CLINICAL STUDY PROTOCOL

ADVATE 2 mL [reconstituted in 2 mL sterile water for injection (SWFI)]
Antihemophilic Factor (Recombinant) Plasma/Albumin Free Method (rAHF-PFM)
Octocog alfa (recombinant human coagulation factor VIII)

TITLE: ADVATE 2 mL (reconstituted in 2 mL SWFI)

POST-AUTHORIZATION SAFETY SURVEILLANCE STUDY

SHORT TITLE: ADVATE 2 mL PASS

PROTOCOL IDENTIFIER: 061101

NON-INTERVENTIONAL OBSERVATIONAL STUDY

AMENDMENT 1: 2013 JUL 26

REPLACES ORIGINAL PROTOCOL: 2012 FEB 23

Study Sponsor(s):	**Baxter Healthcare Corporation** One Baxter Way Westlake Village, CA 91362	**Baxter Innovations GmbH** Industriestrasse 67 A-1220 Vienna, AUSTRIA

1. STUDY PERSONNEL

Authorized Representative (Signatory)

[redacted] MD

[redacted], [redacted]

Baxter Healthcare Corporation

1.1 Study Organization

The name and contact information of the authorized representative and individuals involved with the study (eg, investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs. For information on the definition and assessment of adverse events (AEs), refer to Section 11.1.

ALL SAEs ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT

See SAER form for contact information.

Further details are also available in the study team roster.

For definitions and information on the assessment of these events refer to the following:

- AE, Section 11.1
- SAE, Section 11.1.1
- Assessment of AEs, Section 11.1.9

3. SYNOPSIS

STUDY PRODUCT	
Name of Study Product	ADVATE 2 mL [reconstituted in 2 mL sterile water for injection (SWFI)], Antihemophilic Factor (Recombinant) Plasma/Albumin Free Method (rAHF-PFM) Octocog alfa (recombinant human coagulation factor VIII)
Name(s) of Active Ingredient(s)	recombinant human coagulation factor VIII (FVIII)
CLINICAL CONDITION(S)/INDICATION(S)	
• Treatment and prophylaxis of bleeding in patients with hemophilia A	
PROTOCOL IDENTIFIER	061101
PROTOCOL TITLE	ADVATE 2 mL (reconstituted in 2 mL SWFI) POST-AUTHORIZATION SAFETY SURVEILLANCE STUDY
Short Title	ADVATE 2 mL PASS
STUDY PHASE	Non-interventional observational study (post-authorization safety surveillance [PASS])
PLANNED STUDY PERIOD	
Initiation	November 2012
Completion	March 2016
Duration	42 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
• This is a PASS study designed to collect data on the safety and effectiveness of ADVATE reconstituted in 2 mL SWFI during routine clinical practice in children until 12 years of age. This surveillance study will be a post-licensure commitment for ADVATE reconstituted in 2 mL SWFI.	
Primary Objective	
• To assess incidence of all local and general, hypersensitivity and infusion-related reactions, irrespective of product-related causality for the adverse events [AEs]	
Secondary Objective(s)	
• To assess incidence of all AEs considered by the investigator to be causally related (possibly or probably related) to ADVATE reconstituted in 2 mL SWFI • To assess immunogenicity in all subjects • To assess immunogenicity in previously treated patients (PTPs; > 50 exposure days [EDs]) with baseline FVIII ≤ 2% and with no history of inhibitors prior to study entry • To assess immunogenicity in PTPs (> 50 EDs) with baseline FVIII < 1% and with no history of inhibitors prior to study entry • To assess effectiveness in on-demand treatment • To assess effectiveness in prophylaxis • To assess effectiveness in surgical or dental procedures • To assess FVIII treatment satisfaction and preference ratings from caregiver • To assess infusion volume and time to mix and infuse FVIII treatment	

STUDY DESIGN	
Study Type	Safety, Efficacy
Control Type	None
Study Indication Type	Treatment
Blinding Schema	Open-label
Study Design	This study is a prospective, non-interventional, observational PASS study that assesses the safety and efficacy of ADVATE (rAHF-PFM) reconstituted in 2 mL SWFI during routine clinical practice.
Planned Duration of Subject Participation	6 months
Primary Outcome Measure	
• Incidence of all local and general, hypersensitivity and infusion-related reactions, irrespective of product-related causality for the AEs	
Secondary Outcome Measure(s)	
• Number and type of AEs considered by the investigator to be causally related (possibly or probably related) to ADVATE reconstituted in 2 mL SWFI • Number of inhibitors in all subjects • Number of inhibitors in PTPs (>50 EDs) with baseline FVIII < 1% and with no history of inhibitors prior to study entry • Number of inhibitors in PTPs (> 50 EDs) with baseline FVIII ≤ 2% and with no history of inhibitors prior to study entry • Subjective hemostatic effectiveness rating of ADVATE reconstituted in 2 mL SWFI (excellent, good, fair, or none) for each bleeding episode treated • Number of bleeding episodes treated with 1, 2, 3, ≥ 4 infusions of ADVATE reconstituted in 2 mL SWFI • Total units of ADVATE reconstituted in 2 mL SWFI administered to treat each bleeding episode • Overall effectiveness of prophylaxis in subjects who are on prophylactic regimen, as defined by the investigator, for the full duration of the study • Global assessment rating of hemostatic effectiveness of ADVATE reconstituted in 2 mL SWFI (excellent, good, fair, or none) in surgical or dental procedures • Change in FVIII treatment satisfaction and preference ratings from caregiver between ADVATE reconstituted in 5 mL and 2 mL SWFI • Change in FVIII infusion volume and time to mix and infuse FVIII treatment between ADVATE reconstituted in 5 mL and 2 mL SWFI	
STUDY PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Study Product	**ADVATE** **Dosage form**: powder and solvent for solution for injection **Dosage frequency**: the investigator will determine the dose and dosage frequency in accordance with the ADVATE marketing authorization **Mode of Administration:** intravenous

SUBJECT SELECTION	
Targeted Accrual	73

Inclusion Criteria

- Subject has severe or moderately severe hemophilia A (baseline FVIII ≤ 2%)
- Subject is ≤12 years of age
- Subject's legally authorized representative(s) has provided written informed consent
- Subject is prescribed ADVATE and will only receive ADVATE reconstituted in 2 mL SWFI
- Documented history of prior exposure to ADVATE (for subjects ≤ 2 years old, at least 3 EDs to ADVATE; for subjects with ≤ 50 EDs, all prior EDs must be to ADVATE; for subjects with >50 EDs, the last 20 prior EDs must be to ADVATE)
- Documented evidence of negative inhibitor test result during ≤10 EDs prior to study entry

Exclusion Criteria

- Subject has known hypersensitivity to the active substance or to any of the excipients
- Subject has a known allergic reaction to mouse or hamster proteins
- Subject has no prior exposure to a FVIII concentrate
- Subject has a requirement for a major surgical procedure at the time of enrollment
- Subject is currently being treated with an immune tolerance induction regimen
- Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand disease)
- Subject has participated in another clinical study involving an investigational product (IP) or device within 30 days prior to study enrollment or is scheduled to participate in another clinical study involving an IP or device or PASS registry during the course of this study.

STATISTICAL ANALYSIS

Sample Size Calculation

As hemophilia A is a relatively rare disease, the number of subjects eligible for documentation is limited. Therefore, no formal sample size calculation was performed. The targeted enrollment will be 73 subjects. This number was determined to offset the estimated 17% dropout rate experienced in study 060103, and to provide 60 evaluable subjects.

Planned Statistical Analysis

Statistical analysis will be descriptive in nature. Continuous variables will be described with means, standard deviations, minimum, first quartile, medians, interquartile ranges, third quartile, and maximum. Categorical variables will be expressed as frequencies and percentages. 95% confidence intervals of selected point estimates will be calculated. Paired statistical tests (parametric via t-test and/or non-parametric via Wilcoxon Signed-Rank test) will be employed to test for differences in infusion volume, time (to be captured in minutes and seconds) needed to mix and infuse FVIII, and satisfaction with ADVATE reconstituted in 5mL SWFI prior to enrolling in the study and ADVATE reconstituted in 2mL SWFI.

4. TABLE OF CONTENTS

Tables

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleed rate
AE	Adverse event (or Adverse Experience)
BU	Bethesda unit
BW	Body weight
CHO	Chinese hamster ovary
cm	Centimeter(s)
CRF	Case report form
dL	Deciliter(s)
EASBE	Effectiveness analysis set for bleeding episodes
EASPT	Effectiveness analysis set for prophylactic treatment
EASSDP	Effectiveness analysis set for surgical and dental procedures
EC	Ethics committee
ED	Exposure day
eg	For example
EU	European Union
FDA	Food and Drug Administration
FVIII	Factor VIII
GCP	Good clinical practice
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV-1/2	Human immunodeficiency virus type 1 & 2
IAS1	Immunogenicity analysis set 1
IAS2	Immunogenicity analysis set 2
i.v.	Intravenous
ICF	Informed consent form
ICH	International Conference on Harmonisation
ie	*id est* (Latin for “that is”)
IgG	Immunoglobulin G
IR	Incremental recovery
ITI	Immune tolerance induction
IU	International unit(s)

Abbreviation	Definition
kg	Kilogram(s)
mL	Milliliter(s)
PASS	Post-Authorization Safety Surveillance
PK	Pharmacokinetics
PKAS	PK analysis set
PP	Per protocol
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
rAHF-PFM	Recombinant Antihemophilic Factor Plasma/Albumin-Free Method
SAE	Serious adverse event (or serious adverse experience)
SAER	Serious adverse event report
SAS	Safety analysis set
SIC	Subject identification code
SmPC	Summary of Product Characteristics
SWFI	Sterile water for injection
VWF	von Willebrand factor

6. BACKGROUND INFORMATION

6.1 Description of Study Product

Baxter Healthcare Corporation (hereafter referred to as Baxter), jointly with Wyeth (formerly Genetics Institute, Inc.) previously developed and clinically investigated a recombinant factor VIII (FVIII) concentrate under the trade name of RECOMBINATE.[i] Extensive pre-licensure clinical testing as well as post-licensure pharmaco-surveillance has shown RECOMBINATE (Antihemophilic Factor [Recombinant]) to be a safe, well-tolerated, and effective recombinant FVIII product.[1; 2]

The cell culture process for RECOMBINATE production employs proteins of bovine origin, namely, aprotinin and albumin. In addition, human albumin is used as a stabilizer in the final formulation. Human albumin has demonstrated an exceptional safety record;[3] however, its addition carries the potential for transmission of human viruses. Furthermore, the use of proteins of bovine origin in the manufacturing of recombinant coagulation proteins has become a source of concern for the hemophilia community, due to speculation that the agent(s) of infectivity that cause bovine spongiform encephalopathy could contaminate these reagents.[4-6]

To address these concerns, Baxter developed ADVATE[ii] (Antihemophilic Factor [Recombinant], Plasma/Albumin-Free Method, Octocog alfa), a recombinant FVIII produced by a Plasma/Albumin Free Method that does not employ any human or animal-derived additives in the cell culture, purification, or formulation of the final product. The Chinese hamster ovary (CHO) cell line used for RECOMBINATE production was adapted to a plasma protein-free cell culture medium for the production of ADVATE. These manufacturing process and formulation innovations result in a recombinant FVIII concentrate with virtually no risk of transmission of adventitious agents derived from exogenous human or animal sources.

