OBSERVATIONAL STUDY NUMBER: PASS-INT-004

PROSPECTIVE ADVATE IMMUNE TOLERANCE INDUCTION REGISTRY (PAIR)

AMENDMENT 3 VERSION: April 22, 2010
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AMENDMENT 2 VERSION: October 1, 2008
AMENDMENT 1 VERSION: December 21, 2006
ORIGINAL VERSION: December 4, 2006

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INVESTIGATOR ACKNOWLEDGEMENT

PROSPECTIVE ADVATE IMMUNE TOLERANCE INDUCTION REGISTRY (PAIR)

Observational plan number: PASS-INT-004

Amendment 3

Version: April 22, 2010

By signing below, the Investigator acknowledges that he/she has read and understood this protocol, including the Appendix entitled Data Handling Convention / Self Evident Corrections, and provides assurance that this observational study will be conducted according to all requirements of this protocol, and all applicable regulatory requirements.

________________________________________________________________________
Principal Investigator Date

By signing below, the Baxter representative verifies receipt of the Investigator’s acknowledgment.

________________________________________________________________________
Study Sponsor Date
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1. SYNOPSIS

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<thead>
<tr>
<th>Observational Study Number:</th>
<th>PASS-INT-004</th>
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<tbody>
<tr>
<td>Observational Study Title:</td>
<td>Prospective ADVATE Immune Tolerance Induction Registry (PAIR)</td>
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<tr>
<td>Objectives:</td>
<td>Primary objective:</td>
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<td></td>
<td>- To assess the safety and tolerance in terms of incidence of SAEs and non-serious AEs deemed related to ADVATE among subjects with hemophilia A and inhibitors to FVIII undergoing ITI therapy with ADVATE as primary FVIII therapeutic agent</td>
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<tr>
<td></td>
<td>Secondary objectives:</td>
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<tr>
<td></td>
<td>- To collect information on the incidence of central venous access device-related infections during ITI therapy with ADVATE</td>
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<td>- To collect information on the success rates of ITI therapy performed with ADVATE in hemophilia A subjects and inhibitors to FVIII</td>
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<tr>
<td></td>
<td>- To collect information on the correlation between ITI success rates and a variety of subject characteristics, treatment variables and intercurrent infections</td>
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<tr>
<td>Design:</td>
<td>A prospective, multi-center, uncontrolled, open-label, non-interventional post-authorization study</td>
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<tr>
<td>Treatment(s):</td>
<td>Commercially obtained ADVATE will be prescribed and administered as primary FVIII therapeutic agent according to the center’s preferred ITI regimen during the study observational period. Because this is a non-interventional study, ITI treatment regimens will not be standardized.</td>
</tr>
<tr>
<td>Duration of Participation:</td>
<td>Maximum duration of study participation for each subject will be 33 months, with a 12-month post-observational follow-up</td>
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</table>
| **Subjects:** | Target enrollment is approximately 50 evaluable subjects  
Subjects have hemophilia A of any severity  
Subjects have been previously diagnosed with inhibitor to FVIII (low or high titer)  
Subjects undergoing ITI therapy using ADVATE as the primary FVIII therapeutic for the ITI regimen  
Written ICF, where locally required |

| **Statistical Analysis:** | There is no formal hypothesis testing. The incidence of SAEs and non-serious AEs related to ADVATE will be calculated using point estimates, along with 2-sided 95% confidence intervals. The overall rate of ITI success, as defined as the percentage of inhibitor subjects who had their inhibitor abolished following ITI therapy will also be calculated. Descriptive statistics will be presented for each endpoint and major treatment variables or major subject demographic descriptors. Descriptive statistics will include the mean, median, SD, 25th and 75th percentiles, minimum, maximum and sample size for continuous variables, and frequencies and percentages for categorical variables. Multivariate analysis will be employed when applicable. An interim descriptive analysis will be performed after 20 subjects have completed ITI therapy. |
## 2. LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event (or Adverse Experience)</td>
</tr>
<tr>
<td>BU</td>
<td>Bethesda Unit</td>
</tr>
<tr>
<td>CHO</td>
<td>Chinese Hamster Ovary</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>ECRF</td>
<td>electronic Case Report Form</td>
</tr>
<tr>
<td>ED</td>
<td>Exposure Days</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FVIII</td>
<td>Factor VIII</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HTC</td>
<td>Hemophilia Treatment Center</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITI</td>
<td>Immune Tolerance Induction</td>
</tr>
<tr>
<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>ML</td>
<td>Milliliter</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PTP</td>
<td>Previously Treated Patient</td>
</tr>
<tr>
<td>PUP</td>
<td>Previously Untreated Patient</td>
</tr>
<tr>
<td>RAHF</td>
<td>Recombinant Antihemophilic Factor</td>
</tr>
<tr>
<td>rAHF-PFM</td>
<td>Recombinant Antihemophilic Factor Plasma/Albumin-Free Method</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event (or Serious Adverse Experience)</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>VWF</td>
<td>von Willebrand Factor</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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3. INTRODUCTION

Administration of factor VIII (FVIII) concentrate for the treatment of subjects with hemophilia A can sometimes lead to inhibitor development, most often in subjects with severe disease (FVIII < 1%) and with less than 50 prior FVIII exposure days (EDs). Subjects who develop inhibitors are especially difficult to treat as they may be totally unresponsive to FVIII replacement therapy and require FVIII bypassing agents, which are not always reliable for hemostatic control. Consequently, subjects with FVIII inhibitors generally have poorer long-term outcomes and incur significantly more direct medical costs than hemophilia A subjects without inhibitors.

Inhibitors to FVIII, which oftentimes first manifest as perceived “lack of effect” and can be indicated by decreased \textit{in vivo} recovery and accelerated FVIII half-life, are typically measured in the Bethesda Assay. The Bethesda assay, however, which detects antibodies that inhibit the coagulation process, does not necessarily have the ability to detect the presence of “non-neutralizing” antibodies that alter FVIII pharmacokinetics and that can still impact clinical response to therapy.

One approach to the long-term treatment of subjects with inhibitors that has been accepted by many hemophilia treaters and recommended by some Medical Advisory Organizations is to induce FVIII immune tolerance, in an effort to restore responsiveness to FVIII therapy. It has been demonstrated that FVIII inhibitors can be eradicated in most subjects with repeated high doses of FVIII. Tolerance induction, however, may take up to 1-3 years of treatment, in some cases.

The overall safety of FVIII administration in ITI therapy, the therapeutic strategy that is most effective in achieving FVIII immune tolerance, as well as subject characteristics that may predict ITI success or failure remain inadequately defined despite numerous case-reports, small-scale studies, and evaluations of international and regional registries. A retrospective study recently documented a combined complete and partial success rate of 83% in 36 ITI cases in which RECOMBINATE, a first generation recombinant FVIII, was used as the primary therapeutic. These results appear consistent with reports of other small case studies with plasma-derived products of various purities. Very little has been published however on the product specific safety of ITI therapy, particularly in prospective studies or observational registries, mostly due to the rarity of study subjects.
Prospective safety surveillance programs can be of considerable value by further expanding our knowledge through accurate documentation of clinical experience, current practice patterns and subject outcomes, and in subjects that would not necessarily be eligible to participate in controlled studies involving ITI.

During ITI therapy, high-dose FVIII may be adequate to manage bleeding episodes in some subjects with titers less than 5-10 BU, but subjects with higher titers often require FVIII inhibitor bypassing agents for hemostatic management. In addition, FVIII inhibitor bypassing agents are sometimes administered prophylactically in an effort to prevent frequent bleeding and orthopedic disease progression during ITI. Nevertheless, bleed management and prevention practices during ITI are not well documented.

ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM) is processed using the same CHO cell line that expresses the FVIII molecule in RECOMBINATE. The ADVATE CHO cell-line, however, has been adapted to grow in a proprietary culture medium free of any protein additives of human or animal origin. The murine monoclonal antibody used in immunoaffinity chromatography purification of ADVATE is produced by a hybridoma cell line that has also been adapted to grow in a protein-free cell culture medium. The final formulation of ADVATE employs trehalose for FVIII stabilization and mannitol as bulking agent. The ADVATE manufacturing processes (ie, cell culture, purification and final formulation) employ no additives of human or animal origin, thereby eliminating the risk of transmission of viruses and/or prions that may be associated with these agents. Recent reports of individual ITI cases with ADVATE as the primary therapeutic indicate that ADVATE may be a useful therapeutic in this treatment modality.

The prospective, multi-center, open-label, observational study proposed herein is designed to capture information regarding the “real-life” clinical experience with ADVATE in hemophilia A subjects with inhibitors who undergo ITI therapy. The observational study will complement the limited experience gathered from the Baxter sponsored IND study in PUP and the International, Randomized, Controlled Trial of Immune Tolerance Induction with highly selected study populations. The cohort design will provide a broader view of the management of this known complication. This observational study may reveal what infusion schedules and dosing amounts may work best with ADVATE, as well as some of the subject characteristics that potentially influence ITI success or failure. In addition, this observational study will also document the bleed frequency and bleed management practices in subjects undergoing ITI with
ADVATE. Documentation of the clinical experience with ADVATE will widen the knowledge base from which physicians and their patients make decisions regarding therapeutic strategies and FVIII concentrate choice in their ITI therapeutic regimens.

This study is designed as a prospective, non-interventional, observational cohort study. Patient selection and treatment modalities are based on the local institutional treatment practices. The observational plan does not make any stipulations on diagnostic measures, eg, laboratory tests, which will be dictated only by the individual patient’s needs. Thus, the protocol represents an observational study, which is exempt from GCP requirements.

4. STUDY OBJECTIVES
The overall goal of this observational study is to document safety and tolerance of ADVATE as primary FVIII therapeutic agent in ITI therapy in subjects with hemophilia A and inhibitors.

PRIMARY OBJECTIVE:

- To assess the incidence of SAEs and non-serious AEs deemed related to ADVATE in subjects undergoing ITI therapy with ADVATE

SECONDARY OBJECTIVES AND ADDITIONAL EXPLORATORY ANALYSES:

- To collect information on the incidence of central venous access device-related infections during ITI with ADVATE
- To collect information on the general success rate (Section 8.2) of ITI therapy with ADVATE in all observational study subjects
- To collect information on the precise success rate (Section 8.2) of ITI therapy with ADVATE in the subset of subjects with severe hemophilia A (FVIII ≤ 1%), any titer inhibitor to FVIII, no previous ITI attempt, and primary use of ADVATE as the FVIII immunizing agent during ITI therapy
- To collect information on the precise success rate (Section 8.2) of ITI therapy with ADVATE in the subset of subjects with severe hemophilia A (FVIII ≤ 1%), high-titer (>5 BU) inhibitor to FVIII, no previous ITI attempt, and primary use of ADVATE as the FVIII immunizing agent during ITI therapy
- To collect information on the correlation between ITI success or failure and venous access device-related infections and/or complications
• To collect information on the correlation between time to ITI success and venous access device-related infections and sepsis
• To collect information on the correlation between ITI success or failure and treatment variables
• To collect information on the correlation between ITI success or failure and subject characteristics
• To collect information on the potential relationship between post-ITI maintenance regimens and inhibitor recurrence
• To collect information on the number of bleed events and hemostatic agent(s) used during ITI therapy with ADVATE
• To collect information on the relapse rate for inhibitors

5. SUBJECT POPULATION
Potential observational study subjects will be identified by working with centers known to have patients with inhibitors, as well as prospectively working with large Hemophilia Treatment Centers (HTCs) with sizable pediatric populations that utilize ADVATE in routine clinical practice and are known to prescribe ADVATE for ITI. Centers that participated in a previous retrospective study on the use of RECOMBINATE in ITI therapy will also be invited to participate in PAIR. All subjects will meet the criteria outlined below.

