clinical Laboratory Parameters

Clinical laboratory parameters and vital signs will be summarized for baseline and postbaseline scheduled visits (including the termination visit), as well as their changes from baseline. Number and percent of subjects with clinically significant abnormal results for vital signs and clinical laboratory parameters will be summarized for any postbaseline assessment.

Shift tables will be used to assess the frequency of changes for clinically significant vital signs and clinical laboratory parameters (hematology and clinical chemistry) to note clinically significant changes, or vice versa, after first exposure to ADYNOVATE.

9.7 Pharmacokinetic Analyses

Pharmacokinetic parameters will be estimated for FVIII activity measured by the 1-stage clotting assay following an initial single dose and steady-state dose of ADYNOVATE. Pharmacokinetic parameters, as appropriate but not limited to, will include CL (clearance), V (volume of distribution), AUC (area under the concentration versus time curve between defined timepoints), C_{max} (maximum concentration), $C_{predose}$ (predose concentration), and elimination-phase $T_{1/2}$. For PK subjects, subject to availability of FVIII activity, NCA methodology will be used. For all subjects, the population PK modeling and simulation method will be used, as appropriate, and reported separately.

Factor VIII activity (1-stage clotting assay) in PK samples collected following single-dose and steady-state dose for PK assessments, predose FVIII levels (activity and antigen), FVIII activity and VWF antigen will be tabulated and summarized descriptively. Incremental recovery over the prophylactic treatments will be calculated and summarized descriptively.

9.8 Other Analyses

9.8.1 Patient-reported Outcome Analysis

Health-related quality of life results as assessed using the EQ-5D-5L will be summarized using descriptive statistics in accordance with the questionnaire user guide. Changes from baseline/preinfusion to study completion in this PRO will be estimated using the Hodges-Lehmann estimator.

9.8.2 Healthcare Resource Utilization Analyses

Healthcare resource utilization endpoints, including number and duration of hospitalizations, number of emergency room visits, number of acute care visits, and number of days missed from school/work, will be summarized descriptively. Additional analyses may include mean hospitalizations per subject, mean length of stay, and mean days missed from school/work.

10. REFERENCES

Aledort, L. M., Haschmeyer, R. H. and Pettersson, H. 1994. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med,* 236(4), 391-9.

Berntorp, E. 2009. Joint outcomes in patients with haemophilia: the importance of adherence to preventive regimens. *Haemophilia,* 15(6), 1219-27.

Berntorp, E., Spotts, G., Patrone, L. and Ewenstein, B. M. 2014. Advancing personalized care in hemophilia A: ten years' experience with an advanced category antihemophilic factor prepared using a plasma/albumin-free method. *Biologics,* 2014, 115-27.

Björkman, S. 2003. Prophylactic dosing of factor VIII and factor IX from a clinical pharmacokinetic perspective. *Haemophilia,* 9 Suppl 1, 101-10.

Björkman, S. and Berntorp, E. 2001. Pharmacokinetics of coagulation factors: clinical relevance for patients with haemophilia. *Clin Pharmacokinet,* 40(11), 815-32.

Björkman, S., Folkesson, A. and Jönsson, S. 2009. Pharmacokinetics and dose requirements of factor VIII over the age range 3-74 years : A population analysis based on 50 patients with long-term prophylactic treatment for haemophilia A. *Eur. J. Clin. Pharmacol,* 65(10), 989-98.

Blanchette, V. S., Key, N. S., Ljung, L. R., Manco-Johnson, M. J., van den Berg, H. M. and Srivastava, A. 2014. Definitions in hemophilia: Communication from the SSC of the ISTH. *J Thromb Haemost,* 12(22), 1935-9.

Chinese Medical Association; Hematology Branch Thrombosis and Hemostasis Group 2017. Consensus of Chinese expert on the diagnosis and treatment of hemophilia (version 2017). *Zhonghua xueyexue zazhi,* 38(5), 364-70.

Fischer, K., van der Bom, J. G., Molho, P., Negrier, C., Mauser-Bunschoten, E. P., Roosendaal, G., et al. 2002. Prophylactic versus on-demand treatment strategies for severe haemophilia: a comparison of costs and long-term outcome. *Haemophilia,* 8(6), 745-52.

Gouw, S. C., van der Bom, J. G. and van den Berg, H. M. 2007. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: The CANAL cohort study. *Blood,* 109(11), 4648-54.