The biologics license application for ADVATE reconstituted in 5 mL SWFI was approved by the US Food and Drug Administration (FDA) in 2003. In the European Union (EU), ADVATE reconstituted in 5 mL SWFI is registered through the centralized procedure (EU birth date: 02Mar2004). As of 31 January 2013, ADVATE has active licenses in 58 countries worldwide.

---

[i] RECOMBINATE is a trademark of Baxter International, Inc.
[ii] ADVATE is a trademark of Baxter International, Inc.

The application for ADVATE reconstituted in 2 mL SWFI was approved by Health Canada on 15 November 2011, the US FDA on 15 December 2011 and by the European Commission on 19 December 2011.

6.2 Clinical Condition/Indication

ADVATE is indicated for the prevention and control of bleeding episodes and the perioperative management of patients with hemophilia A (congenital FVIII deficiency).

6.3 Population to Be Studied

The study population will include 60 evaluable subjects aged ≤ 12 years with severe or moderately severe hemophilia A (FVIII ≤ 2%) with documented prior exposure to FVIII concentrates. Thirty (30) subjects will be ≤ 6 years and the remaining 30 subjects will be > 6 to ≤ 12 years of age. Of the 30 subjects ≤ 6 years of age, at least 15 subjects will be ≤ 2 years old. Ongoing enrollment will carefully be monitored to help ensure that the study population reflects the age categories specified.

The targeted enrollment will be 73 subjects. This number was determined to offset the projected dropout rate of 17% experienced in the ADVATE previously untreated patient (PUP) study (060103)[iii,7], and to ensure that there are 60 evaluable subjects.

The patient population to be studied (pediatric patients, aged ≤ 12 years) is of an age that the participants are not able to provide informed consent. However, appropriate consent procedures will be in place, and the consent of the patient's legally authorized representative(s) will be obtained.

6.4 Findings From Nonclinical and Clinical Studies

6.4.1 Studies with ADVATE Reconstituted in 5 mL SWFI

Study 069901 was the pivotal study in the clinical development program for ADVATE.8 This study enrolled and treated 108 previously treated patients (PTPs) who were ≤10 years of age with moderately severe to severe hemophilia A (baseline FVIII ≤ 2%). This study demonstrated bioequivalence of ADVATE and RECOMBINATE with respect to certain pharmacokinetic (PK) parameters (area under the plasma concentration vs. time curve [AUC] and adjusted recovery). The treatment of bleeding episodes was rated excellent or good in 86% of cases, and 93% of bleeding episodes required 1 or 2 infusions for hemostatic control. One non-persistent low titer inhibitor (2.0 Bethesda units [BU]) was detected in 1 PTP that was undetectable 8 weeks after its initial report. No high titer or other low titer inhibitors were detected. No subject developed allergic or

[iii] Data on File, Clinical Study Report (060103). Baxter BioScience, Westlake Village, CA.

hypersensitivity responses to heterologous proteins (ie, CHO cell protein, murine immunoglobulin G [IgG], and human von Willebrand Factor [VWF]). No subjects died or withdrew due to an adverse event (AE). A total of 877 AEs were reported: 10 serious adverse events (SAEs) and 867 non-serious AEs. No SAEs were considered related to the administration of ADVATE. The majority (17/19) of treatment-related, non-serious AEs were rated as mild or moderate.

Study 060102 was a Phase 2/3 continuation study, open only to subjects who completed treatment on study 069901.[iv] This study involved 82 PTPs who were to be treated until the licensed product was commercially available. The PK parameters of ADVATE at the onset of treatment were similar to those after at least 75 exposure days (EDs). Eleven subjects who were treated on prophylactic regimens did not report a bleeding episode. The treatment of bleeding episodes was rated excellent or good in 80.3% of cases, and 88.4% of bleeding episodes required 1 or 2 infusions for hemostatic control. No FVIII inhibitors were detected. No subject developed allergic or hypersensitivity responses to heterologous proteins (ie, CHO cell protein, murine IgG, and human VWF). No subjects died or withdrew due to AEs. A total of 506 AEs were reported: 11 SAEs and 495 non-serious AEs. None of the SAEs were considered related to administration of ADVATE. All (4/4) treatment-related, non-serious AEs were rated as mild or moderate.

Study BLB-200-01 was a Phase 2/3 study involving 15 Japanese PTPs who were to be treated for a minimum of 24 weeks.[v] This completed study demonstrated equivalence of ADVATE and RECOMBINATE with respect to AUC. The treatment of bleeding episodes was rated excellent or good in 97.1% of cases, and 87.0% of bleeding episodes required 1 or 2 infusions for hemostatic control. No FVIII inhibitors were detected. No subject developed allergic or hypersensitivity responses to heterologous proteins (ie, CHO cell protein, murine IgG, and human VWF). No subjects died or withdrew due to AEs. A total of 59 AEs were reported: 2 SAEs and 57 non-serious AEs. None of the SAEs were considered related to administration of ADVATE. All (4/4) treatment related, non-serious AEs were rated as mild or moderate.

Study 060101 was a Phase 2/3 study involving 53 pediatric PTPs under 6 years of age who were to be treated for ≥ 50 ED or 6 months.[9] PK parameters were consistent with those observed in older subjects who participated in study 069901. Six subjects who were treated on prophylactic regimens did not report a bleeding episode. The treatment of bleeding episodes was rated excellent or good in 93.8% of cases, and 90.1% of bleeding

[iv] Data on File, Clinical Study Report (069901). Baxter BioScience, Westlake Village, CA.
[v] Data on File, Clinical Study Report (BLB-200-01). Baxter BioScience, Westlake Village, CA.

episodes required 1 or 2 infusions for hemostatic control. No FVIII inhibitors were detected. No subject developed allergic or hypersensitivity responses to heterologous proteins (ie, CHO cell protein, murine IgG, and human VWF). No subjects died or withdrew due to AEs. A total of 522 AEs were reported: 15 SAEs and 537 non-serious AEs. No SAEs were considered related to the administration of ADVATE. All (6/6) treatment-related, non-serious AEs were rated as mild or moderate.

Study 069902 was a Phase 2/3 study that investigated the efficacy and safety of ADVATE for perioperative management in 58 PTPs who underwent 65 invasive procedures.[10] Intra- and post-operative treatment (either by bolus infusion or continuous infusion) was rated excellent or good in 61/61 (100%) and 62/62 (100%) of the procedures rated, respectively. No FVIII inhibitors were detected. No subjects died or withdrew due to AEs. A total of 156 AEs were reported: 7 SAEs and 149 non-serious AEs. None of the SAEs were considered related to the administration of ADVATE. The majority (6/8) of treatment-related, non-serious AEs were rated as mild or moderate.

Study 060201 was a Phase 4 study that investigated the efficacy and safety of ADVATE in the comparison of 2 prophylactic regimens following a 6 month period of on-demand treatment.[11] In this study, 73 PTPs with severe or moderately severe hemophilia A (baseline FVIII ≤ 2%) received ADVATE for 6 months of on-demand treatment followed by randomization to 12 months of either standard (20-40 IU/kg every 48 ± 6 hours) or PK-driven (20-80 IU/kg every 72 ± 6 hours, targeting FVIII trough levels ≥1%) prophylaxis. A per protocol (PP) group was defined as subjects receiving >90% and ≤110% of the predicted number of prophylactic infusions. The annualized bleed rates (ABRs) for the PP set for on-demand, standard prophylaxis, PK-driven prophylaxis, and either prophylaxis regimen were 43.98, 0.99, 1.00, and 1.00, respectively. There were no statistically significant differences for the median ABRs for the 2 prophylaxis regimens. The median differences in annualized bleed rates between on-demand and standard prophylaxis, on-demand and PK-driven prophylaxis, and on-demand and any prophylaxis were all statistically significant ($p < 0.0001$). No subject developed a FVIII inhibitor during this study. One subject recorded a possible low-titer FVIII inhibitor, which was considered a related, mild SAE. However, upon review, this report of inhibitor was not upheld by the sponsor as it was not confirmed, as mandated by the study protocol. The subject's subsequent test at his next scheduled study visit was <0.4 BU/mL. No subjects died or withdrew due to AEs. A total of 200 AEs were reported: 14 SAEs and 186 non-serious AEs. One of the SAEs was considered related to the administration of ADVATE, described above. There were 19 non-serious AEs considered related to the administration of ADVATE; of these, 16 were rated as mild and 3 were rated as moderate.

Study 060103 was a Phase 3b study that investigated the safety and efficacy of ADVATE in 55 PUPs under 6 years of age with severe or moderately severe hemophilia A.[vi] Of 517 treated bleeding episodes, 90% were managed with 1 or 2 infusions. Hemostatic efficacy was considered excellent or good in 93% of 466 rated bleeding episode treatments. Twenty-seven surgical procedures were performed, with intra- and postoperative hemostatic efficacies considered excellent or good in 22/22 (100%) and 25/25 (100%) of the procedures rated, respectively. Inhibitory antibodies to FVIII developed in 16/55 (29.1%; 95% CI: 17.1%-41.1%) subjects. All the subjects who developed inhibitors had severe hemophilia (FVIII <1%). At the time of inhibitor diagnosis, 7 subjects were categorized with high-titer inhibitors (>5 BU/mL confirmed with a new blood sample) and 9 subjects were categorized with low-titer inhibitors (≤5 BU/mL). An immunogenicity analysis set of 50 subjects was used for the calculation of the odds ratio (OR) of risk factors for inhibitor development, which included all 16 subjects with inhibitors and subjects without inhibitors who had at least 10 EDs. Univariate analysis identified statistically significant OR results for 3 risk factors: family history of inhibitor (4.95 [95% CI: 1.29-19.06]), non-Caucasian ethnicity (4.18, [95% CI: 1.18-14.82]), and intensive treatment at high dose[vii] within the first 20 EDs (4.50, 95% CI: 1.05-19.25). Intensive treatment at high dose in all but 1 subject, where it was administered for a bleeding episode, consisted of perioperative infusions in the context of port placement. Inhibitor incidence in low-risk subpopulations of subjects who lacked the risk factors confirmed in this study was also examined. While 16/55 (29.1%) subjects in the entire study population developed inhibitors, 7/37 (18.9%) subjects who were Caucasian and 2/25 (8.0%) subjects who were both Caucasian and had no family history developed inhibitors. In the 20 subjects who were Caucasian, had no family history of inhibitors, and did not receive intensive treatment at high dose (lacked all 3 risk factors) there was no inhibitor development (0/20 [0.0%]).[7] No subjects died or withdrew due to AEs. A total of 931 AEs were reported: 46 SAEs and 885 non-serious AEs. All 16 SAEs considered related to the administration of ADVATE were inhibitor development. There were 14 non-serious AEs considered related to the administration of ADVATE; of these, 6 were rated as mild and 8 were rated as moderate.

