NON-INTERVENTIONAL STUDY PROTOCOL

PRODUCT: OBIZUR® [ANTIHEMOPHILIC FACTOR (RECOMBINANT), PORCINE SEQUENCE]

STUDY TITLE: POST-MARKETING non-interventional safety evaluation of obizur in the treatment of bleeding episodes for patients with acquired hemophilia A

PROTOCOL IDENTIFIER: 241302

VERSION: 11 MAR 2015

Study Sponsor: **Baxalta U.S. Inc.**
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TITLE PAGE: POST MARKETING SAFETY STUDY

PROTOCOL TITLE	Post Marketing Non-Interventional Safety Evaluation of Obizur in the Treatment of Bleeding Episodes for Patients with Acquired Hemophilia A
PROTOCOL ID #	241302
ORIGINAL	2015 MAR 11
OTHER REGISTER	Study not registered
MEDICINAL PRODUCT	
Active Ingredient(s)	Antihemophilic Factor (Recombinant), Porcine Sequence
Medicinal Product	Antihemophilic Factor (Recombinant), Porcine Sequence
PRODUCT REF. #	NA
PROCEDURE #	NA
MARKETING AUTHORISATION HOLDER (MAH)	**Baxalta U.S. Inc.** One Baxter Way Westlake Village, CA USA 91362 **Baxalta Innovations GmbH** Industriestrasse 67 A-1221 Vienna, AUSTRIA

RESEARCH QUESTION & OBJECTIVES

The overall objective is to assess data on aspects of safety, treatment, and treatment outcomes among patients with acquired hemophilia A (AHA) who are prescribed and treated with Obizur in a real-world setting.

Research Question

The study is designed to assess safety and to describe factors related to the safety, utilization and effectiveness of Obizur in real-world clinical practice.

Primary Objective

The primary objective is to determine the incidence of therapy-related SAEs in patients with AHA who are prescribed and treated with Obizur in routine clinical practice.

Secondary Objective(s)

1. To describe hemostatic effectiveness of Obizur in the treatment of bleeding episodes.
2. To describe the frequency, total dose, and total number of infusions of Obizur required to control bleeding episodes.
3. To describe concomitant medication use.
4. To describe the clinical setting in which patients first present with symptoms of AHA, patient co-morbidities, time from presentation of symptoms to a positive diagnosis, and time from a positive diagnosis to first treatment with Obizur.
5. To describe the immunogenicity of Obizur during the course of treatment.

COUNTRY OF STUDY	United States
AUTHOR	[redacted], MD One Baxter Parkway Deerfield, IL 60015 USA [redacted] [redacted]

MARKETING AUTHORIZATION HOLDER(S)

MAH	**Baxalta U.S. Inc.** Westlake Village, CA 91362 USA
MAH CONTACT PERSON	[redacted], MD [redacted] Global Clinical Development BioScience Baxalta U.S. Inc.

SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ethics committee(s) (ECs).

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

See SAER form for contact information.
Further details are also available in the study team roster.

ADVERSE EVENT DEFINITIONS AND ASSESSMENT

For information on the definitions and assessment of these events refer to: definitions of AE in Section 11.1.1, SAE in Section 11.1.1.1 and assessment of AEs in Section 11.1.2.

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AHA	acquired hemophilia A
aPPCs	activated prothrombin complex concentrates
B19V	parvovirus B19
BHK	baby hamster kidney
CRF	case report form
CSR	case study report
DDVAP	Demopressin
EC	ethics committee
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
F	Factor
FDA	Food and Drug Administration
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
ICF	informed consent form
IRB	institutional review board
MAH	marketing authorization holder
MedDRA	medical dictionary for regulatory activities
NMC	non-medical complaint
pFVIII	porcine FVIII
rFVIIa	recombinant activated FVII
rpFVIII	Recombinant pFVIII
SAE	serious adverse event
SAER	serious adverse event report
SIC	subject identification code
U	Units
WHO	World Health Organization

3. RESPONSIBLE PARTIES

3.1 MAH's Authorized Representative (Signatory)/Responsible Party

[redacted], MD
[redacted] Global Clinical Development BioScience
Baxalta U.S. Inc.

3.2 Investigator(s)

The name and contact information of all investigators will be maintained by the MAH in a separate file and provided to the individual investigators (see Annex 14.1).

3.3 Other Individuals Involved in the Study

The name and contact information of other individuals involved with the study (e.g., MAH's medical expert and study monitor, MAH's representative(s), laboratories, steering committees, and oversight committees (including ethics committees [ECs]), as applicable) will be maintained by the MAH and provided to the investigator (see Annex 14.1).

4. ABSTRACT

Title:

Post Marketing Non-Interventional Safety Evaluation of Obizur in the Treatment of Bleeding Episodes for Patients with Acquired Hemophilia A

Rationale and background:

Acquired hemophilia A (AHA) is a rare autoimmune disorder in which non hemophilic persons develop auto-antibodies directed against circulating blood coagulation factor (F) VIII.[1] These auto-antibodies are distinct from the alloantibodies that form in patients with congenital hemophilia A in response to factor replacement therapy.[2] In approximately 50% of cases FVIII autoantibodies occur in patients with no concomitant disease, while the remaining cases may be associated with an underlying medical condition such as pregnancy, hematological or solid tumors, infections, use of medications, or autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and thyroid disorders.[2] The estimated incidence rate of AHA is approximately one case per million persons annually, though it is likely that this figure is underestimated in the elderly population.[3] This presumption is underscored by evidence indicating that the incidence of AHA increases with age. The incidence rate in children under 16 years is estimated to be 0.045 per million persons annually, compared to an estimated rate of 14.7 per million persons annually in individuals over the age of 85 years.[3]

A recently developed highly purified antihemophilic recombinant porcine sequence FVIII therapy (Obizur®) was approved for marketing for the treatment of AHA. While data from the clinical trial on Obizur demonstrated a positive safety and efficacy profile of porcine FVIII (pFVIII) in patients with AHA after 90 days, additional data are needed regarding longer-term safety (up to 180 days post-treatment), utilization, and the effectiveness of pFVIII in the real-world setting. Therefore, Baxalta plans to conduct the present study to assess safety of Obizur based on incidence of serious adverse events (SAEs), and to describe the hemostatic effectiveness of Obizur in the treatment of bleeding episodes, determine frequency and dosage, describe concomitant medications and AHA diagnosis, and describe immunogenicity of Obizur during the course of routine treatment.

Research question and objectives:

The overall objective is to enroll patients with AHA who are prescribed and treated with Obizur, to assess safety, and to describe factors related to safety, utilization and effectiveness.