5.1 Inclusion Criteria
• Subject has hemophilia A of any severity
• Subject has been previously diagnosed with inhibitor to FVIII (low or high titer; developed following the use of any FVIII therapeutic)
• Subject has been prescribed ADVATE as the primary FVIII therapeutic for use in ITI therapy. The choice of prescription of ADVATE is to be made independent of and prior to any decision to participate in this observational study.
• Subject may be of any age
• Subject or subject’s parent/legally authorized representative has provided written ICF, where required

5.2 Exclusion Criteria
• Subject has known hypersensitivity to the active substance or to any of the excipients in ADVATE
6. STUDY DESIGN

This is a prospective, multi-center, uncontrolled, open-label, non-interventional post-authorization safety surveillance study on the use of ADVATE for ITI therapy as the primary FVIII therapeutic agent. The observational study follows a cohort design, and does not make binding stipulations on treatment or observation schedule. The investigator shall assess the eligibility and suitability of the subject for enrollment in this observational study. Commercially obtained ADVATE will be prescribed by the participating investigator according to the preferred ITI regimen at that institution. Principally, the observational study aims to collect subject and treatment-related data during ADVATE ITI therapy. Data collection will start from the time ITI is initiated and continue until ITI is completed. Post-observation follow-up will be performed 12 months following ITI therapy completion to determine whether FVIII immune tolerance has been maintained. ITI completion is defined as the time at which the subject achieves complete success, partial success or failure to ITI (see Section 8.2). If the inhibitor is still present after 33 months of ITI therapy, the subject will be considered to have failed ITI, and his participation in the observational study will end at this time. If ITI therapy was started within the 9 months prior to observational study enrollment, data collected retrospectively will be used for the purposes of the clinical outcome analysis. All serious and non-serious AEs that are judged at least possibly related to ADVATE will be collected retrospectively, and all AEs will be reported during the prospective data collection. However, a focus will be placed on prospectively collected safety data for a more precise estimate of related AE incidence. Written ICF, where required, will be obtained from the subject at the screening and enrollment visit. It is intended that the data to be collected on the CRF will be obtained during routinely scheduled or unscheduled visits of the subject to the HTC. The participating investigators are encouraged to include all case files on patients who have been prescribed ADVATE for ITI in their subject record databases from their routine clinical practice that fit the inclusion criteria in order to reduce the appearance of any case selection bias. In light of the recently announced premature closure of the International, Randomized, Controlled Trial of Immune Tolerance Induction24 in November 2009, it is anticipated that patients who would have been eligible for that study may now be considered for enrollment into PAIR. Therefore, the PAIR subject recruitment period is being extended and the enrollment target is...
increased from 30 to 50 evaluable subjects. In addition, the PAIR protocol has been amended to gather additional data related to individual bleed management during ITI, in an effort to better document this important aspect of safety and disease management.

7. **STUDY DURATION**

The observation period for each subject will be from the time ITI is initiated through up to 33 months of ITI therapy, with an additional 12-month post-observation follow-up after ITI is considered successful or partially successful. If ITI success or partial success is not achieved within 33 months of ITI initiation, participation in the observational study will end. Thus, the longest observation period for a subject in the observational study would be 45 months or 33 months of ITI, plus 12-month follow up afterwards. The post-observation follow-up will be performed at 12 months after ITI success or partial success and ITI therapy termination. The investigator will complete a post-observation follow-up CRF using data collected from subject records accumulated during the 12-month post-observation period. No clinic visit is specifically required for the collection of these data. If the subject starts on ADVATE ITI before observational study enrollment, all attempts will be made to collect data retrospectively. This includes subject diary data. A maximum of 9 months of retrospective data collection will be permitted; subjects who began ITI more than 9 months prior to observational study screening will not be eligible for PAIR.

8. **STUDY PROCEDURES**

Hemophilia physicians at institutions caring for a large cohort of pediatric patients and who use ADVATE in their routine clinical practice and investigators from the Retrospective Assessment of ITI with RECOMBINATE and who are also known to prescribe ADVATE will be approached to participate in the observational study. All assessments are to be made from routine clinical examinations, thus reflecting the medical practice at the respective treatment centers.

Written ICF, where required, from each subject is to be obtained before data entry on the case report forms (CRFs). The investigator, or his/her designee, is to enter the required data on the CRFs, and provide optional information if available. CRFs will be submitted to the data management center in accordance with instructions from the Sponsor or designee.

All assessments within the observational plan are to be made from routine examinations, thus reflecting the medical practice at the individual treatment center. No investigations are to be done specifically for the purpose of the surveillance. This pertains specifically
to laboratory, or other invasive procedures. Patient visits at the center are to be scheduled
according to medical needs, consistent with the policies at the center.

INFORMATION TO BE COLLECTED AT BASELINE, IF AVAILABLE:

- Month and year of birth
- Ethnicity
- Gender
- Height and weight
- A medical history, including concomitant diseases and medications
- Baseline FVIII level
- FVIII mutation genotype
- Previous surgeries, including dates of surgeries
- FVIII inhibitor:
  - FVIII EDs prior to inhibitor detection
  - Name of FVIII therapy subject was receiving at time of inhibitor
diagnosis
  - Type of FVIII product used, dosing regimen, start and stop dates, and
reason for any change in therapy (if any) in 12-month period prior to
inhibitor development, if available
  - Date of inhibitor diagnosis
  - Inhibitor titer at time of diagnosis and assay type
  - Peak inhibitor titer, assay type and date of detection, prior to ITI
therapy, if available
  - Inhibitor titer prior to current ADVATE ITI initiation (if ITI started
prior to baseline visit), date and assay type
- FVIII recovery and half-life studies:
  - Prior to inhibitor development (if available)
  - After inhibitor development and prior to ITI therapy start (if available)
- Number/location of bleeding events (per month or year) and regimen type:
  - Prior to inhibitor diagnosis
  - Between inhibitor diagnosis and ITI start
- History of previous ITI attempts, including factor product, ITI regimen, start
and stop dates and reason for change in therapy, prior to ADVATE ITI
treatment, if any
• Family history of inhibitor, inhibitor outcome, history of ITI therapy, max titer and ITI outcome, if any
• ADVATE ITI start date with dosage regimen and body weight at time of ITI start if ITI already started
• Use of FVIII inhibitor bypassing agents (eg, FEIBA, rFVIIa, and/or porcine FVIII) in the 6 months prior to ADVATE ITI therapy, if available
• Vaccinations within 3 months prior to ITI therapy along with the corresponding inhibitor levels pre- and post-vaccination, if available
• Use of central venous access devices and the incidence of device-associated infections and/or sepsis, if any
• History of SAEs and non-serious AEs possibly related to ADVATE during ADVATE ITI therapy if ITI therapy was started prior to observational study enrollment
• If the inhibitor development, that occurred prior to ADVATE ITI initiation date, had not been reported according to applicable laws and regulations, the inhibitor should be documented on the Serious Adverse Event Report forms (form codes: SAE1, SAE2, SAE3)

INFORMATION TO BE COLLECTED DURING INTERVAL VISITS, IF AVAILABLE:
• Subject diary
• Height and weight
• Concomitant medications, including vaccinations and ITI-related medications such as cyclophosphamide, immunoglobulin, and corticosteroids (sourced from diaries or clinic records)
• ADVATE ITI start date and dosage regimen if not collected during baseline visit
• ADVATE ITI therapy adjustments, if any
• Inhibitor titer and assay type, if measured
• Inhibitor disappearance date, if applicable
• FVIII recovery and half-life studies, if performed
• Vaccinations during ITI therapy along with the corresponding inhibitor titers pre- and post-vaccination, if available
• Placement/replacement/removal of central venous access devices and the incidence of device-associated infections and/or complications, if applicable
• If an access device-associated infection occurs, the inhibitor titer prior to and after resolution of the infection, if available
• All serious and non-serious AEs that occurred since last visit
• The number of bleeding episodes that required treatment since the last visit
• The name, dose, and start and stop infusion times of the factor concentrate(s) used to treat each bleeding episode
• The global efficacy assessment of individual bleeding episode treatment
• Type and dose of FVIII inhibitor bypassing agents (eg, FEIBA, rFVIIa), if used for bleeding treatment or prophylaxis during ADVATE ITI therapy
• Data to be collected upon review of the subject diary and/or clinic records:
  • Number, location, cause, start and stop date and/or type of new bleeding events since last clinic visit
  • Name, dose, and start and stop infusion times of the factor concentrate(s) used to treat each bleeding episode
  • The global efficacy assessment of individual bleeding episode treatment

INFORMATION TO BE COLLECTED AT TERMINATION VISIT, IF AVAILABLE:

• Subject diary
• Height and weight
• Concomitant medications, including vaccinations and ITI-related medications such as cyclophosphamide, immunoglobulin, and corticosteroids (sourced from diaries or clinic records)
• ADVATE ITI therapy adjustments, if any
• ADVATE ITI end date
• Inhibitor titer and assay type, if measured
• Inhibitor disappearance date, if applicable
• FVIII recovery and half-life studies, if performed
• FVIII recovery and half-life studies following inhibitor disappearance, if performed
• Vaccinations during ITI therapy along with the corresponding inhibitor titers pre- and post-vaccination, if available
• Placement/replacement/removal of central venous access devices and the incidence of device-associated infections and sepsis, if any
• If an access device-associated septic condition occurs, the inhibitor titers prior
to and after sepsis resolution, if available, along with the sepsis resolution
description on the AE CRF
• All serious and non-serious AEs that occurred since last visit
• Number of bleeding episodes that required treatment
• Name, dose, and start and stop infusion times of the factor concentrate(s) used
to treat each bleeding episode
• The global efficacy assessment of individual bleeding episode treatment
• Type of FVIII inhibitor bypassing agents (eg, FEIBA, rFVIIa), if used for
bleeding treatment or prophylaxis during ADVATE ITI therapy
• Reason for discontinuation of ITI, such as achievement of success, expected
lack of success, or unwillingness of subject to continue
• Criteria used for determination of success, partial success, or failure if
different from that defined in study protocol
• Data to be collected upon review of the subject diary and/or clinic records:
  • Number, body site location and/or type of new bleeding events since last
    clinic visit
  • Name, dose, and start and stop infusion times of the factor concentrate(s) used
to treat each bleeding episode
  • The global efficacy assessment of individual bleeding episode treatment

INFORMATION TO BE COLLECTED AT THE END OF THE POST-
OBSERVATION 12-MONTH FOLLOW UP, IF AVAILABLE:

• FVIII treatment regimen(s) during the post-observation period
• Information on disappearance/reappearance of inhibitors during the post-
  observation period
• Inhibitor titer(s), if measured, and record date(s)
• FVIII recovery percent and half-life studies, if performed, and record date(s)
• Serious and non-serious AEs that were identified from available clinic and/or
  subject record and were judged related to ADVATE by the investigator
• End of study date and primary reason for study exit

8.1 Randomization

There is no randomization involved in this observational study. The observational study
will be open-label, with all subjects having made prior independent choice of ADVATE
for use as the primary FVIII therapeutic for ITI therapy being eligible for inclusion. Any subject having met all eligibility criteria, none of the exclusion criteria, and signed the ICF will be allotted a unique identification number consisting of the 4-digit study site number (eg, 0002) and a sequential 3-digit subject number (eg, 003), reflecting the order in which enrollment took place at that site. The study site is responsible for maintaining a current log of subjects correlating their personal data (full name, date of birth) to the number they have been assigned to in this surveillance in order to avoid assignment errors, such as duplicating or skipping numbers, and to allow subject tracking and study coordination. This log will be kept in strictest confidence at the HTC, so that only the attending physician and other authorized research personnel will have full knowledge about the subject’s identity. The subject’s unique identification number will be entered on all study documentation (ie CRF).

8.2 Clinical Outcome Assessments
The protocol does not stipulate FVIII pharmacokinetic (PK) assessments, however, the precise assessment of ITI success, partial success and failure will be based on PK assessments as performed in the International, Randomized, Controlled Trial of Immune Tolerance Induction Study. Because PK information may not be available in all cases, the general success for all observational study subjects will be assessed using the general success criterion.

GENERAL SUCCESS CRITERIA: achievement of negative FVIII inhibitor titer (< 0.6 BU or local laboratory cut off) in any observational study subjects.

PRECISE SUCCESS CRITERIA: where available, PK information as described in the following definitions will be used to assess the clinical outcome of ITI therapy in subjects with severe hemophilia A and inhibitors to FVIII.