6.4.2 Studies with ADVATE Reconstituted in 2 mL SWFI

A local tolerance study (Baxter study PV2030701) in rabbits showed that ADVATE reconstituted with 2 mL of sterile water for injection (SWFI) is well tolerated after

[vi] Data on File, Clinical Study Report (060103). Baxter BioScience, Westlake Village, CA.
[vii] Intensive treatment and high dose: defined as 5 consecutive study days of a mean infusion dose of FVIII >50 IU/kg.

intravenous (i.v.) administration.[viii] Slight transient reddening at the administration site was observed after intraarterial application and after paravenous administration of ADVATE reconstituted in 2 mL SWFI. However, no correlating adverse histopathological changes could be observed indicating a transient nature of this finding. This reaction was not observed with ADVATE reconstituted in 5 mL SWFI. This effect was also observed for the 2 mL reconstituted buffer control.

Study 060702 was a Phase 1 study that investigated the pharmacokinetics and safety of ADVATE reconstituted in 2 mL SWFI, compared with ADVATE reconstituted in 5 mL SWFI in 42 PTPs (15 pediatric subjects ≥ 2 to < 12 years and 27 adults/adolescents aged ≥ 12 to ≤ 65 years) with severe hemophilia A (baseline FVIII ≤ 1%).[ix] This study demonstrated bioequivalence of ADVATE reconstituted in 2 mL SWFI and ADVATE reconstituted in 5 mL SWFI with respect to area under the plasma concentration vs. time curve from 0 to 48 hours ($AUC_{0\text{-}48h}$). No FVIII inhibitors were detected. No subjects died or withdrew due to AEs. A total of 36 AEs were reported: 1 SAE and 35 non-serious AEs. No AEs were considered related to the administration of ADVATE. In the pediatric cohort, 1 SAE and 19 non-serious AEs occurred in 10 subjects. The 1 SAE was a case of severe pyrexia which occurred a day after an infusion and resolved. The most frequently occurring non-serious AEs in the pediatric cohort were contusion with 5 cases (1 moderate, 4 mild) in 5 subjects, hematoma with 3 cases (1 moderate, 2 mild) in 3 subjects, and arthropod bite with 2 cases rated mild in 2 subjects. There was 1 occurrence of the remaining AEs: conjunctival hemorrhage, catheter thrombosis, injection site hematoma, injection site swelling, allergy to arthropod sting, ear infection, hemarthrosis, joint range of motion decreased, and joint swelling. With the exception of the 1 case of hemarthrosis which was rated moderate, the remaining AEs were rated mild. There were 2 AEs in 2 pediatric subjects that were infusion site reactions after infusion of ADVATE reconstituted in 2 mL SWFI. The infusion site reactions were induration/swelling and bruising, both of which were rated as mild. The investigators considered these reactions to be related to study procedure and not related to ADVATE. In the adult/adolescent cohort, there were 16 non-serious AEs in 8 subjects which consisted of 1 occurrence each of the following AEs: eye discharge, oral herpes, rash pustular, sinusitis, arthropod bite, contusion, head injury, joint effusion, joint swelling, headache, dysuria, cough, nasal congestion, rhinorrhea, erythema, and hypertension. With the exception of the 1 case of sinusitis which was rated moderate, all AEs were rated mild. There were no infusion site reactions in the adult/adolescent cohort.

[viii] Data on File, Preclinical Study Report (PV2030701). Baxter BioScience, Westlake Village, CA.
[ix] Data on File, Clinical Study Report (060702). Baxter BioScience, Westlake Village, CA.

6.5 Evaluation of Anticipated Risks and Benefits of the Study Product(s) to Human Subjects

The results derived from the ADVATE clinical development and post-authorization safety surveillance (PASS) programs suggest that ADVATE is efficacious, safe, and well-tolerated in adults and pediatric subjects with severe to moderately severe hemophilia under a variety of clinical settings.[8-10; 12; 13] The safety and efficacy profile for ADVATE is consistent with that observed for other currently licensed recombinant FVIII products including RECOMBINATE.

6.5.1 Hypersensitivity

As with any i.v. protein, product allergic type hypersensitivity reactions are possible. Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported as part of the post-marketing experience with ADVATE and have been manifested by dizziness, paresthesias, rash, flushing, face swelling, urticaria, and pruritus. The product contains traces of mouse and hamster proteins. Patients should be informed of the signs of immediate-type hypersensitivity reactions including hives, pruritus, generalized urticaria, angioedema, hypotension (eg, dizziness or syncope), shock and acute respiratory distress (eg, tightness in the chest, wheezing). If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physicians. In case of anaphylactic shock, the current medical standards for shock treatment should be followed.

Due to the decrease in infusion volume for ADVATE reconstituted in 2 mL SWFI, if hypersensitivity reactions occur there is less time to react by stopping the infusion. Therefore, caution is advised during infusion of ADVATE reconstituted in 2 mL SWFI, especially in children.

6.5.2 Inhibitor Development

The formation of neutralizing antibodies (inhibitors) against FVIII is a known complication in the management of individuals with hemophilia A. These inhibitors are usually IgGs directed against the FVIII procoagulant activity, which are quantified in BU per mL of plasma using the modified Bethesda assay. In patients who develop inhibitors to FVIII, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialized hemophilia centre be contacted. The risk of developing inhibitors is correlated to the extent of exposure to FVIII, the risk being highest within the first 20 EDs, and to other genetic and environmental factors. Rarely, inhibitors may develop after the first 100 EDs. Cases of recurrent inhibitor (low titer) have been observed after switching from one FVIII product to another in previously

treated patients with more than 100 EDs who have a history of inhibitor development. Patients treated with coagulation FVIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

The formation of inhibitors to FVIII is a known complication in the management of patients with hemophilia A. The risk of developing inhibitors correlates to the extent of prior exposure to FVIII, with the risk being highest within the first 20 EDs. *De novo* inhibitor formation is less commonly observed after 100 EDs.

6.5.3 Injection-Site Reactions/CVAD-Related

For ADVATE reconstituted with 2 mL SWFI, misapplication (intra-arterially or paravenously) may lead to mild, short term injection site reactions, such as bruising and erythema.

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

6.5.4 Sodium Content

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

6.6 Compliance Statement

This study will be conducted in accordance with this protocol and local and applicable national regulatory requirements.[14; 15] Efforts are taken to follow the principles set forth in the International Conference on Harmonization Guideline for Good Clinical Practice E6 (ICH GCP, April 1996) to the extent possible for a non-interventional study.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to collect data on the safety and effectiveness of ADVATE reconstituted in 2 mL SWFI during routine clinical practice. This non-interventional study will be a post-licensure commitment for ADVATE reconstituted in 2 mL SWFI.

7.2 Primary Objective

The primary objective of the study is to assess incidence of all local and general, hypersensitivity and infusion-related reactions, irrespective of product-related causality for the AEs.

7.3 Secondary Objectives

7.3.1 Safety

- To assess incidence of all AEs considered by the investigator to be causally related (possibly or probably related) to ADVATE reconstituted in 2 ml SWFI
- To assess immunogenicity in all subjects
- To assess immunogenicity in PTPs (> 50 EDs) with baseline FVIII ≤ 2% and with no history of inhibitors prior to study entry
- To assess immunogenicity in PTPs (> 50 EDs) with baseline FVIII < 1% and with no history of inhibitors prior to study entry

7.3.2 Effectiveness

- To assess effectiveness in on-demand treatment
- To assess effectiveness in prophylaxis
- To assess effectiveness in surgical or dental procedures

7.3.3 Non-clinical Outcomes

- To assess FVIII treatment satisfaction and preference ratings from caregiver
- To assess FVIII infusion volume and time to mix and infuse FVIII treatment

8. STUDY DESIGN

8.1 Overall Study Design

This study is a prospective, non-interventional PASS study that assesses the safety and effectiveness of ADVATE reconstituted in 2 mL SWFI during routine clinical practice. Subjects with severe or moderately severe hemophilia A (FVIII ≤2%) and documented prior exposure to FVIII concentrates, aged ≤12 years, who are prescribed ADVATE and will only receive ADVATE reconstituted in 2 mL SWFI, will be asked to participate. The study will prospectively capture ADVATE related data for 6 months from the date of enrollment. Subjects should receive all FVIII therapy with ADVATE reconstituted in 2 mL SWFI during the study observation period. The investigators shall determine all treatment regimens according to product labeling information and standard practice. For all bleeding episodes requiring treatment, the subject should be treated until adequate hemostasis is achieved. The investigators will also determine all monitoring schedules, including the frequency of clinic visits and laboratory testing. A screening visit during which the investigator determines whether the enrolled subject (ie, one whose legally authorized representative(s) has signed an informed consent form [ICF]) meets all inclusion criteria and none of the exclusion criteria is required. All other study visits, including the last visit, should coincide with the routinely and emergently scheduled

clinic and hospital visits that the subject has in the 6-month period following enrollment. Caregivers will be asked to complete a short survey at the beginning and end of the 6-month observation period. The survey will capture data on their infusion experience and satisfaction with ADVATE reconstituted in 5 mL SWFI at the beginning of the study and with ADVATE reconstituted in 2 mL SWFI at the end of the study. The follow-up survey will also ask caregivers about their preferences between ADVATE reconstituted in 2 mL and 5mL SWFI on a variety of factors. This survey is strictly optional and will only be offered where such a survey is in concordance with non-interventional study regulations and after ethics committee (EC) approval of its use.

8.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is 42 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The recruitment period is expected to be 36 months.

The subject participation period is 6 months from enrollment to subject completion (ie, last study visit), unless prematurely discontinued.

8.3 Outcome Measures

8.3.1 Primary Outcome Measure

The primary outcome measure is the incidence of all local and general, hypersensitivity and infusion-related reactions, irrespective of product-related causality.