Study design:

This study is a multi-center, uncontrolled, open-label, non-interventional postauthorization safety surveillance study to describe the use of Obizur in patients with AHA, and secondarily, where data are available, to describe the hemostatic effectiveness and immunogenicity of Obizur. Approximately 40 male and female patients ≥18 years of age with AHA in the United States will be enrolled over a three and a half year period with follow-up from the date of treatment through 180 days; it is expected this prospective study will enroll up to two patients per month. Patients should be enrolled within five days of initiating Obizur to ensure unbiased prospective observation.

In addition, in an attempt to collect all safety and utilization data on patients treated with Obizur since Food and Drug Administration approval in October 2014, Baxalta will conduct a retrospective chart review on persons treated with Obizur prior to the prospective study start date. Baxalta expects there will be approximately 30 to 40 patients who were treated with Obizur prior to the study start date, on whom retrospective data will be collected.

Prospective data will be collected for each subject over a period of approximately 180 days from the time of Obizur treatment; in addition, data points that are retrospective in nature (such as comorbidities and prior medical treatment) will be obtained from the medical chart for the time period prior to Obizur treatment. A subject or a subject's legally authorized representative will provide signed informed consent according to local regulations, prior to data collection initiation. Signed informed consent should be obtained within five days of Obizur treatment for patients newly treated with Obizur.

Among patients in the retrospective cohort, for whom Obizur treatment occurred prior to initiation of the prospective study, signed informed consent will be obtained at the time the patient has a clinic visit. If the patient is deceased or lost to follow-up, only anonymized data will be collected from the medical chart and entered into the electronic data capture (EDC) system.

The choice of Obizur use is to be made *independent of and prior to* any decision by the subject or the subject's legally authorized representative to participate in this study. The treating physician will determine the treatment regimen, as well as frequency of laboratory and clinical assessments, according to routine clinical practice.

Data collection will be limited to existing information and for the purposes of this study will be collected if data are (a) part of routine clinical practice or (b) elected by an investigator. Available data from patient visits shall be entered into an EDC system and checked for data quality. Keeping with the non-interventional study design, there will be no *required* visits, medical tests, laboratory tests and/or procedures, or interventions during the study duration. Baxalta will provide the option for physicians to use a central laboratory to process anti-human and anti-porcine FVIII antibodies

If these assessments are made, it is recommended that a Bethesda assay using the Nijmegen modification be undertaken for antibodies measurement, and that pFVIII antibodies be tested before and during treatment administration, and in the follow-up. Lab results from local or other central laboratories available in the medical chart will be recorded; it is not a requirement of the study that these lab tests be completed.

Population:

In this study, Baxalta plans to enroll a prospective cohort of approximately 40 patients with AHA who have had a bleeding episode and are being newly treated with Obizur in a hospital setting. In addition, Baxalta will collect retrospective clinical data on AHA patients with a bleeding episode, who were treated with Obizur prior to the prospective study start date. Data elements for collection will be the same for both groups. The study will be conducted in the United States, and the majority of sites will be hematology departments, where patients are being treated by hematologists. Sites will be pre-selected and will obtain institutional review board (IRB) approval prior to subject enrollment.

The study enrollment and collection period will be 4 years in length; including start-up closure, and dissemination of the final report, the entire study will take approximately 4.5 years.

Variables:

- Demographics (age, sex, weight, race, ethnicity)
- Pregnant, breast-feeding, or post-partum
- Medical history
    - Bleed description
        - spontaneous/traumatic, superficial/internal
        - location: intramuscular, retroperitoneal, gastrointestinal, intracranial, specify

- Hematology laboratory results (baseline and any follow-up)
  - Hemoglobin [<8 g/considered severe], hematocrit, red blood cell count, white blood cell count with differential, platelet count
- Bleed severity (baseline)
  - Physician assessment (severe/not severe)
- FVIII activity levels (baseline)
- Anti-human and anti-porcine FVIII antibody titers (baseline)
- Prior treatment with hemostatic agents (baseline)
  - Regimen received
  - Medication start/stop dates (retrospective cohort only)
- Comorbidities (baseline)
  - Physician assessment of association with AHA (possibly associated with causation of AHA/not associated with AHA)
- Current medications not related to AHA (taken within 14 days)
- AHA diagnosis
- Presentation of AHA symptoms

- Immunosuppressive agents received to treat underlying AHA during current Obizur treatment (baseline and follow-up)
- Obizur utilization (baseline and follow-up)
- Length of hospital stay per bleed (days)
- Safety (collect all SAEs; endpoint is therapy-related SAEs)
  - Key safety concerns:
    - Inhibitor development against pFVIII (follow-up)
    - Hypersensitivity reactions including anaphylaxis
    - Thrombogenicity
    - Outcomes, including date of death
- Physician bleed cessation assessment
  - Bleeding stopped versus not stopped
  - Date bleeding stopped

  - If bleeding not stopped, note reason (e.g., death, new treatment)
- FVIII activity measurements throughout treatment
- Human and porcine FVIII antibody titers. [Requirement to have a reference lab for anti-porcine FVIII antibody measurement (Central lab available if physician chooses to use it)]
- Concurrent bleeding episodes (baseline or follow-up)
  - Appearance of bleeding at a new site
- Treatment for bleeding episodes that occur greater than 72 hours after stopping treatment for the original bleed

Data sources:

Data wil be extracted from existing patient medical charts.

All prospective data shall be transcribed into the EDC system within 14 days of entry into the patient chart.

Retrospective data collection (for subjects who were treated with Obizur prior to initiation of the prospective study) will be completed within approximately 2 months of IRB approval.

Post-electronic data entry, medical dictionary for regulatory activities (MedDRA) coding will be conducted for all medical conditions reported and WHODRUG coding for all reported medications.

Study size:

There will be one cohort of approximately 40 patients with AHA who have had a bleeding episode and are being treated with Obizur. In addition, Baxalta expects there will be approximately 30 to 40 patients who were treated with Obizur prior to the initiation of the prospective study, on whom retrospective data will be collected.

Data analysis:

Sample Size Calculation

The proposed sample size of 40 patients will be adequate to address the primary objective of evaluating the safety profile for Obizur. No formal sample size calculations were performed for the determination of the number of subjects for documentation, as this is primarily a descriptive study and is not designed to test a specific statistical hypothesis.

Planned Statistical Analysis

The analysis plan for reports will be fully described in a written and approved statistical analysis plan (SAP). Descriptive statistics will include specifically, but not exclusively, arithmetic mean, medians, standard deviations, minimum, maximum, proportions, frequency counts, 25th and 75th percentiles, and 95% confidence intervals of select point estimates. Figures will be prepared to illustrate data patterns over time where appropriate. Analyses will be performed using available data, though missing values are expected due to the non-interventional nature of the study. Full details on handling missing data, which are common in observational studies, will be described separately in the SAP.