• COMPLETE SUCCESS:
  Within 33 months of ITI initiation, inhibitor titer < 0.6 BU and FVIII recovery data ≥ 66% of expected recovery (following 50 IU/kg dose, recovery measured at 30 ± 5 minutes post FVIII infusion) and FVIII half-life ≥ 6 hours. Both PK parameters should be measured following minimal 48-hour treatment-free washout period. If the cut-off limit for inhibitor detection at the local laboratory is different from 0.6 BU, the standards at local laboratory will prevail.
- **PARTIAL SUCCESS:**
  Upon termination of ITI therapy (no fewer than 9 months and no more than 33 months of ITI treatment), inhibitor titer remains below 5 BU or negative titer (< 0.6 BU or local laboratory cut off) with FVIII recovery of < 66% of expected recovery, or FVIII recovery > 66% of expected recovery but FVIII half-life < 6 hours associated with clinical response to FVIII therapy.

- **FAILURE:**
  Does not meet complete or partial success criterion, OR
  Following the first 3 months of treatment and prior to completing 33 months of ITI, failure to achieve an ongoing ≥ 20% reduction in inhibitor titer, during each interim non-overlapping 6-month period of ITI in the absence of documented infection. This implies that 9 months is the minimum treatment period and 33 months the maximum possible duration of unsuccessful ITI. This criterion for ITI failure will cease to apply once the subject achieves a titer of ≤ 5 BU.

- **UNASSESSABLE Per Protocol:**
  Does not meet criteria for complete or partial success, or failure.

- **RELAPSE:** (determined during post-observation 12-month follow-up after inhibitor disappearance)
  - Following inhibitor disappearance, positive inhibitor titer (per local laboratory criteria) – should be confirmed within a 2-week period OR
  - Following inhibitor disappearance, negative inhibitor titer (per local laboratory criteria) but recovery < 66% (when measured at 1 hour ± 30 min post FVIII infusion) – should be confirmed within a 2-week period OR
  - Following inhibitor disappearance, negative inhibitor titer (per local laboratory criteria) but FVIII half-life of < 6 hours (when measured after a 48-hour treatment-free washout period) – should be confirmed within 2 weeks

### 8.3 Subject Diary

The subject or subject’s legally authorized representative may maintain a diary during the subject’s participation in the study. The diary will include the following information:

- ITI infusion record including date of the infusion, lot number, and total units infused
- Treatment of new bleeding episodes including start and stop times of the bleeding episode, cause of the bleeding episode, name, dose, and lot number of factor concentrate(s) used, start and stop times of factor infusion, and the overall efficacy rating of individual bleeding episode treatment
- All AEs
- Concomitant medications taken (including vaccinations)

The diary will be presented to the investigator during each clinic visit. The investigator will also review the diary, discuss it with the subject or subject’s legally authorized representative, and enter the information on the appropriate CRF.

### 8.4 Laboratory Assessments

All testing will be done at the local laboratory at the participating site according to the established procedures and methods. The FVIII assay and inhibitor assay methods and reference standard used will be reported in the CRFs for FVIII level and inhibitor determination (per local laboratory criteria). The protocol does not mandate laboratory testing. However, if the investigator chooses, he/she may utilize the procedure followed in the International, Randomized, Controlled Trial of Immune Tolerance Induction to determine the disappearance of the inhibitor as guidance for this observational study.24

Highlights of the PK assessment protocol therein are summarized below:

- Within a month after the first negative inhibitor titer, the Bethesda assay may be repeated.
- If titer is still considered negative, FVIII recovery may be determined after the administration of 50 IU/kg of FVIII. If FVIII recovery is still <66% of expected recovery, inhibitor titer and recovery may be monitored at monthly intervals until the recovery is ≥ 66% of expected recovery. Inhibitor and recovery measurements should be taken at the longest possible interval after the previous FVIII dose that is permissible on the treatment regimen. Two negative Bethesda titers are preferably obtained within a 2-month period prior to initiating recovery/half-life studies.
- When the FVIII recovery is found to have normalized (≥ 66% of expected recovery), the FVIII half-life may be estimated within 1 month, after a 48-hour washout period and following a dose of FVIII of 50 IU/kg.
- If the half-life is still < 6 hours, the subject may continue ITI; inhibitor titer is measured monthly; and half-life measurements are repeated approximately every 3 months until reaching ≥ 6 hours.
• When/if the FVIII half-life and recovery levels return to the “normal” range then ITI will be considered successful.

8.4.1 Pharmacokinetic Analyses

The protocol does not stipulate FVIII PK assessments. However, where available, the following PK assessments, as described in the International, Randomized, Controlled Trial of Immune Tolerance Induction study\textsuperscript{24}, could prove useful to assess clinical outcomes. While inhibitor titers may be detected and quantified by utilizing the Bethesda Assay, non-neutralizing antibodies that can negatively impact treatment can still be present even in those subjects that test negative. A recent study has suggested that PK parameters may be a useful way to measure the presence of low-titer inhibitors that may be at or below the limits of detectability in the Bethesda Assay.\textsuperscript{25}

PK assessments are an important part of medical routine practice. To assess FVIII recovery levels, sampling times recommended by the International Society of Thrombosis and Haemostasis are as follows:\textsuperscript{26}

- Immediately prior to ADVATE infusion (baseline)
- 30 ± 5 minutes following infusion of 50 IU/kg body weight
- A wash-out period of up to 48 hrs is recommended prior to this procedure

Suggested minimal sampling schedule for PK determination is as follows:

- Prior to ADVATE infusion (baseline)
- 30 minutes post infusion
- 1-3 hours post infusion
- 6-9 hours post infusion
- 18-24 hours post infusion
- 32-36 hours post infusion

8.5 ITI Regimen with ADVATE

The choice of ITI regimen will be at the discretion of the investigator and in accordance with established treatment practices at the treating center. It is recommended that ITI regimens described in the peer-reviewed literature\textsuperscript{9; 10; 11; 12; 13; 14; 15; 16; 17} or similar to those described in the Prospective International, Randomized, Controlled Trial of Immune Tolerance Induction be followed.\textsuperscript{24}
8.5.1 Management of Bleeding Episodes During ITI

Bleeding episodes and management will be documented through review of subject diaries and clinic records. The approach to bleed management is to be determined by the treating physician. Information on the number and type of bleed events, the factor concentrate used, the global efficacy assessment of the individual bleeding episode treatment, and the respective lot number, if appropriate, will be collected. Bleed events and hemostatic agent(s) received in the clinic will be recorded on the Bleeding Episode Treatment Record CRF (form code BET). Bleed events and hemostatic agent(s) received at home will be recorded by the subject in the subject diary and transcribed to the BET CRF during clinic visit. All AEs associated with ADVATE administration during bleed management, except for the bleed event during ITI, should be reported on the AE CRF (form code AE). All bleed events are to be documented on the BET form. If the AE is serious, the event must be recorded using the SAE forms (form codes SAE1, SAE2, and SAE3). Any and all AEs possibly related to the use of other hemostatic agents including FVIII inhibitor by-passing therapies should be reported to the manufacturer(s) according to all applicable regional/country regulations.

8.5.2 Global Efficacy Assessment of Individual Bleeding Episode Treatment

Clinical efficacy following treatment of each bleeding episode will be assessed by the subject or subject’s legally authorized representative for home infusion, or by the investigator for hospital/clinic-based treatment according to the definitions provided in Table 8.5-1.

| Table 8.5-1 |
| 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\(^b\) 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\(^b\) and slight improvement in signs of bleeding within approximately 8 hours after the infusion. Requires more than 1 infusion for complete resolution. |
| **Poor** | No improvement or condition worsens. |

\(^a\) In subjects below 3 years of age, pain assessments may not be possible.
8.6 Summary Description of ADVATE

ADVATE is indicated in hemophilia A (classical hemophilia) for the prevention and control of bleeding episodes. ADVATE is also indicated in the perioperative management of subjects with hemophilia A. ADVATE can be of therapeutic value in subjects with FVIII inhibitors not exceeding 10 BU/mL. However, in subjects with a known or suspected inhibitor to FVIII, the plasma FVIII level should be monitored frequently and the dose of ADVATE should be adjusted accordingly.

ADVATE is a purified glycoprotein consisting of 2,332 amino acids that is synthesized by a genetically engineered CHO cell line. In culture, the CHO cell line expresses rAHF into the cell culture medium. The rAHF is purified from the culture medium using a series of chromatography columns. The cornerstone of the purification process is an immunoaffinity chromatography step in which a monoclonal antibody directed against FVIII is employed to selectively isolate the rAHF from the medium. The cell culture and purification processes used in the manufacture of ADVATE employ no additives of human or animal origin. The production process includes a dedicated, viral inactivation solvent-detergent treatment step. The rAHF synthesized by the CHO cells has the same biological effects as Antihemophilic Factor (Human) [AHF (Human)]. Structurally, the recombinant protein has a similar combination of heterogeneous heavy and light chains as found in AHF (Human).

ADVATE is formulated as a sterile, non-pyrogenic, white to off-white powder for intravenous injection. When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximum amounts: 38 mg/mL mannitol, 10 mg/mL trehalose, 108 mEq/L sodium, 12 mM histidine, 12 mM Tris, 1.9 mM calcium, 0.15 mg/mL polysorbate-80, and 0.10 mg/mL glutathione. VWF is co-expressed with FVIII, and helps to stabilize it in culture. The final product contains no more than 2 ng VWF/IU rAHF, which will not have any clinically relevant effect in subjects with von Willebrand’s disease. The product contains no preservative.

Each vial of ADVATE is labeled with the AHF activity expressed in IU per vial. Biological potency is determined by an in vitro assay, which employs a FVIII concentrate standard that is referenced to a WHO International Standard for FVIII: C concentrates. The specific activity of ADVATE is 4000 to 10,000 IU per milligram of protein.
8.6.1 Packaging and Labeling

In the US, EU, and Canada, ADVATE is available in single-dose vials that contain the following nominal dosage strengths: 250, 500, 1000, 1500, 2000, and 3000 IU per vial. ADVATE is packaged with 5 mL of Sterile Water for Injection, USP/EP, BaxJect II or a combination of a double-ended needle and a filter needle, one full prescribing physician insert (not available in EU), and one patient insert.

8.6.2 Shelf-Life and Storage

ADVATE should be refrigerated (2° - 8°C [36° - 46°F]) in powder form. ADVATE may be stored at room temperature (up to 30°C [86°F] and 28°C [82°F] or 25°C [77°F], respectively) for a period of up to 6 months not to exceed the expiration date. The date that ADVATE is removed from refrigeration should be noted on the carton. Do not use beyond the expiration date printed on the vial or six months after date noted on the carton, whichever is earliest. After storage at room temperature, the product must not be returned to the refrigerator. Avoid freezing to prevent damage to the diluent vial.

8.6.3 Reconstitution

Reconstitution Using the BAXJECT II Device:

1. Do not use the BAXJECT II device if its sterile barrier system or its packaging is damaged or shows any signs of deterioration.
2. Bring the ADVATE (dry concentrate) and Sterile Water for Injection (diluent) to room temperature.
3. Remove caps from the concentrate and diluent vials.
4. Cleanse stoppers with germicidal solution, and allow to dry prior to use.
5. Open the BAXJECT II device package by peeling away the lid, without touching the inside. Do not remove the device from the package.
6. Turn the package over. Press straight down to fully insert the clear plastic spike through the diluent vial stopper.
7. Grip the BAXJECT II package at its edge and pull the package off the device. Do not remove the blue cap from the BAXJECT II device. Do not touch the exposed white plastic spike.
8. Turn the system over, so that the diluent vial is on top. Quickly insert the white plastic spike fully into the ADVATE vial stopper by pushing straight down. The vacuum will draw the diluent into the ADVATE vial.
9. Swirl gently until all material is dissolved. Be sure that ADVATE is completely dissolved, otherwise active materials will be removed by the device filter.