8.3.2 Secondary Outcome Measures

8.3.2.1 Safety

- Number and type of AEs considered by the investigator to be causally related (possibly or probably related) to ADVATE reconstituted in 2 mL SWFI
- Number of inhibitors in all subjects
- Number of inhibitors in PTPs (> 50 EDs) with baseline FVIII < 1% and with no history of inhibitors prior to study entry
- Number of inhibitors in PTPs (> 50 EDs) with baseline FVIII ≤ 2% and with no history of inhibitors prior to study entry

8.3.2.2 Effectiveness

- Subjective hemostatic effectiveness rating of excellent, good, fair, or none for each bleeding episode treated

- Number of bleeding episodes treated with 1, 2, 3, ≥ 4 infusions of ADVATE reconstituted in 2 mL SWFI
- Total units of ADVATE reconstituted in 2 mL SWFI administered to treat each bleeding episode
- Overall effectiveness of prophylaxis in subjects who are on a prophylactic regimen, as defined by the investigator, for the full duration of the study
- Global assessment rating of hemostatic effectiveness of ADVATE reconstituted in 2 mL SWFI (excellent, good, fair, or none) in surgical or dental procedures

8.3.2.3 Non-Clinical Outcomes

- Change in FVIII treatment satisfaction and preference ratings from caregiver between ADVATE reconstituted in 5 mL and 2 mL SWFI
- Change in FVIII infusion volume and time to mix and infuse FVIII treatment between ADVATE reconstituted in 5 mL and 2 mL SWFI

8.4 Randomization and Blinding

This is a non-randomized, open-label, non-interventional PASS study.

8.5 Study Stopping Rules

Stopping rules will not be established for this non-interventional PASS study since all treatment regimens will be prescribed at the discretion of the investigators according to the product marketing authorization.

8.6 Study Product

8.6.1 Packaging, Labeling, and Storage

Each ADVATE pack contains a powder vial, a 2 mL solvent vial (both type I glass closed with chlorobutyl rubber stoppers) and a device for reconstitution (BAXJECT II).

ADVATE has a shelf life of 2 years when stored in a refrigerator (2°C – 8°C). Do not freeze. During the shelf life, the product may be kept at room temperature (up to 25°C) for a single period not exceeding 6 months. Please record the beginning of storage at room temperature on the product carton. The product may not be returned to refrigerated storage after storage at room temperature. Keep the vial in the outer carton in order to protect from light.

After reconstitution, ADVATE should be administered at room temperature within 3 hours. From a microbiological viewpoint, the product should be used immediately after reconstitution.

8.6.2 Administration

ADVATE should be administered via the i.v. route. The solution should be administered slowly at a rate as determined by the patient's comfort level, not to exceed 10 mL/minute.

8.6.3 Description of Treatment

The treatment regimen, dosing and duration of treatment are at the discretion of the treating physician.

For subject's ≤ 2 years of age, use of the 250 IU size vials is recommended.

Information on treatment is provided in the SmPC as follows:

The posology and duration of the substitution therapy depend on the severity of the FVIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

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

One IU of FVIII activity is equivalent to that quantity of FVIII in one mL of normal human plasma. The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg body weight (BW) raises the plasma FVIII activity by 2 IU/dL. The dose is determined using the following formula:

$$\text{Required units (IU)} = \text{BW (kg)} \times \text{desired FVIII rise (\%)} \times 0.5$$

In case of the following hemorrhagic events, the FVIII activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period. The following table (Table 8.6-1) can be used to guide dosing in bleeding episodes and surgery:

Table 8.6-1
Guide for Dosing in Bleeding Episodes and Surgery

Degree of Hemorrhage / Type of Surgical Procedure	FVIII Level Required (% or IU/dL)	Frequency of Doses (Hours) / Duration of Therapy (Days)
Hemorrhage		
Early hemarthrosis, muscle bleeding or oral bleeding.	20 – 40	Repeat injections every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for at least 1 day, until the bleeding episode, as indicated by pain, is resolved or healing is achieved.
More extensive hemarthrosis, muscle bleeding or hematoma.	30 – 60	Repeat injections every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for 3 – 4 days or more until pain and acute disability are resolved.
Life threatening hemorrhages.	60 – 100	Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.
Surgery		
Minor Including tooth extraction.	30 – 60	Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.
Major	80 – 100 (pre- and postoperative)	Repeat injections every 8 to 24 hours (6 to 24 hours for patients under the age of 6) until adequate wound healing, then continue therapy for at least another 7 days to maintain a FVIII activity of 30% to 60% (IU/dL).

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

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

For long-term prophylaxis against bleeding in patients with severe hemophilia A, the usual doses are 20 to 40 IU of FVIII per kg BW at intervals of 2 to 3 days. In patients under the age of 6, doses of 20 to 50 IU of FVIII per kg BW 3 to 4 times weekly are recommended.

8.6.4 Study Product Accountability

Commercially available ADVATE will be used in this open-label, non-interventional, PASS study. No study product accountability will be employed. All exposure will be captured in subject diaries provided to the subjects (or routinely kept by the subjects) and clinical records routinely kept at the study site and will be transposed to the study case report forms (CRFs).

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

- Subject has severe or moderately severe hemophilia A (baseline FVIII ≤ 2%)
- Subject is ≤12 years of age
- Subject's legally authorized representative(s) has provided written informed consent
- Subject is prescribed ADVATE and will only receive ADVATE reconstituted in 2 mL SWFI
- Documented history of prior exposure to ADVATE (for subjects ≤ 2 years old, at least 3 EDs to ADVATE; for subjects with ≤ 50 EDs, all prior EDs must be to ADVATE; for subjects with >50 EDs, the last 20 prior EDs must be to ADVATE)
- Documented evidence of negative inhibitor test result during ≤10 EDs prior to study entry

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

- Subject has known hypersensitivity to the active substance or to any of the excipients
- Subject has a known allergic reaction to mouse or hamster proteins
- Subject has a requirement for a major surgical procedure at the time of enrollment
- Subject has no prior exposure to a FVIII concentrate
- Subject is currently being treated with an immune tolerance induction (ITI) regimen
- Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand disease)
- Subject has participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device or PASS registry during the course of this study

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw consent for continued participation and data collection. The reason for withdrawal will be recorded on the CRF Completion/Discontinuation page. Assessments to be performed at the termination visit (including in cases of withdrawal or discontinuation) are described in Section 10.6 and Section 21.1. The data collected on withdrawn subjects will be used in the analysis and included in the clinical study report.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action).

Subjects will be withdrawn from further study participation if a subject develops a low-titer inhibitor and can no longer be adequately managed with ADVATE reconstituted in 2 mL SWFI or if a subject develops a high-titer inhibitor.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient whose legally authorized representative(s) provides informed consent (ie, legally authorized representative(s) signs and dates the ICF and patient signs and dates assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the subject identification code (SIC): protocol identifier (eg, 061101) to be provided by the sponsor, 2-digit number study site number (eg, 02) to be provided by the sponsor, and 4-digit subject number (eg, 0003) reflecting the order of enrollment (ie, signing the ICF). For example, the third subject who signed an ICF at study site 02 will be identified as Subject 061101-020003. All study documents (eg, CRFs, clinical documentation, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject does not satisfy ALL inclusion criteria at screening, the subject may be re-screened at a later time at the discretion of the investigator. The investigators will determine all monitoring schedules, including the frequency of clinic visits and laboratory testing. A screening visit during which the investigator determines whether the enrolled subject (ie, one whose legally authorized representative(s) has signed an ICF) meets all inclusion criteria and none of the exclusion criteria is required. All other study visits, including the last visit, should coincide with the routinely and emergently scheduled clinic and hospital visits that the subject has in the 6-month period following enrollment.

10.3.1 Screening Visit

The following data will be collected at the **screening visit**:

- Date of birth
- Gender
- Race

- Ethnicity
- Height (cm)
- Weight (kg)
- Medical history
  - History of local and general infusion-related reactions
  - History of hypersensitivity reactions
  - History of FVIII inhibitor, if any
    - Date of inhibitor detection
    - Date of inhibitor disappearance
    - Titer at time of inhibitor detection
    - Maximum historical titer
    - Total FVIII ED at time of inhibitor detection
    - FVIII product used at time of inhibitor detection
    - FVIII regimen used at time of inhibitor detection
    - History of ITI therapy, if any, including FVIII product and regimen used
    - Most recent FVIII inhibitor titer
- Concomitant medications, including vaccinations
- Vaccination status for hepatitis A virus (HAV) and hepatitis B virus (HBV), if available
- Serology for hepatitis C virus (HCV) and human immunodeficiency virus type 1 & 2 (HIV-1/2), if available
- Baseline FVIII level
- FVIII mutation genotype, if available
- Family history of inhibitors
- Local laboratory cut off value for positive inhibitor titer
- Current treatment regimen (eg, prophylaxis or on-demand) with ADVATE reconstituted in 2 mL SWFI
  - Weight adjusted dose and dosing interval (frequency of infusions)
  - Regimen start date
  - Total FVIII ED at study entry
    - For subjects with ≤50 EDs at study entry, exact number of total EDs must be recorded

    - For subjects with >50 EDs, exact number of total ED is preferred, however, if this data is not available, one of the following ranges should be selected: 51 – 100, 101 – 150, > 150 ED
  - FVIII inhibitor titer at study entry
  - FVIII incremental recovery (IR; IU/dL per IU/kg) at study entry, if available
- Prior to study entry (maximal retrospective time period of 2 years)
  - Treatment regimen (eg, prophylaxis, on-demand, or ITI)
    - Weight adjusted dose and dosing interval (frequency of infusions)
    - Regimen start and end date
  - Name and/or type of products prior to ADVATE, if applicable
    - Plasma-derived FVIII with VWF, intermediate purity
    - Plasma-derived FVIII without VWF, high purity
    - Recombinant FVIII: generation category; full-length vs. B-domain deleted molecule

10.3.2 Interval and Termination Visits

The following data, if available, will be collected at **interval and termination visits**:

- Height (cm)
- Weight (kg)
- Treatment regimen (eg, prophylaxis or on-demand) with ADVATE reconstituted in 2 mL SWFI
  - Weight adjusted dose and dosing interval (frequency of infusions)
  - Regimen change date
- All serious and non-serious AEs, regardless of causal relationship to ADVATE reconstituted in 2 mL SWFI
- All local and general, hypersensitivity and infusion-related reactions (see Appendix A for example only)
- FVIII inhibitor titer
- Serology for HCV and HIV-1/2, if available
- FVIII IR (IU/dL per IU/kg)
- Total ED from ADVATE reconstituted in 2 mL SWFI during study
- Total ED from all FVIII therapies

- Concomitant medications, including vaccinations
- Bleeding episodes, including anatomical location, etiology, and severity
- Subjective hemostatic effectiveness rating of excellent, good, fair, or none for each bleeding episode
- Number of ADVATE reconstituted in 2 mL SWFI infusions used to treat each bleeding episode
- Total units of ADVATE reconstituted in 2 mL SWFI administered to treat each bleeding episode
- Overall effectiveness assessment for prophylaxis for subjects who are on a prophylactic regimen for full duration of study (6 months), at termination visit
- Number of days subject missed from school/daycare due to each bleeding episode
- Number of days subject's caregiver missed from work/school/normal daily activities due to each bleeding episode

Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 21.1 Schedule of Study Procedures and Assessments.