SAEs will be described in listings and tables, and incidence rates will be calculated. Tables outlining the hemostatic effectiveness and immunogenicity of Obizur, frequency, total dose, and total number of infusions of Obizur required to control bleeding episodes will be developed. Tables displaying concomitant medications and patient comorbidities will also be developed. Time from symptoms to diagnosis to treatment will be reported.

Milestones:

The study will either end 4 years from the time the first patient is enrolled, or will be assessed at the point 40 patients have been enrolled in the prospective portion of the study, whichever is earlier.

5. AMENDMENTS AND UPDATES

Not applicable.

6. MILESTONES

Milestone	Planned Date
Final protocol submission	31MAR2015
Start of all data collection/First site initiated	30SEP2015
Last subject in	31MAR2019
Last subject out	30SEP2019
Data lock for prospective data collection	01OCT2016
Data lock for prospective data collection	01OCT2017
Data lock for prospective data collection	01OCT2018
Data lock for prospective data collection, final report	31OCT2019
Data lock for Report on retrospective data	15DEC2015
Report on retrospective data results	30JAN2016
Annual study update report	15DEC2016
Annual study update report	15DEC2017
Annual study update report	15DEC2018
Final clinical study report	31JAN2020

7. RATIONALE AND BACKGROUND

7.1 Medicinal Product Safety Profile

Acquired hemophilia A (AHA) is a rare autoimmune disorder in which non hemophilic persons develop auto-antibodies directed against circulating blood coagulation factor (F) VIII.[1] These auto-antibodies are distinct from the alloantibodies that form in patients with congenital hemophilia A in response to factor replacement therapy.[2] In approximately 50% of cases FVIII autoantibodies occur in patients with no concomitant disease, while the remaining cases may be associated with an underlying medical condition such as pregnancy, hematological or solid tumors, infections, use of medications, or autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and thyroid disorders.[2] The estimated incidence rate of AHA is approximately one case per million persons annually, though it is likely that this figure is underestimated in the elderly population.[3] This presumption is underscored by evidence indicating that the incidence of AHA increases with age. The incidence rate in children under 16 years is estimated to be 0.045 per million persons annually, compared to an estimated rate of 14.7 per million persons annually in individuals over 85 years of age.[3]

Patients with AHA often experience serious subcutaneous bleeding episodes in the muscles or soft tissues and mucous membrane. This varies from the clinical manifestations of patients with congenital hemophilia A in which bleeds into the joint spaces are common.[4,5] Severe bleeds occur in up to 90% of patients with AHA and may result in an estimated mortality rate due to bleeding ranging from 3% to 22%.[2]

Treatment for AHA focuses on treating and preventing the occurrence of bleeding episodes and eradicating the autoantibodies. Treatment choice is dependent on the site and severity of the hemorrhage, patient characteristics, concomitant disorders, and inhibitor titer.[3] On the whole, treatment modalities include normalization of factor deficiency via pFVIII, plasma, or recombinant FVIII, bypassing inhibitor activity with recombinant activated FVII (rFVIIa) or activated prothrombin complex concentrates (aPCCs), neutralization of the autoantibodies by high-dose immunoglobulin, and removal of the pathogenic autoantibodies by plasmapheresis or immunoadsorption.

Bypassing agents such as rFVIIa and aPCCs are recommended as first-line treatment for acute bleeds due to demonstrated efficacy in the literature.[6,7,8] The choice of agent depends on several factors, including knowledge of the patient's previous response, convenience of dosing, use of plasma-derived products and cost.[9] Treatment with demopressin (DDVAP) may increase FVIII levels in some patients, though literature indicates that this treatment may be contraindicated in some patients due to

comorbidities.[9] The international recommendations on the diagnosis and treatment of patients with AHA also recommend pFVIII as alternative therapy, however the drug was not available at the time of writing. Therefore, the authors indicated that the therapy may be added to an updated version of the guidelines after efficacy and safety had been established.

A recently developed highly purified antihemophilic recombinant porcine FVIII (rpFVIII) therapy (Obizur) was approved for the treatment of AHA. In AHA patients, Obizur temporarily replaces inhibited human FVIII with an rpFVIII based on the rationale that it is less susceptible to inactivation by circulating human FVIII antibodies. Twenty-nine adult subjects having autoimmune inhibitory antibodies to human FVIII and experiencing serious bleeding episodes that required hospitalization, were enrolled in a multi-center, prospective, open-label clinical trial that evaluated the safety and efficacy of Obizur. One of the subjects considered evaluable at study entry was later found to not have AHA, leaving 28 subjects evaluable for efficacy. Patients were treated with Obizur until resolution of bleeding or dosing was continued at the physician's discretion.

Each of the 28 evaluable patients with AHA showed an effective (bleeding stopped) or partially effective (bleeding reduced) response and clinical improvement at 24 hours after initial infusion. Additionally, a total of 86 percent (24/28) had successful treatment of the initial bleeding episode. Data from this study demonstrate an acceptable safety profile of Obizur. Of the ten subjects with detectable anti-porcine factor VIII antibodies at baseline, two (20%) experienced an increase in antibody titer, while eight experienced a decreasing to a non-detectable titer. Five of the 19 subjects that were negative for anti-porcine FVIII antibodies at baseline developed anti-porcine FVIII antibodies following exposure to Obizur. All subjects were also monitored for development of binding antibodies to baby hamster kidney (BHK) protein by a validated sequential ELISA (enzyme-linked immunosorbent assay). No patients developed *de novo* anti-BHK antibodies.[10]

7.2 Critical Review of Available Data

Data from the clinical trial demonstrated a positive safety and efficacy profile of pFVIII in patients with AHA, yet data are needed regarding safety and effectiveness of Obizur in the real-world setting. Therefore, Baxalta plans to conduct the present study to assess safety of Obizur based on incidence of related serious adverse events (SAEs) to describe the homeostatic effectiveness of Obizur in the treatment of bleeding episodes, determine frequency and dosage, describe concomitant medications and AHA diagnosis, and describe immunogenicity of Obizur during the course of routine treatment.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The study is designed to assess safety and to describe factors related to the safety, utilization and effectiveness of Obizur in real-world clinical practice.

8.2 Primary Objective

The primary objective is to determine the incidence of therapy-related SAEs in patients with AHA who are prescribed and treated with Obizur in routine clinical practice.