Hacker, M. R., Geraghty, S. and Manco-Johnson, M. 2001. Barriers to compliance with prophylaxis therapy in haemophilia. *Haemophilia,* 7(4), 392-6.

Hoots, W. K. and Nugent, D. J. 2006. Evidence for the benefits of prophylaxis in the management of hemophilia A. *Thromb. Haemost,* 96(4), 433-40.

Konkle, B. A., Stasyshyn, O., Chowdary, P., Bevan, D. H., Mant, T., Shima, M., et al. 2015. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. *Blood,* 126(9), 1078-85.

Krishnan, S., Vietri, J., Furlan, R. and Duncan, N. 2015. Adherence to prophylaxis is associated with better outcomes in moderate and severe haemophilia: results of a patient survey. *Haemophilia,* 21(1), 64-70.

Langer, A. L., Etra, A. and Aledort, L. 2018. Evaluating the safety of emicizumab in patients with hemophilia A. *Expert Opin Drug Saf,* 17(12), 1233-7.

Lee, C. A. 2007. Prevention of haemophilic synovitis: prophylaxis. *Haemophilia,* 13 Suppl 3, 20-5.

Löfqvist, T., Nilsson, I. M., Berntorp, E. and Pettersson, H. 1997. Haemophilia prophylaxis in young patients--a long-term follow-up. *J Intern Med,* 241(5), 395-400.

Mahlangu, J., Powell, J. S., Ragni, M. V., Chowdary, P., Josephson, N. C., Pabinger, I., et al. 2014. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood,* 123(3), 317-25.

Manco-Johnson, M. 2007. Comparing prophylaxis with episodic treatment in haemophilia A: implications for clinical practice. *Haemophilia,* 13 Suppl 2, 4-9.

Manco-Johnson, M. J., Abshire, T. C., Shapiro, A. D., Riske, B., Hacker, M. R., Kilcoyne, R., et al. 2007. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med,* 357(6), 535-44.

Manco-Johnson, M. J., Nuss, R., Geraghty, S., Funk, S. and Kilcoyne, R. 1994. Results of secondary prophylaxis in children with severe hemophilia. *Am J Hematol,* 47(2), 113-7.

Morado, M., Villar, A., Jiménez-Yuste, V., Quintana, M. and Hernandez-Navarro, F. 2005. Prophylactic treatment effects in inhibitor risk: experience in one centre. *Haemophilia,* 11(2), 79-83.

Mullins, E. S., Stasyshyn, O., Alvarez-Roman, M. T., Osman, D., Liesner, R., Engl, W., et al. 2017. Extended half-life pegylated, full-length recombinant factor VIII for prophylaxis in children with severe haemophilia A. *Haemophilia,* 23(2), 238-46.

National Hemophilia Foundation 2007. Recommendation concerning prophylaxis (Regular administration of clotting factor concentrate to prevent bleeding). *MASAC 241. 4-11-2007.*

National Hemophilia Foundation. 2006. Recommendation concerning prophylaxis (regular administration of clotting factor concentrate to prevent bleeding). *MASAC 170. 4-22-2006.*

Roosendaal, G. and Lafeber, F. 2007. Prophylactic treatment for prevention of joint disease in hemophilia--cost versus benefit. *N Engl J Med,* 357(6), 603-5.

Royal, S., Schramm, W., Berntorp, E., Giangrande, P., Gringeri, A., Ludlam, C., et al. 2002. Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients. *Haemophilia,* 8(1), 44-50.

Song, X., Zhong, J., Xue, F., Chen, L., Li, H., Yuan, D., et al. 2021. An overview of patients with haemophilia A in China: Epidemiology, disease severity and treatment strategies. *Haemophilia,* 27(1), e51-e9.

Valentino, L. A., Mamonov, V., Hellmann, A., Quon, D. V., Chybicka, A., Schroth, P., et al. 2012. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J. Thromb. Haemost,* 10(3), 359-67.

White, G. C., Courter, S., Bray, G. L., Lee, M. and Gomperts, E. D. 1997. A multicenter study of recombinant factor VIII (Recombinate) in previously treated patients with hemophilia A The Recombinate Previously Treated Patient Study Group. *Thromb Haemost,* 77(4), 660-7.

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 International Council for Harmonisation (ICH) E6 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, contract research organization [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 Good Clinical Practice (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 electronic case report forms (eCRFs) 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 (IP) 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 CRO 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 nonpediatric 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 institutional review boards (IRBs)/ethics committees (ECs) are notified as appropriate. Additionally, the discontinuation of a registered clinical study that has been posted to a designated public website will be updated accordingly

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

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) and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available 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 subinvestigators 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 ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any subinvestigators 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 IP, 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

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the clinical study agreement.

Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor 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 eCRFs that have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log.

The clinical research associate (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. Alternative approaches may be used to ensure data quality, data integrity, and subject safety (eg, remote source data review via phone) as permitted by regional and local regulations. Additional details are in the monitoring plan.

The eCRFs must 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's eDiary/electronic patient-reported outcomes device, 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 eCRF 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, data obtained using electronic devices and associated technologies [if applicable], 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 (eg, the United States [US] Food and Drug Administration [FDA], European Medicines Agency [EMA], United Kingdom Medicines and Healthcare products 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 the IP; and any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations 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 eCRF 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 eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF 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 sponsor'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.

Appendix 1.5 Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable, from all study subjects prior to any study-related procedures, including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP:

The subject must receive 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. The investigational site is responsible for the consenting process.

After the subject has received and read (or been read) the subject information, the subject and/or the subject's legally authorized representative (as applicable), is/are requested to sign and date the subject informed consent form or a certified translation if applicable.

A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be provided 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 at the site and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form and assent form, where applicable, that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

Additional Pharmacokinetic Sampling Consent Procedure

Informed consent must also be obtained for patients who self-identify as Asian and agree to additional pharmacokinetic (PK) sampling before any additional PK samples are drawn.

Institutional Review Board or Ethics Committee

It is the responsibility of the investigator to submit this protocol, the informed consent form and assent form, where applicable, (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.

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. The investigator must also keep the local IRB/EC informed of any serious and significant adverse events 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 review(s) 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 ADYNOVATE; national or local regulatory authorities; and the IRBs/ECs that 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 numbers, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries that 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 multisite study results are published in a cooperative publication or for a period of 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 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 multisite study publication, if any, or the fact that the study results are a subset of data resulting from a larger multisite study.

Takeda is committed to transparent dissemination of all scientific, technical, and medical manuscripts generated from Takeda-supported research. Therefore, after 01 Jan 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 reuse 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 and analyzed by a central and/or local laboratory:

Clinical Chemistry (local laboratory)	Hematology (local laboratory)
• Sodium • Potassium • Chloride • Bicarbonate • Total protein • Albumin • ALT • AST • GGT • Bilirubin • ALP • Urea/BUN test • Creatinine • Glucose • Cholesterol • Very low-density lipoprotein • Low-density lipoprotein • High-density lipoprotein • Triglycerides	• Hemoglobin • Hematocrit • Erythrocytes (ie, RBC count) • Leukocytes (ie, WBC count) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils) • Platelet count
Immunology (local laboratory as first choice and central laboratory as back-up)	**Coagulation Function (local laboratory)**
• HIV-1/HIV-2 antibody • HCV antibody • HCV PCR testing [a] • HbsAg • HbsAb • HbcAb • CD4 Counts [b]	• aPTT [d] • INR

Immunogenicity (central laboratory) • Inhibitory antibodies to FVIII [c] • Binding antibodies to ADYNOVATE • Binding antibodies to CHO proteins	Others (central and/or local laboratory) • FVIII activity levels (central and/or local laboratory) • FVIII antigen levels (central laboratory) • VWF antigen levels (central laboratory) • Blood typing (local laboratory)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CHO=Chinese hamster ovary; FVIII=factor VIII; GGT=gamma-glutamyl transferase; HbcAb=hepatitis B core antibody; HbsAb=hepatitis B surface antibody; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; PCR=polymerase chain reaction; RBC=red blood cell; VWF=von Willebrand factor; WBC=white blood cell

[a] Polymerase chain reaction will be used to confirm a positive HCV titer

[b] If a subject is HIV-positive, CD4 count is measured to determine the subject's eligibility.

[c] Emergency clinical management of the subject may be based on FVIII inhibitor results generated at the local laboratory. An additional blood sample will need to be drawn for testing at the central laboratory to confirm the result determined at the local laboratory.

[d] Assessed, as needed, for surgery.

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

Appendix 3.1 Adverse Event Definitions

Per standard definition, 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 (IP) 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).

For this study, AEs are collected from the time informed consent is signed.

