TITLE PAGE – PASS INFORMATION

PROTOCOL TITLE	Prospective and retrospective, non-interventional study to evaluate the safety and effectiveness of Obizur in real-life practice
PROTOCOL ID #	241501
AMENDMENT	Amendment 3: 20 JUL 2018 ALL VERSIONS: Amendment 3: 20 JUL 2018 Amendment 2: 24 MAY 2017 Amendment 1: 03 JUN 2016 Original: 21 MAR 2016
EU PAS REGISTER	EU PAS Register Number: EUPAS16055
MEDICINAL PRODUCT	
Active Ingredient(s)	ATC code: B02BD14 Antihaemorrhagics / Antihaemophilic Factor (Recombinant), Porcine Sequence International non-proprietary name: Susoctocog alfa
Medicinal Product	Obizur®
PRODUCT REF. #	EMEA/H/C/002792
PROCEDURE #	EMA/CHMP/471356/2015
MARKETING AUTHORISATION HOLDER (MAH)	Baxalta Innovations GmbH[i] Industriestrasse 67 A-1221 Vienna, AUSTRIA
JOINT PASS	No
RESEARCH QUESTION & OBJECTIVES	
Research Question	
The present Post-Authorisation Safety Study (PASS) addresses the safety, utilisation and effectiveness of Obizur in the treatment of bleeding episodes in real-life clinical practice in Europe and in the United States (US). It will collect further information, in particular regarding safety concerns, as established in the Risk Management Plan (RMP).	
Primary Objective	
The primary objective is to document the safety of subjects treated with Obizur in real-life clinical practice (any Adverse Event [AE]), including, but not limited to hypersensitivity reactions, thromboembolic events and dose dispensing medication errors.	

[i] Baxalta is now part of Shire

Secondary Objective(s)
To monitor Obizur use in real-life clinical practice including: 1. Immunogenicity corresponding to the development of newly recognised anti-porcine FVIII (pFVIII) inhibitors or an increase in titre of pFVIII inhibitors from pre-treatment levels (if known). 2. To describe the haemostatic effectiveness of Obizur in the treatment of bleeding episodes. 3. To describe the frequency, initial and total dose, and total number of infusions of Obizur administered to control bleeding episodes. 4. To describe concomitant medication use. 5. To describe the complete remission rate (inhibitors eradication)
Exploratory Objective(s)
[redacted]

COUNTRY(-IES) OF STUDY	Approximately 12 European countries: Germany, Austria, Italy, the Netherlands, Poland, Spain, France, Belgium, Portugal and potential other European countries (to be selected) Approximatively 6 sites in United States
AUTHOR	[redacted], MD Shire International GmbH Zählerweg 10 6301 Zug, Switzerland

MARKETING AUTHORIZATION HOLDER(S)

MAH	**Baxalta Innovations GmbH**[i] **Industriestrasse 67** **A-1221 Vienna, AUSTRIA**
MAH CONTACT PERSON	**[redacted], MD** [redacted] **Global Clinical Development Operations** **Baxalta Innovations GmbH**[i]

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.

NON-SERIOUS ADVERSE EVENT REPORTING

Any non-serious adverse events (AEs), all therapies/procedures to treat the non-serious AEs, and the outcome of the non-serious AEs must be reported in the Electronic Data Capture (EDC) system and transmitted to the MAH within seven business days from the site becoming aware of the non-serious AE. If the EDC system is out of order for more than seven days, the non-serious AEs must be reported on a paper Non-Serious Adverse Event Report Form (see Non-Serious Adverse Event Report Form for contact information).

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, and assessment of AEs in Section 11.1.2 and SAE in Section 11.1.1.1.

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AH	acquired haemophilia A
APCC	activated prothrombin complex concentrate
APTT	activated partial thromboplastin time
B19V	parvovirus B19
BHK	baby hamster kidney
CHA	congenital haemophilia A
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CRO	contract research organisation
DDVAP	desmopressin
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
EC	ethics committee
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EDC	electronic data capture
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FEIBA	factor eight inhibitor bypassing activity
FVIII	factor VIII
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
hFVIII	human FVIII
HIV	human immunodeficiency virus
IRB	Institutional Review Board

Abbreviation	Definition
LSO	last subject out
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
NMC	non-medical complaint
PAS	post-authorisation study
PASS	post-authorisation safety study
pFVIII	porcine FVIII
PL	package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
Q	quarter
rFVIIa	recombinant activated factor VII
RMP	risk management plan
SAE	serious adverse event
SAER	serious adverse event report
SAP	statistical analysis plan
SIC	subject identification code
SPC	summary of product characteristics
TLFs	tables, listings and figures
vWF	von Willebrand Factor
WHO	World Health Organisation
US	United States

3. RESPONSIBLE PARTIES

3.1 MAH's Authorised Representative (Signatory)

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH[i]

3.2 Investigator(s)

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

3.3 Other Individuals Involved in the Study

The names 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 Section 14.1).

4. ABSTRACT

Title: Prospective and retrospective, non-interventional study to evaluate the safety and effectiveness of Obizur in real-life practice

Original protocol version 1.0, date: 21 MAR 2016;
Protocol Amendment 1: 03 JUN 2016;
Protocol Amendment 2: 24 MAY 2017
Protocol Amendment 3: 20 JUL 2018

Main author: [redacted], MD, [redacted]

Rationale and background: Acquired haemophilia A (AH) is an uncommon and potentially life threatening autoimmune disease in which non-haemophilic persons develop autoimmune inhibitors directed against circulating blood coagulation factors, including factor VIII (FVIII). Obizur (susoctocog alfa) is a purified, recombinant, B-domain-deleted porcine sequence FVIII (pFVIII). Obizur temporarily replaces inhibited FVIII with a recombinant pFVIII, based on the rationale that it is sufficiently similar to human FVIII (hFVIII) to have a haemostatic effect, yet sufficiently different so as to be less susceptible to inactivation by circulating inhibitors.

The haemostatic efficacy and safety of Obizur in subjects with AH was demonstrated by a pivotal phase II/III study, a multi-centre, international, prospective, open-label clinical trial that evaluated Obizur in 29 adult subjects (28 with confirmed AH) having autoimmune inhibitors to hFVIII.

As with all medicinal products, the population exposed during clinical trials and duration of follow-up is limited. The risk management plan (RMP) of Obizur highlights the need to continue monitoring the use of Obizur in clinical practice. At the time of approval of the marketing authorisation it was agreed with the European Medicines Agency (EMA) to further monitor the safety profile of the medicinal product, which includes the conduct of a non-interventional post-authorisation safety study (PASS). This PASS will collect further safety information on hypersensitivity reactions, will routinely monitor thromboembolic events and dose dispensing medication errors. In addition, it will also collect other adverse events (AEs), information on inhibitory antibodies to Obizur, potential lack of efficacy, according to clinical practice at the participating centres.

Research question and objectives: The present PASS addresses the safety, utilisation, and effectiveness of Obizur in the treatment of bleeding episodes in real-life clinical practice in Europe and in the United States (US). The study is designed to collect further information in particular regarding safety concerns, as established in the Risk Management Plan (RMP).

The primary objective of the study is to document the safety of subjects treated with Obizur in real-life clinical practice by collecting any AE including but not limited to:

- Hypersensitivity reactions
- Thromboembolic events
- Dose dispensing medication errors.

The secondary objectives of the study are to monitor Obizur use in real-life practice including:

- Immunogenicity corresponding to the development of newly recognised anti-pFVIII inhibitors or an increase in titre of anti-pFVIII inhibitors from pre-treatment levels (if known) during the course of treatment and up to 180 days after the last administration of Obizur, where available
- To describe the haemostatic effectiveness of Obizur in the treatment of bleeding episodes
- To describe the frequency, total dose, and total number of infusions of Obizur administered to control bleeding episodes
- To describe concomitant medication use.
- To describe the complete remission rate (inhibitors eradication)

Exploratory objective: [redacted]

Study design: This study is a non-interventional post-authorisation safety study (PASS), designed as a single cohort, uncontrolled, multi-centre European and US study based on prospective and retrospective data collection. It aims to describe Obizur overall safety in real-life clinical practice.

The decision to administer Obizur, as well as the frequency of laboratory and clinical assessments will be made by the investigator, independent of the study, and is not mandated by study design or protocol. The study will be implemented in countries sequentially, as the product becomes commercially available. At each study site, all subjects to whom the treating physician decides to administer Obizur, and who meet inclusion/exclusion criteria, will be offered participation in the study and their data will be collected prospectively. The inclusion of prospective European subjects will be complemented by a retrospective chart review of existing data collected routinely for patients treated with Obizur (See Figure 1).

As available, subjects' demographics, clinical characteristics, comorbidities and other medical history, indication for treatment, characteristics of bleeding episode prompting treatment by Obizur, inhibitor levels (anti-hFVIII and anti-pFVIII), prior treatments to Obizur, Obizur treatment details, bleeding control, concomitant medications and AEs/ serious adverse events (SAEs) including death for any cause will be collected at baseline as available in the medical records, and as available from routine follow-up visits or from patients existing records for up to 180 days after the last administration of Obizur.

In case of bleeding episodes occurring more than 72 hours after initial bleeding control with subsequent re-administration of Obizur, all data elements described above will be captured, apart from data related to the prior Obizur treatment episode. Data can be collected for up to 180 days after the last dose of Obizur for this subsequent bleeding episode, or until the end of the study, whichever occurs first.

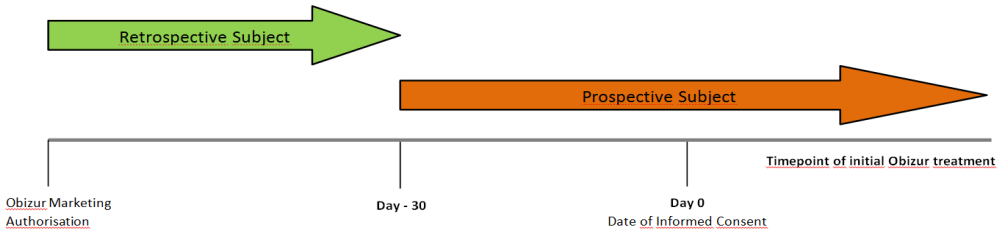
Population: During the assessment of the marketing authorisation application, the European Medicine Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommended this study should include as many subjects as possible in order to provide substantial safety information on Obizur treatment in real-life clinical practice. The overall duration of the study from study initiation (i.e., initiation of first site) to study completion (i.e., end of data collection) is not predetermined.