8.3 Secondary Objectives

1. To describe hemostatic effectiveness of Obizur in the treatment of bleeding episodes.
2. To describe the frequency, total dose, and total number of infusions of Obizur required to control bleeding episodes.
3. To describe concomitant medication use.
4. To describe the clinical setting in which patients first present with symptoms of AHA, patient co-morbidities, time from presentation of symptoms to a positive diagnosis, and time from a positive diagnosis to first treatment with Obizur.
5. To describe the immunogenicity of Obizur during the course of treatment.

9. RESEARCH METHODS

9.1 Study Design

This study is a multi-center, uncontrolled, open-label, non-interventional postauthorization safety surveillance study to describe the use of Obizur in patients with AHA, and secondarily, where data are available, to describe the hemostatic effectiveness and immunogenicity of Obizur. Approximately 40 male and female patients ≥18 years of age with AHA in the United States will be enrolled over a 3.5 year period with follow-up from the date of treatment through 180 days; it is expected this prospective study will enroll up to two patients per month. Patients should be enrolled within five days of initiating Obizur to ensure unbiased prospective observation.

In addition, in an attempt to collect all safety and utilization data on patients treated with Obizur since Food and Drug Administration approval in October 2014, Baxalta will conduct a retrospective chart review on persons treated with Obizur prior to the prospective study start date. Baxalta expects there will be approximately 30 to 40 patients who were treated with Obizur prior to the study start date, on whom retrospective data will be collected.

Prospective data will be collected for each subject over a period of approximately 180 days from the time of Obizur treatment; in addition, data points that are retrospective in nature (such as comorbidities and prior medical treatment) will be obtained from the medical chart for the time period prior to Obizur treatment. A subject or a subject's legally authorized representative will provide signed informed consent according to local regulations, prior to data collection initiation. Signed informed consent should be obtained within five days of Obizur treatment for patients newly treated with Obizur.

Among patients in the retrospective cohort, for whom Obizur treatment occurred prior to initiation of the prospective study, signed informed consent will be obtained at the time the patient has a clinic visit. If the patient is deceased or lost to follow-up, only anonymized data will be collected from the medical chart and entered into the electronic data capture (EDC) system.

The choice of Obizur use is to be made *independent of and prior to* any decision by the subject or the subject's legally authorized representative to participate in this study. The treating physician will determine the treatment regimen, as well as frequency of laboratory and clinical assessments, according to routine clinical practice.

Data collection will be limited to existing information and for the purposes of this study will be collected if data are (a) part of routine clinical practice or (b) elected by an investigator. Available data from patient visits shall be entered into an EDC system and checked for data quality. Keeping with the non-interventional study design, there will be no *required* visits, medical tests, laboratory tests and/or procedures, or interventions during the study duration. Baxalta will provide the option for physicians to use a central laboratory to process anti-human and anti-porcine FVIII antibodies, should they choose to do so.

If these assessments are made, it is recommended that a Bethesda assay using the Nijmegen modification be undertaken for antibodies measurement, and that pFVIII antibodies be tested before and during treatment administration, and in the follow-up. Lab results from local or other central laboratories available in the medical chart will be recorded; it is not a requirement of the study that these lab tests be completed.

9.1.1 Primary Outcome

The primary outcome is patient safety in terms of AEs, their seriousness and severity. In particular, describing:

- Incidence of therapy-related SAEs and level of severity

9.1.2 Secondary Outcomes

Secondary outcomes will describe:

- Effectiveness assessment for resolution of bleeding, determined as either bleeding stopped or didn't stop
  - If bleeding did not stop, a reason should be provided (e.g., death)
- Time to bleeding resolution, death, or switch to another treatment.
- Number of Obizur units/kg required for control of bleeding (bleeding stopped)
- Number of Obizur infusions required for control of bleeding (bleeding stopped)
- Newly recognised anti-pFVIII inhibitors or increase in titer of anti-pFVIII inhibitors from pre-treatment level, impact on hemostatic efficacy and associated clinical manifestations if any, and evolution of titer over time
- Occurrence of hypersensitivity reactions
- Occurrence of any thrombogenic event

9.2 Setting

9.2.1 Medicinal Product(s)/Medical Device(s)

Administration, packaging, labeling, and storage for the product are described in the product labeling.

The active ingredient in Obizur is a recombinant analogue of porcine factor VIII (pFVIII) with an approximate molecular weight of 170 kDa. The rpFVIII molecule in Obizur is a glycoprotein containing a 90 kDa heavy chain and a 80 kDa light chain. The B-domain normally present in naturally occurring pFVIII has been replaced with a twenty-four amino acid linker. Once activated, the resulting rpFVIIIa has a comparable activity to the endogenous human FVIIIa.

Obizur is expressed in a genetically engineered baby hamster kidney (BHK) cell line which secretes rpFVIII into the cell culture medium, and the rpFVIII protein is then purified using a series of chromatography and filtration steps. The production process includes two dedicated viral clearance steps - a solvent/detergent treatment step for viral inactivation and a nanofiltration step through a series of two 15-nm filters for removal of viruses. No additives of human or animal origin are used in the formulation of Obizur.

Obizur is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with the diluent (Sterile Water for Injection). Obizur is available in single-use vials that nominally contain 500 units (U) per vial. When reconstituted with the diluent, the product contains the following components per mL: 8.8 mg sodium chloride, 0.04 mg Tris-base, 0.73 mg Tris-HCl, 1.47 mg tri-sodium citrate dehydrate, 0.15 mg calcium chloride dehydrate, 1.9 mg sucrose, and 0.05 mg polysorbate 80.

Each vial of Obizur is labeled with the actual rpFVIII activity expressed in U determined by a one-stage clotting assay, using a reference rpFVIII material calibrated against the World Health Organization (WHO) 8th International Standard for human FVIII concentrates. The specific activity of Obizur is in the range of 11000 - 18000 U per milligram of protein. The potency values of Obizur determined by the chromogenic assay vary and are approximately 20-50% lower than those of the one-stage clotting assay.

9.2.2 Duration of Study Period(s) and Subject Participation

For the prospective portion of the study, the overall study enrollment and collection period will be 4 years from study initiation (i.e., first site initiated) to study completion (i.e., last subject out). The recruitment period is expected to be 3.5 years. Subject participation period is 180 days for each qualifying bleeding episode. Including start-up and closure, the entire study will take approximately 4.5 years.

Retrospective chart review will be conducted for approximately six weeks after the first site is initiated for the patients with a bleeding episode during which they were treated with Obizur prior to the start date of the prospective study. Utilization data for this group of patients will be presented in a one-time Retrospective Utilization Data Report.