Reconstitution: Using the Double-Ended Needle:

1. Bring the ADVATE (dry concentrate) and Sterile Water for Injection (diluent) to room temperature.
2. Remove caps from the concentrate and diluent vials.
3. Cleanse stoppers with germicidal solution, and allow to dry prior to use.
4. Remove protective covering from one end of the double-ended needle and insert exposed needle through the center of the stopper.
5. Remove protective covering from the other end of the double-ended needle. Invert diluent bottle over the upright ADVATE bottle, then rapidly insert the free end of the needle through the ADVATE bottle stopper at its center. The vacuum in the bottle will draw in the diluent.
6. Disconnect the two bottles by removing the needle from the diluent bottle stopper, then remove the needle from the ADVATE bottle. Swirl gently until all material is dissolved. Be sure that ADVATE is completely dissolved, otherwise active materials will be removed by the filter needle.

• **NOTE**: Do not refrigerate after reconstitution.

Administration: Use Aseptic Technique

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless in appearance. If not, do not use the solution and notify Baxter immediately. ADVATE should be administered at room temperature not more than 3 hours after reconstitution.

A) Using the BAXJECT II Device:

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

B) Using the double-ended needle for reconstitution and the filter needle for preparing the administration. Plastic syringes must be used with this product, since proteins such as ADVATE tend to stick to the surface of glass syringes:

1. Attach filter needle to a disposable syringe and draw back plunger to admit air into the syringe.
2. Insert needle into reconstituted ADVATE.
3. Inject air into bottle and then withdraw the reconstituted material into the syringe.
4. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously as instructed under Administration by bolus infusion.
5. If a subject is to receive more than one bottle of ADVATE, the contents of the multiple bottles may be drawn into the same syringe by drawing up each bottle through a separate unused filter needle. Filter needles are intended to filter the contents of a single bottle of ADVATE only.

8.6.4 Administration by Bolus Infusion

A dose of ADVATE should be administered over a period of \( \leq 5 \) minutes (maximum infusion rate, 10 mL/min). The pulse rate should be determined before and during administration of ADVATE. Should a significant increase in pulse rate occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

8.6.5 Dosing Schedule and Requirements

Dosing schedule for ADVATE ITI regimen is made at the discretion of the investigator.

8.7 Adverse Events

An AE is defined as any unfavorable medical occurrence in a subject administered a medicinal product and which does not necessarily have a causal relationship with the
treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory function), symptom, or disease temporally associated with the use of the observational product, whether or not the event is considered causally related to the product. For the purposes of this registry, observational product refers to ADVATE.

- Laboratory and vital sign abnormalities qualify as AEs if medical intervention is required to treat or address the abnormality.
- An elective procedure/surgery that occurs during the course of a study, but is being performed for a documented pre-existing condition and was pre-planned prior to study entry will not qualify as an AE. If, however, the pre-existing condition unexpectedly deteriorates during the study requiring the procedure/surgery to be performed earlier than planned, the condition for which the procedure/surgery is being performed will qualify as an AE.

During the course of the study, the investigator shall routinely monitor each subject for the occurrence of any AEs. If an AE occurs, a full description of the event should be recorded including the date of onset, severity, time course, description, actions taken, and causal relationship of the AE to the observational product. Additionally an alternative cause for the event, based on the facts of the case should be provided if the category chosen is “not related to the observational product.”

AEs should be actively solicited and recorded by the investigator at defined visits during the course of the study. Additionally, any AE voluntarily reported by the subject should be recorded by the investigator on the appropriate CRF. All SAEs, irrespective of the relationship to the observational product, must be reported to the Sponsor’s representative within 24 hours of the investigative site becoming aware of its occurrence. All non-serious AEs must be reported to the Sponsor’s representative within 5 business days of the investigative site becoming aware of its occurrence.

All AEs should be followed by the investigator until a conclusion for the AE can be determined.

An AE can result from the use of the observational product in accordance with the locally specified ITI regimen, as well as from an accidental or intentional overdose of the observational product above and beyond the prescribed dose or any other medications administered during the course of the registry. An AE can also occur subsequent to observational product withdrawal.
8.7.1 Summary of Known and Potential Risks of ADVATE to Human Subjects (ie labeled AEs)

An integrated analysis of the safety of rAHF-PFM across the clinical program utilized final data from the completed Baxter clinical studies 069901, 060102, BLB-200-01, 060101, and 069902. Data collected through 27 March 2006 were utilized for the ongoing Baxter clinical study 060103. A total of 234 unique subjects received at least 1 infusion of study product. Total exposure to rAHF-PFM was 84,539,784 IU (47 lots) in 44,926 infusions. The median duration of participation per subject was 370.5 days (range: 1 to 1,256 days) and the median exposure per subject to rAHF-PFM was 128.0 days (range: 1 to 598 days).

A total of 2,507 AEs were reported in 215 (91.9%) subjects; 19 treated subjects reported no AEs during their participation. There were no deaths and none of the treated subjects withdrew due to an AE. Only 59 AEs in 41 (17.5%) subjects were serious, and all but 5 SAEs were judged by the investigator to be possibly or probably related to study product. Non-serious AEs comprised the majority (2,448/2,507) of all AEs. Of the 2,448 non-serious AEs, the majority were mild (n=1,741; 85.9%) or moderate (n=649; 59.4%) events. The most common AEs occurring in at least 5% of subjects were pyrexia (32.48% of subjects), cough (29.06% of subjects), headache (27.35% of subjects), and nasopharyngitis (26.50% of subjects). Overall, the majority of the AEs appear to have been related to trauma, intercurrent mild respiratory and gastrointestinal diseases, or well-described complications of hemophilia.

Of all AEs, only 56 were considered by the investigator to be possibly or probably related to the administration of rAHF-PFM (Table 8.7-1). Of these, 5 in 5 subjects were serious and 51 in 24 subjects were non-serious. The 5 SAEs that were considered related to rAHF-PFM, all involved the development of a FVIII inhibitor in a PUP in ongoing study 060103. None led to the discontinuation of study product. One of the 5 PUPs who developed a FVIII inhibitor began immune tolerance therapy with study product according to the protocol and discontinued from the study. This subject continued immune tolerance therapy with commercial rAHF-PFM (ADVATE) and was successfully tolerized.

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\[ ^{i} \] Estimated from reported dose.

\[ ^{ii} \] One of the 5 PUPs who developed a FVIII inhibitor began immune tolerance therapy with study product according to the protocol and discontinued from the study. This subject continued immune tolerance therapy with commercial rAHF-PFM (ADVATE) and was successfully tolerized.
<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>MedDRA Preferred Term</th>
<th>Number of Patients</th>
<th>AE Rate (% Patients)</th>
<th>AE Rate Frequency Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Lymphangitis</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Eye inflammation</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal pain upper</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>2</td>
<td>0.85%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General Disorders and Administrative Site Conditions</td>
<td>Chest pain</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Feeling abnormal</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Oedema peripheral</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>3</td>
<td>1.28%</td>
<td>Common</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Influenza</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laryngitis</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>Post procedural complication</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Post procedural haemorrhage</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Procedural site reaction</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Investigations</td>
<td>Alanine aminotransferase increased</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Anti FVIII antibody positive</td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.14%</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Coagulation FVIII decreased</td>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Haematocrit decreased</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laboratory test abnormal</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Dizziness</td>
<td>3</td>
<td>1.28%</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
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<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>5</td>
<td>2.14%</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Memory impairment</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
Table 8.7-1
Summary of Adverse Drug Reactions from the rAHF-PFM Clinical Program

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>MedDRA Preferred Term</th>
<th>Number of Patients</th>
<th>AE Rate (% Patients)</th>
<th>AE Rate Frequency Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, Thoracic and Mediastinal disorders</td>
<td>Dyspnoea</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Dermatitis diaper</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hyperhidrosis</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pruritis</td>
<td>2</td>
<td>0.85%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>2</td>
<td>0.85%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Haematoma</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hot flush</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pallor</td>
<td>1</td>
<td>0.43%</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Abbreviations: MedRA = Medical Dictionary for Regulatory Activities, AE = adverse event.

a. Baxter rAHF-PFM clinical program included 234 unique, treated subjects from: completed studies 069901, 060102, BLB-200-01, 060101, and 069902 and ongoing study 060103 (database snapshot 27 March 2006).

b. Frequency has been evaluated using the following criteria: very common (≥ 10%), common (< 10% to ≥ 1%), uncommon (< 1% to ≥ 0.1%), rare (< 0.1% to ≥ 1/10,000) and very rare (< 1/10,000).

c. As specified in the protocol of Baxter clinical study 060103, a FVIII inhibitor titer ≥ 0.6 BU was reported as an SAE.

d. The unexpected decreased coagulation FVIII levels in association with an infected central catheter occurred in 1 patient during CI of rAHF-PFM following surgery (postoperative Days 10-14). Hemostasis was maintained at all times during this period and both plasma FVIII levels and clearance rates returned to appropriate levels by postoperative Day 15. FVIII inhibitor assays performed after completion of CI and at study termination were negative.

For the integrated analysis across 1 ongoing and 5 completed studies, the risk of developing a FVIII inhibitor for subjects (PUPs and PTPs) was estimated (at the 95% level) using the Poisson distribution based on previous exposure history. For the 25 PUPs with no previous treatment experience with other FVIII concentrates at study entry and 0 to 3 exposure days (EDs) with rAHF-PFM in the 28 days prior to screening, the overall incidence of any FVIII inhibitor was 20.0% (data collected through 27 March 2006)iii The 95% confidence intervals for the risk of developing a FVIII inhibitor were

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iii Study 060103 is ongoing; data were collected for the integrated analysis through 27 March 2006.
8.22 to 39.85% for any titer inhibitor. Taking into consideration the early stage of this PUP study, the FVIII inhibitor events detected during this period (5 in 25 treated subjects) were within the expected and previously observed range. In a more recent report (data collected through 20 June 2007), inhibitor formation was reported in 12 of 49 PUPs over the course of study 060103.

Of 198 PTPs evaluated for FVIII inhibitors, only 1 (0.51%) subject developed a low-titer inhibitor (2.4 BU in the modified Bethesda assay) after 26 EDs. Follow-up inhibitor tests performed for this subject after withdrawal from the study were negative. The 95% confidence interval for the risk of developing a FVIII inhibitor among PTPs was 0.026 to 2.91%. Across all studies, median exposure to rAHF-PFM was 128.0 EDs per subject. The incidence of FVIII inhibitors in PTPs in the rAHF-PFM clinical development program was similar to that reported in studies of PTPs who received REFACTOiv (1 of 113 subjects)22 or KOGENATEv (1 of 85 subjects).23 In contrast to the low titer inhibitor observed in study 069901, the inhibitors observed in the ReFacto and Kogenate studies were high titer inhibitors (> 5 BU). Furthermore, thus far in the rAHF-PFM clinical development program, there were no clusters of reports associated with individual lots of study product and no reports in documented, low-risk subjects. In light of these considerations, the inhibitor events that were reported most likely represent the natural history of severe hemophilia A following early or intense exposure to FVIII replacement.

In conclusion, the results derived from the rAHF-PFM clinical development program suggest that rAHF-PFM is efficacious and safe for adults and pediatric subjects with severe to moderately severe hemophilia under a variety of clinical settings. The safety and efficacy profile for rAHF-PFM is consistent with that observed for other currently licensed rAHF products including RECOMBINATE rAHF.

8.7.1.1 Definition of Adverse Event Terms

Observational product: ADVATE

Date of onset: The date that the signs and symptoms of the AE began.

Signs & symptoms vs. diagnosis: If a definitive diagnosis has been medically established by the physician caring for the subject or by the investigator, this diagnosis should then

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iv REFACTO is a registered trademark of Wyeth Pharmaceuticals, Inc.
v KOGENATE is a registered trademark of Bayer Healthcare, LLC.
be recorded as the AE. If a definitive diagnosis has not been medically established, the
signs and symptoms should then be recorded as the AE.

**Diagnosis vs. complications:** If a subject experiences not only a diagnosis, but
additionally a complication of the diagnosis (i.e., myocardial infarction with congestive
heart failure), both the diagnosis and the medical complication should be collected and
recorded as separate AEs on separate CRFs.