The target number of subjects to be enrolled is at least 50. Recruitment of these 50 subjects, with a maximum of 15 European retrospectively enrolled and 15 US prospectively enrolled subjects, is planned for an initial period of five years, and will be reassessed annually along with the yearly status update report and data summary provided for the annual assessment of the marketing authorisation under exceptional circumstances.

Data will be collected, where available, for each subject for up to 180 days following the last Obizur treatment during routine follow-up visits.

The definition of retrospective and prospective subjects has been defined as follows.

Figure 1
Subject classification (Prospective vs Retrospective)



- A prospective subject is a subject who is being treated with Obizur, i.e. informed consent is obtained within 30 days of Obizur administration
- A retrospective subject is a subject who was treated with Obizur between its marketing authorisation and more than 30 days before the date of the Informed Consent (Day -30). All subjects who do not have to sign an informed consent due to local regulations or do not have a screening visit (e.g. deceased patients) will also be considered as "retrospective patients".

In order to be enrolled, a subject must be prescribed Obizur by a physician for the treatment of a bleeding episode, independent of and prior to the decision to enrol the subject in the study. Subjects who meet ALL of the following criteria are eligible for this study:

- Adult subject (or legal representative) is willing to provide informed consent, unless informed consent is not required (e.g., deceased subjects, as local regulations allow).
- Subject is being treated or was treated with Obizur in routine clinical practice.

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

- Subject has known anaphylactic reactions to the active substance, hamster protein, or to any of the excipients of Obizur.
- Subject has participated in a clinical study involving a medicinal product or device within 30 days prior to enrolment, or is scheduled to participate in a clinical study involving a medicinal product or device.
- US Subject who has participated in the post-marketing study, NCT02610127.

Variables: The following variables are key to addressing the study objectives and will be collected as they are available:

- Safety variables: adverse events of special interest (AESIs) including hypersensitivity reactions, thromboembolic events, dose dispensing medication errors and, if available, immunogenicity (newly recognised anti-pFVIII inhibitors or titre increase of anti-pFVIII inhibitors from pre-treatment level); SAEs and AEs, both assessed by level of severity, relationship to Obizur, outcome, and whether associated with treatment discontinuation;
- Effectiveness variables: overall bleeding control (bleeding stopped or not with consequence); time to achieve bleeding control with Obizur; Obizur dosage to achieve bleeding control and overall Obizur treatment course to control bleeding;
- Demographics: age, sex, race/ethnicity (if allowed per local regulations), and any case of pregnancy/lactation;
- Hospital stay: initial hospitalisation and readmission (admission and discharge date, reason for admission, length of stay per level of care, destination upon discharge);
- Medical History: date and circumstances of diagnosis of anti-FVIII inhibitors; previous bleeding episodes (date, site, circumstances, severity, and treatment); history of cardiovascular disease/thromboembolic events; and other available significant medical history;
- Available comorbidities and patient specific characteristics (e.g. viral status of patients)
- Description of bleeding episode for which Obizur was prescribed: date, indication and circumstances of Obizur treatment, and description of bleeding episode (date of occurrence, bleeding site, circumstances of occurrence, severity, and type);
- Treatments (medications and procedures): treatments prior to Obizur; current Obizur treatments (number of units administered, dosage, dates and time of administration); additional treatments and procedures undertaken to control bleeding episodes; immunosuppressive agents and/or other treatments received to eradicate anti-FVIII inhibitors during the episode for which Obizur is being administered (name, treatment dose, start date, stop date, number of units and reason for administration/switch); and other concomitant medications;
- Physical examinations: vital signs, height, and weight;
- Clinical laboratory parameters: haematology and coagulation tests.

Data sources: All data will be abstracted from the subject's medical records at baseline, where available, and as available during the routine follow-up visits, with respect to both in-hospital stays and out-patient visits or laboratory tests, through prospective or retrospective data collection. Investigators (or clinical staff trained for data entry) will enter data required by the protocol into the electronic data capture (EDC) system. Data for entry could come from an electronic medical record, a paper medical record, or laboratory forms.

Study size: During the pivotal phase II/III study, seven out of 29 subjects (24%) treated by Obizur either developed de novo anti-pFVIII inhibitors or experienced a rise of anti-pFVIII inhibitors from baseline titres. Assuming that the expected proportion of subjects with any AESI is 25%, for instance, a sample of 50 subjects will provide the following 95% confidence interval (CI): 13.8, 39.3 (Clopper-Pearson method). The study aims to recruit as many subjects as possible, with a minimum target of 50 subjects, in order to provide substantial safety information on Obizur in real-life.

Data analysis: Categorical variables will be summarised by absolute and relative frequencies (number of valid and missing observations and percentages). Continuous variables will be summarised by descriptive statistics (number of valid and missing observations, mean, standard deviation, median, interquartile range, minimum, and maximum). Time-to-event data will be assessed using the Kaplan-Meier method. Two-sided 95% CIs will be provided for the main statistical estimator.

Analyses will characterise the overall subject population by presenting descriptive statistics on subject demographics, baseline characteristics, medical history and current comorbidities, physical examination, description of bleeding episode for which Obizur was prescribed, treatment history (prior and concomitant to the bleeding episode, including Obizur and other medications/procedures), hospital stays, and laboratory values.

Analysis of limited demographic characteristics of subjects, such as age and sex, not enrolled in the study at participating sites will help evaluate the representativeness of the subject population compared to current practice, where feasible and allowed by local regulation.

Milestones:

- Protocol approval: Q2 2016
- Study initiation: Q4 2016
- Annual reports
- End of data collection: Not predetermined

5. AMENDMENTS AND UPDATES

Amd. No.	Version Date	Section of Protocol	Amendment	Reason
3	20 JUL 2018	Main changes: Study title update 4. ABSTRACT 5. AMENDMENTS AND UPDATES 7. RATIONAL AND BACKGROUND 7.3 Medicinal Product Safety Profile 8. RESEARCH QUESTION AND OBJECTIVES 8.1 Research Question 8.3 Secondary Objectives 9. RESEARCH METHODS 9.1 Study Design 9.2 Setting 9.4 Data Sources 9.7 Data Analysis 9.9 Limitations of the Research Methods 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS	Refer to Section 14.4 for the detailed Summary of Changes	Updating study design to include EU retrospective data collection and addition of US study sites to collect prospective data.
2	24MAY2017	Main changes: MAH contact person update **6. MILESTONES** 9.6.2 Laboratory and Reader Standardization 11.1.2.3 Safety Reporting	Refer to Section 14.4 for the detailed Summary of Changes	To update actual information To update the type of laboratory processing anti-hFVIII and anti pFVIII inhibitor activity assays To address changes in required reporting for non-serious adverse events (AEs)
1	03JUN2016	Main changes: 8.2 Primary Objective 8.3 Secondary Objectives 9.1.1 Primary Endpoints 9.1.2 Secondary Endpoints 9.2.2.2 Exclusion Criteria 9.3.7.2 Coagulation Tests 9.5 Study Size 9.6.2 Laboratory and Reader Standardization 9.8.4 Monitoring	Refer to Section 14.4 of Protocol Amendment 1 for the Summary of Changes	To address Pharmacovigilance Risk Assessment Committee (PRAC) requirements for this non-interventional study

6. MILESTONES

Milestone	Planned Date
Original protocol submission to the PRAC	Q1 2016
Protocol approval	Q2 2016
Registration in EU PAS Register	EUPAS16055
Study initiation	Q4 2016
End of data collection[a]	Not predetermined as per regulatory requirements
Annual reports	On the anniversary date of the Commission Decision granting the Marketing Authorisation
Final Report of study results	Six months after LSO

Abbreviations: LSO = Last subject out; PRAC = Pharmacovigilance Risk Assessment Committee; Q1 = First quarter; Q2 = Second quarter; Q4 = Fourth quarter

[a] There is no predetermined end date for this study and it will continue until agreement of termination with European Medicine Agency (PRAC and Committee for Medicinal Products for Human Use).

7. RATIONALE AND BACKGROUND

7.1 Background

Acquired coagulation inhibitors are generated in response to immune-mediated signals to deplete or inhibit of a coagulation factor. Inhibitors are most commonly directed against FVIII and von Willebrand Factor (vWF).[1] It is a well-known phenomenon that approximately 25-30% of subjects with severe congenital haemophilia A (CHA) develop neutralising inhibitors, typically during the first 20-50 exposure days to FVIII concentrates.[2] Acquired haemophilia A (AH) is an uncommon and potentially life-threatening autoimmune disease in which non-haemophilic persons develop autoimmune inhibitors directed against circulating blood coagulation factors, including FVIII. These inhibitors are distinct from the ones that form in patients with CHA as inhibitors formed during AH target the subject's own plasma coagulation factors, rather than coagulation factor replacement therapy.[3] AH is characterised by spontaneous haemorrhage or by bleeding induced by surgery, trauma, or procedures (invasive or minor) in subjects with no previous familial or personal history of bleeding.[4,5] The reported incidence of AH is approximately 1.5 cases per million per year, worldwide.[1,6]

7.2 Medicinal Product Efficacy Profile

Obizur (susoctocog alfa) is a purified, recombinant, B-domain-deleted porcine sequence FVIII (pFVIII) that is expressed by a genetically-engineered baby hamster kidney (BHK) cell line with a deoxyribonucleic acid (DNA) construct coding for 1,448 amino acids.

In AH subjects, Obizur temporarily replaces inhibited FVIII with a recombinant porcine sequence FVIII, based on the rationale that it is sufficiently similar to human (hFVIII) to have a haemostatic effect in humans, yet sufficiently different so as to be less susceptible to inactivation by circulating FVIII inhibitors.

Currently, the first-line treatment of bleeding in AH are bypassing agents. The two available treatments are recombinant activated factor VII (rFVIIa – NOVOSEVEN®) and the activated prothrombin complex concentrate (APCC, Factor Eight Inhibitor Bypassing Activity – FEIBA).[1,3,7] There is a risk of thromboembolic events associated with these treatments that may be enhanced by a patient's underlying disease and comorbid conditions.[1,3] High-dose replacement therapy with hFVIII concentrates is less successful in AH subjects with high-titre inhibitors, unless it is associated with removal of the pathogenic inhibitors by plasmapheresis or immunoadsorption.[1,8] Desmopressin (DDVAP) is reserved for minor bleeding episodes and very low titre inhibitors; it carries an unfavourable safety profile, particularly in an elderly subject population.[1,3] Immunosuppression is recommended to eradicate the autoantibody.