Persons with a bleeding episode prior to study start date will be asked to provide written informed consent, so data can be collected for up to 180 days post-treatment. For several patients, this will require some retrospective and some prospective data collection. Subjects from both groups (prospective and retrospective) will be included in the Annual Study Update Report, and their inclusion in the overall analysis will be outlines in the statistical analysis report (SAP).

- First site initiated: September 2015
- Data lock for retrospective data collection: December 2015
- Report of retrospective utilization results: January 2016
- Last subject in: March 2019
- Last subject out: September 2019
- Final clinical study report (CSR): January 2020

Subjects who have a bleeding episode successfully controlled by Obizur may be retreated with Obizur for any subsequent bleeding episode; these subjects will not be double-counted in the total 40 patients, but will be deemed a separate bleeding episode in analysis. Subsequent bleeds are defined as bleeds that occur greater than 72 hours after finalizing initial treatment For each bleed newly treated with Obizur, the 180-day follow-up period will restart. If a subject experiences a new bleed within the ongoing 180-day follow-up period, the subject will (a) still be followed for the original 180 days and (b) will also be followed for 180 days post the 2nd bleed, or until the study ends (i.e., there will be overlap in the follow-up period).

9.2.3 Subject Selection Criteria

Subjects must be prescribed Obizur for the treatment of a bleeding episode by a physician, prior to the decision to enroll in the study.

9.2.3.1 Inclusion Criteria

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

1. Subject is ≥18 years of age at the time of informed consent.
2. Subject has AHA, and is being treated/was treated with Obizur.
3. Subject is willing and able to comply with the requirements of the protocol.

9.2.3.2 Exclusion Criteria

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

1. Subject has a known anaphylactic reaction to the active substance, to any of the excipients, or to hamster protein.
2. Subject has a concomitant bleeding disorder(s) other than AHA.
3. Subject has participated in another clinical study involving a medicinal product or device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving a medicinal product or device during the course of the study.

9.2.4 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study. A legally authorized surrogate may also sign the informed consent. If the patient is deceased or lost to follow-up, only anonymized data will be collected from the medical chart and entered into the electronic data capture (EDC) system.

9.2.5 Subject Identification Code

The following series of numbers will comprise the subject identification code (SIC): protocol identifier 241302 to be provided by the MAH, two- or three-digit study site number (e.g., 02) to be provided by the MAH, and three- or four-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form [ICF]). For example, the third subject who signed an ICF at study site 02 will be identified as Subject 161302-020003. All study documents pertaining to the subject (e.g., case report forms [CRFs], clinical documentation, etc.) will be identified with the SIC.

Alternative uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

9.2.6 Screening and Follow-up

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure or decision to not enroll. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in Figure 1.

Figure 1
Study Design for Baxalta Non-Interventional Study Protocol 241302

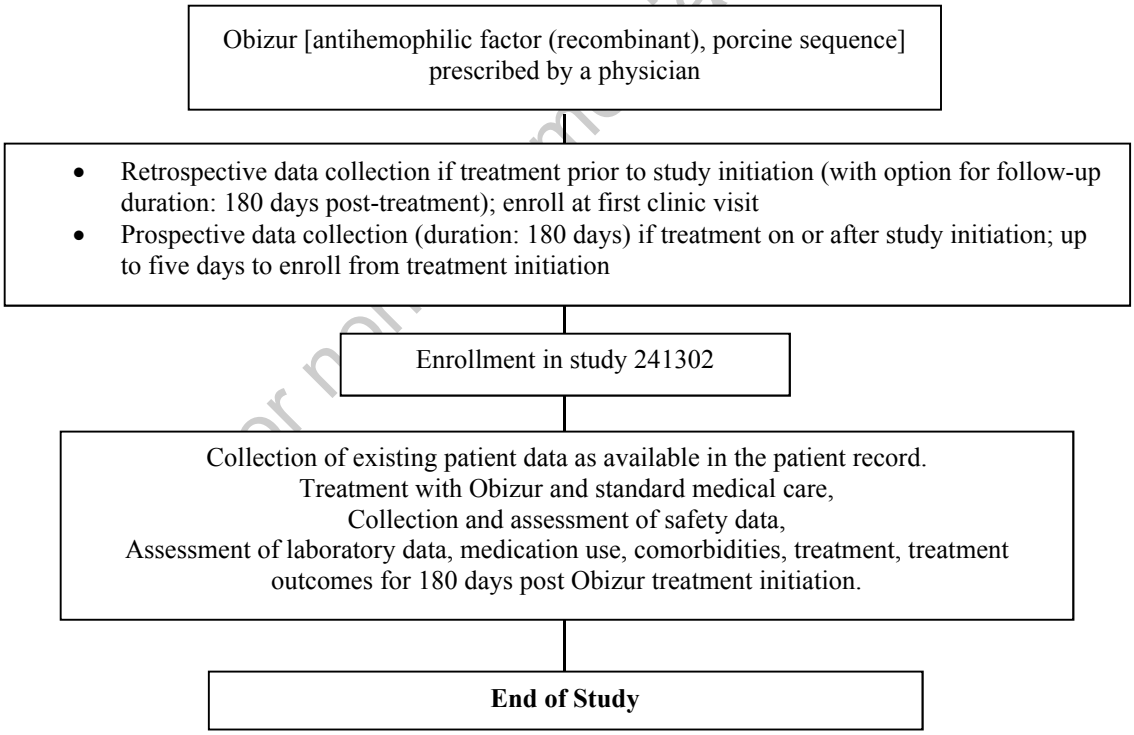

Table 1.
Schedule of Study Assessments

Assessments	Screening	Baseline	Interval/Data available per existing patient visits, medical charts						Study Completion/ Termination[a]
			Time A	Time B	Time C	Time D	Time E	Time F, etc.	
Informed Consent [b]	X								
Eligibility Criteria [b]	X								
Demographic Information		X							
AHA Information		X	X	X	X	X	X	X	
Medical History		X	X	X	X	X	X	X	
Concomitant Medications		X	X	X	X	X	X	X	X
Safety: SAEs		X	X	X	X	X	X	X	X
Laboratories (as available) [c]		X	X	X	X	X	X	X	X
Obizur Treatment Information		X	X	X	X	X	X	X	X
Concurrent Bleeding Episodes		X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	

[a] Include for cases of withdrawal or discontinuation.
[b] Occurs before start of data collection.
[c] For laboratory assessments, see Table 2.
[d] Only if additional bleeds occur.