**Severity:** The severity of each AE should be recorded as mild, moderate, or severe
according to the following definition:

- **Mild:** transient and well-tolerated by the study subject
- **Moderate:** causes discomfort and a temporary interference with daily living
- **Severe:** substantially interferes with daily living to the point of being
  incapacitating and/or life threatening

**Causality:** The relationship of the AE to the use of the observational product should be
assigned by the investigator according to the following category definitions:

- **Related:** The AE has a strong and medically reasonable temporal relationship
to the start of the observational product, and no other more likely medical
etiology is present in the facts of the case. Supporting evidence may include a
  negative dechallenge and/or a positive rechallenge.
- **Not Related:** The AE is considered to be “not related” to the observational
  product because of temporal implausibility, biological implausibility and/or
  because a more likely cause for the event, such as an underlying or concurrent
  illness or an effect of another medicinal product, is present in the facts of the
  case.

**Causality reasoning:** If the causality category of “not related” is chosen by the
investigator, his/her reason for this choice should be provided. This can consist of an
alternative cause for the event based on the case facts, and/or temporal or biologic
implausibility (if applicable).

### 8.7.1.2 Serious Adverse Events (SAEs)

The following regulatory criteria qualify an AE as an SAE:

**Death of Subject:** An event resulting in the death of the subject.
**Life-Threatening**: In the opinion of the investigator, an event that would have resulted in immediate death if medical intervention had not been undertaken. This does not include an event that would have been fatal if it had occurred in a more severe form.

**Hospitalization**: An event resulting in formal inpatient admission of the subject to the hospital. Visits to the emergency room or outpatient facility do not constitute hospitalization for the purpose of the definition.

**Prolongation of Hospitalization**: An event that prolongs the subject’s stay in the hospital. By definition, this is a different event from the event that resulted in the hospitalization.

**Congenital Abnormality**: An abnormality detected at or after birth in the offspring of a study subject.

**Persistent or Significant Disability/Incapacity**: An event that substantially interferes with the subject’s usual daily activities of living. This category is not intended to include events of relatively minor medical significance such as minor trauma, diarrhea, nausea, etc.

**Important Medical Event**: Although not resulting in death or hospitalization, as important medical event should be considered as SAE if, based on medical judgment, it significantly jeopardize the subject and/or require medical or surgical intervention to prevent one of the other serious outcomes from occurring.

### 8.7.1.2.1 Hospitalization

Adverse events associated with inpatient hospitalization or prolongation of existing hospitalization are considered serious. Inpatient hospitalization refers to any inpatient admission, regardless of length of stay. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Routine emergency room admissions
- Same day surgeries (as outpatient/same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Social admission (e.g., subject has no place to sleep)
- Administrative admission (e.g., for yearly physical exam)
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol)
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery)
- Pre-planned treatments or surgical procedures, which should be noted in the baseline documentation for the entire protocol and/or for the individual subject

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.7.1.2.2 Inhibitors

Inhibitors are considered SAEs. If the inhibitor has not yet been reported, it must be reported now, since Baxter is obligated to report inhibitor cases to the regulatory agencies. The name of the FVIII product prescribed when the subject developed the inhibitor is important for the causality assessment to be made. All patients who enter PAIR for whom inhibitor development has not been reported to the appropriate manufacturer, must have an SAE report completed, regardless of product prescribed when the inhibitor developed.

8.7.1.3 Non-Serious Adverse Events

A non-serious AE is an AE that does not meet the categories that define an SAE.
8.7.2 Adverse Events Reporting

8.7.2.1 Investigator to Baxter

All AEs, whether deemed possibly related to observational product or not, are to be recorded on the AE CRF (form code AE).

All SAEs, irrespective of the relationship to the observational product, must also be recorded on the SAE forms (form codes SAE1, SAE2, and SAE3).

If the inhibitor event, that occurred prior to ADVATE ITI initiation date, had not been reported according to applicable laws and regulations, the inhibitor event should be documented on the Serious Adverse Event Report forms (form codes: SAE1, SAE2, SAE3). There is no need to report the inhibitor event on the AE CRF.

All SAEs must be reported to Sponsor’s representative within 24 hours of the investigative site becoming aware of its occurrence.

All non-serious AEs must be reported to Sponsor’s representative within 5 calendar days of the investigative site becoming aware of its occurrence.

The completed AE CRFs and SAE forms are to be FAXED to:

INC Research
15360 Barranca Parkway
Irvine, CA  92618-2215 USA
T: +1-949-202-3240
F: +1-484-322-1499

8.7.2.2 Investigator to IRB/EC

It is the investigators’ responsibility to comply with local IRB/EC reporting procedures.

8.8 Laboratory Abnormalities

The investigator must assess the clinical significance of all abnormal laboratory values obtained in the course of the study. Any clinically significant abnormalities should be fully reported.
Clinically significant is defined as any abnormality that the investigator feels of major clinical concern, requires medical intervention, or that otherwise meets the definition of a “serious” AE. Additional tests and other evaluations required to establish the significance, or etiology of an abnormal result, or to monitor the course of an AE may be obtained when clinically indicated.

8.9 **Intercurrent Illnesses and Pre-Existing Diseases**

Diseases that are present at or before ADVATE administration (pre-existing disease), and that manifest with the same severity, frequency or duration subsequent to ADVATE administration, will not be considered an AE. However, incidents where there is an increase in severity or duration of the pre-existing disease should be reported on the AE CRF (form code AE) if it is judged by the treating physician to be possibly related to observational product. All new illnesses, whether deemed possibly related to observational product or not, should be recorded on the AE CRF.

8.10 **Prior and Concomitant Medications**

All relevant prior and concomitant medications (“Medical History”) taken or administered during the study will be documented in the subject’s clinic/hospital and study records, examples of which include previous FVIII exposure (and product brand potentially associated with inhibitor development), vaccination history, use of FVIII/FIX inhibitor bypass therapy, and immune-suppressant therapies. The subject’s prior and concomitant medication information will be documented on the appropriate CRF. Documentation of the use of any blood or plasma product and lot numbers is also required.

8.11 **Subject Withdrawal**

Any subject may withdraw from the study for any reason at any time. Additionally, the investigator may withdraw any subject from the study at his/her discretion. The investigator should provide the Sponsor with a written account of any reasons for early withdrawal.
8.12 Study Completion

The end-of-study CRF will be completed at study termination. The primary reason for termination will be listed on the CRF. One of the following conditions should be met:

a. Subject completed study protocol
b. Subject was withdrawn by the primary investigator for non-study drug related reasons
c. Subject or legally authorized representative voluntarily withdrew consent
d. Subject was lost to follow-up during the maximum observational period
e. Subject was lost to follow-up during the 12-month post-observational period
f. Subject died
g. Other reason for premature study termination

Regardless of the reason for termination, all data available for the subject up to the time of termination should be recorded onto the appropriate CRF, prior to retrieval by the Sponsor. The investigator shall provide follow-up information on subjects who experienced SAEs until a diagnosis and final outcome are established.

9. STATISTICAL ANALYSIS

9.1 Data Management

Each subject will be allotted a unique identification number consisting of the 4-digit study site number and a sequential 3-digit subject number, reflecting the order in which enrollment took place at that site. The subject’s unique identification number is required for data allocation and evaluation.

All data collected during the study will be entered into an electronic database for statistical analysis. Plausibility checks will be done, and attempts will be made to resolve inconsistencies.

The Sponsor’s clinical data management department or designee will correct without notification to site staff the CRF issues outlined in the Data Handling Conventions / Self Evident Corrections document (Section 12.1).
9.2   Endpoints and Exploratory Analyses
If the subject was started on ADVATE ITI prior to the observational study enrollment, all attempts will be made to collect data retrospectively. Both retrospective and prospective data will be combined for the efficacy endpoint analysis. All SAEs and non-serious AEs collected retrospectively and prospectively will be reported. However, a focus on prospectively collected AEs will be used for a more precise estimate of observational product-related AE incidence rates.

An interim descriptive analysis will be performed after 20 subjects have completed ITI therapy. The rationale for this analysis is to share the ongoing experience with the investigators and provide an up to date view of the safety profile that is emerging from this very long-term, ongoing study. The interim analysis will be descriptive in nature and will not impact the study design, nor interfere with study completion and analysis of final results.

9.2.1   Primary Endpoints
Incidence of SAEs and non-serious AEs possibly related to ADVATE during the ITI therapy in any observational study subject.

9.2.2   Secondary Endpoints
- Incidence of venous access device-related infections and sepsis during ITI therapy with ADVATE
- Rate of general ITI success as defined in Section 8.2, expressed as a percentage of all subjects achieving negative FVIII inhibitor titer (< 0.6 BU or cut-off limit of inhibitor detection per local laboratory)
- Rate of precise ITI success and partial success as defined in Section 8.2, expressed as a percentage of subjects with severe hemophilia A, any titer inhibitors, no history of previous ITI attempt with other FVIII concentrates, and exclusive use of ADVATE as the FVIII immunizing agent during ITI therapy
- Rate of precise ITI success and partial success as defined in Section 8.2, expressed as a percentage of subjects with severe hemophilia A and high-titer or high-responding (> 5 BU) inhibitors, no history of previous ITI attempt with other FVIII concentrates, and exclusive use of ADVATE as the FVIII immunizing agent during ITI therapy
Additional analyses, for exploratory purposes, as data become available:

- The time from the start of ITI to successful tolerance
- Number of bleeding episodes during ITI
- Global efficacy assessment of individual bleeding episode treatment
- The inhibitor recurrence (relapse) rate in the first 12 months after successful ITI
- The correlation between:
  a. Venous access device-related infections and sepsis, success rate and time to success
  b. Success rate and time to start ITI
  c. The dose-regimen, success rate and time to ITI
  d. The starting inhibitor titer, success rate and time to ITI
  e. The peak historical inhibitor titer, success rate and time to ITI
  f. The peak inhibitor titer after starting ITI, success rate and time to success
  g. The age at the time of inhibitor detection, success rate and time to success
  h. Immunizations and success rate and time to success
  i. The number of FVIII treatment days between inhibitor detection and initiation of ITI, success of ITI
  j. Post ITI maintenance regimen and inhibitor recurrence

9.3 Sample Size Considerations

The target study population includes approximately 50 subjects. In addition, the observational study may be expanded to include ITI data prospectively collected in the Baxter sponsored IND study of ADVATE in PUPs, and in the International, Randomized, Controlled Trial of Immune Tolerance Induction Study. By eventually combining the various ADVATE ITI databases we will gain a more comprehensive view of the overall safety of ITI therapy with ADVATE in a wider variety of subjects and clinical treatment scenarios. In addition, the data collected in this observational study (and proposed combined ADVATE ITI database) may complement and expand the current knowledge base gathered in other registries and investigational studies, thus increasing our power to

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vi Study terminated early.
identify practice patterns and patient demographic variables predictive of therapeutic outcomes.

In the 32 months since launch of ADVATE (August 2003 in the US and March, 2004 in Europe), more than 1.2 billion IU have been distributed to the market worldwide.\(^2^7\) Licensure in Europe was expanded in early 2005 to include treatment of children less than 6 years of age and PUPs. Licensure has also been granted in Australia, Canada, and Japan, thus, there will be a broad patient population with access to ADVATE during the observational study enrollment period.

During the post-launch period, Baxter has received reports of PUPs or minimally treated patients with less than 50 FVIII EDs who received ADVATE therapy and went on to develop an inhibitor. Of these, at least 10 have thus far reported that they either have undergone or are undergoing ITI, or are planning to begin ITI therapy\(^2^3;^2^7\); each of these cases would have qualified for inclusion in the observational study. In addition, Baxter has received anecdotal information on other cases of ADVATE use in ITI therapy with patients who developed inhibitors on other FVIII products. Thus, it is reasonable to assume that with continued market utilization in the US and EU member states, etc., and licensure in Australia in 2005, and Canada and Japan in 2006, that 50 cases of ITI therapy with ADVATE outside of formal clinical studies may be identified within the 4-year enrollment window. Although the anticipated patient sample size is small, it is expected that enrolled participants will receive a large number of ADVATE EDs (from several days/weeks to up to 33 months of daily infusion), and at a relatively higher frequency of infusion than for most licensed indications (ie, on-demand therapy and prophylaxis, in some geographies). The high frequency of infusions and complications associated with venous access pose special problems not studied in the formal prospective clinical study program done prior to licensure, as well as in formal phase IV studies.