However, relapses may occur in about 15–33% of cases between one week and several months after cessation of immunosuppressive therapy.[3]

The haemostatic efficacy and safety of Obizur in subjects with AH was demonstrated by a pivotal phase II/III study, a multi-centre, international, prospective, open-label clinical trial that evaluated Obizur in 29 adult subjects (28 with confirmed AH) having autoimmune inhibitors to hFVIII.[9] The initial dose utilised during the study was 200 U/kg. Subjects were treated with Obizur until resolution of bleeding or dosing was continued at the physician's discretion. The decision to administer additional Obizur doses was made by the investigator based on the subject's FVIII activity trough levels (>80% for a bleeding episode of particular concern, >50% for all other serious bleeds). After cessation of the bleed, the subject could receive further therapy with Obizur until the healing process was completed, at the discretion of the investigator.

The primary endpoint of this clinical trial was the proportion of serious bleeding episodes responsive to Obizur therapy at 24 hours after the initiation of treatment. All the 28 evaluable subjects had a positive response to treatment for the initial bleeding episodes (either bleeding stopped completely, or bleeding was reduced) at 24 hours after dosing. A positive response was observed in 95% (19/20) of subjects evaluated at eight hours and 100% (18/18) at 16 hours. In addition to response to treatment, the overall treatment success was determined by the investigator based on the subject's ability to discontinue or reduce the dose and/or dosing frequency of Obizur. A total of 24/28 (86%) subjects had successful treatment (i.e. complete cessation of bleeding episode) of the initial bleeding episode. Of those subjects treated with Obizur as first-line therapy, defined as no immediate previous use of anti-haemorrhagic agents prior to the first Obizur treatment, 16/17 (94%) reported eventual treatment success. Eleven subjects reported to receive anti-haemorrhagics (e.g. rFVIIa, APCC, tranexamic acid) prior to first treatment with Obizur. Of these 11 subjects, eight had eventual successful treatment (73%).

7.3 Medicinal Product Safety Profile

Data from the above mentioned pivotal clinical trial demonstrated an acceptable safety profile of Obizur. No serious adverse event (SAE) was considered related to Obizur. Of the 29 subjects treated with Obizur, 19 subjects (65.5%) did not have detectable anti-pFVIII inhibitors at baseline and 10 (34.5%) had detectable inhibitors to pFVIII. Five of the 19 (26%) subjects developed anti-pFVIII inhibitors following exposure to Obizur. Of the 10 subjects with detectable anti-pFVIII inhibitors at baseline, two (20%) experienced an increase in titre and eight (80%) experienced a decrease to a non-detectable level.

All subjects were also monitored for development of BHK protein binding inhibitors by a validated sequential enzyme-linked immunosorbent assay (ELISA). No subjects developed de novo anti-BHK inhibitors.

The risk management plan (RMP) of Obizur comprehensively describes the safety profile of the medicinal product resulting from the thorough analysis of all data available from the clinical development program. The following safety concerns are highlighted:

- Identified risks:
  - Inhibitory antibodies to Obizur which may result in lack of response to treatment. Risk groups may include populations with high titre anti-pFVIII inhibitors and potential corresponding lack of efficacy (evidence source: final clinical study report of OBI-1-301/OBI-1-301a). During the pivotal phase II/III study, seven out of 29 subjects (24%) treated by Obizur either developed *de novo* anti-pFVIII inhibitors or experienced a rise of anti-pFVIII inhibitors from baseline titres. However, there have been no reports of lack of efficacy in the Obizur clinical studies.
- Potential risks:
  - Hypersensitivity and allergic reactions to the active substance, any of the excipients or to BHK protein: these reactions might range from a rash to fatal anaphylactic reactions which, depending on the severity, may require medical intervention and hospitalisation (no reports were observed during clinical trials but based on scientific literature this risk cannot be disregarded).
  - Lack of efficacy due to neutralising inhibitory antibodies against the product: this safety concern is related to the previously identified risk. However, no lack of efficacy was observed during the clinical development program even in subjects that developed inhibitors against Obizur.
  - Thromboembolic events: no related events were observed with Obizur during the clinical trials but have been observed with bypassing agents currently recommended as first-line treatment to control bleeds in AH subjects. Subjects with AH are often at higher risk for thromboembolic events due to a high prevalence of risk factors (advanced age, recent surgical procedures and comorbid conditions including liver disease, malignancy and autoimmune disorders). Thromboembolic events may lead to prolonged hospitalisation, costly treatment, and can have life-threatening or fatal outcomes. Therefore, the Marketing Authorisation Holder (MAH) considers this an important potential risk.

- Catheter-related complications: as with other FVIII products, there is a potential for localised, catheter related complications (e.g., infection, thrombosis, hematoma, arterial injury) in Obizur-treated subjects. Those complications would lead to additional treatment measures and prolonged hospitalisation. Although none were observed during the Obizur clinical development program, this potential risk cannot be excluded.
- Dose dispensing medication errors: in order to administer the appropriate dose of Obizur, multiple vials may be required. If a large number of vials are required, there is potential for miscalculation which could result in dose error. As Obizur administration will occur in acute care or highly attended in subject wards, dosing errors are unlikely. Although no errors were observed during the Obizur clinical development programme, this potential risk should not be excluded.

Obizur, being a B-domain deleted porcine sequence FVIII and a biological product, is metabolised the same way as other plasma proteins. No interaction studies have been performed with Obizur, and to date, no interactions of Obizur with other medicinal products have been reported. Incompatibility studies have not been performed with Obizur. In the absence of compatibility studies with Obizur, it should not be mixed with other medicinal products.

Instructions for proper dosing and administration are provided in the Summary of Product Characteristics (SPC) and Package Leaflet (PL). Obizur is intended for inpatient administration only and should be administered under the supervision of a physician experienced in the treatment of haemophilia.

In addition, an educational brochure contains recommendations and product information for European physicians and events of special interest are followed-up using specific questionnaires. These measures are intended to minimise identified risks, prevent potential risks and avoid use in populations not studied in clinical trials for which the benefit-risk balance is not established. Measures to specifically minimise the risk of dose dispensing medication errors include the distribution of a healthcare professional's brochure including a detailed description about the method for calculation of vials for a patient weighing for example 70 kg and a link to an on-line video that further elaborates on the required calculation and administration of the drug.

In addition to the abovementioned measures, it was agreed upon with the European Medicines Agency (EMA) to further monitor the safety profile of the medicinal product, which includes the conduct of a United States (US) and a European post-authorisation study.

This protocol describes the European Union (EU) post-authorisation safety study (PASS) which will collect real-world information on the use of Obizur, without interfering with routine clinical practice. The safety profile of the medicinal product will be actively monitored to identify any safety signals and allow timely measures to minimise risks and maximise benefits of Obizur.

7.4 Critical Review of Available Data

Results of single-dose toxicity, repeat-dose toxicity, and general safety pharmacology studies in animal models revealed no concerns with regard to safety up to doses of 1000 U/kg. However, no reproductive or developmental toxicity studies have been performed so the safety in pregnant women is unknown.

Three clinical studies with Obizur have been completed to date: OBI-1-101, a phase I study [10]; OBI-1-201, a phase II study [11,12]; and OBI-1-301/OBI-1-301a (expanded access protocol in the US), a phase III study.[9]

Data from the clinical development programme demonstrated a positive safety and efficacy profile of Obizur in subjects with AH. However, these data were obtained in a limited sample of adult subjects with AH who had a follow-up duration of 90 days after the last administration of the product. Very few subjects have required, and been exposed to, a second treatment course with Obizur.

As with all medicinal products, there are limitations to adverse event (AE) detection common to the clinical trial development programme, such as:

- Limitation to detect rare AEs: AH is a rare disease, and despite the number of subjects exposed to Obizur in clinical studies meeting the required sample size, the ability to detect rare adverse reactions is limited;
- Limitation to detect AEs due to prolonged exposure: In clinical studies with Obizur, 43 subjects had a total of 355 exposure days. The ability to detect adverse reactions due to prolonged exposure is limited and prolonged or high exposure does correlate with a likelihood of anti-porcine inhibitor development.

- Limitation to detect AEs due to cumulative effects: Clinical studies involved at least one infusion with Obizur in different clinical settings and cumulative effects were not seen in this limited subject population. However, adverse reactions due to cumulative effects in the target population in the post-marketing setting are not expected to differ from those seen in the clinical setting.
- Limitation to detect AEs which have a long latency: Subjects were followed for time periods specified by the study protocols. In the pivotal study OBI-1-301, subjects were followed for 90 days. It is possible that AEs with longer latency may be seen during a prolonged follow-up period.
- Effect of exclusion criteria: In clinical studies, subjects were relatively medically stable and able to follow instructions and attend study visits. In real-world clinical practice, subjects with different severity and clinical presentations might receive treatment at the discretion of the treating physician. The SPC/PL communicates warnings and contraindications that should be followed.

As with all medicinal products, routine use of Obizur may differ from the subject population studied in the clinical development program. Obizur was approved by the US Food and Drug Administration (FDA) in the US in October 2014 and by the European Commission on 11 November 2015 and to date no additional risks have been identified.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The study addresses the safety, utilisation and effectiveness of Obizur in the treatment of bleeding episodes in real-life clinical practice in Europe and in the US. The study is designed to collect further information, in particular regarding safety concerns, as established in the RMP.

8.2 Primary Objective

The primary objective of the study is to document the safety of subjects treated with Obizur in real-life clinical practice by recording any AEs, including but not limited to:

- Hypersensitivity reactions
- Thromboembolic events
- Dose dispensing medication errors.