Table 2. Clinical Laboratory Data Collection
Clinical Laboratory Data Collection

Assessments	Screening	Baseline	Interval/Data available per existing patient visits, medical charts						Study Completion/Terminationa
			Time A	Time B	Time C	Time D	Time E	Time F, etc.	
Hematology*									
Hemoglobin		X----------→							
Hematocrit		X----------→							
CBC with differential, if consistent with local practice		X----------→							
FVIII anti-human and anti-porcine antibodies±		X----------→							

*Given the observational nature of this study, data will be collected as recorded. No laboratory assessments are mandated by this Protocol.
± Baxalta will provide the option for physicians to use a central laboratory to process FVIII anti-human and anti-porcine antibodies

9.2.7 Subject Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF.

The data collected on withdrawn subjects will be used in the analysis and included in the non-interventional study report.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and responsible party have the discretion to discontinue any subject from the study if, in their judgment,

continued participation would pose an unacceptable risk for the subject.

9.2.8 Study Stopping Rules

Enrollment into the study will end if the following criteria are met:

1. At least 40 subjects have been enrolled in the prospective study.

9.3 Variables

9.3.1 Baseline subject information

- Demographics (age, sex, weight, race, ethnicity)
- Pregnant or breast-feeding

9.3.2 Medical history

- Bleed description
  - Spontaneous/traumatic, superficial/internal
  - Location: intramuscular, retroperitoneal, gastrointestinal, intracranial, specify
- Hematology laboratory results (baseline and any follow-up)
  - Hemoglobin [< 8g/dL, severe]
  - Hematocrit
  - Complete blood count with differential.
  - Date of blood draw (include baseline and any follow-up)

- Bleed severity (severe/not severe)
  - Measured by physician
  - Hemoglobin levels [< 8, severe]
    - Date of draw and results
- FVIII activity levels (baseline)
  - Date of draw and results
- Anti-human and anti-porcine FVIII antibody titers (baseline)
  - Date of draw and results
- Prior treatment with hemostatic agents (baseline)
  - Regimen received
  - Medication start and stop dates (retrospective cohort only)
- Comorbidities (baseline)
  - List of all comorbidities with start dates
  - Physician relationship assessment (possibly associated with causation of AHA/not associated with AHA)
- Current medications not related to AHA (taken within 14 days)
  - Name of medication
  - Medication start/stop dates
  - Medication dose
- AHA diagnosis
  - Date
- Presentation of AHA symptoms
  - Symptom
  - Date

9.3.3 Medication during treatment

- Immunosuppressive agents received to treat underlying AHA
  - Dose and frequency
  - Date

9.3.4 Obizur Utilization

- Date and time of infusion
- Dose per infusion (U/kg)
- Total number of days of Obizur use

9.3.5 Safety (collect all SAEs; endpoint is therapy-related SAEs)

For the purpose of this study only serious adverse events (SAEs) will be collected. Reasons for collecting SAEs only include the following: Patients enrolled in this study are often elderly with a multitude of comorbidities and high medication intake. Additionally, they are seriously diseased receiving treatment in intensive care units. Thus, making qualified assessments of non-serious AEs with respect to isolated medicinal products is next to impossible given the multitude of treatments administered concomitantly.

- Key safety concerns:
  - Inhibitor development against pFVIII (post baseline)
    - Date of inhibitor draw
  - Hypersensitivity reactions including anaphylaxis
  - Thrombogenicity
  - Outcomes, including death (yes/no, date of death)

9.3.6 Bleed cessation assessment

- Overall effectiveness assessment for therapy response
  - Bleeding stopped versus not stopped
  - Date bleeding stopped
  - If bleeding not stopped, note reason (e.g., death, new treatment)
- FVIII activity measurements throughout treatment
  - Date assay performed
- Human and pFVIII antibody titers
  - Human and pFVIII antibody titers
    - Requirement to have a reference lab for anti-porcine FVIII antibody measurement (Central lab available if physician chooses to use it)

- Date and titer levels, starting at baseline through 180 days

- Concurrent bleeding episodes
  - Exacerbation of bleeding at an existing site
    - Date of exacerbation
    - Site of bleed
  - Appearance of bleeding at a new site
    - Date
    - Site of bleed

- Treatment for bleeding episodes that occur greater than 72 hours after stopping treatment for the original bleed
  - Bleed start date
  - Bleed stop date
  - Date of treatment

- Length of hospital stay per bleed (days)
  - Hospital admission/discharge dates
  - Location within hospital (ER, ICU, etc.)
  - Primary reason for hospitalization

9.3.7 Medical History, Medications, and Non-Drug Therapies

At screening, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 11.1.2.1) or surgery and start and end dates: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received within the 14 days prior to product administration until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

Pregnant women will be followed for one year post-treatment for any evidence of teratogenicity, birth defects and other congenital complications in their offspring.

9.3.8 Physical Examinations

At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. During follow-up, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the SAE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Section 11.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

9.3.9 Clinical Laboratory Parameters

Baxalta will provide the option for physicians to use a central laboratory to process, anti-human and anti-porcine FVIII antibodies, should they choose to do so. If these assessments are made, it is recommended that a Bethesda assay using the Nijmegen modification be undertaken for antibodies measurement, and that pFVIII antibodies be tested before and during treatment administration, and in the follow-up. Lab results from local or other central laboratories available in the medical chart will be recorded; it is not a requirement of the study that these lab tests be completed.

Hematology

Laboratory parameters may include Hematology parameters (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count), and will be documented in the CRFs if collected in regular clinical practice.

9.3.10 Vital Signs

Vital signs will include height (cm) and weight (kg), and will be reported at enrollment, and whenever else as available in the medical records as close to the time of Obizur dosing as possible. Vital signs will be recorded on the CRF.

9.3.11 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed the study according to the protocol.

Reasons for completion/discontinuation will be reported on the Completion/ Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up, dropout), study terminated by the MAH, or other (reason to be specified by the investigator). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF and will be used in the analysis and included in the study report.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations performed as part of the evaluation of the event will be reported to the MAH. Details of the outcome may be reported to the appropriate regulatory authorities by the responsible party.

9.4 Data Sources

Investigators (or clinical staff trained for data entry) will enter data required by the protocol into the EDC system; all data shall be transcribed within 14 days of entry into the patient chart. Designated staff will have access to the data entry system after they have been fully trained.

Data for entry could come from an electronic medical chart, a paper chart or from laboratory forms. It is expected that the majority of the data will be obtained from hematology departments in hospitals; however, there is potential that other sources of documentation may be used. Source type will be captured in the CRF.

Validation programs will be designed to check for data discrepancies. Data will be reviewed for completeness and accuracy; any necessary data changes will be communicated to the clinical site.

Post-electronic data entry, MedDRA coding will be conducted for all medical conditions reported and WHODRUG coding for all reported medications.