10.3.3 Surgical or Dental Procedures

For subjects who undergo surgical or dental procedures during the study, the following data will also be collected, as available:

- Type of procedure
- Date and time of procedure
- Mode of ADVATE administration
- Total weight-adjusted dose of ADVATE infused in the preoperative, intraoperative, and postoperative periods
- Total number of days of FVIII replacement therapy
- Global assessment of intraoperative and postoperative hemostatic effectiveness as determined by the investigator (excellent, good, fair, or none)

10.4 Medications and Non-Drug Therapies

The use of another FVIII concentrate, other than ADVATE reconstituted in 2 mL SWFI, is **not** permitted during the course of the study. A subject who uses a FVIII concentrate other than ADVATE will be considered a protocol violation. The use of ADVATE reconstituted in 5 mL SWFI will be considered a protocol deviation.

Subjects may receive ADVATE reconstituted in 5 mL SWFI if a higher potency is needed for adequate hemostatic coverage during emergent surgical procedures, but this will be considered a protocol deviation. As the administration of ADVATE reconstituted in 5 mL SWFI for surgical prophylaxis would constitute a discrete episode, these subjects may be able to continue participation in the study. Please liaise with the medical monitor for the study when any such deviation is foreseen.

10.5 Data Sources

10.5.1 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subject diaries, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study.

The data to be entered directly onto the CRF and to be considered source data are referenced in Section 18.2. The use of subject diaries is described in Section 10.5.2.

10.5.2 Subject Diary

In many centers, it is considered standard practice for subjects with hemophilia to maintain a diary which captures FVIII treatment and disease related data. Therefore, a subject diary will be provided to each subject at the screening visit, as needed, to help with the standardization of data collection method. Nevertheless, the completion of the diary is a voluntary effort by the individual subject or subject's legally authorized representative. A subject diary should allow for capture of the following information:

- Infusion log
- AEs
- Bleed events, date-time and anatomical location
- Subjective hemostatic effectiveness rating for each bleeding episode treated
- Total units of ADVATE reconstituted in 2 mL SWFI administered to treat each bleeding episode

- Number of ADVATE reconstituted in 2 mL SWFI infusions used to treat each bleeding episode
- Number of days subject missed from school/daycare due to each bleeding episode
- Number of days subject's caregiver missed from work/school/normal daily activities due to each bleeding episode

All AEs regardless of causality, bleed occurrences and location, subjective hemostatic effectiveness ratings for each bleeding episode treated, total units of ADVATE reconstituted in 2 mL SWFI administered and infusions used to treat each bleeding episode, and number of days missed by subject from school/daycare, respectively and by caregiver from work/school/normal daily activities, recorded in subject diary during study participation period will be transcribed onto the CRF.

The subject diary will serve as source documentation. Entries in the subject diaries will be transcribed onto the appropriate CRFs. Any entry on the CRF that does not correspond with an entry in the subject diary will be explained by the investigator on the relevant subject diary page.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations). Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, adverse event (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, protocol violation(s)), study terminated by sponsor, or other (reason to be specified by the investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. The reason for discontinuation will be recorded on the CRF, and data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. Assessments to be performed at the termination visit (including in cases of withdrawal or discontinuation) can be found in Supplement 21.1 Schedule of Study Procedures and Assessments.

10.7 Procedures for Monitoring Subject Compliance

There is no procedure for monitoring subject compliance. All treatment regimens and monitoring schedules will be determined by the treating physician. The protocol does not require for any additional testing or monitoring than what is judged necessary by the treating physician.

11. ASSESSMENT OF SAFETY

11.1 Adverse Events

The following data will be collected at **interval and termination visits**:

- All serious and non-serious AEs, regardless of causal relationship to ADVATE reconstituted in 2 mL SWFI, including but not limited to
  - All local and general, hypersensitivity and infusion related-reactions
  - FVIII inhibitor titer

An AE is defined as any untoward medical occurrence in a subject administered study product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), or disease (eg, peritonitis, bacteremia, etc.) temporally associated with the use of the study product (ie, ADVATE reconstituted in 2 mL SWFI), whether or not considered causally related to the study product. An AE includes any event, regardless of the presumed causality between the event and the study product.

11.1.1 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - 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 HIV, HAV, HBV, HCV, hepatitis E virus, or parvovirus B19
- FVIII inhibitor formation should always be considered an SAE.

11.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

11.1.3 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

11.1.4 Causality

Causality is a determination of whether there is a reasonable possibility that the study product is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the study product and the AE using his/her clinical expertise and judgement according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the study product (ie, does not follow a reasonable temporal relationship to the administration of study product or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the study product
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of study product
  - An alternative etiology is equally or less likely compared to the potential relationship to the study product
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of study product, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the study product as evidenced by measurement of the study product concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

These causality definitions will also be used to assess the causality of an AE with a study-related procedure(s), if necessary.

11.1.5 Hypersensitivity and Infusion-Related Reactions

Hypersensitivity and infusion-related reactions are defined as AEs associated with infusion. These typically occur during the infusion or within 24 hours after the infusion. However, they may occur beyond this period. These reactions include both local and systemic events.

Hypersensitivity or infusion-related reactions include, but are not limited to, dyspnea, wheezing/bronchospasm, chest tightness, rash, hives, pruritus, angioedema, flushing, cyanosis, dizziness/light headedness, weak pulse, loss of consciousness, pyrexia, hypotension, cardiac arrest, nausea, headache, fatigue.

Local infusion-related reactions include, but are not limited to, erythema, pain, tenderness, swelling, and induration.

A hypersensitivity/infusion-related reaction questionnaire (see Appendix A for example only) is included as a supplement to the CRF to capture further information regarding these reactions.

11.1.6 Preexisting Diseases

Preexisting diseases that are present before entry in to the study, described in the medical history, and that manifest with the same severity, frequency, or duration after study product exposure, will not be recorded as AEs. However, when there is an increase in the severity or duration of a preexisting disease, the event must be described on the AE CRF. Bleeding events are excluded from this provision.

11.1.7 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB and the Reference Safety Information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

For the purposes of this study, each unexpected AE experienced by a subject undergoing on-demand or prophylaxis therapy with ADVATE will be recorded on the AE CRF.

11.1.8 Untoward Medical Occurrences Not Considered Adverse Events

Each **serious** untoward medical occurrence experienced before the first study product exposure (eg, from the time of signed informed consent up to but not including the first study product exposure) will be described on the SAER. However, these events will not be considered as SAEs or included in the analysis of SAEs.

For the purposes of this study, each of the following non-serious events experienced after the first study product exposure will not be considered an AE, and thus, not included in the analysis of AEs:

- Hemorrhagic events that are considered non-serious by the investigator

11.1.9 Assessment of Adverse Events

Each AE from the first study product exposure until study completion/discontinuation date will be described on the AE CRF (ie, 1 AE per form) using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom, or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 11.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 11.1.1
- Severity as defined in Section 11.1.3
- Causal relationship to study product exposure or study procedure as defined in Section 11.1.4
- Local and general, hypersensitivity and infusion-related reaction as defined in Section 11.1.5

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal) and action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until the study completion/termination visit. 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 separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including overdosing, underdosing, abuse, and withdrawal), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule),

failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness; no additional reporting on CRFs is necessary.

11.1.10 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE**. NMCs include but are not limited to the following:

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

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

11.2 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 11.1.3) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

11.3 Physical Examinations

At screening and subsequent study visits (as described in Table 21.1-1), a physical examination will be performed on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF.

11.4 Clinical Laboratory Parameters

11.4.1 FVIII Inhibitor Titer

Documentation of a negative inhibitor test during ≤10 EDs before initiation of ADVATE reconstituted in 2 mL SWFI is an inclusion criterion. Thereafter, the investigators shall determine the frequency for inhibitor testing based on routine screening schedule, as appropriate within respective countries and subject to relevant clinical guidelines, or clinical signs. It is recommended that inhibitor testing is performed in the presence of clinical signs suggesting inhibitor development: increased bleeding tendency, high consumption, lack of response or efficacy, decreased IR, shortened half life. If an inhibitor is suspected, it is also recommended to look at FVIII IR. If the IR appears greatly reduced and/or no FVIII is detected, an inhibitor is suspected. It should be kept in mind that the normal PK range may be age-related, with children exhibiting different kinetics (shorter half-life and lower IR) compared to adults.

The inhibitor assay methods and reference standard used will be reported in the CRF. In the case a positive inhibitor titer is detected, a confirmatory test on a second, separately drawn sample should be performed. This second sample should be taken prior to any change of treatment and shortly (within 1 month) after the previous positive test. Results of FVIII IR and half-life tests should be recorded with associated washout period, FVIII dose administered and sampling times. All laboratory testing will be done at the local lab.

Negative inhibitor titer: any titer below the limit of inhibitor detection of the local lab; if local lab reference value is not available, any titer <0.6 BU by the Nijmegen modification Bethesda assay, or < 1 BU by a non-Nijmegen modification Bethesda assay.

Low-titer inhibitor titer: any titer higher than the limit of inhibitor detection of the local lab and ≤ 5 BU; if local lab reference value is not available, any titer ≥0.6 BU by the Nijmegen modification Bethesda assay, or ≥1 BU by a non-Nijmegen modification Bethesda assay.

High-titer inhibitor titer: any titer > 5 BU at any time after diagnosis.

11.4.2 Assessment of Laboratory Values

11.4.2.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal laboratory value is to be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is also considered an AE (see definition in Section 11.1). If yes, the sign, symptom, or medical diagnosis will be recorded on the AE CRF. If the abnormal value was not deemed an AE because it was due to a lab error, was due to a preexisting disease (described in Section 11.1.6), was not clinically significant, was a symptom of a new/worsened condition already recorded as an AE, or was due to another issue that will be specified, the investigator will record the justification on the CRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result 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.

11.5 Vital Signs

Vital signs will be collected.