8.3 Secondary Objectives

The secondary objectives of the study are to monitor Obizur use in real-life clinical practice, including:

- Immunogenicity corresponding to the development of newly recognised anti-pFVIII inhibitors or an increase in titre of pFVIII inhibitors from pre-treatment levels (if known) during the course of treatment and up to 180 days after the first administration of Obizur, if available in routine practice
- To describe the haemostatic effectiveness of Obizur in the treatment of bleeding episodes
- To describe the frequency, total dose, and total number of infusions of Obizur administered to control bleeding episodes
- To describe concomitant medication use
- To describe the complete remission rate (inhibitors eradication)

8.4 Exploratory Objectives

[redacted]

9. RESEARCH METHODS

9.1 Study Design

This study is a non-interventional, post-authorisation, prospective and retrospective, single cohort, uncontrolled, multi-centre European and US study to describe Obizur overall safety profile in real-life clinical practice, with particular attention to adverse events of special interest (AESIs) and other SAEs reporting. In addition, this study aims to document the haemostatic effectiveness and utilisation patterns of Obizur in real-life clinical practice. The overall study design is illustrated in Figure 3.

In an attempt to collect all safety and utilization data on patients treated with Obizur since the Marketing Authorisation, all subjects treated with Obizur and meeting the defined inclusion/exclusion criteria could be invited to participate in this study. US subjects who have been enrolled in the post-marketing study, NCT02610127 can not be enrolled.

Approximatively 50 subjects are expected to be enrolled in the study consisting of at least 20 European prospective subjects, a maximum of 15 European retrospective patients and a maximum of 15 US prospective subjects.

Because this study is non-interventional, the decision to administer Obizur will be made prior to the enrolment of study subjects and is not mandated by study design or protocol.Data will not be actively requested if not available as the intention is to describe real-life clinical practice.

The study will be implemented in selected countries sequentially, as the product becomes commercially available. The overall duration of the study from initiation (i.e., initiation of first site) to completion (i.e., end of data collection) is not predetermined. At each study site, all subjects to whom the treating physician decides to administer Obizur, and who meet inclusion/exclusion criteria, will be offered participation in the study. As Obizur is administered to control bleeding episodes in a medical/surgical emergency context, informed consent will be solicited from the subject or legal representative at the earliest possible time point, but should not exceed 30 days following the initiation of Obizur therapy. In case of death before subject's consent has been obtained, informed consent will be solicited from the next of kin, according to local regulations. In the event such consent cannot be solicited, data will be anonymised and source data verification will not occur, in order to maintain data privacy. This will occur where allowed by local regulations.

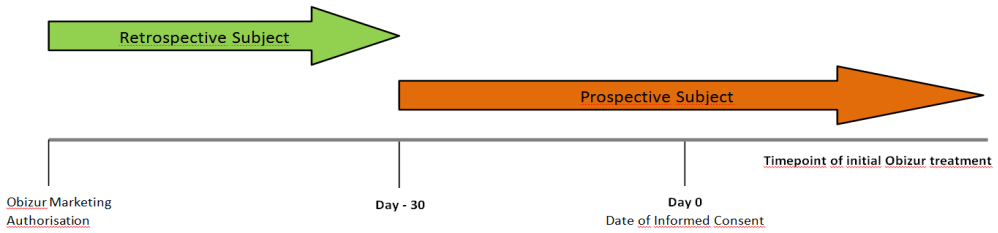
In an attempt to collect as many data as possible and given the challenges of prospective data collection in patients with such a rare disease, the prospective European data-set will be complemented by a retrospective chart review of existing data collected routinely for patients in the EU treated with Obizur (see Figure 1).

The inclusion of these retrospective data from patients already treated with Obizur allows the primary objective study to be met fully, whilst expediting study results.

Both, prospective and retrospective enrolled patients, will fulfil the same eligibility criteria.

The definition of retrospective and prospective subjects has been defined as follows:

Figure 1
Subject classification (Prospective vs Retrospective)



- A prospective subject is a subject who is being treated with Obizur, i.e. informed consent is obtained within 30 days of Obizur administration.
- A retrospective subject is a subject who was treated with Obizur between its marketing authorisation and more than 30 days before the date of the Informed Consent (Day -30). All subjects who do not have to sign an informed consent due to local regulations or do not have a screening visit (e.g. deceased patients) will also be considered as "retrospective patients".

The treating physician will determine the treatment regimen, as well as the frequency of laboratory and clinical assessments according to routine clinical practice. The decision to carry out any laboratory and/or clinical assessments lies completely with the investigator, who is responsible for the treatment, and is not mandated by study design or protocol. Subjects' demographics, clinical characteristics, comorbidities and other medical history, indication for treatment, characteristics of bleeding episode prompting treatment by Obizur, inhibitor levels (anti-hFVIII and anti-pFVIII), prior treatments to Obizur, Obizur treatment details, bleeding control, concomitant medications and AEs/SAEs will be collected.

Data will be collected and registered in the electronic case report forms (eCRFs) on each subject for a period of 180 days from the time of Obizur treatment; in addition, data points that are retrospective in nature prior to initiation of Obizur (such as comorbidities and prior medical treatment) should be obtained from the patient's medical chart records for the time period prior to Obizur treatment.

The collection of data on immunogenicity (newly recognised anti-pFVIII neutralising inhibitors or increase in titres from pre-treatment values, if known) during the course of the study will depend on whether anti-pFVIII testing is performed as part of the routine clinical practice. [redacted]

In case of bleeding episodes occurring more than 72 hours after initial bleeding control with subsequent re-administration of Obizur, all data elements described above will be captured, apart from data related to the prior Obizur treatment episode. Data can be collected for up to 180 days after the last dose of Obizur for this subsequent bleeding episode or until the end of the study, whichever occurs first.

Subjects who present with ongoing SAEs, AESI, or non-serious AE considered attributable to Obizur at the end of the planned follow-up period will be monitored until resolution or stabilisation of the AE/SAE as part of routine pharmacovigilance activities.

Available data from routine visits shall be transcribed onto the eCRFs.

9.1.1 Primary Endpoints

The primary endpoint is safety, which will be assessed by AE/SAE frequency, seriousness, severity and outcome (subject recovered/ recovered with sequelae, not recovered/ fatal). Particular attention will be given to the following AESIs: hypersensitivity reactions, thromboembolic events and dose dispensing medication errors, defined as follows:

Hypersensitivity:

An allergic/ hypersensitivity/ anaphylaxis reaction is a disorder characterized by an acute local or general inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells due to exposure to an allergen, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.

Hypersensitivity reactions may include urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension; these reactions can be severe and can be systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported.

Thromboembolic Events:

A thromboembolic event is determined by blood clots that break off and migrate to other areas of the circulation via the blood stream.

Thromboembolic events may include disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction, and stroke. Patients with a history of coronary heart disease, liver disease, DIC, arterial or venous thrombosis, post-operative immobilisation and elderly patients may have an increased risk of developing thromboembolic events.

Thromboembolic events should be confirmed by appropriate diagnostic procedures (e.g., sonography).

Dose dispensing medication error:

Miscalculation of dose while prescribing (calculation of the correct dose based on the patient's weight) or administration of the incorrect dose.

The following will be assessed for the above mentioned AESIs:

- Incidence of SAEs (inclusive of death due to any cause) and AEs by level of severity, relationship to Obizur, SAE/AE outcome, and whether it was associated with treatment discontinuation
- Incidence, level of severity, relationship to Obizur, and outcome of AESI, including the following:
  - Hypersensitivity reactions
  - Any thromboembolic event
  - Dose dispensing medication error.

9.1.2 Secondary Endpoints

- Immunogenicity, upon availability: newly recognised anti-pFVIII inhibitors or increase in titre of anti-pFVIII inhibitors from pre-treatment level (if known) and evolution of titre over time
- Clinical characteristics of the treated subject population Obizur treatment and concomitant medications use
- Overall effectiveness assessment for resolution of bleeding determined as either bleeding stopped or did not stop (if bleeding did not stop, a reason should be provided [e.g., death])
- Time and dosage (dose per infusion and number of infusions) administered to achieve bleeding control (all bleeding stopped), death, or switch to haemostatic treatment other than Obizur

9.1.3 Exploratory Endpoints

[redacted]

9.2 Setting

9.2.1 Duration of Study Period(s) and Subject Participation

As mentioned in Section 7.2, a very limited sample of subjects were included in the clinical development programmes of Obizur due to the low prevalence of the disease. Therefore, during the assessment of the marketing authorisation application, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended that this study should include as many prospective subjects as possible in order to provide substantial safety information on Obizur treatment in real-life clinical practice. The overall duration of the study from study initiation (i.e., initiation of first site) to study completion (i.e., end of data collection) is not predetermined. The target number of subjects to be enrolled is at least 50 (with a maximum of 15 European retrospectively enrolled subjects and 15 US prospectively enrolled subjects). The recruitment is planned for an initial period of five years.

Data will be collected, where available, for each subject for up to 180 days following the last Obizur treatment dose.

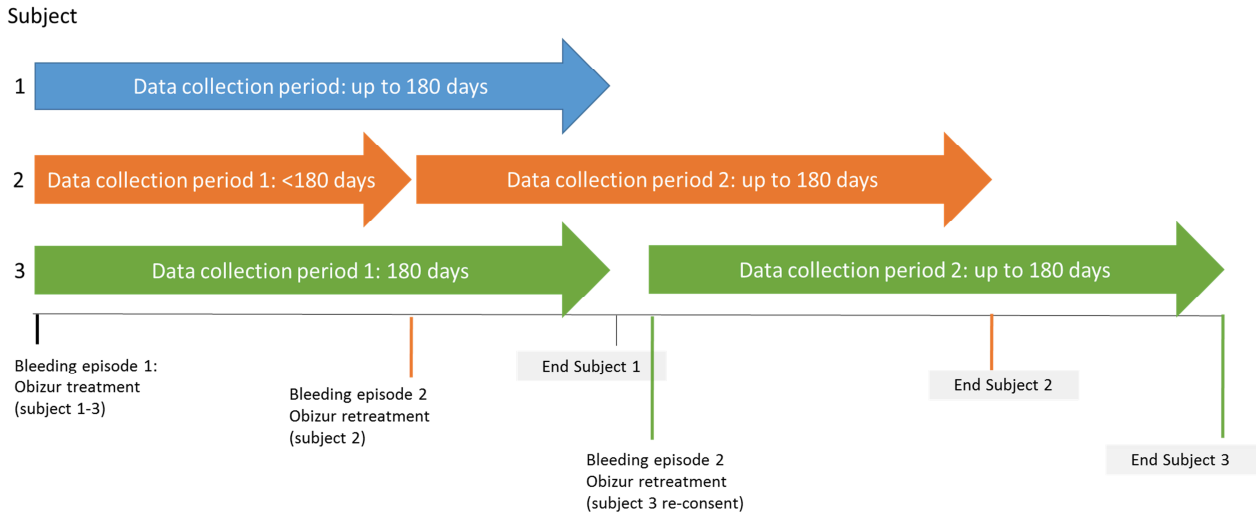
If another bleed occurs it will be classified as:

- Re-bleed if it occurs in the same anatomical location and within 72 hours of the resolution of the previous bleeding;
- Concurrent bleed if it occurs at the same time (i.e. during treatment or within 72 hours of resolution) as the previous bleed but at a different anatomical location
- Subsequent bleed if it is a new bleed occurring 72 hours after the resolution of the previous bleed (either in the same anatomical location or in a new one).