9.4.1 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, pharmacy dispensing records, recorded data from automated instruments, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

Data will be extracted from existing patient medical charts; all data shall be transcribed into the EDC system within 14 days of entry into the patient chart. Post-electronic data entry, MedDRA coding will be conducted for all medical conditions (including medical history) reported and WHODRUG coding for all reported medications.

9.5 Study Size

There will be one prospective cohort of approximately 40 patients with AHA who have had a bleeding episode and are being treated with Obizur prospectively. This sample size of 40 will be adequate to assess the number of therapy-related safety events experienced by this group of Obizur-treated AHA patients. In the event that some data from the retrospective group are assessed with the prospective cohort, (raising the total number of evaluable patients from 40 to 50), the following 95% confidence intervals (CIs) would be obtained.

The following calculations were completed to assess the two-sided 95% CIs around the proportion of subjects experiencing a true safety event in this population being treated with Obizur; the exact (Clopper-Pearson) method was used for calculation. These confidence limits are defined for the proportion (number of subjects with an event divided by the number of treated subjects) only. For the gray highlighted areas below, assuming 5% of subjects experience a related safety event within the population of AHA patients administered Obizur, a sample size of 40 subjects yields a two-sided 95% CI of (0.6%, 16.9%) and a sample size of 50 persons yields a two-sided 95% CI of (0.8%, 15.1%).

	Actual Width[a]	Proportion (P)[b]	95 % CI[c] Lower Limit[d]	95% CI[c] Upper Limit[e]
40 Subjects	10.7%	1%	0.0%	10.7%
	13.8%	3%	0.1%	13.9%
	16.3%	5%	0.6%	16.9%
	18.4%	7%	1.3%	19.7%
	20.9%	10%	2.7%	23.7%
	24.1%	15%	5.7%	29.8%
50 Subjects	9.0%	1%	0.0%	9.0%
	12.0%	3%	0.2%	12.2%
	14.3%	5%	0.8%	15.2%
	16.2%	7%	1.7%	17.9%
	18.5%	10%	3.3%	21.8%
	21.5%	15%	6.4%	27.9%

[a] Actual Width: Value of the distance from the lower limit to the upper limit of the 95% CI. Width if P = 0.5 is the maximum width for a confidence interval with the given sample size.
[b] Proportion (P): Proportion of the sample assumed to have the outcome (i.e., SAE).
[c] Confidence level = 0.95.
[d] Lower Limit (lower limit of the 95% CI).
[e] Upper Limit (upper limit of the 95% CI).

9.6 Data Management

9.6.1 Data Collection Methods

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as “source data” (see Section 9.4.1) records detailing the progress of the study for each subject, signed ICFs, correspondence with the Ethics Committee (EC) and the study monitor/MAH, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), subject diaries (if used), and data clarifications requested by the MAH.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: (1) the first entry will be crossed out entirely, remaining legible; and (2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

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

If electronic format CRFs are provided by the MAH, only authorized study site personnel will record or change data on the CRFs. If data are not entered on the CRFs during the study visit, the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site.

The handling of data by the MAH, including data quality assurance, will comply with regulatory guidelines and the standard operating procedures of the MAH. Data management and control processes specific to the study will be described in the data management plan (see Section 14.1).

9.6.2 Software

The software for data management will be determined by the CRO conducting the study.

All computations and generation of tables, listings, and data for figures will be performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA), or a comparable statistical software.

9.7 Data Analysis

9.7.1 Datasets and Analysis Cohorts

All treated subjects will be included in the analysis dataset.

9.7.2 Handling of Missing, Unused, and Spurious Data

Analyses will be performed using available data, because, due to the non-interventional nature of the study, missing values are expected. There will be no imputation. All reasonable attempts should be made by the site to limit the amount of missing data.

9.7.3 Methods of Analysis

The analysis plan will be fully described in a written and approved SAP. Briefly, descriptive statistics will include specifically but not exclusively, arithmetic mean, medians, standard deviations, minimum, maximum, proportions, frequency counts, 25th and 75th percentiles, and 95% confidence intervals of select point estimates. Figures will be prepared to illustrate patterns of data over time where appropriate. Analyses will be performed using available data (missing values are expected due to the non-interventional nature of the study).

Therapy-related SAEs will be described in listings and tables and will presented by MedDRA system organ class (SOC) and preferred term (PT) and incidence rates will be calculated. Incidence will be interpreted as incidence proportion (number of patients with events/number of patients treated) and incidence rate (xx events per xx year of follow-up). Tables outlining the hemostatic effectiveness and immunogenicity of Obizur, frequency, total dose, total number of infusions of Obizur required to control bleeding episodes will be developed. Tables displaying concomitant medications and patient comorbidities will also be created. Time from symptoms to diagnosis to treatment will be reported. Where feasible, analyses may be performed within meaningful subgroups.

9.7.3.1 Primary Outcome

The primary outcome (see Section 9.1.1) is patient safety in terms of AEs, their seriousness and severity. In particular, describing:

- Incidence of therapy-related SAEs and level of severity

These data will be described in tables and listings.

9.7.3.2 Secondary Outcomes

The secondary outcomes will be descriptive in nature.

Secondary outcomes will describe effectiveness of Obizur as measured by:

- Effectiveness assessment for resolution of bleeding, determined as either bleeding stopped or didn't stop.
  - If bleeding did not stop, a reason should be provided (e.g., death)
- Time to bleeding resolution, death, or switch to another treatment.
- Number of Obizur units/kg required for control of bleeding (bleeding stopped)
- Number of Obizur infusions required for control of bleeding (bleeding stopped)
- Newly recognised anti-pFVIII inhibitors or increase in titer of anti-pFVIII inhibitors from pre-treatment level, impact on hemostatic efficacy and associated clinical manifestations if any, and evolution of titer over time
- Occurrence of hypersensitivity reactions
- Occurrence of any thrombogenic event

9.7.4 Planned Interim Analysis of the Study

Annual study report updates will be completed, which will include basic demographic and safety information. Complete information on these reports will be outlines in the SAP. No formal interim analyses are planned for this study.

9.8 Quality Control

Examples for quality control and quality assurance planning and implementation for the construction of the analytical data and the analysis of data are detailed in CDER's Manual of Policy and Procedures (MAPP) 6700.2 Standards for Data Management and Analytic Processes in the Office of Surveillance and Epidemiology (OSE), (FDA MAPP 6700.2).[i]

9.8.1 Investigator's Responsibility

The Investigator will comply with the protocol (which has been approved/given favorable opinion by the competent/health authority and/or EC, as applicable), and applicable regulatory requirements as described in the Non-interventional Trial Agreement.