12. ASSESSMENT OF THERAPY HEMOSTATIC EFFECTIVENESS

12.1 On-Demand Hemostatic Effectiveness and Prophylactic Effectiveness Data Collection

The following data will be collected at **interval and termination visits**:

- Subjective hemostatic effectiveness rating of excellent, good, fair, or none for each bleeding episode treated (see definitions in Table 12.1-1)
- Number of ADVATE infusions used to treat each bleeding episode
- Number of ADVATE units used to treat each bleeding episode
- Overall effectiveness assessment for prophylaxis therapy (at termination visit only)

12.1.1 Assessment of Hemostatic Effectiveness for Bleeding Episodes

The number of ADVATE infusions and ADVATE units used to treat each bleeding episode and subjective hemostatic effectiveness ratings for each bleeding episode treated will be recorded in:

- Subject diary for all on-demand treatment administered at home
- Subject's medical record for all on-demand treatment administered in hospital/clinic

Individual bleed treatment data will be transcribed to the CRFs. During the interval and termination visits, the investigator will review the diary with the subject or the subject's legally authorized representative and transcribe the relevant data on the CRF.

The subjective assessment of hemostatic effectiveness of ADVATE following the on-demand treatment of each bleeding episode will be assessed by the subject's legally authorized representative for treatments given at home, or by the investigator for treatments given in the hospital/clinic according to the definitions provided in Table 12.1-1. The hemostatic effectiveness assessment will be recorded on the CRF.

Table 12.1-1
Rating Scale for the Treatment of Bleeding Episodes

Excellent	Full relief of pain[a] and cessation of bleeding as evidenced by objective signs (eg, swelling, tenderness, irritability, inconsolability, and decreased range of motion in the case of musculoskeletal hemorrhage) within approximately 8 hours of 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[a] and/or improvement in signs of bleeding within approximately 8 hours after the infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable or slight relief of pain[a] and slight improvement in signs of bleeding within approximately 8 hours after the infusion. Requires more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

a. In subjects below 3 years of age, pain assessments may not be possible.

12.1.2 Overall Effectiveness Assessment for Prophylaxis Therapy

For the purpose of this study, prophylaxis regimen is defined as regular infusions of FVIII replacement, as prescribed by the investigator, and a subject documented by the investigator as being on a prophylactic regimen in the CRF will be analyzed accordingly.

At the termination visit, the investigator will assess the overall effectiveness of ADVATE for prophylaxis in subjects who receive continuous and regular prophylaxis therapy for the full duration of the study. The assessment should be based upon the following: the investigator's professional opinion; the subject's current health status, including the presence or absence of inhibitor; the response to ADVATE in relation to previous experience with prior FVIII therapies; and performance in prophylaxis for the prevention of breakthrough bleeding. Using the following definitions in Table 12.1-2, the investigators will assign an overall effectiveness rating. The overall effectiveness assessment will be recorded on the CRF.

Table 12.1-2 Overall Effectiveness Assessment for Prophylaxis Therapy	
Excellent	Same or lower breakthrough bleed rate within the last 6 months compared with previous prophylaxis therapy; If subject did not receive previous prophylaxis therapy with ADVATE or another FVIII, same or better than expected outcome according to investigator's expectation.
Good	Minor increase in breakthrough bleed rate within the last 6 months compared with previous prophylaxis therapy; If subject did not receive prophylaxis therapy with ADVATE or another FVIII, slightly less than expected outcome according to investigator's expectation.
Fair	Moderate increase in breakthrough bleed rate in the last 6 months compared with previous prophylaxis therapy; If subject did not receive prophylaxis therapy with ADVATE or another FVIII, somewhat less than expected outcome according to investigator's expectation.
None	Significant increase in breakthrough bleed rate in the last 6 months compared with previous prophylaxis therapy; If subject did not receive prophylaxis therapy with ADVATE or another FVIII, little to no benefit according to investigators' expectation.

12.2 Hemostatic Effectiveness for Surgical or Dental Procedures

For subjects who undergo surgical or dental procedures during the observation period of the study, the hemostatic effectiveness of ADVATE reconstituted in 2 mL SWFI will be assessed using the physician's global assessment rating.

A global assessment of intraoperative and postoperative hemostatic effectiveness will be determined by the investigator according to the scale defined in Table 12.2-1.

Table 12.2-1 Definitions of Hemostatic Effectiveness for Intraoperative and Postoperative Bleeding	
Excellent	Perioperative hemostasis achieved was unequivocally as good as or better than that expected for the type of procedure performed.
Good	Perioperative hemostasis achieved was probably as good as expected for the type of procedure performed.
Fair	Perioperative hemostasis was clearly less than optimal for the type of procedure performed but was maintained without the need for a change in therapeutic regimen.
None	Subject experienced bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change in therapeutic regimen.

If a bleeding episode occurs at the site of a surgical procedure during the postoperative period, the event would be counted as a bleeding episode in the corresponding CRF.

13. NON-CLINICAL OUTCOMES

13.1 FVIII Satisfaction and Preference Survey

The baseline and follow-up surveys are included in Appendix B. Each paper and pencil survey will be completed by the caregiver for the patient (typically the parent). This survey is strictly optional and will only be offered where such a survey is in concordance with non-interventional study regulations and after EC approval of its use.

The baseline survey will be completed at the screening visit and consists of 14 questions about the experience with ADVATE reconstituted in 5 mL SWFI prior to starting the study. The first 6 questions capture data on the infusion experience including:

- How many vials needed per dose
- Presence of a catheter / port
- Who infuses the dose
- Time needed to mix and infuse dose
- On average, what percent of the time do you lose access to your child's vein after starting the infusion
- If you've lost access to your child's vein, what percent of the time do you re-stick the needle to complete the infusion

The next 8 questions capture the level of satisfaction with the following items using a 5-point Likert scale:

- The amount of liquid volume needed for infusion
- The time needed to mix FVIII treatment
- The time needed to infuse FVIII treatment
- The ease of infusing FVIII treatment
- The amount of anxiety the child has over his FVIII infusions
- The amount of anxiety the caregiver has infusing child's FVIII treatment
- The overall convenience of FVIII treatment
- The FVIII treatment in general

The follow-up survey will be completed at the termination visit. The same 14 questions from the baseline survey are included, but instead ask about the satisfaction with ADVATE reconstituted in 2 mL SWFI during the study. An additional 8 questions in the follow-up survey ask if there is a preference between ADVATE reconstituted in 5 mL and 2 mL SWFI on the same items included in the satisfaction question.

14. STATISTICS

14.1 Sample Size and Power Calculations

As hemophilia A is a relatively rare disease, the number of subjects eligible for documentation is limited. Therefore, no formal sample size calculation was performed. The targeted enrollment will be 73 subjects. This number was determined to offset the estimated 17% dropout rate experienced in study 060103, and to provide 60 evaluable subjects.

14.2 Datasets and Analysis Cohorts

There are no cohorts in this study.

14.2.1 Safety Analysis Set

The safety analysis set (SAS) will consist of data for all subjects that receive at least 1 dose of ADVATE reconstituted in 2 mL SWFI.

14.2.1.1 Immunogenicity Analysis Set for FVIII < 1%

The immunogenicity analysis set of PTPs (> 50 EDs) with baseline FVIII < 1% (IAS1) and with no history of inhibitor prior to study entry will be a subset of the safety analysis set.

14.2.1.2 Immunogenicity Analysis Set for FVIII ≤ 2%

The immunogenicity analysis set of PTPs (> 50 EDs) with baseline FVIII ≤ 2% (IAS2) and with no history of inhibitor prior to study entry will be a subset of the safety analysis set.

14.2.2 Effectiveness Analysis Set for Bleeding Episodes

The effectiveness analysis set for bleeding episodes (EASBE) will consist of all data for all subjects who report at least 1 new bleeding episode treated with ADVATE reconstituted in 2 mL SWFI.

14.2.3 Effectiveness Analysis Set for Prophylactic Treatment

The effectiveness analysis set for prophylactic treatment (EASPT) will include all subjects who were assigned by their Medical Doctor (site investigator) as being on prophylactic treatment during the whole course of this study.

14.2.4 Pharmacokinetic Analysis Set

The PK analysis set (PKAS) will include all subjects with one or more determinations of IR.

14.2.5 Surgical and Dental Procedures Analysis Set

The effectiveness analysis set for surgical and dental procedures (EASSDP) will include all subjects who underwent surgical or dental procedures during the study.

14.3 Handling of Missing, Unused, and Spurious Data

There will be no imputation on any outcome measure in this study. Missing data will be reported as such.

If a subject weight is missing from any infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.

If FVIII activity levels are reported as inequalities, the < or > sign will be dropped for use in numeric analyses.

14.4 Methods of Analysis for Primary and Secondary Outcome Measures

Statistical analysis will be descriptive in nature. Continuous variables will be described with means, standard deviations, minimum, first quartile, medians, interquartile ranges, third quartile, and maximum. Categorical variables will be expressed as frequencies and percentages. 95% confidence intervals of selected point estimates will be calculated. Paired statistical tests (parametric via t-test and/or non-parametric via Wilcoxon Signed-Rank test) will be employed to test for differences in infusion volume, time (to be captured in minutes and seconds) needed to mix and infuse FVIII, and satisfaction with ADVATE reconstituted in 5mL SWFI prior to enrolling in the study and ADVATE reconstituted in 2mL SWFI. Figures will be prepared to illustrate the patterns of data over time where appropriate.

14.4.1 Primary Outcome Measure

The primary outcome measure is to assess the incidence of all local and general, hypersensitivity and infusion-related reactions, irrespective of product-related causality for the AEs. The SAS will be employed to compute this outcome measure.

14.4.2 Secondary Outcome Measures

Each secondary outcome measure will be calculated by employing the applicable analysis set:

- Number of AEs considered by the investigator to be causally related (possibly or probably related) to ADVATE reconstituted in 2 mL SWFI, SAS
- Number of inhibitors in all subjects, SAS

- Number of inhibitors in PTPs (>50 EDs) with baseline FVIII < 1% and with no history of inhibitors prior to study entry, IAS1
- Number of inhibitors in PTPs (> 50 EDs) with baseline FVIII ≤ 2% and with no history of inhibitors prior to study entry, IAS2
- Subjective hemostatic effectiveness rating of excellent, good, fair, or none for each unique bleeding episode treated, EASBE
- Number of bleeding episodes treated with 1, 2, 3, ≥ 4 infusions of ADVATE reconstituted in 2 mL SWFI, EASBE
- Total units of ADVATE reconstituted in 2 mL SWFI administered to treat each bleeding episode, EASBE
- Overall effectiveness of prophylaxis in subjects who are on a prophylactic regimen for the full duration of the study, EASPT
- Global assessment rating of hemostatic effectiveness of ADVATE reconstituted in 2 mL SWFI (excellent, good, fair, or none) in surgical or dental procedures, EASSDP
- Change in FVIII treatment satisfaction and preference ratings from caregiver between ADVATE reconstituted in 5 mL and 2 mL SWFI, SAS
- Change in FVIII infusion volume and time to mix and infuse FVIII treatment between ADVATE reconstituted in 5 mL and 2 mL SWFI, SAS

14.5 Planned Safety Reports for the Study

Regular safety updates and progress reports and regular data transfers are to be scheduled.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Non-Interventional Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Non-Interventional Study Agreement.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Non-Interventional Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol, and in study documents refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

16.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

16.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Non-Interventional Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

16.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Non-Interventional Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

16.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate 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, but within 1 calendar day after the change is implemented. The sponsor (Baxter) will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

17. ETHICS

17.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Non-Interventional Study Agreement.