For each bleed newly treated with Obizur, the 180-day post-treatment data collection period will restart.

Figure 2 presented below shows different subject data collection scenarios.

Figure 2
Subject data collection scenarios



Notes:

Subject 1 has one bleeding event treated with Obizur and data are collected routinely (as available) for up to 180 days. Subject 2 is being followed after a first Obizur treatment but presents with a subsequent bleeding episode during the first data collection period and is retreated with Obizur; in this case, the first data collection period is interrupted and a new 180-day data collection period starts as part of initial consent (no re-consenting would be required as the first 180 period was not completed when the second bleeding occurred). Subject 3 has a first bleed treated with Obizur and data are collected routinely (as available) for up to 180 days; later, Subject 3 presents another bleed retreated with Obizur and is followed after re-consenting for another 180-day post-treatment period. The second data collection period will last for the full 180 days if Subject 3 is not retreated again within this time frame.

For the retrospective data collection if the available data already covers more than one 180-day follow-up period only one informed consent will be required.

Subjects being retreated will not be double counted in the analyses but bleeding episodes will be counted separately in the analyses. All SAEs/AEs occurring during the data collection period will be collected along with the corresponding treatment.

Given the observational nature of the study, procedures and follow-up visits are not mandated by the protocol and data will only be collected as available per routine practice.

Subjects who present with an ongoing SAE, AESI, or non-serious AE considered related to Obizur (non-serious adverse drug reaction [ADR]) at the end of the planned follow-up period, will be monitored until the resolution or stabilisation of the SAE/AEs, as part of routine pharmacovigilance activities (i.e. outside the present study) if this is in agreement with clinical routine and local regulations.

9.2.2 Subject Selection Criteria

A subject must be prescribed Obizur for the treatment of a bleeding episode by a physician, independent of and prior to the decision to enrol the subject in the study.

9.2.2.1 Inclusion Criteria

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

- Adult subject or legal authorised representative is willing to provide informed consent, unless informed consent is not required (e.g. subjects who are deceased), as local regulations allow.
- Subject is being treated or was treated with Obizur in routine clinical practice

9.2.2.2 Exclusion Criteria

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

- Subject has participated in a clinical study involving a medicinal product or device within 30 days prior to enrolment or is scheduled to participate in a clinical study involving a medicinal product or device at study entry
- Subject has known anaphylactic reactions to the active substance, hamster protein, or to any of the excipients of Obizur listed in the SPC /PL
    - The following list of excipients can be found in the SPC/PL:
        - Powder:
            - Polysorbate 80
            - Sodium chloride

        - Calcium chloride dihydrate
        - Sucrose
        - Tris Base
        - Tris HCl
        - Tri-sodium citrate dihydrate
    - Solvent:
        - Sterilised water for injections
- US Subject who has participated in the post-marketing study, NCT2610127

9.2.3 Informed Consent and Enrolment

Any subject who provides informed consent (i.e., signs and dates the informed consent form) is considered enrolled in the study. A legally authorised representative may also sign the informed consent. Informed consent may not be required (e.g. deceased subjects) as local regulations allow.

9.2.4 Subject Identification Code

The following series of numbers will comprise the subject identification code (SIC): protocol identifier (241501), 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 enrolment. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 241501-020003. All study documents pertaining to the subject (e.g., eCRFs, 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. Patients re-consenting would be given the same SIC.

9.2.5 Screening and Follow-up

The study site is responsible for maintaining a screening log that includes all subjects eligible for enrolment. The log also will serve to document the reason for screening failure (e.g. not consenting, not meeting the eligibility criteria, investigator decision not to include the subject). All screening data will be collected and reported in eCRFs (inclusive of demographic data, such as sex and age), regardless of screening outcome where allowed by local regulation. If a subject is re-screened after a first data collection period of 180 days has passed, a new ICF should be signed, the subject will be re-enrolled into the study using the same subject identifier.

New forms are required for that subject apart from data already captured during the last treatment cycle.

The overall study design is illustrated in Figure 3. Details on data to be recorded for baseline and follow-up can be found in Table 1 and Table 2. Detailed data to be collected are described in Section 9.3.

Figure 3
Study Design for Baxalta Non-Interventional Study 241501

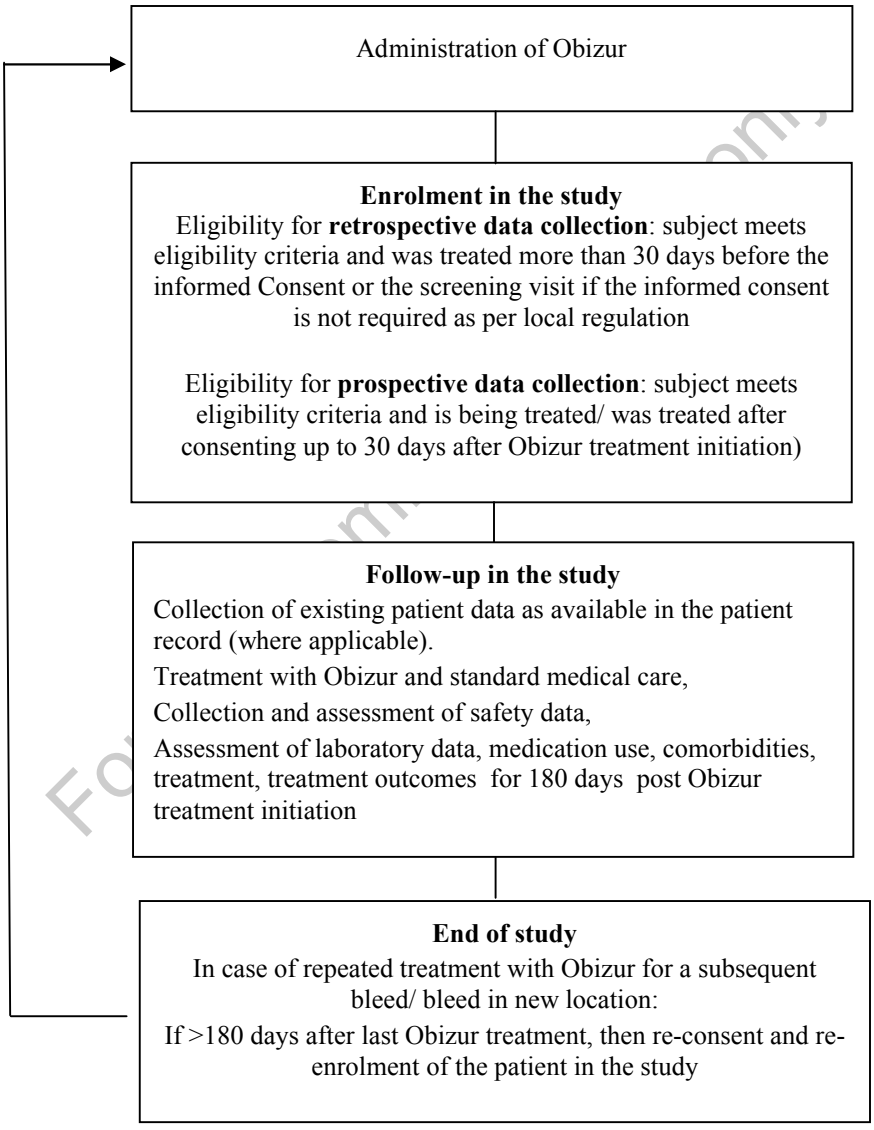


Table 1
Schedule of Study Assessments

Assessments	Baseline (as available)	At routine follow-up visits[e] (as available)	Up to 180 days after last administration of Obizur (as available)
Informed Consent [a]	X		
Eligibility Criteria	X		
Demographics	X		
Vital signs, Weight and Height[b]	X		
Pregnancy/nursing status[b]	X	X	X
Disease and treatment history[b]	X		
Other medical history[b]	X		
Comorbidities	X	X	X
Prior/concomitant medication within 14 days of Obizur initiation[b]	X		
Initial bleeding event description[b]	X	X	
Obizur treatment details	X		
Other medication administered for haemostatic control[b]	X	X	X
Surgical/medical procedures[b]	X	X	X
Haemostatic effectiveness[b]	X	X	
Hospital days[b]	X	X	X
Additional bleeding events[b]	X	X	X
Adverse Events[c]	X	X	X
Laboratory tests (as available)[d]	X	X	X
End of follow-up			X

[a] Occurs before start of data collection (for subjects enrolled retrospectively) and within 30 days of Obizur administration (for subjects enrolled prospectively). In case of repeated treatment with Obizur for a subsequent bleed/ bleed in a new location if >180 days after last Obizur treatment, then re-consent and re-enrolment of the patient in the study .

[b] As available

[c] Adverse events (AEs) including serious and non-serious AEs ongoing at that time point must be followed up until resolution or stabilisation or as available in the existing medical records (for retrospective data collection).

[d] For laboratory assessments, see Table 2

[e] In case of a long in-hospital stay, follow-up visit would be entered every 2 weeks

Table 2
Clinical Laboratory Data Collection

Parameters	Obizur treatment period (as available)	At routine follow-up visits[c] (as available)	Up to 180 days after last administration of Obizur (as available)
Haemoglobin[a]	X	X	X
Haematocrit	X	X	X
Complete blood count with differential	X	X	X
APTT levels	X	X	X
Prothrombin time	X	X	X
FVIII levels	X	X	X
anti-hFVIII and anti-pFVIII inhibitor levels and assay method[b]	X	X	X
Anti-BHK levels	X	X	X

Abbreviations: APTT: activated partial thromboplastin time; BHK: baby hamster kidney; FVIII: coagulation factor VIII; h: human; p: porcine.