[i] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm#ODS

The Investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the MAH. The term "Investigator" as used in this protocol as well as in other study documents, refers to the Investigator or authorized study personnel that the Investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the Investigator, except where the Investigator's signature is specifically required.

The Investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Non-interventional Trial Agreement.

9.8.2 Direct Access to Source Data/Documents

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

9.8.3 Training

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

9.8.4 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Non-interventional Trial Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan (see Section 14.1).

9.8.5 Auditing

The MAH and/or MAH's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, and applicable regulatory guidelines/requirements. The Investigator will permit auditors to visit the study site, as described in the Non-interventional Trial Agreement. Auditing processes specific to the study will be described in the clinical quality management plan (see Section 14.1).

9.8.6 Non-Compliance with the Protocol

If monitoring and/or auditing activities identify serious and/or persistent non-compliance with the protocol, the MAH may terminate the Investigator's participation in the study.

9.9 Limitations of the Research Methods

A challenge when conducting a study among patients with a rare disease is to identify enough patients for the study. Based on the clinical trial data, there is an expectation that this is feasible.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Compliance Statement

This study will be conducted in accordance with this protocol and applicable national and local requirements for good pharmacovigilance practices.

10.2 Subject Privacy

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

10.3 Ethics Committee(s) and Regulatory Authorities

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

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

10.4 Informed Consent

Investigators will choose patients for enrollment in consideration of the study eligibility criteria. The Investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an ICF before entering into the study according to applicable regulatory requirements. Before use, the ICF will be reviewed by the MAH and approved by the EC and regulatory authority(ies), where applicable, (see Section 10.3). The ICF will include a comprehensive explanation of the study without any exculpatory statements, in accordance with the elements required by applicable regulatory requirements. Patients or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree to the use of their data for the study, unless they withdraw voluntarily or are terminated from the study for any reason.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Adverse Events

11.1.1 Definitions

An AE, in this study, is defined as any untoward medical occurrence in a subject administered Obizur. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death.

11.1.1.1 Serious Adverse Event

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

- Outcome is fatal/results in death (including fetal death).
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
    - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
    - Thrombotic or embolic event (e.g., stroke, TIA, myocardial infarction, DVT, pulmonary embolism, etc.)

Uncomplicated pregnancies, following maternal or paternal exposure to product are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

11.1.1.2 Non-Serious Adverse Event

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

11.1.1.3 Unexpected Adverse Events

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

11.1.1.4 Preexisting Diseases

Preexisting diseases that are present before entry into the study are described in the medical history, and those that manifest with the same severity, frequency, or duration during the study, will not be recorded as SAEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, and the event is considered an SAE, it must be described on the AE CRF.

11.1.2 Assessment of Adverse Events

Each SAE from time of Obizur treatment until study completion will be described on the SAE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the SAE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definitions in Section 11.1). For the purpose of this study only SAEs will be collected. Reasons for collecting SAEs only include: patients enrolled in this study are often elderly with a multitude of comorbidities and high medication intake. Additionally, they are seriously diseased receiving treatment in intensive care units. Thus, making qualified assessments of non-serious AEs with respect to isolated medicinal products is next to impossible given the multitude of treatments administered concomitantly. Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 11.1.1.1
- Severity as defined in Section 11.1.2.1
- Causal relationship to Obizur exposure as defined in Section 11.1.2.2

For each SAE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving SAEs will be followed until resolution, or 180 days post Obizur administration, which is first. If the severity rating for an ongoing SAE changes before the event resolves, the original SAE report will be revised (i.e., the event will not be reported as separate SAE). During the course of any SAE, the highest severity rating will be reported.

Any pregnancy that occurs after administration of medicinal product Obizur will be reported on a Pregnancy Form and followed-up at one year post-delivery, if feasible.

11.1.2.1 Severity

The Investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below; only AEs considered serious will be reported in this study:

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

11.1.2.2 Causality

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

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

11.2 Non-Medical Complaints

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

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

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The investigator will comply with the publication policy as described in the Non-interventional Trial Agreement.

13. REFERENCES

1. Huth-Kühne A, Baudo F, Collins P et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica. 2009;94:566-575.

2. Franchini M, Mannucci PM. Inhibitors of propagation of coagulation (factors VIII, IX and XI): a review of current therapeutic practices. Br.J.Clin.Pharmacol. 2011;72:553-562.

3. Franchini M, Mannucci PM. Acquired haemophilia A: A 2013 update. Thromb.Haemost. 2013;110:1114-1120.

4. Srivastava A, Brewer AK, Mauser-Bunschoten EP et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19:e1-e47.

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6. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. Blood. 2004;104:3858-3864.

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8. Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. Haemophilia. 2004;10:169-173.

9. Collins PW, Chalmers E, Hart D et al. Diagnosis and management of acquired coagulation inhibitors: A guideline from UKHCDO. Br.J.Haematol. 2013;162:758-773.

10. Baxter Healthcare Corporation. Package Insert: OBIZUR [antihemophilic factor (recombinant), porcine sequence] lyophilized powder for solution for intravenous injection. 10. 2014. OBIZUR.

14. ANNEXES

14.1 List of Stand-Alone Documents

Documents listed in Annex 1 are maintained separately from the study protocol. They can be provided on request.

No.	Document Reference No.	Date	Title
1	Number	Not finalized	Study Organization
2	Number	Not finalized	Clinical Monitoring Plan
3	Number	Not finalized	Data Management Plan

14.2 ENCePP Checklist for Study Protocols

A copy of the ENCePP Checklist for Study protocols completed and signed by the main author of the study protocol should be included. The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

- "Study start" means "Start of data collection"
- "Study progress" means "Progress report(s)"
- "Study completion" means "End of data collection"
- "Reporting" means "Final report of the study results"]

Refer to the completed ENCePP Checklist.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: ANTIHEMOPHILIC FACTOR (RECOMBINANT), PORCINE SEQUENCE (OBIZUR)

STUDY TITLE: POST MARKETING NON-INTERVENTIONAL SAFETY EVALUATION OF OBIZUR IN THE TREATMENT OF BLEEDING EPISODES FOR PATIENTS WITH ACQUIRED HEMOPHILIA A

PROTOCOL IDENTIFIER: 241302

ORIGINAL: 2015 MAR 11

OTHER PROTOCOL ID(s)

NCT Number: Not applicable

EudraCT Number: Not applicable

IND/IDE NUMBER: Not applicable

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

Signature of Principal Investigator Date

Print Name of Principal Investigator

Signature of MAH Representative Date

[redacted], MD

[redacted] Global Clinical Development BioScience