10. **OBLIGATIONS OF THE SPONSOR AND THE INVESTIGATOR**

This observational study will be conducted in accordance with this observational protocol and national regulations applicable to post-authorization surveillance studies.

The Sponsor will select investigators on the basis of their expertise in the treatment of subjects diagnosed with hemophilia A and the study site's willingness to conduct an observational study of this nature.
The Sponsor and investigator must comply with all applicable regulations. In addition, the investigator must follow local and institutional requirements including, but not limited to, clinical research, obtaining signed informed consent (ICF), and IRB/IEC regulations. The Sponsor will provide notification to the investigator of protocol and amendment approvals by regulatory authorities, if applicable.

Except where the investigator's signature is specifically required, it is understood that the term "investigator" as used in this observational protocol and on CRFs refers to the investigator or appropriate personnel that the investigator designates to perform a certain duty. The investigator is ultimately responsible for the conduct of all aspects of the surveillance. Sub-investigators or other appropriate personnel are eligible to sign for the investigator on designated CRFs.

The investigator and site observational study coordinator will provide the Sponsor notification of relocation to another institution.

The investigator is responsible for maintaining the following:

- Appropriate source documentation of all study data. Source documents are original documents, data, and records from which the subject’s CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
- Subject files containing completed CRFs, ICFs, and supporting copies of source documentation, as required.
- Study files containing the protocol with all amendments, package insert, copies of study documentation, and all correspondence to and from the IEC/IRB and the Sponsor or designee.

10.1 Institutional Review Board / Independent Ethics Committee

Prior to enrollment of subjects into this observational study, the approved protocol and the ICF will be sent for notification, or approval, to the appropriate IRB/IEC, in accordance with local requirements. The ICF is provided for data protection reasons, and not for ITI therapy or ADVATE use. Choice of treatment and therapeutic is an independent decision between subject and physician.

Where applicable, the IRB/IEC letter of notice/approval of the protocol will be signed by the chairperson or recording secretary of the IRB/IEC prior to the start of this
observational study, and a copy will be provided to the Sponsor. Notification of the IRB/IEC's composition, or a statement that the IRB meets regulatory criteria for the composition of such an IRB/IEC will be provided to the Sponsor.

Should amendments to the protocol be required, the Sponsor will write the amendments in a standard format and provide them to the investigator for submission to the IRB/IEC.

10.2 Informed Consent

Investigators will choose subjects in accordance with the eligibility criteria detailed in Section 5. Where required, all subjects or their legally authorized representative (in case of observational study participants < 18 years of age) must sign an informed consent form (ICF) before entering the observational study. An assent form may be provided to and signed by participants less than 18 years of age.

Prior to enrollment into the observational study, subjects and/or their legally authorized representative(s) will receive a comprehensive explanation of the nature and purpose of the observational study, and the other elements that are part of obtaining proper ICF. Subjects or their legally authorized representative(s) will be allowed sufficient time to consider participation in the PAIR, after having the nature of the surveillance explained to them. The ICF must not include any exculpatory statements. It will be reviewed by the IRB/IEC prior to use, where required.

The Sponsor will provide the investigator in writing any new information that significantly bears on the subjects' risk to receive ADVATE. This new information will be communicated by the investigator to subjects that consent to participate in the observational study in accordance with IRB/IEC requirements. The ICF will be updated, if necessary.

By signing the ICF, this implies that the subject agrees to the transfer of their medical data to the Sponsor of the observational plan. Subjects are free to decide if they will utilize the provided patient diary.

Every attempt will be made to protect subjects’ rights to privacy within legal limits. However, records associated with subjects’ participation in the observational study, including medical histories (case histories) that may identify the subject, and the ICF signed by the subject will be made available for inspection on request by the IRB or IEC, Baxter Healthcare Corporation, Baxter Innovations GmbH or designee, or any competent
or regulatory authorities. In addition, the results of treatment and laboratory data may be published for scientific purposes, but subjects’ identity will not be disclosed. In the event the observation plan and data collection is utilized to support a regulatory application, the study Sponsor may require access to associated individual subjects records for source data verification purposes.

10.3 Study Records and Case Report Forms
Questions or interpretations of the protocol or CRFs will be referred to the Sponsor. The Sponsor is responsible for providing interpretation of all data questions.

10.3.1 Study Records
During the observational study period, the investigator will maintain complete and accurate documentation for the observational study, including medical records, records detailing the progress of the observational study for each subject, laboratory reports, CRFs, signed ICF, correspondence with the IRB/IEC and the observational study monitor/Sponsor, AE reports and information regarding subject screening, enrollment, discontinuation, and completion of the study observation period.

10.3.2 Case Report Forms
Paper CRFs will be supplied by the Sponsor for the recording of all subject information and study data as specified by this observational study. Original CRFs should be handled in accordance with instructions from the Sponsor. CRFs must be completed by the appropriate study personnel or data coordinator and signed by the principal investigator as indicated. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports. Data reported on the CRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. The investigator/institution should maintain all study documents as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

When paper CRFs are used, all required data will be clearly and accurately recorded by authorized personnel on the CRFs provided by the Sponsor. CRFs will be completed legibly using ballpoint pen with black ink. Any manual data correction on the original CRFs will be made by deleting the initial value with a single line, and recording the revised value along with the date and initials of the individual making the change.
Correction fluid and erasing are not permitted on CRFs. Only designated site personnel shall record or change data on a CRF.

CRFs should be completed within 1 week of data becoming available. CRFs will remain at the site until they are reviewed by the Sponsor or designee. The original CRFs will be collected by the Sponsor or designee. CRFs should be handled and sent to the data management center in accordance with instructions from the Sponsor or designee. An identical copy of the complete set of CRFs for each subject will remain at the clinical study site.

The Data Handling Conventions / Self Evident Corrections document (Section 12.1) outlines the method by which the Sponsor’s clinical data management department or designee handle certain ambiguous data recorded on CRFs without notification to site staff.

10.4 Confidentiality
The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval by the Sponsor.

10.5 Retention of Data
The investigator will maintain all records pertaining to this observational study for a minimum of five years after study end, or up to the maximum period required by local law.

The investigator will obtain permission from the Sponsor in writing before destroying any observational study records and the Sponsor will notify the investigator in writing when observational study records can be destroyed.

10.6 PAIR Monitoring
The Sponsor or designee shall ensure that the investigator understands all requirements of the protocol and his/her regulatory responsibilities as an investigator. The Sponsor or delegated representative will follow up with each clinical observational study site regularly to ensure compliance with the protocol and to verify the accuracy and completeness of data reported on the CRFs.
11. RESPONSIBILITIES

Baxter Healthcare Corporation and Baxter Innovations GmbH will act as the responsible Sponsor for the initiation, conduct, reports and publications of the observational study.

12. APPENDICES

This section contains additional information to assist in the interpretation of protocol requirements, ie flow charts for visit schedules, clinical events, and laboratory assessments.

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<th>POST-OBSERVATION 12-MONTH FOLLOW UP</th>
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* All visits should coincide with routinely scheduled or urgent visits by the subject to the center. Laboratory tests are not mandated, but if performed, all laboratory values listed are requested.
12.1 Data Handling Conventions / Self Evident Corrections

1. Missing or illegible header information may be corrected when the information can be determined without question.

2. Dates may be converted to Day/Month/Year format, where Day is numeric with leading zero as appropriate and Month is the first three letters. The Year is the last two digits with the exception of the subject’s Date of Birth which is 4 digits.

3. Entries with write-overs may be entered into the database when the information is considered to be legible.

4. Misspellings that do not change the meaning of the word (excluding adverse events and medications) will be corrected.

5. Standard time may be converted to the 24-hour clock format.

6. Decimals may be rounded up or down as appropriate to the nearest whole number (eg .4 or below will be rounded down and .5 or above will be rounded up).

7. The last recorded data above ditto marks or down arrows may be entered in the database in place of symbol.

8. Items recorded in units different from those specified may be converted to the appropriate units when the conversion can be made logically (e.g. Celsius to Fahrenheit).

9. Writing in margins or outside of designated entry fields will be queried only if deemed essential to the integrity of the study, otherwise this information will not be entered. On page 3 “none” may be entered into the database if written indicating the patient has not received a factor VIII concentrate prior to ADVATE.

10. Leading zeros will be entered in the database if omitted from CRF.

11. Continuous values entered as a range will be averaged (eg, 3-4 times per week will be entered as 3.5 times per week).

12. Errors of logic will be corrected if the correct data can be ascertained from other data within the CRF: eg, abnormality within a body system is recorded but an abnormality in that system has not been denoted by a tick, and then body system will be ticked to reflect an abnormality is present.

13. Dates from early in the year without reflecting the new year will be changed to reflect the correct date (e.g. 12 Dec 2004 through 30 Jan 2004 will be clarified as 12 Dec 2004 through 30 Jan 2005).
14. The pink or yellow copy of the CRF will only be entered into the database if the original white copy is not available. A note will be made to file stating the pink/yellow copy serves as the original.
15. Blank fields not identified as “critical” will NOT be queried. “Optional” pages will not be queried.
16. In reference to the pages where more than one may be completed and submitted (e.g. multiple concomitant medication pages), if subsequent CRF pages are not numbered, the additional page will be assigned the next available number.
17. Data located on an incorrect CRF/field may be relocated to the appropriate CRF/field (e.g.: moving lab results from a comments field to the appropriate lab field).
18. Zeroes (0s) in LOT NUMBERS are always entered as zeroes and never the alpha letter “O”. 1s are always entered as the number one and never the lowercase alpha letter “L”.
19. Clarifying “other, specify” if data are provided (eg, race, physical exam).
20. If both the end date and a status of continuing are indicated (eg. for adverse events, concomitant medication, hospitalization) the end date will supersede.
21. Deletion of obvious duplicate data (eg, same results sent twice with the same date but different clinical visit CRFs – interim visit and early termination)
22. For adverse events that record action taken code “none” and any other action code, “none” may be deleted as it is superseded by other existing data.
23. If equivalent units or terms are recorded instead of the acceptable data management standard (eg, cc for mL, SQ for SC route, Not Examined for Not Done), the data management standard units or terms will be used.
24. If the answer to a YES or NO question is blank or obviously incorrect (eg, answers to the following questions do not reflect the data that are recorded or missing: Were there any adverse events? Concomitant medications? Hospitalizations?), the question will be queried only if deemed essential to the integrity of the study, otherwise this information will not be entered.
12.2 List of Changes

Observational Plan Number PASS-INT-004
Amendment 3
Version 21 April 10

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

Original text: SAE CRF
Revised text: SAE forms
Purpose for change: To increase clarity. Data reported on the SAE forms (form codes SAE1, SAE2, and SAE 3) are entered in the Baxter pharmacovigilance database and are not entered in the clinical database.

Original text: EMEA
Revised text: EMA
Purpose for change: To reflect the current name of the Agency.

2. Throughout the Document Except in Study Title (Prospective ADVATE Immune Tolerance Induction Registry [PAIR])
Original text: registry
Revised text: observational study, or study
Purpose for change: to reflect the type of study more accurately.

3. Cover Page 2
Original text: Version dates of protocol and amendments, together with signatures of Baxter personnel are listed.
Revised text: delete entire page
Purpose for change: to follow current protocol template.

4. Investigator Acknowledgement Page
Original text: The Baxter Medical Affairs manager or designee
Revised text: The Baxter representative
Purpose for change: To reflect current structure of Baxter Global Research and Development.
5. **Section 1.0 Synopsis**

**Original text:** Target enrollment is approximately 30 subjects  
**Revised text:** Target enrollment is approximately 50 evaluable subjects  
**Purpose for change:** To reflect the revised target enrollment and recruitment extension in order to capture patients who would be eligible for the recently closed International ITI study.