[a] Given the observational nature of this study, data will be collected as recorded and if available. No laboratory assessments are mandated by this Protocol.

[b] Physicians will have the option to use a certified laboratory to process anti-hFVIII and pFVIII inhibitors.

[c] In case of a long in-hospital stay, follow-up visit would be entered every 2 weeks

Retrospective chart review for data collection covering 180 days post-treatment will be conducted for patients with a bleeding episode during which they were treated with Obizur between the marketing authorisation and more than 30 days before the informed consent. Data for this group of patients will be presented in a one-time Retrospective Data Report.

9.2.6 Subject Withdrawal and Discontinuation

Any subject may voluntarily withdraw consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study eCRF. Subjects may withdraw consent to participate in the study at any time with no effect on their medical care or access to treatment.

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).

As the subjects will be followed-up according to routine medical care, it is possible that subject will not see their treating physician within the 180-day data collection period after last dose of Obizur.

Subjects will also be discontinued from further study participation for the following reasons:

- Violation of eligibility criteria
- Investigator decision to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

9.2.7 Study Stopping Rules

There is no predetermined end date for this study and it will continue until agreement of termination with Committee for Medicinal Products for Human Use (CHMP)/PRAC.

9.3 Variables

The following data will be collected at the time points described in Section 9.2.5 Screening and Follow-up.

9.3.1 Safety Variables

9.3.1.1 Adverse Events of Special Interest (AESI)

There is a particular interest in monitoring AESIs, the AEs related to the safety concerns from the RMP. Therefore, any occurrence of the following AEs will be reported and monitored with the same level of priority as an SAE as defined in Section 11.1.1.

The AESIs include hypersensitivity reactions, thromboembolic events, dose dispensing medication errors (these three AESIs are primary endpoints of the study and are defined in Section 9.1.1) and, if available, immunogenicity (newly recognised or titre increase of anti-pFVIII inhibitors from pre-treatment level, if known). [redacted]

9.3.1.2 Serious Adverse Events (SAEs) (including death of any cause)

Each SAE will be assessed by level of severity, relationship to Obizur and outcome. For details on definition, collection and assessment of these variables please see Section 11.

9.3.1.3 Non-Serious Adverse Events (AEs)

Each non-serious AE will be assessed by level of severity, relationship to Obizur, and AE outcome. For details on the definition, collection and assessment of this variable please see Section 11.

9.3.1.4 Serious Adverse Events (SAEs)/Adverse Events (AEs) Associated with Treatment Discontinuation

Each SAE/AE will be assessed to determine whether it led to Obizur discontinuation. For the details on the definition, collection and assessment of this variable please see Section 11.

9.3.2 Effectiveness Variables

9.3.2.1 Overall Bleeding Control

Each episode will be assessed to determine whether bleeding stopped. If bleeding did not stop, the consequence will be recorded (e.g. death, need for secondary treatment).

9.3.2.2 Time to Achieve Bleeding Control with Obizur

Bleeding control duration will be assessed from initiation of Obizur therapy (start time) to the time to achieve bleeding control (stop time).

9.3.2.3 Obizur Dosage to Achieve Bleeding Control

For bleeding episodes successfully controlled by Obizur (bleeding stopped), number of Obizur infusions and dose required to stop the bleeding (initial dose of Obizur administration, will be recorded).

9.3.2.4 Overall Obizur Treatment Course to Control Bleeding

For the bleeding episodes successfully controlled by Obizur (bleeding stopped) the initial bleeding control phase and healing phase (i.e., once bleeding has responded based on clinical assessment, usually within the first 24 hours) if applicable, the duration of therapy, total number of infusions of Obizur and total dose administered during the complete treatment course will be collected.

9.3.3 Demographics

The following variables will be collected for each subject at the in-hospital treatment period (where available and allowed by local regulations):

- Age
- Sex
- Race/ethnicity (if allowed per local regulations)
- If pregnant: date of last menstrual period, expected due date, overall number of pregnancies, number of normal deliveries
- If breast-feeding: date of delivery, pregnancy outcome

9.3.4 Hospital Stay

- Initial hospitalisation: admission and discharge dates, reason for admission, length of stay per level of care, destination upon discharge
- Hospital readmissions: admission and discharge dates, reason for admission, length of stay per level of care, destination upon discharge

9.3.5 Medical History, Medications, and Non-Drug Therapies

9.3.5.1 Medical History

- Date and circumstances of diagnosis of anti-FVIII inhibitors (e.g., inaugural bleeding episode, prolonged activated partial thromboplastin time [APTT], other)
- Previous bleeding episodes: date, site(s), circumstances (spontaneous, trauma, procedure, post-partum), severity, and treatment (type of treatment, total dose administered, and duration of use, if available)
- History of cardiovascular disease/thromboembolic events
- Other available significant medical history
- Available comorbidities and patient specific characteristics (e.g. viral status of patients)

9.3.5.2 Description of Bleeding Episode for Which Obizur Was Prescribed

- Date, indication and circumstances of Obizur treatment, and description of bleeding episode:
  - Circumstances of occurrence (e.g., spontaneous, subsequent to trauma, surgical procedure)
  - Bleeding site(s), type (skin, intramuscular, gastrointestinal/abdominal, genital/urinary, retroperitoneal, thoracic, intracranial, other), and date(s) of occurrence
  - Bleed severity (life-threatening, limb threatening, other) as determined by the prescribing physician
  - Bleeding episode type:
    - Initial bleed: The first bleeding event for which the patient received Obizur treatment.
    - Concurrent bleeding episode(s): a bleed that occurs at the same time (i.e., during treatment or within 72 hours of resolution) as the initial/subsequent bleed but at a different anatomical location
    - Rebleed: a bleed that occurred within 72 hours after resolution of the initial/subsequent bleed at the same anatomical location
    - Subsequent bleed: a new bleeding event (at the same or different anatomical location as the initial bleed) with onset greater than 72 hours after resolution of the initial bleed

9.3.5.3 Treatments (Medications and Procedures)

- Treatments taken prior to Obizur
  - History of immunosuppressive agents and/or other treatments received to eradicate anti-FVIII inhibitors prior to Obizur initiation
  - Prior medication received within 14 days of Obizur administration
  - Haemostatic agents received prior to Obizur initiation for the current bleeding episode (name, start and stop dates, number of units, dosage and/or total dose administered, reason for switch to Obizur)
- Obizur treatment
  - Number of units, dosage, date and time of administration of Obizur, treatment target of each infusion (bleeding control or healing phase)

- Additional medications, treatments and procedures undertaken to control bleeding episode (during Obizur treatment episode or to treat subsequent bleeding episodes that occur at the follow-up period)
    - Name, number of units, dosage and/or total dose administered, start and stop dates, reason for administration/switch
- Immunosuppressive agents and/or other treatments received to eradicate anti-FVIII inhibitors during the episode for which Obizur is being administered, including name, treatment dose, start and stop date
- Other concomitant medications

9.3.6 Physical Examinations

Vital signs (i.e. pulse, blood pressure, respiratory rate, and body temperature), as well as height (cm) and weight (kg), will be reported at baseline.

9.3.7 Clinical Laboratory Parameters

9.3.7.1 Haematology

The following will be collected for each treatment course of Obizur, where available per routine practice:

- Haemoglobin (assessed as severe if level is < 8 g/dL)
- Haematocrit
- Complete blood count, with white blood cells differential
- Date of blood draw (include baseline and any follow-up)

9.3.7.2 Coagulation Tests

The following will be collected for each treatment course of Obizur (prior and during treatment course) if available per routine practice:

- APTT
- Prothrombin time
- FVIII levels, before treatment, during treatment course and at follow-up visits (as available)
- Anti-hFVIII inhibitor titres before treatment, during treatment course and at follow-up visits (as available)

- Anti-pFVIII inhibitor titres before treatment, during treatment course and at follow-up visits (as available)
- Assay method used for anti-hFVIII and anti-pFVIII testing

9.3.8 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 eCRF, 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 eCRF 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

All data about subjects demographics, clinical characteristics, disease and other medical history, indication for treatment, characteristics of bleeding episode prompting treatment by Obizur, inhibitor levels (anti-hFVIII and anti-pFVIII), treatment by Obizur, clinical and haemostatic effectiveness, concomitant medications administered for bleeding control, comorbid conditions, AEs and death will be collected as available from routine visits, both with respect to in-hospital stays and out-patient visits or laboratory tests, through prospective or retrospective data collection. In case of a long in-hospital stay, follow-up visit would be entered every 2 weeks (refer to Table 1).

Investigators (or clinical staff trained for data entry) will enter data required by the protocol into the electronic data capture (EDC) system. Sites are recommended to enter data within 14 days of entry into the subject chart for prospective data collection or 14 days of ICF signature for retrospective data collection. Designated staff will have access to the EDC 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 the majority of the data will be obtained from haematology departments in hospitals; however, other sources of documentation may be used.

Subjects will be treated and followed up according to standard of care practice in participating study centres. There will be no mandatory visits or procedures associated with the study.

9.4.1 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings and observations. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subject pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, 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 subject medical records and entered into the EDC system. Following data entry into the EDC system, Medical Dictionary for Regulatory Activities (MedDRA) coding will be conducted for all medical conditions (including medical history) reported and World Health Organisation (WHO) WHODRUG dictionary coding for all reported medications.

For additional information on study documentation and eCRFs see Section 9.6.1.

9.5 Study Size

The study defines four AESIs: hypersensitivity reactions, thromboembolic events, dose dispensing medication errors and, if available, immunogenicity. Among those events, only immunogenicity was observed in the clinical development programme; therefore the sample size is calculated based on its reported incidence.

During the pivotal phase II/III study, seven out of 29 subjects (24%) treated by Obizur either developed de novo anti-pFVIII inhibitors or experienced a rise of anti-pFVIII inhibitors from baseline titres. Hence, as an example, assuming that the expected proportion of subjects with any AESI is 25%, a sample of 50 subjects will provide precision for an AESI proportion with the following 95% confidence interval (CI) [13.8, 39.3] (Clopper-Pearson method). The higher the sample size, the smaller the width of the CI.

For instance, as described in Table 3 below, achieving a sample size of 60 subjects would provide a 95% CI [14.7, 37.9] for the same expected proportion, and hence decrease the width of the CI and increase the precision by approximately 2%.