Treatment-emergent Adverse Event

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

Non–treatment emergent AEs are events occurring before the first exposure to IP and are not considered TEAEs. However, each **serious** non-TEAE experienced before the first IP exposure (ie, from the time of signed informed consent up to but not including the first IP exposure) will be described on the serious AE (SAE) electronic case report form (eCRF) in English, or the paper Takeda Safety Report Form (as back-up). These events will be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each nonserious non-TEAE occurrence experienced by a subject undergoing study-related procedure(s) before the first IP exposure will be recorded on the AE eCRF; these events will be considered as AEs and will not be included in the analysis of AEs.

Serious Adverse Event

An SAE is any untoward clinical manifestation of signs, symptoms, or outcomes (whether considered related to IP or not and at any dose) that:

- 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 that hypothetically might have caused death if it were 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:
  - Any hospitalization due to a planned surgical intervention or the placement or planned removal of a central venous device is not considered an SAE. However, any planned surgery becoming necessary due to a worsening condition of the subject during the study period constitutes an SAE.
  - Development of a confirmed inhibitory antibody based on a second blood draw to factor VIII within 2 weeks of study site notification of an inhibitor determined at the central laboratory with an inhibitor level ≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for human immunodeficiency virus, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus, hepatitis E virus, or parvovirus B19
  - Thromboembolic events (eg, stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism)
  - Severe hypersensitivity/allergic reactions to ADYNOVATE

Unexpected Adverse Event

Per standard definition, an unexpected AE 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 investigator's brochure (IB) and/or prescribing information 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 SAEs will be determined by the sponsor using the IB and/or prescribing information as the RSI (as applicable). This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

For this study, expectedness of SAEs will be determined by the sponsor using the RSI section of the IB.

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

Symptoms of the disease under study should not be classified as AEs as long as they are within the normal day-to-day fluctuation or expected disease progression and are part of the efficacy or effectiveness data collected in the study. Significant worsening of symptoms should be recorded as an AE.

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 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 eCRF.

Clinical Laboratory and Other Safety Assessments

A change in the value of a clinical laboratory parameter or vital sign measure can represent an AE if the change is clinically relevant or if, during administration of IP, 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 IP), 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 values (such as hematology panel or clinical chemistry panel) or vital signs that 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 or vital sign is clinically significant and represents an AE.

Appendix 3.2 Collection of Adverse Events

All AEs are collected from the time the informed consent document is signed until the defined follow-up period stated in Section 8.1.4. This includes events occurring during the screening phase of the study, regardless of whether or not IP is administered.

All AEs must be followed to closure (ie, the subject's health has returned to their 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. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as a separate AE). During the course of any AE, the highest severity rating will be reported. However, worsening medical conditions, signs, or symptoms present prior to initiation of IP must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the IP and the dyspepsia becomes severe and more frequent after the 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, significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship Categorization

A physician/investigator must make the assessment of relationship to IP 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 IP. 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 IP 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 A1. 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.

For the purposes of this study, the following nonserious events experienced after the first IP exposure will not be considered an AE and thus not included in the analysis of AEs:

- Hospital or clinic visits for administration of ADYNOVATE
- Hospitalization for routine bleeding episode management that could be managed in the clinic or home setting but for which the subject was hospitalized
- Hospitalizations for planned medical or surgical procedures, eg, placement of a central venous line
- Hospitalization or prolongation of hospitalization intended only for social reasons
- Hospital admittance without in-patient hospitalization or emergency room visit/admittance in itself (although the event triggering the visit may be an SAE)
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period
- Bleeding episodes/hemophilia-related events:

  Bleeding episodes are part of the underlying disease and therefore are not AEs. If a bleeding episode was caused by an injury (eg, a fall), the injury would not be reported as an AE unless it resulted in a medical finding other than a bleeding episode (eg, abrasion of skin; fractured tibia). Therefore, **any hemophilia-related event** (eg, hemarthrosis, bruising, hemorrhage) **will not be reported as an AE, but these events will be recorded on the bleeding event CRF**. However, hemophilia-related events meeting the criteria for seriousness (eg, a gastrointestinal hemorrhage requiring hospitalization) will be reported as SAEs and described on the SAE report.

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 eCRF.

Appendix 3.4 Safety Reporting

Reference Safety Information

The RSI for this study is the RSI section of the IB. The sponsor has provided the IB under separate cover to all investigators.

Reporting Procedures

The investigator should complete an SAE eCRF in English, or report via the paper Takeda Safety Report Form (as back-up), 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 Appendix 3.9) unless they result in an SAE. The fax number and e-mail address are provided in the Form Completion Instructions.