**Original text:** None  
**Revised text:** An interim descriptive analysis will be performed after 20 subjects have completed ITI therapy.  
**Purpose for change:** To reflect current plan for data analysis.

**Original text:** SADR Suspected Adverse Drug Reaction  
**Revised text:** Delete  
**Purpose for change:** To avoid using the term SADR.

**Original text:** The registry will compliment the limited experience gathered from the Baxter sponsored IND study in PUP and interventional studies with highly selected study populations.  
**Revised text:** The observational study will compliment the limited experience gathered from the Baxter sponsored IND study in PUP and the International, Randomized, Controlled Trial of Immune Tolerance Induction [24] with highly selected study populations.  
**Purpose for change:** To increase clarity.

**Original text:** Patient selection and treatment modalities are based on the nationally approved SPC or local institutional treatment practices.  
**Revised text:** Patient selection and treatment modalities are based on the local institutional treatment practices.  
**Purpose for change:** To reflect the fact that immune tolerance induction is not an approved indication on any EU Summaries of Product Characteristics.

6. **Section 6.0 Study Design**

**Original text:** The investigator may also assess eligibility and suitability of the subject for inclusion in the International, Randomized, Controlled Trial of Immune Tolerance Induction [24]. Participation in this, or another controlled study does not necessarily preclude inclusion of data in the PAIR registry. Those who choose to participate in a controlled study may have their data transferred to the PAIR database after they complete
the study and as the data may become available.
Revised text: Delete
Purpose for change: To reflect the fact that the International, Randomized, Controlled Trial of Immune Tolerance Induction was stopped prematurely in November 2009.

Original text: Data collection will start from the time ITI is initiated and continue until the inhibitor is abolished.
Revised text: Data collection will start from the time ITI is initiated and continue until ITI is completed.
Purpose for change: To reflect the fact that not all inhibitors will be abolished.

Original text: All serious and non-serious sADRs will be collected retrospectively.
Revised text: All serious and non-serious AEs that are judged at least possibly related to ADVATE will be collected retrospectively.
Purpose for change: To avoid using the term SADR.

Original text: However, a focus will be placed on prospectively collected safety data for a more precise estimate of sADR incidence.
Revised text: However, a focus will be placed on prospectively collected safety data for a more precise estimate of related AE incidence.
Purpose for change: To avoid using the term SADR.

Original text: None
Revised text: In light of the recently announced premature closure of the International, Randomized, Controlled Trial of Immune Tolerance Induction [24] in November 2009, it is anticipated that patients who would have been eligible for that study may now be considered for enrollment into PAIR. Therefore, the PAIR subject recruitment period is being extended and the enrollment target is increased from 30 to 50 evaluable subjects. In addition, the PAIR protocol has been amended to gather additional data related to individual bleed management during ITI, in an effort to better document this important aspect of safety and disease management.
Purpose for change: To reflect the revised target enrollment and recruitment extension in order to capture patients who would be eligible for the recently closed International ITI study.
7. **Section 8.0 Study Procedures**

**Original text:**
- Severity of disease
- Inhibitor titer
- Type of FVIII product used, dosing regimen, and reason for any change in therapy (if any) in 12-month period prior to inhibitor development, if available
- History of previous ITI attempts, including ITI regimen, and reason for change in therapy, prior to ADVATE ITI treatment, if any
- Family history of inhibitor, inhibitor outcome, history of ITI therapy, and ITI outcome, if any
- ADVATE ITI start date with dosage regimen if ITI already started
- Use of FVIII inhibitor bypassing agents (eg, FEIBA, rFVIIa, and/or porcine FVIII) in the 9 months prior to ADVATE ITI therapy, if available
- Use of central venous access devices and the incidence of device-associated infections and/or complications, if any
- Type of FVIII inhibitor bypassing agents (eg, FEIBA, rFVIIa), if used for bleeding treatment or prophylaxis during ADVATE ITI therapy
- Number, location, and/or type of new bleeding events since last clinic visit
- None

**Revised text:**
- Baseline FVIII level
- Inhibitor titer and assay type
- Type of FVIII product used, dosing regimen, start and stop dates, and reason for any change in therapy (if any) in 12-month period prior to inhibitor development, if available
- History of previous ITI attempts, including factor product, ITI regimen, start and stop date and reason for change in therapy, prior to ADVATE ITI treatment, if any
- Family history of inhibitor, inhibitor outcome, history of ITI therapy, max titer and ITI outcome, if any
- ADVATE ITI start date with dosage regimen and body weight at time of ITI start if ITI already started
- Use of FVIII inhibitor bypassing agents (eg, FEIBA, rFVIIa, and/or porcine FVIII) in the 6 months prior to ADVATE ITI therapy, if available
- Use of central venous access devices and the incidence of device-associated infections and/or sepsis, if any
- Type and dose of FVIII inhibitor bypassing agents (eg, FEIBA, rFVIIa), if used for bleeding treatment or prophylaxis during ADVATE ITI therapy
- Number, location, cause, start and stop date and/or type of new bleeding events since last clinic visit
- Information on disappearance/reappearance of inhibitors during the post-observation period
- End of study date and primary reason for study exit

Purpose for change: To reflect what is currently on the case report form.

Original text:
- Date of inhibitor diagnosis
- FVIII ED prior to inhibitor detection
- Type of FVIII product used, dosing regimen, start and stop dates, and reason for any change in therapy (if any) in 12-month period prior to inhibitor development, if available
- Name of FVIII therapy subject was receiving at time of inhibitor diagnosis
- Inhibitor titer at time of diagnosis and assay type
- Inhibitor titer prior to current ADVATE ITI initiation (if ITI started prior to baseline visit), date and assay type
- Peak inhibitor titer, assay type and date of detection, prior to ITI therapy, if available
- FVIII recovery and half-life studies prior to inhibitor development (if available)
- FVIII recovery and half-life studies post inhibitor development and prior to ITI therapy start (if available)
- Number/location of bleeding events (per month or year) and regimen type prior to inhibitor diagnosis
- Number/location of bleeding events (per month or year) and regimen type between inhibitor diagnosis and ITI start

Revised text:
- FVIII inhibitor:
  - FVIII ED prior to inhibitor detection
  - Name of FVIII therapy subject was receiving at time of inhibitor diagnosis
• Type of FVIII product used, dosing regimen, start and stop dates, and reason for any change in therapy (if any) in 12-month period prior to inhibitor development, if available
• Date of inhibitor diagnosis
• Inhibitor titer at time of diagnosis and assay type
• Peak inhibitor titer, assay type and date of detection, prior to ITI therapy, if available
• Inhibitor titer prior to current ADVATE ITI initiation (if ITI started prior to baseline visit), date and assay type

- FVIII recovery and half-life studies:
  • Prior to inhibitor development (if available)
  • After inhibitor development and prior to ITI therapy start (if available)

- Number/location of bleeding events (per month or year) and regimen type:
  • Prior to inhibitor diagnosis
  • Between inhibitor diagnosis and ITI start

Purpose for change: To improve stylistic format.

Original text: None
Revised text: If the inhibitor development, that occurred prior to ADVATE ITI initiation date, had not been reported according to applicable laws and regulations, the inhibitor should be documented on the Serious Adverse Event Report forms (form code: SAE1, SAE2, SAE3).
Purpose for change: To clarify the reporting procedure for inhibitor events.

Original text: None
Revised text:
- Name, dose, and start and stop infusion time of the factor concentrate(s) used to treat each bleeding episode
- The global efficacy assessment of individual bleeding episode treatment

Purpose for change: to capture additional data on bleed management during ITI

8. Section 8.2 Clinical Outcome Assessments

Original text: PARTIAL SUCCESS: Upon termination of ITI therapy (no sooner than 9 months minimal and no later than 33 months of ITI treatment), inhibitor titer remains below 5 BU but FVIII recovery levels are <66% (when measured at 30 ± 5 minutes post FVIII infusion) and/or FVIII half-life <6 hours and not followed by a treatment limiting
anamnestic rise in inhibitor to > 5 BU over a period of 6 months of on-demand treatment or 12 months of prophylaxis.

Revised text: PARTIAL SUCCESS: Upon termination of ITI therapy (no fewer than 9 months and no more than 33 months of ITI treatment), inhibitor titer remains below 5 BU or negative titer (< 0.6 BU or local laboratory cut off) with FVIII recovery of < 66% of expected recovery, or FVIII recovery > 66% of expected recovery but FVIII half-life < 6 hours associated with clinical response to FVIII therapy.

Purpose for change: To reflect the definition according to the latest amendment of the International, Randomized, Controlled Trial of Immune Tolerance Induction.

Original text: FAILURE: Does not meet complete or partial success criterion, OR
A less than 20% reduction in inhibitor titer, relative to the peak inhibitor titer on ITI, over any 6-month period after the first 3 months of treatment. This implies that 9 months is the minimum treatment period and 33 months the maximum possible duration of unsuccessful ITI.

Revised text: FAILURE: Does not meet complete or partial success criterion, OR
Following the first 3 months of treatment and prior to completing 33 months of ITI, failure to achieve an ongoing ≥ 20% reduction in inhibitor titer, during each interim non-overlapping 6-month period of ITI in the absence of documented infection. This implies that 9 months is the minimum treatment period and 33 months the maximum possible duration of unsuccessful ITI.

This criterion for ITI failure will cease to apply once the subject achieves a titer of ≤ 5 BU.

Purpose for change: To reflect the definition according to the latest amendment of the International, Randomized, Controlled Trial of Immune Tolerance Induction.

Original text: None

Revised text: UNASSESSABLE Per Protocol:
Does not meet criteria for complete or partial success, or failure.

Purpose: For patients that do not meet criteria for complete or partial success, or failure.

Original text: RELAPSE: At the end of the 12-month follow-up period, negative inhibitor titer (per local laboratory criteria) but FVIII half-life of < 6 hours (when measured after a 48-hour treatment-free washout period) confirmed within 2 weeks.

Revised text: RELAPSE: Following inhibitor disappearance, negative inhibitor titer (per local laboratory criteria) but FVIII half-life of < 6 hours (when measured after a 48-hour treatment-free washout period) confirmed within 2 weeks.

Purpose for change: To increase clarity.
9. **Section 8.3 Subject Diary**

**Original text**: The subject or subject’s legally authorized representative will maintain a diary during the subject’s participation in the study.

**Revised text**: The subject or subject’s legally authorized representative may maintain a diary during the subject’s participation in the study.

**Purpose for change**: To reflect the observational nature of the study.

**Original text**: Treatment of new bleeding episodes including start and stop time of the bleeding episode, cause of the bleeding episode, name of factor concentrate used, and lot number.

**Revised text**: Treatment of new bleeding episodes including start and stop times of the bleeding episode, cause of the bleeding episode, name, dose, and lot number of factor concentrate(s) used, start and stop times of factor infusion, and the overall efficacy rating of individual bleeding episode treatment.

**Purpose for change**: To capture additional data on bleed management during ITI.

10. **Section 8.4 Laboratory Assessments**

**Original text**:

- If titer is still considered negative, FVIII recovery may be determined after the administration of 50 IU/kg of FVIII. If FVIII recovery is still < 66%, recovery may be monitored at monthly intervals until achieving ≥ 66%. Inhibitor and recovery measurements should be taken at the longest possible interval after the previous FVIII dose that is permissible on the treatment regimen. Two negative Bethesda titers are preferably obtained within a 2-month period prior to initiating recovery/half-life studies.

- When the FVIII recovery is found to have normalized (≥ 66%), the FVIII half-life may be estimated within 1 month, after a 48-hour washout period and following a dose of FVIII of 50 IU/kg.

- If the half-life is still < 6 hours, the subject may continue ITI and half-life measurement repeated approximately every 3 months until reaching ≥ 6 hours.
Revised text:

- If titer is still considered negative, FVIII recovery may be determined after the administration of 50 IU/kg of FVIII. If FVIII recovery is still < 66% of expected, inhibitor titer and recovery may be monitored at monthly intervals until the recovery is ≥ 66% of expected. Inhibitor and recovery measurements should be taken at the longest possible interval after the previous FVIII dose that is permissible on the treatment regimen. Two negative Bethesda titers are preferably obtained within a 2-month period prior to initiating recovery/half-life studies.
- When the FVIII recovery is found to have normalized (≥ 66% of expected), the FVIII half-life may be estimated within 1 month, after a 48-hour washout period and following a dose of FVIII of 50 IU/kg.
- If the half-life is still < 6 hours, the subject may continue ITI; inhibitor titer is measured monthly; and half-life measurement is repeated approximately every 3 months until reaching ≥ 6 hours.

Purpose for change: To increase clarity.

11. Section 8.5.1 Management of Bleeding Episodes during ITI

Original text: Information on the number and type of bleed events, the factor concentrate used and the respective lot number, if appropriate, will be collected.

Revised text: Information on the number and type of bleed events, the factor concentrate used, the global efficacy assessment of the individual bleeding episode treatment, and the respective lot number, if appropriate, will be collected.

Purpose for change: To capture additional data on bleed management during ITI.

12. Section 8.5.2 Global Efficacy Assessment of Individual Bleeding Episode Treatment

Original text: None

Revised text: Clinical efficacy following treatment of each bleeding episode will be assessed by the subject or subject’s legally authorized representative for home infusion, or by the investigator for hospital/clinic-based treatment according to the definitions provided in Table 8.5-1.
Table 8.5-1
Rating Scale for the Treatment of Bleeding Episodes

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excellent</strong></td>
<td>Full relief of pain and cessation of bleeding as evidenced by objective signs (e.g., 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.</td>
</tr>
<tr>
<td><strong>Good</strong></td>
<td>Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after the infusion. Possibly requires more than 1 infusion for complete resolution.</td>
</tr>
<tr>
<td><strong>Fair</strong></td>
<td>Probable or slight relief of pain and slight improvement in signs of bleeding within approximately 8 hours after the infusion. Requires more than 1 infusion for complete resolution.</td>
</tr>
<tr>
<td><strong>Poor</strong></td>
<td>No improvement or condition worsens.</td>
</tr>
</tbody>
</table>

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

13. **Section 8.6.3 Reconstitution**

Original text: None

Revised text: Reconstitution Using the BAXJECT II Device

1. Do not use the BAXJECT II device if its sterile barrier system or its packaging is damaged or shows any signs of deterioration.
2. Bring the ADVATE (dry concentrate) and Sterile Water for Injection (diluent) to room temperature.
3. Remove caps from the concentrate and diluent vials.
4. Cleanse stoppers with germicidal solution, and allow to dry prior to use.
5. Open the BAXJECT II device package by peeling away the lid, without touching the inside. Do not remove the device from the package.
6. Turn the package over. Press straight down to fully insert the clear plastic spike through the diluent vial stopper.
7. Grip the BAXJECT II package at its edge and pull the package off the device. Do not remove the blue cap from the BAXJECT II device. Do not touch the exposed white plastic spike.
8. Turn the system over, so that the diluent vial is on top. Quickly insert the white plastic spike fully into the ADVATE vial stopper by pushing straight down. The vacuum will draw the diluent into the ADVATE vial.
9. Swirl gently until all material is dissolved. Be sure that ADVATE is completely dissolved, otherwise active materials will be removed by the device filter.
A) Using the BAXJECT II Device:

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

B) Using the double-ended needle for reconstitution and the filter needle for preparing the administration.

14. Section 8.6 Summary Description of ADVATE

Original text: When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximal amounts: 38 mg/mL mannitol, 10 mg/mL trehalose, 108 mEq/L sodium, 12 mM histidine, 12 mM Tris, 1.9 mM calcium, 0.17 mg/mL polysorbate-80, and 0.10 mg/mL glutathione.

Revised text: When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximum amounts: 38 mg/mL mannitol, 10 mg/mL trehalose, 108 mEq/L sodium, 12 mM histidine, 12 mM Tris, 1.9 mM calcium, 0.15 mg/mL polysorbate-80, and 0.10 mg/mL glutathione.

Purpose for change: To reflect the current release specifications for ADVATE.

Original text: In the US, EU and Canada, ADVATE is available in single-dose vials that contain the following nominal dosage strengths: 250, 500, 1000, 1500, and 2000 IU per vial.

Revised text: In the US, EU and Canada, ADVATE is available in single-dose vials that contain the following nominal dosage strengths: 250, 500, 1000, 1500, 2000, and 3000 IU per vial.

Purpose for change: To reflect the fact that dosage strength of 3000 IU per vial is available.
ADVATE should be refrigerated (2° - 8°C [36° - 46°F]) in powder form. In the US and Canada, ADVATE may be stored at room temperature (up to 30°C [86°F] and 28°C [82°F], respectively) for a period of up to 6 months not to exceed the expiration date. In EU, ADVATE may be stored at room temperature (up to 25°C [77°F]) for a period of up to 2 months not to exceed the expiration date.

Purpose for change: To reflect current recommended storage condition.

15. Section 8.7.2 Adverse Event Reporting
Original text: None
Revised text: If the inhibitor event, that occurred prior to ADVATE ITI initiation date, had not been reported according to applicable laws and regulations, the inhibitor event should be documented on the Serious Adverse Event Report forms (form code: SAE1, SAE2, SAE3). There is no need to report the inhibitor event on the AE CRF.
Purpose for change: To clarify the reporting procedure for inhibitor events.

Original text:
Attn: Baxter PAIR Medical Reviewer
MDS Pharma Services
King of Prussia, PA USA
T: +1-610-239-7900, Extension x 463
F: +1-484-322-1499
Revised text:
INC Research
15360 Barranca Parkway
Irvine, CA 92618-2215 USA
T: +1-949-202-3240
F: +1-484-322-1499
Purpose for change: To reflect current contact information.

16. Section 8.9 Intercurrent Illnesses and Pre-Existing Diseases
Original text: Illnesses (including signs/symptoms of a pre-existing disease state) that are present at or before ADVATE administration (pre-existing disease).
Revised text: Diseases that are present at or before ADVATE administration (pre-existing disease).
Purpose for change: To increase clarity.
Original text: However, incidents where there is an increase in severity or duration of the pre-existing disease should be reported on the AE CRF (form code AE) if it is judged by the treating physician to be possibly related to observational product.
Revised text: However, incidents where there is an increase in severity, frequency or duration of the pre-existing disease should be reported on the AE CRF (form code AE).

Purpose for change: To increase clarity.

17. Section 9.1 Data Management
Original text: A combined biometrical and medical report will be prepared by the clinical project manager.
Revised text: Delete

Purpose for change: To remove non-applicable sentence.

18. Section 9.2 Endpoints and Exploratory Analyses
Original text: However, a focus on prospectively collected sADRs will be used for a more precise estimate of observational product related AE incidence rates.
Revised text: However, a focus on prospectively collected AEs will be used for a more precise estimate of observational product related AE incidence rates.

Purpose for change: to avoid using the term SADR.

Original text: None
Revised text: An interim descriptive analysis will be performed after 20 subjects have completed ITI therapy. The rationale for this analysis is to share the ongoing experience with the investigator's and provide an up to date view of the safety profile that is emerging from this very long-term, ongoing study. The interim analysis will be descriptive in nature and will not impact the study design, nor interfere with study completion and analysis of final results. Purpose for change: to reflect the current plan for data analysis.

Original text: Rate of general ITI success as defined in section 8.2, expressed as a percentage of all subjects achieving negative FVIII inhibitor titer (< 0.6 BU or cut-off limit of inhibitor detection per local laboratory) or as defined by the investigator.
Revised text: Rate of general ITI success as defined in section 8.2, expressed as a percentage of all subjects achieving negative FVIII inhibitor titer (< 0.6 BU or cut-off limit of inhibitor detection per local laboratory).

Purpose for change: To increase clarity.
Original text: Additional analyses, for exploratory purposes
Revised text: Additional analyses, for exploratory purposes, as data become available:
Purpose for change: To increase clarity.

Original text: None
Revised text: Global efficacy assessment of individual bleeding episode treatment.
Purpose for change: To capture additional data on bleed management during ITI.

19. Section 9.3 Sample Size Considerations
Original text: The target study population includes approximately 30 subjects.
Revised text: The target study population includes approximately 50 subjects.
Purpose for change: To reflect the revised target enrollment and recruitment extension in order to capture patients who would be eligible for the recently closed International ITI study.

Original text: Thus it is reasonable to assume that with continued market utilization in the US and EMEA member states, etc., and licensure Australia in 2005, and Canada and Japan in 2006, that more than 30 cases of ITI therapy with ADVATE outside of formal clinical studies may be identified within the 2-year enrollment window.
Revised text: Thus it is reasonable to assume that with continued market utilization in the US and EMA member states, etc., and licensure Australia in 2005, and Canada and Japan in 2006, that 50 cases of ITI therapy with ADVATE outside of formal clinical studies may be identified within the 4-year enrollment window.
Purpose for change: To reflect the revised target enrollment and recruitment extension in order to capture patients who would be eligible for the recently closed International ITI study.

20. Section 10.0 Obligations of the Sponsor and the Investigator
Original text: This observational study will be conducted in accordance with this observational protocol, the Declaration of Helsinki, and national regulations applicable to post-authorization surveillance studies.
Revised text: This observational study will be conducted in accordance with this observational protocol and national regulations applicable to post-authorization surveillance studies.
Purpose for change: Deletion of Declaration of Helsinki per FDA recommendation, as the Declaration is subject to revision independent of FDA authority and may lead to confusion regarding FDA’s acceptance of non-IND data.
21. **Section 10.2 Informed Consent**

*Original text:* By signing the ICF, subjects (or legally authorized representative(s)) agree that they will complete all evaluations and documentation if required by the surveillance, unless they withdraw voluntarily or are terminated from the observational study for any reason.

*Revised text:* Delete

*Purpose for change:* To reflect the observational nature of the study.

22. **Section 10.3.2 Case Report Forms**

*Original text:* CRFs or the electronic equivalent will be supplied by the Sponsor for the recording of all subject information and study data as specified by this registry. Original CRF and electronic equivalent should be handled in accordance with instructions from the Sponsor. CRFs or the electronic equivalent must be completed by the appropriate study personnel or data coordinator and signed by the principal investigator as indicated.

*Revised text:* Paper CRFs will be supplied by the Sponsor for the recording of all subject information and study data as specified by this observational study. Original CRFs should be handled in accordance with instructions from the Sponsor. CRFs must be completed by the appropriate study personnel or data coordinator and signed by the principal investigator as indicated.

*Purpose for change:* To reflect the fact that electronic case report forms are not used in study.

*Original text:* When paper CRFs are used, all required data will be clearly and accurately recorded by authorized personnel on the CRFs provided by the Sponsor.

*Revised text:* All required data will be clearly and accurately transcribed by authorized personnel from source documents into the CRFs provided by the Sponsor.

*Purpose for change:* To reflect the fact that electronic case report forms are not used in study.

*Original text:* CRFs should be completed within 1 week of data becoming available.

*Revised text:* CRFs should be completed as soon as data becomes available.

*Purpose for change:* To reflect current procedure for case report form completion.

*Original text:* CRF and electronic equivalent should be handled and sent to data management center in accordance with instructions from the Sponsor or designee.

*Revised text:* CRFs should be handled and sent to data management center in accordance with instructions from the Sponsor or designee.
Purpose for change: To reflect the fact that electronic case report forms are not used in study.

23. **Section 11.0 Responsibilities**

Original text: Baxter Global Clinical & Medical Affairs (Westlake Village, CA)

Revised text: Baxter Healthcare Corporation and Baxter Innovations GmbH

Purpose for change: To reflect current organizational name.
13. REFERENCES


2. DiMichele D. Inhibitors: resolving diagnostic and therapeutic dilemmas. Haemophilia

3. Hay CRM, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and
   management of factor VIII and IX inhibitors: a guideline from the United Kingdom

   91.

5. Gringeri A and Mannucci PM for the Italian Association of Haemophilia Centres.
   Italian guidelines for the diagnosis and treatment of patients with haemophilia and

   recommendations for immune tolerance therapy in type A haemophiliacs with