As already described in Section 9.2.1, the study aims to recruit as many subjects as possible, with a minimum of 50 subjects, and the study duration has not been pre-defined as required by European regulatory authorities.

Table 3
Sample Size Calculation for a Precision of an AESI Proportion and its Corresponding Two Sided 95% CI

Confidence Level	Sample Size (N)	Actual Width	Proportion (P)	Lower Limit	Upper Limit
95	40	28.5	25	12.7	41.2
95	40	30.0	30	16.6	46.5
95	40	31.1	35	20.6	51.7
95	40	31.8	40	24.9	56.7
95	50	25.4	25	13.8	39.3
95	50	26.8	30	17.9	44.6
95	50	27.7	35	22.1	49.8
95	50	28.4	40	26.4	54.8
95	60	23.1	25	14.7	37.9
95	60	24.4	30	18.9	43.2
95	60	25.3	35	23.1	48.4
95	60	25.9	40	27.6	53.5

Note: Confidence Interval Formula: Exact (Clopper-Pearson)

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 informed consent forms, correspondence with the EC/IRB (Institutional Review Boards) and the study monitor/MAH, enrolment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), 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 initialled 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 eCRFs are provided by the MAH, only authorised study site personnel will record or change data on the eCRFs. If data is not entered on the eCRFs during the study visit, the data will be recorded on paper; and this documentation will be considered source documentation. Changes to eCRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of forms 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 Laboratory and Reader Standardisation

Data on immunogenicity ([redacted]) will be collected only if this assessment is part of routine clinical practice or decided by the investigator as described in Section 9.1. If these assessments are made and in compliance with the Guideline on the clinical investigation of recombinant FVIII and human plasma-derived FVIII products (EMA/CHMP/BPWP/144533/2009 Rev 1), physicians will have the option to use their local laboratory or a certified laboratory to process anti-hFVIII and anti-pFVIII inhibitor activity assays. The sponsor recommends that the laboratory performs the analysis of inhibitory antibodies using the Nijmegen modification of the Bethesda assay.

9.6.3 Software

The software for data management will be determined in accordance with the sponsor or the mandated contract research organisation (CRO).

All computations and generation of tables, listings, and figures (TLFs) 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 subjects who sign informed consent, have a designated representative sign an ICF or are exempt from signing informed consent (patients with consent waived by the EC/IRB), on whom data has been entered into the EDC, will be included in the analysis dataset.

The Full Analysis Set (FAS) will include all subjects in the study who fulfil inclusion and exclusion criteria.

9.7.2 Handling of Missing, Unused, and Spurious Data

Analyses will be performed using available data. Due to the observational nature of the study, missing values are expected. However, no imputation of missing values will be considered unless otherwise stated in the statistical analysis plan (SAP). All reasonable attempts should be made by the site to limit the amount of missing data. If there are missing or partial dates for Obizur treatment, or bleed outcome, there will be no time estimates reported for that treatment or bleed, but the treatment or bleed will still be included in the reporting of other summaries.

9.7.3 Methods of Analysis

A detailed SAP has been created for the study before the first annual analysis and will be updated as necessary during the course of the study.

Categorical variables will be summarised by absolute and relative frequencies (number of valid and missing observations and percentages). Continuous variables will be summarised by descriptive statistics (number of valid and missing observations, mean, standard deviation, median, interquartile range, minimum, and maximum). Two-sided 95% CI will be provided for the main statistical estimator.

All analysis will be performed on the FAS unless otherwise stated in the SAP. Where subjects have received two or several courses of Obizur therapy, data pertaining to the second and subsequent treatment periods will be described separately.

The analysis will characterise the overall subject population by presenting descriptive statistics on subject demographics and baseline characteristics, medical history and current comorbidities, physical examination, description of bleeding episode for which Obizur was prescribed, treatment history (prior and concomitant to the bleeding episode including Obizur and other medications/ procedures), hospital stay episodes and laboratory values. Subject disposition will be summarised for prospective (3 different sub-populations: combined EU and US prospective patients and EU and US patients separately) and retrospective subjects.

Analysis of the characteristics of subjects not enrolled in the study at participating sites will help evaluate the representativeness of the subject population compared to current practice, where feasible and allowed by local regulation.

9.7.3.1 Primary Endpoint

The descriptive methods of analysis for the primary endpoints (see Section 9.1.1) are the following:

Depending of available data, the AE incidence will be summarised by MedDRA system organ class and preferred term using frequency distributions and by severity. The incidence rate will be calculated as the number of events during the follow-up period divided by person-time of patients at risk during the same follow-up period.

AESI and SAEs, inclusive of death of any cause, will be described by suspected drug relationship and whether they were leading to treatment discontinuation. Incidence rates of SAEs and AESI, inclusive of death of any cause, will be estimated by dividing the number of incident cases by the person-time at risk.

All information pertaining to AE noted during the study will be listed by subject, detailing the verbatim term given by the investigator, MedDRA preferred term and system organ class, start/end dates, severity, seriousness, relationship to Obizur and action taken. The AE onset will be shown relative (in number of days) to the date of initial dose.

For the purpose of summaries and listings, the durations of AEs will be calculated as follows: (stop date [day] – start date [day]) + 1 [day], which yields the number of days during which the AE occurred.

9.7.3.2 Secondary Endpoints

The methods of analysis for the secondary safety endpoints (see Section 9.1.2) are mainly descriptive.

Laboratory data (e.g., antibody titres and other tests) will be described by assessment and presented by shift tables where applicable. Newly recognised anti-pFVIII inhibitors or increase in titre of anti-pFVIII inhibitors from pre-treatment level (if known) will be described.

Relevant medical history (inclusive of current comorbidities) will be summarised by system organ class and preferred term MedDRA. Severity of bleeding episodes will be evaluated based on subject's haemoglobin level before treatment start.

Administration of Obizur will be described in terms of number of units, number of infusions, treatment targets and treatment duration for the overall course of administration and per treatment phase (bleeding control phase, healing phase if applicable).

Treatment history and concomitant medications will be summarised by class of the WHO DRUG Reference List and using frequency distributions. Non-medication therapies undertaken for bleeding control will be described. Hospital stay episodes will be described.

Tables outlining the haemostatic effectiveness of Obizur; frequency, total dose, and total number of infusions of Obizur; and time Obizur was administered in order to control bleeding episodes will be developed.

9.7.3.3 Exploratory Endpoints

[redacted]

9.7.4 Planned Interim Analysis of the Study

Annual analyses are planned for this study concurrent with the annual assessment of the marketing authorisation under exceptional circumstances.

9.8 Quality Control

9.8.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favourable opinion by the competent/health authority and/or EC/IRB, as applicable), and applicable regulatory requirements as described in the Non-interventional Trial Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the MAH. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorised study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorised 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 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

It is planned that an onsite monitoring visit will take place at each site once the first patient from that specific site will have been included in the study. Thereafter, remote monitoring visits will take place once per year. Some ad-hoc on-site visits may be triggered as detailed in the clinical monitoring plan. 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 and may be revisited during the conduct of the study. (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 audit plan (see Section 14.1).

9.8.6 Non-Compliance with the Protocol

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

9.9 Limitations of the Research Methods

A challenge when conducting a study among subjects with a rare disease is to identify enough subjects for the study. Based on the clinical trial data, there is an expectation that this recruitment and follow-up of patients could be challenging as administration of Obizur occurs in an emergency setting where patients are not routinely followed. To mitigate this risk and ensure timely data collection, the protocol is amended to include retrospective data collection of patients treated with Obizur since its Marketing Authorisation in the EU and more than 30 days before the informed consent.

In addition, as with all observational studies, being dependent on the routine practice, cooperation and collaboration of the healthcare professionals, incomplete and missing data are expected. Data on immunogenicity ([redacted]) depends on laboratory tests and clinical assessments during the conduct of this study. Those may not be routinely required by all the treating physicians. Therefore, it is anticipated that the amount of data to assess this endpoint might be lower than for the others. Nevertheless, all available data to describe the immunogenicity of Obizur (newly recognised anti-pFVIII neutralising inhibitors or increase in titres from pre-treatment values [if known]) during the course of treatment and up to a minimum of 180 days after the last administration of Obizur will be transcribed onto the eCRFs.

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 (GVP).

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 enrolment of subjects into this study, the protocol, informed consent form, and any other written information to be provided to subjects will be reviewed and approved/given favourable opinion by the EC and applicable regulatory authorities. The study will commence only upon the MAH's receipt of approval/favourable 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 favourable 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 subjects for enrolment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All subjects/ and/or their legally authorised representative must sign an informed consent form according to applicable regulatory requirements. Before use, the informed consent form will be reviewed by the MAH and approved by the EC and regulatory authority(ies), where applicable, (see Section 10.3). The informed consent form will include a comprehensive explanation of the study without any exculpatory statements, in accordance with the elements required by applicable regulatory requirements. Subjects or their legally authorised representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, subjects or their legally authorised 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 (AEs)

11.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteraemia, etc.), or outcome of death temporally associated with the use of a medicinal product, whether or not considered causally related to the medicinal product.

11.1.1.1 Serious Adverse Event (SAE)

A 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 foetal 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 hospitalisation or results in prolongation of an existing hospitalisation – inpatient hospitalisation 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 hospitalisation but may jeopardise 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 hospitalisation, 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)

AESI listed below should be considered and reported as SAE:

- Hypersensitivity reactions
- Thromboembolic events
- Dose dispensing medication errors
- New (i.e., de novo)/titre increase of pFVIII inhibitors

11.1.1.2 Non-Serious Adverse Events (AEs)

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

11.1.1.3 Unexpected Adverse Events (AEs)

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., SPC/PL). "Unexpected" also refers to the 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 AEs/SAEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE Report Forms.

11.1.2 Assessment of Adverse Events (AEs)

Each AE from enrolment until study completion will be described on the AE Report Form using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definitions in Section 11.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 11.1.1.1, Section 11.1.1.2, and/or Section 11.1.1.3.
- Severity as defined in Section 11.1.2.1.
- Causal relationship to medicinal product exposure as defined in Section 11.1.2.2.