Medical Device Safety Reporting

All serious injuries and UADEs must be reported to the sponsor as an SAE in the same process as described above. Serious injury is defined as:

- Led to death
- Led to a serious deterioration in health of a patient, user, or others that:
  - resulted in a life-threatening illness or injury
  - resulted in permanent impairment/damage of a body function or body structure

- required inpatient hospitalization or prolongation of existing hospitalization
- resulted in medical or surgical intervention to prevent permanent impairment/damage to a 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 IP) are collected from the time the subject signs the informed consent form until the defined follow-up period stated in Section 8.1.4 and must be reported via the eCRF in English, or the paper Takeda Safety Report Form (as back-up), within 24 hours of becoming aware of the event.

In addition, any SAE(s) considered "related" to the IP and discovered by the investigator at any interval after the study has completed must be reported to the Takeda Global Patient Safety Evaluation (GPSE) 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 date 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, 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 IP action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the IP should be recorded as "dose not changed" or "not applicable" (if the subject never received IP). The IP 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 defined follow-up period stated in Section 8.1.4.

Any report of pregnancy for any partner of a study participant must be reported within 24 hours to the Takeda GPSE using the pregnancy report form. The fax number and e-mail address are provided in the form completion instructions.

A copy of the pregnancy report form (and any applicable follow-up reports) must also be sent to the CRO/sponsor using the details specified in the emergency contact information section of the protocol.

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 abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the same procedure described for SAE reporting.

In addition to the above, if the reported pregnancy meets serious criteria, it must be reported as an SAE using the same procedure described for SAE reporting as well as the pregnancy report form. The test date of the first positive serum/urine β-human chorionic gonadotropin 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 using the Takeda Safety Report Form whether or not they result in an AE/SAE as described in 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 IP when used for a nonmedical 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 IP other than as directed or indicated at any dose (Note: this includes a situation where the IP is not used as directed at the dose prescribed by the protocol)
- Overdose – Intentional or unintentional intake of a dose of IP higher than the protocol-prescribed dose
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an IP. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the IP 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 IP should be considered as a reportable medication error.

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 do 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 Authority, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor or designee is responsible for reporting all SUSARs and any other applicable SAEs to regulatory authorities, investigators, and ECs/institutions as applicable, in accordance with national regulations in the countries where the study is conducted. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the ADYNOVATE program.

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

Appendix 4 SCALES AND ASSESSMENTS

The following scale/assessment will be utilized in this study:

Full Title of Scale/Assessment	Version Number	Date Issued
European Quality of Life Questionnaire in 5 dimensions (EQ-5D)	EQ-5D 5-level version (EQ-5D-5L)	30 Nov 2021

A separate master file containing the scale/assessment listed above will be provided to the site. Updates to scale/assessment during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.

Appendix 5 ABBREVIATIONS

Abbreviation	Definition
ABR	annualized bleeding rate
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve between defined timepoints
BU	Bethesda unit(s)
BUN	blood urea nitrogen
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
$C_{predose}$	predose concentration
COVID-19	coronavirus disease of 2019
CRA	clinical research associate
CRO	contract research organization
EC	ethics committee
eCRF	electronic case report form
ED	exposure day
eDiary	electronic diary
EHL	extended half-life
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life Questionnaire in 5 dimensions 5-level version
EUDRACT	European Union clinical trials database
FAS	full analysis set

Abbreviation	Definition
FDA	Food and Drug Administration
FIX	factor IX
FVIII	factor VIII
GCP	Good Clinical Practice
GHEA	Global Hemostatic Efficacy Assessment
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IR	incremental recovery
IRB	institutional review board
IU	international units
MRT	mean residence time
NCA	noncompartmental analysis
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PK AS	pharmacokinetic analysis set
PK FAS	pharmacokinetic full analysis set
PPAS	per protocol analysis set
pRBC	packed red blood cell
PRO	patient-reported outcome
PT	preferred term
PTP	previously treated patient
PUP	previously untreated patient
rFVIII	recombinant human coagulation factor VIII

Abbreviation	Definition
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SA set	safety analysis set
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SWFI	sterile water for injection
$T_{1/2}$	half-life
UADE	unanticipated adverse device effect
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
V	volume of distribution
VWF	von Willebrand factor

Appendix 6 PROTOCOL HISTORY

Document	Date	Amendment Type	Global/Country/Site Specific
Amendment 1	16 Apr 2023	Non-substantial	China
Original Protocol	21 Jun 2022	Not applicable	China