17.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, ICF, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Non-Interventional Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

17.3 Informed Consent

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

All patients' legally authorized representative(s) must sign an ICF before entering into the study according to applicable regulatory requirements and ICH GCP. An assent form may be provided and should be signed by patients less than 13 years of age. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 17.2). The ICF will include a

comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients' legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the ICF, patients' legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with study product exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF, which has been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study (see Section 17.3).

17.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be used for this study for the following reasons:

- Subjects are on study product which is a product that is already licensed.
- The expected related AEs in this study are as described in the prescribing information of ADVATE, the already licensed product.

18. DATA HANDLING AND RECORD KEEPING

18.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Non-Interventional Study Agreement.

18.2 Study Documents and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Documentation may include information defined as "source data" (see Section 10.5.1)medical records, records detailing the progress of the study for each subject, signed ICFs, drug disposition records, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and

initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

18.2.1 Case Report Forms

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

Only authorized study site personnel will record or change data on the CRFs. All data should preferably be entered on the CRFs during the study visit. If this is not possible due to time restrictions, the data will be recorded on paper; this documentation will be considered source data. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 18.2).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

18.2.2 Data Recorded Directly on Case Report Forms

The following documents/data are to be entered directly onto the CRF or submitted directly to the sponsor, and therefore, are considered source documents/data: laboratory forms/notes, memoranda, enrollment/screening logs, subject diaries, evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, and subject files.

18.3 Document and Data Retention

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 Non-Interventional Study Agreement.

19. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Non-Interventional Study Agreement.

20. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Non-Interventional Study Agreement.

21. SUPPLEMENTS

21.1 Schedule of Study Procedures and Assessments

Table 21.1-1
Schedule of Study Procedures and Assessments

Procedures/Assessments	Screening Visit	Interval Study Visits	Study Completion/ Termination Visit[a]
Informed Consent[b]	X		
Eligibility Criteria	X		
Medical History	X	X	X
Medications	X	X	X
Physical Exam	X	X	X
Surgical or Dental Procedures		X	X
Subject Diary	X	X	X
Adverse Events		X	X
Laboratory Tests[c]	X	X	X
Vital Signs	X	X	X
Satisfaction/preference caregiver survey[d]	X		X

a. Includes cases of withdrawal or discontinuation.
b. Occurs at enrollment (before screening).
c. No non-routine laboratory tests are mandated by this protocol; laboratory data that has been collected through routine practice should be recorded in the CRFs.
d. This survey is strictly optional and will only be offered where such a survey is in concordance with non-interventional study regulations and after EC approval of its use.

22. REFERENCES

1. White GC, II, Courter S, Bray GL et al: A multicenter study of recombinant factor VIII (Recombinate) in previously treated patients with hemophilia A. The Recombinate Previously Treated Patient Study Group. Thromb.Haemost. 1997;77: 660-667.

2. Bray GL, Gomperts ED, Courter S et al: A multicenter study of recombinant factor VIII (recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A. Blood. 1994;83: 2428-2435.

3. McClelland DB: Safety of human albumin as a constituent of biologic therapeutic products. Transfusion. 1998;38: 690-699.

4. Schonberger LB: New variant Creutzfeldt-Jakob disease and bovine spongiform encephalopathy. Infect.Dis.Clin.North Am. 1998;12: 111-121.

5. Ironside JW: Variant Creutzfeldt-Jakob disease: risk of transmission by blood transfusion and blood therapies. Haemophilia. 2006;12 Suppl 1: 8-15.

6. Peden A, McCardle L, Head MW et al: Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia. 2010;16: 296-304.

7. Auerswald G, Thompson AA, Recht M et al: Experience of Advate rAHF-PFM in previously untreated patients and minimally treated patients with haemophilia A. Thromb.Haemost. 2012;107: 1072-1082.

8. Tarantino MD, Collins PW, Hay PW et al: Clinical evaluation of an advanced category antihaemophilic factor prepared using a plasma/albumin-free method: pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A. Haemophilia. 2004;10: 428-437.

9. Blanchette VS, Shapiro AD, Liesner RJ et al: Plasma and albumin free recombinant factor VIII (rAHF-PFM): pharmacokinetics, efficacy and safety in previously treated pediatric patients. J.Thromb.Haemost. 2008;6: 1319-1326.

10. Negrier C, Shapiro A, Berntorp E et al: Surgical evaluation of a recombinant factor VIII prepared using a plasma/albumin-free method: efficacy and safety of ADVATE in previously treated patients. Thromb.Haemost. 2008;100: 217-223.

11. Valentino LA, Mamonov V, Hellmann A et al: A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. J.Thromb.Haemost. 2012;10: 359-367.

12. Shapiro A, Gruppo R, Pabinger I et al: Integrated analysis of safety and efficacy of a plasma- and albumin-free recombinant factor VIII (rAHF-PFM) from six clinical studies in patients with hemophilia A. Expert Opin.Biol.Ther. 2009;9: 273-283.

13. Oldenburg J, Goudemand J, Valentino L et al: Postauthorization safety surveillance of ADVATE [antihaemophilic factor (recombinant), plasma/albumin-free method] demonstrates efficacy, safety and low-risk for immunogenicity in routine clinical practice. Haemophilia. 2010;16: 866-877.

14. Committee for Medicinal Products for Human Use: Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products. European Medicines Agency (EMA) 7/21/2011. Report number: EMA/CHMP/BPWP/144533/2009. Link to Publisher's Site: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109692.pdf.

15. European Commission, European Medicines Agency: The rules governing medicinal products in the European Union -- Volume 9A Guidelines on pharmacovigilance for medicinal products for human use. European Medicines Agency (EMEA / EMA) 9/2008. Link to Publisher's Site: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf.

23. SUMMARY OF CHANGES

In this section, changes from the previous version of the Protocol, dated 2012 FEB 23, are described and their rationale is given.

1. **Throughout the document**
   Minor grammatical and/or administrative changes have been made to improve the readability and/or clarity of the protocol.

2. **Title page and throughout the document**
   Description of Change: Revised study title: ADVATE 2 mL (reconstituted in 2 mL SWFI) POST-AUTHORIZATION SAFETY SURVEILLANCE STUDY.
   Purpose of Change: Extension of the study from the EU to North America.

3. **Section 1 "Study Personnel"**
   Description of Change: Change from [redacted] to [redacted].
   Reason for Change: Change in personnel and title.

4. **Section 2 and throughout the document**
   Description of Change: Re-wording of the SAE Reporting.
   Purpose of Change: To add clarity to the fax-numbers to be used.

5. **Section 6.6, Compliance Statement**
   Description of Change: Added text: this protocol, and applicable.
   Purpose of Change: To comply with internal procedures.

6. **Section 9.3 Withdrawal and Discontinuation**
   Description of Change: Added text indicating that assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.6 and Section 21.2.
   Purpose of Change: To align with most recent template recommendations.

7. **Section 10.5, Data Sources**
   Description of Change: Added new section.
   Purpose of Change: To comply with internal procedures.

8. **Section 10.6, Subject Completion/Discontinuation**
   Description of Change: Added text: completed all study procedures according with the protocol (with or without protocol deviations), and indicated that assessments to be performed at the termination visit (including in cases of withdrawal or discontinuation) could be found in Supplement 21.2 Schedule of Study.
   Purpose of Change: To align protocol with current protocol template recommendations.

9. **Section 11.1, Adverse Events**
   Description of Change: Added text: considered causally.
   Purpose of Change: To add clarity on study procedure.

10. **Section 11.1.3, Sev**erity
    Description of Change: Added text: These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.
    Purpose of Change: To add clarity on study procedure.

11. **Section 11.1.7, 11.1.7 Unexpected Adverse Events**
    Description of Change: Added text: "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.
    Purpose of Change: to add clarity on study procedure.

12. **Section 11.1.9, Assessment of Adverse Events**
    Description of Change: Added text: that if no diagnosis could be established at the time of reporting an AE, a symptom or sign in standard medical terminology be used, and also that if an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness; no additional reporting on CRFs is necessary. Also added that the AEs will be evaluated for causal relationship to study product OR study procedure. Also added that 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 separate AE). During the course of any AE, the highest severity rating will be reported. Also added information regarding deviations in dosage, failures of pharmacologic action and unexpected clinical benefits).
    Purpose of Change: To add clarity on study procedure.

13. **Added Section 11.1.10, Non-Medical Complaints**

Description of Change: Added text: A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE. NMCs include but are not limited to the following:

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

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

Purpose of Change: To comply with internal procedures.

14. **Section 16.5, 16.5 Non-Compliance with the Protocol**

Description of Change: Added text: The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate 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, but within 1 calendar day after the change is implemented. The sponsor (Baxter) will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

Purpose of Text: To comply with internal procedures.

15. **Section 18.2, 18.2 Study Documents and Case Report Forms**

Description of Change: Added text: information defined as “source data” (see Section 10.5.1), also updated language regarding paper documentation to align with protocol template.

Purpose of Change: Cross reference to the newly introduced Section 10.5.1.

16. **Table 21.1-1 Schedule of Study Procedures and Assessments**

Description of Change: Indicated that subjects who withdraw or discontinue are to complete the Termination Visit.

Purpose of Change: To align with most recent template recommendations.

17. **Section 23 References**

Description of Change: Changed reference #11 (Valentino et al. 2012) from "in press" reference to current citation, and added new reference #7 for Auerswald et al.
Purpose of Change: To update to current publication information.

APPENDIX A: HYPERSENSITIVITY AND GENERAL REACTION QUESTIONNAIRE

ADVATE 2 mL [reconstituted in 2 mL sterile water for injection (SWFI)]

Antihemophilic Factor (Recombinant) Plasma/Albumin Free Method (rAHF-PFM)

Octocog alfa (recombinant human coagulation factor VIII)

TITLE: ADVATE 2 mL (reconstituted in 2 mL SWFI)

POST-AUTHORIZATION SAFETY SURVEILLANCE STUDY

SHORT TITLE: ADVATE 2 mL PASS

PROTOCOL IDENTIFIER: 061101

NON-INTERVENTIONAL OBSERVATIONAL STUDY

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

HYPERSENSITIVITY AND GENERAL REACTION QUESTIONNAIRE

Questionnaire will be filled out at every study visit.