For each AE, 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 Report Form. Recovering/resolving AEs will be followed until resolution, or 180 days post Obizur administration, whichever occurs first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the dosage specified in the SPC/PL (including overdosing, underdosing, abuse, and withdrawal, treatment errors including incorrect route of administration, use of an incorrect product, and deviations from the dosing schedule defined in the SPC/PL which is one of the AESIs of the study), use for indications other than the approved one, failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities. Any pregnancy that occurs after administration of medicinal product will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year post-delivery, if feasible under routine pharmacovigilance activities.

11.1.2.1 Severity of Adverse Events (AEs)

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

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.

- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

11.1.2.2 Causality of Adverse Events (AEs)

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

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the medicinal product (i.e., does not follow a reasonable temporal relationship to the administration of product or has a much more likely alternative aetiology).
- Unlikely related (either one or both circumstances are met)
  - Has little or no temporal relationship to the medicinal product
  - A more likely alternative aetiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of medicinal product
  - An alternative aetiology is equally or less likely compared to the potential relationship to the medicinal product
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of medicinal product, which may include but is not limited to the following:

- Reappearance of a similar reaction upon re-administration (positive rechallenge)
- Positive results in a drug sensitivity test (skin test, etc.)
- Toxic level of the product as evidenced by measurement of the product concentrations in the blood or other bodily fluid

➢ Another aetiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within each Obizur treatment episode, the investigator shall provide the alternative aetiology.

11.1.2.3 Safety Reporting

AEs/SAEs will be assessed at all study visits as outlined in the Schedule of Study Assessments (see Table 1) and Section 11.1 above.

AEs/SAEs are to be recorded on AE/SAE Report Form. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the study product, must be reported **immediately** (within 24 hours of the study centre's first knowledge of the event) using the paper SAER Form.

For the prospective subject: any non-serious AE which occurs during this study, whether or not related to the study product, must be reported through EDC within seven business days from the site becoming aware of the non-serious AE. If the EDC system is out of order for more than seven days, the non-serious AEs must be reported on a paper Non-Serious Adverse Event Report Form.

For the retrospective subject: any non-serious **AE related to Obizur** must be reported through EDC within seven business days from the date of enrollment of the subject. If the EDC system is out of order for more than seven days, the non-serious AEs must be reported on a paper Non-Serious Adverse Event Report Form

The initial AE/SAE information reported must at least include the following:

- Protocol number
- Subject identification number and demographics (sex, age at onset of event and/or date of birth)
- Study drug exposure

- Medical term for event (diagnosis preferably)
- Description of the AE/SAE, including:
  - Date of onset
  - AE/SAE treatment (drug, dose, route of administration)
  - Causal relationship determined by the Investigator
  - Measures taken (i.e., action taken regarding investigational product in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion), if applicable
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting Investigator (for paper SAER)

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 mislabelled 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 1 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.

The investigator, or coordinating investigator(s) for multicentre studies, will sign the study report.

13. REFERENCES

1. Collins PW, Chalmers E, Hart D, et al. Diagnosis and management of acquired coagulation inhibitors: A guideline from UKHCDO. *Br J Haematol*. 2013;162(6):758-773.

2. Coppola A, Tagliaferri A, Calizzani G, et al. Clinical use and the Italian demand for activated prothrombin complex and activated recombinant factor VII concentrates. *Blood Transfus*. 2013;11 Suppl 4:S101-S109.

3. 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(4):553-562.

4. 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(4):566-575.

5. Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: Results from the European Acquired Haemophilia (EACH2) Registry. *J Thromb Haemost*. 2012;10(4):622-631.

6. Mulliez SM, Vantilborgh A, Devreese KM. Acquired hemophilia: a case report and review of the literature. *Int J Lab Hematol*. 2014;36(3):398-407.

7. Baudo F, Collins P, Huth-Kuehne A, et al. Management of bleeding in acquired hemophilia A (AHA): Results from the European Acquired Hemophilia (EACH2) Registry. *Blood*. 2012;120(1):39-46.

8. Sakurai Y, Takeda T. Acquired hemophilia A: A frequently overlooked autoimmune hemorrhagic disorder. *J Immunol Res*. 2014;2014:320674.

9. Kruse-Jarres R, St Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. *Haemophilia*. 2015;21(2):162-170.

10. Kempton CL, Abshire TC, Deveras RA, et al. Pharmacokinetics and safety of OBI-1, a recombinant B domain-deleted porcine factor VIII, in subjects with haemophilia A. *Haemophilia*. 2012;18(5):798-804.

11. Mahlangu J, Andreeva T, Macfarlane D, et al. A phase II open-label study evaluating the hemostatic activity, pharmacokinetics and safety of recombinant porcine factor VIII (OBI-1) in hemophilia A patients with inhibitors directed against human FVIII. *Haemophilia*. 2008;14 Suppl 2:15-16.

12. Toschi V. OBI-1, porcine recombinant Factor VIII for the potential treatment of patients with congenital hemophilia A and alloantibodies against human Factor VIII. *Curr Opin Mol Ther*. 2010;12(5):617-625.

14. ANNEXES

14.1 List of Stand-Alone Documents

No.	Document Reference No.	Date	Title
1	Version 1.0	15 APR 2016	**Recruitment Strategy Plan**
2	Version 2.0 / Version 1.0	08 DEC 2016 / 13 JUN 2016	**Clinical Operations Plan**
3	Number	Not finalised	**Data Management Plan**
4	Version 1.0	01 DEC 2016	**Audit Plan**
5	Version 1.0	21 APR 2016	**Project Communication Plan**
6	Version 1.0	17 AUG 2017	**Statistical Analysis Plan**

14.2 ENCePP Checklist for Study Protocols

Refer to the completed ENCePP Checklist.

14.3 Additional Information

Not Applicable.

14.4 Summary of Changes

PROTOCOL 241501

AMENDMENT 3
20 JULY 2018

Replaces: Amendment 2, 24 MAY 2017

Amd. No.	Section of Protocol	Description of Change	Purpose for Change
3	Throughout the document	Versioning update	To update of the version
3	Throughout the document	Minor grammatical and/or administrative changes	To improve the readability and/or clarity of the protocol
3	Protocol title	Adding of "retrospective"	To reflect that both prospective and retrospective data collection will be performed
3	Title page	Author name updated	To reflect new author
3	Research question and country (ies) of study	Adding of US Adding of US update of European countries	To reflect the participating countries
3	SECONDARY OBJECTIVES	Inclusion of "To describe the complete remission rate (inhibitors eradication)"	To be consistent with abstract
3	4. ABSTRACT	Abstract updated in line with the protocol amendment changes listed below Definition of prospective and retrospective patients has been added	To update of the study design to include EU retrospective data Collection and addition of US study sites to collect prospective data.
3	5. AMENDMENTS AND UPDATES	Section updated to reflect the main changes	To reflect the changes of the protocol amendment 3
3	8.1 Research Question, 9.1 Study Design, 9.2.1 Duration of Study Period(s) and Subject Participation, 9.2.2 Subject Selection Criteria	Inclusion of United States	To allow the inclusion of US prospective Sites
3	8.3 SECONDARY OBJECTIVES	Inclusion of To describe the complete remission rate (inhibitors eradication)	To be consistent with abstract

Amd. No.	Section of Protocol	Description of Change	Purpose for Change
3	9.1 STUDY DESIGN	Introduction of EU retrospective data collection and US prospective patients. Approximatively 50 subjects are expected to be enrolled in the study consisting of at least 20 European prospective subjects, a maximum of 15 European retrospective patients and a maximum of 15 US prospective subjects	To reflect that both prospective and retrospective data collection will be performed in order to reach the target number of patients
3	9.2.1 DURATION OF STUDY PERIOD(S) AND SUBJECT PARTICIPATION	Maximum 15 European retrospective subjects and maximum of 15 US prospective subjects will be enrolled. For the retrospective data collection if the available data already covers more than one 180-day follow-up period only one informed consent will be required	Clarification of the numbers of patients to be enrolled in order to balance the study population Clarification on the informed consent requirement for retrospective subject
3	9.2.2 SUBJECT SELECTION AND EXCLUSION CRITERIA	Include clarification for the criteria applicable to enrollement of US prospective and EU retrospective subjects New exclusion criteria: US Subject who has participated in the post-marketing study, NCT02610127 can not be enrolled. Excipients list and reference linked with SPC and LP. The list of excipients was removed.	To reflect the inclusion of EU retrospective and US prospective subjects.
3	9.2.3 INFORMED CONSENT AND ENROLMENT	Clarification about the requirement of Informed consent: Informed consent may not be required (e.g. deceased subjects) as local regulations allow.	To reflect the inclusion of retrospective subjects.
3	9.2.5 SCREENING AND FOLLOW-UP	Update of Figure 3: Study Design and footnotes for the Table 1: Schedule of Study Assessments and Table 2: Clinical Laboratory Data Collection	To reflect the inclusion of retrospective subjects and add clarification in case of long in-hospital stay
3	9.4 DATA SOURCES	Inclusion clarification that prospective and retrospective data collection will be performed. Clarification in case of long in-hospital stay	To reflect the inclusion of retrospective subjects and add clarification in case of long in-hospital stay
3	9.7.1 DATASETS AND ANALYSIS COHORTS	Inclusion of clarification on Informed consent collection	To add clarification

Amd. No.	Section of Protocol	Description of Change	Purpose for Change
3	9.7.3 METHODS OF ANALYSIS	Subject population defined for prospective subjects (3 sub-populations) and retrospective patient.	To reflect the inclusion of EU retrospective and US prospective subjects
3	9.9 LIMITATIONS OF THE RESEARCH METHODS	Added information that retrospective data collection will mitigate the recruitment of patients but the amount of missing data in these patients is likely to be higher	To reflect the benefits and risks of the implementation of retrospective data collection
3	11.1.2.3 SAFETY REPORTING	For the retrospective subjects, only AE related to Obizur should be reported	To add clarification on AE collection
3	14.1 List of Stand-Alone Documents	Version and date of statistical plan updated	Update
3	INVESTIGATOR ACKNOWLEDGEMENT	Dates updated	To reflect new protocol amendment version

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT Obizur®

STUDY TITLE: Prospective and retrospective, non-interventional study to evaluate the safety and effectiveness of Obizur in real-life practice

PROTOCOL IDENTIFIER: 241501

PROTOCOL AMENDMENT 3: 20 JUL 2018

Replaces **PROTOCOL AMENDMENT 2: 24 MAY 2017**

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 Operations