PRODUCT INFORMATION:

ADVATE 2 mL infusion: Date:_____ Time (local):_____
Lot Number:_____
Reason for infusion: Prophylaxis___ On-demand___
Number of total exposure days (EDs) to ADVATE 2 mL:_____

HYPERSENSITIVITY AND GENERAL REACTION INFORMATION: Check if not applicable____

Reaction Start: Date:_____ Time (local):_____
Reaction Stop: Date:_____ Time (local):_____

SYMPTOM(S)

Respiratory:	**Latency:**	**Severity:**	**Mild=M, Moderate=D, Severe=S**	
Difficulty Breathing	_____	M___	D___	S___
Tightness in throat or chest	_____	M___	D___	S___
Wheezing/Bronchospasm	_____	M___	D___	S___
Other	_____	M___	D___	S___
Skin:				
Swelling	_____	M___	D___	S___
Hives	_____	M___	D___	S___
Itching	_____	M___	D___	S___
Rash	_____	M___	D___	S___
Flushing	_____	M___	D___	S___
Cyanosis/Turning blue	_____	M___	D___	S___
Other	_____	M___	D___	S___

Others:				
Dizziness/Lightheadedness	_____	M___	D___	S___
Weak Pulse	_____	M___	D___	S___
Loss of Consciousness	_____	M___	D___	S___
Fever	_____	M___	D___	S___
Hypotension	_____	M___	D___	S___
Cardiac Arrest	_____	M___	D___	S___
Nausea	_____	M___	D___	S___
Headache	_____	M___	D___	S___
Fatigue	_____	M___	D___	S___
Other	_____	M___	D___	S___

How long after the onset did the reaction(s) resolve?_____
Was treatment given for the reaction? Yes___ No___
If yes, please describe the
treatment:_____
_____
Was the patient hospitalized? Yes___ No___
If yes, please provide hospitalization date:
Admission date:_____
Discharge date:_____

OUTCOME:

Would you consider this an anaphylactic reaction? Yes___ No___
Was the drug given again after this reaction? Yes___ No___
Did the patient develop a reaction again? Yes___ No___

PATIENT INFORMATION:

Allergies to other Factor VIII products? Yes___ No___
If yes, please provide name of Factor VIII product:_____
Allergies to mouse or hamster proteins? Yes___ No___
Allergies to other substances (dust, ragweed, etc)? Yes___ No___
Patient history of eczema? Yes___ No___
Patient history of asthma? Yes___ No___

EVENT DESCRIPTION:

Worksheet completed by: **Date:**

APPENDIX B: ADVATE 2 ML STUDY CAREGIVER SURVEYS

ADVATE 2 mL [reconstituted in 2 mL sterile water for injection (SWFI)]

Antihemophilic Factor (Recombinant) Plasma/Albumin Free Method (rAHF-PFM)

Octocog alfa (recombinant human coagulation factor VIII)

TITLE: ADVATE 2 mL (reconstituted in 2 mL SWFI)

POST-AUTHORIZATION SAFETY SURVEILLANCE STUDY

SHORT TITLE: ADVATE 2 mL PASS

PROTOCOL IDENTIFIER: 061101

NON-INTERVENTIONAL OBSERVATIONAL STUDY

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

ADVATE 2mL Study

Caregiver Survey

Baseline Assessment

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

We are interested in your experiences prior to enrolling in this study. Please complete the questions below with your prior ADVATE 5mL treatment in mind. Please answer each question to the best of your ability. There are no right or wrong answers.

Infusion Questions

1. Please select the number for each vial size you normally use to infuse your child's prescribed ADVATE dose. *For example, if you are infusing 2 vials of 500 IU and 1 vial of 250 IU for your child, please complete the table as follows:*

Number of Vials	**EXAMPLE: Vial Sizes Needed to Infuse ADVATE Dose**					
	250	**500**	**1000**	**1500**	**2000**	**3000**
1	☑	☐	☐	☐	☐	☐
2	☐	☑	☐	☐	☐	☐
3	☐	☐	☐	☐	☐	☐
4	☐	☐	☐	☐	☐	☐

Number of Vials	**Vial Sizes Needed to Infuse ADVATE Dose**					
	250	**500**	**1000**	**1500**	**2000**	**3000**
1	☐	☐	☐	☐	☐	☐
2	☐	☐	☐	☐	☐	☐
3	☐	☐	☐	☐	☐	☐
4	☐	☐	☐	☐	☐	☐

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

2. Does your child have a Central Venous Access Catheter / Port?
   - ❑ Yes
   - ❑ No

3. How does your child receive his ADVATE infusions?
   - ❑ He infuses himself
   - ❑ I (parent/caregiver) infuse him
   - ❑ Nurse/healthcare professional infuses him

4. How long, on average, does it take to:
   a) Mix (reconstitute) your child's prescribed ADVATE dose?
   _____minutes _____seconds

   b) Infuse your child's prescribed ADVATE dose after the needle is in place?
   _____minutes _____seconds

   c) Complete the whole infusion process (from setting up the vial(s) to cleaning up)?
   _____minutes _____seconds

5. On average, what percent of the time do you lose access to your child's vein after starting the infusion?
   _____%

6. If you've lost access to your child's vein, what percent of the time do you re-stick the needle to complete the infusion?
   _____%

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

Satisfaction with ADVATE treatment

Please rate your level of satisfaction with…	**Very satisfied**	**Satisfied**	**Neither satisfied nor dissatisfied**	**Dissatisfied**	**Very dissatisfied**
7. The amount of liquid volume needed for my child's infusion	❑	❑	❑	❑	❑
8. The time needed to mix my child's factor VIII treatment	❑	❑	❑	❑	❑
9. The time needed to infuse my child's factor VIII treatment	❑	❑	❑	❑	❑
10. The ease of infusing my child's factor VIII treatment	❑	❑	❑	❑	❑
11. The amount of anxiety my child has over his factor VIII infusions	❑	❑	❑	❑	❑
12. The amount of anxiety I have infusing my child's factor VIII treatment	❑	❑	❑	❑	❑
13. The overall convenience of my child's factor VIII treatment	❑	❑	❑	❑	❑
14. My child's factor VIII treatment in general	❑	❑	❑	❑	❑

Thank you for completing this survey!

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

ADVATE 2ML STUDY

CAREGIVER SURVEY

FOLLOW-UP ASSESSMENT

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

We are interested in your experiences during this study. Please complete the questions below with your prior ADVATE 2mL treatment in mind. Please answer each question to the best of your ability. There are no right or wrong answers.

Infusion Questions

1. Please select the number for each vial size you normally use to infuse your child's prescribed ADVATE dose during this study. *For example, if you are infusing 2 vials of 500 IU and 1 vial of 250 IU for your child, please complete the table as follows:*

Number of Vials	**EXAMPLE: Vial Sizes Needed to Infuse ADVATE 2 mL Dose**	
	250	**500**
1	☑	☐
2	☐	☑
3	☐	☐
4	☐	☐

Number of Vials	**Vial Sizes Needed to Infuse ADVATE 2 mL Dose**	
	250	**500**
1	☐	☐
2	☐	☐
3	☐	☐
4	☐	☐

2. Does your child have a Central Venous Access Catheter / Port?
   - ❑ Yes
   - ❑ No

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

3. How does your child receive his ADVATE infusions?
   - ❑ He infuses himself
   - ❑ I (parent/caregiver) infuse him
   - ❑ Nurse/healthcare professional infuses him

4. Prior to enrolling in this study, how long, on average, did it take to:
   a) Mix (reconstitute) your child's prescribed ADVATE dose?
   _____minutes _____seconds

   b) Infuse your child's prescribed ADVATE dose after the needle is in place?
   _____minutes _____seconds

   c) Complete the whole infusion process (from setting up the vial(s) to cleaning up)?
   _____minutes _____seconds

5. On average, what percent of the time do you lose access to your child's vein after starting the infusion?
   _____%

6. After you've lost access to your child's vein, what percent of the time do you re-stick the needle to complete the infusion?
   _____%

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

Satisfaction with ADVATE treatment

Please rate your level of satisfaction with…	**Very satisfied**	**Satisfied**	**Neither satisfied nor dissatisfied**	**Dissatisfied**	**Very dissatisfied**
7. The amount of liquid volume needed for my child's infusion	❑	❑	❑	❑	❑
8. The time needed to mix my child's factor VIII treatment	❑	❑	❑	❑	❑
9. The time needed to infuse my child's factor VIII treatment	❑	❑	❑	❑	❑
10. The ease of infusing my child's factor VIII treatment	❑	❑	❑	❑	❑
11. The amount of anxiety my child has over his factor VIII infusions	❑	❑	❑	❑	❑
12. The amount of anxiety I have infusing my child's factor VIII treatment	❑	❑	❑	❑	❑
13. The overall convenience of my child's factor VIII treatment	❑	❑	❑	❑	❑
14. My child's factor VIII treatment in general	❑	❑	❑	❑	❑

Baxter BioScience	PROTOCOL NO 061101	SUBJECT IDENTIFICATION NO. SITE NO. ☐☐ SUBJECT NO. ☐☐☐☐	**Study Visit and Date**: ☐ Follow-up Visit date: _____

Preference

Now that your child has received ADVATE 2mL for his hemophilia, please indicate your preference between ADVATE 2mL and ADVATE 5mL (before enrolling in this study) on the following features….

	Prefer ADVATE 2 mL	**No Preference**	**Prefer ADVATE 5 mL**
15. The amount of liquid volume needed for my child's infusion	❑	❑	❑
16. The time needed to mix my child's factor VIII treatment	❑	❑	❑
17. The time needed to infuse my child's factor VIII treatment	❑	❑	❑
18. The ease of infusing my child's factor VIII treatment	❑	❑	❑
19. The amount of anxiety my child has over his factor VIII infusions	❑	❑	❑
20. The amount of anxiety I have infusing my child's factor VIII treatment	❑	❑	❑
21. The overall convenience of my child's factor VIII treatment	❑	❑	❑
22. My child's factor VIII treatment in general	❑	❑	❑

Thank you for completing this survey!

INVESTIGATOR ACKNOWLEDGEMENT

ADVATE 2 mL [reconstituted in 2 mL sterile water for injection (SWFI)]

Antihemophilic Factor (Recombinant) Plasma/Albumin Free Method (rAHF-PFM)

Octocog alfa (recombinant human coagulation factor VIII)

TITLE: ADVATE 2 mL (reconstituted in 2 mL SWFI)

POST-AUTHORIZATION SAFETY SURVEILLANCE STUDY

SHORT TITLE: ADVATE 2 mL PASS

PROTOCOL IDENTIFIER: 061101

NON-INTERVENTIONAL OBSERVATIONAL STUDY

AMENDMENT 1: 2013 JUL 26

REPLACES ORIGINAL PROTOCOL: 2012 FEB 23

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, non-interventional study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator