

Summary Basis for Regulatory Action

Date	22 October 2014
From	Natalya Ananyeva, PhD, Committee Chairperson
Subject	Summary Basis for Regulatory Action
BLA #	STN 125512/0
Applicant	Baxter Healthcare Corporation
Date of Submission	25 November 2013
PDUFA Goal Date	25 October 2014
Proprietary Name / Established name	OBIZUR / Antihemophilic Factor (Recombinant), Porcine Sequence
Dosage form	OBIZUR is available as a white lyophilized powder in single-use glass vials containing nominally 500 units per vial. Each vial is reconstituted with 1 mL of Sterile Water For Injection prior to intravenous injection.
Proposed Indications	OBIZUR is indicated for the treatment of bleeding episodes in adults with acquired hemophilia A.
Orphan Designation	Yes
Recommended Action	Approval
Signatory Authorities Action	<p>Jay S. Epstein, MD _____ Office Signatory Authority:</p> <p><input type="checkbox"/> <i>I concur with the summary review</i></p> <p><input type="checkbox"/> <i>I concur with the summary review and include a separate review or addendum to add further analysis</i></p> <p><input type="checkbox"/> <i>I do not concur with the summary review and include a separate review or addendum</i></p> <p>Mary Malarkey _____ Office Signatory Authority:</p> <p><input type="checkbox"/> <i>I concur with the summary review</i></p> <p><input type="checkbox"/> <i>I concur with the summary review and include a separate review or addendum to add further analysis</i></p> <p><input type="checkbox"/> <i>I do not concur with the summary review and include a separate review or addendum</i></p>

Discipline	Reviewers and Consultants
Clinical	Lisa Faulcon, MD, OBRR/DHCR/CRB
Clinical Pharmacology	Carl-Michael Staschen, MD, PhD, OBRR/DHCR/HPRB
Bio-Statistics	Boris Zaslavsky, PhD, DrSci, OBE/DB
Pharmacology/Toxicology	La’Nissa Brown-Baker, PhD, OBRR/DHCR/HPRB
CMC – Product	Natalya Ananyeva, PhD, OBRR/DHRR/LH Alexey Khrenov, PhD, OBRR/DHRR/LH Ze Peng, PhD, OBRR/DHRR/LH
CMC – Facility	Qiao Bobo, PhD, OCBQ/DMPQ/BII Jie He, OCBQ/DMPQ/BII Jeremy Wally, PhD, OCBQ/DMPQ/BII
Bioresearch Monitoring	Dennis Cato, MS, OCBQ/DIS/BMB
Labeling	Loan Nguyen, PharmD, OCBQ/DCM/APLB
Epidemiology	Wambui Chege, MD, OBE/DE/AEB
Lot Release Testing Plan / In-Support Testing	Karen Campbell, OCBQ/DBSQC Lokesh Bhattacharyya, PhD, OCBQ/DBSQC/LACBRP Alfred Del Grosso, PhD, OCBQ/DBSQC/LACBRP Catherine Poole, OCBQ/DBSQC/LACBRP Hyesuk Kong, PhD, OCBQ/DBSQC/LACBRP Grainne Tobin, PhD, OCBQ/DBSQC/LACBRP Igor Bacik, PhD, OCBQ/DBSQC/LACBRP
Regulatory Project Manager	Thomas Maruna, MS, MLS(ASCP), OBRR/IOD/RPMS Nannette Cagungun, MS, PD, RAC, OBRR/IOD/RPMS
Advisory Committee	Product not presented to Advisory Committee

1. Introduction

Baxter Healthcare Corporation (Baxter) submitted an original Biologics License Application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant), Porcine Sequence. The commercial product is a sterile lyophilized powder in single-use glass vials containing nominally 500 units per vial. The product is reconstituted with Sterile Water for Injection (SWFI) provided in a pre-filled syringe. The proprietary name of the U.S. marketed product is OBIZUR.

OBIZUR is indicated for the treatment of bleeding episodes in adults with acquired hemophilia A (AHA). OBIZUR is not indicated for the treatment of congenital hemophilia A (CHA) or von Willebrand disease.

The active component in OBIZUR is a recombinant (r) analogue of porcine (p) Coagulation Factor VIII (FVIII) in which the B-domain of the molecule was replaced with a twenty-four amino acid linker.

The safety and efficacy of OBIZUR was evaluated in a prospective, open-label, multicenter clinical trial of 29 subjects with AHA who received OBIZUR to treat a serious bleeding episode. All subjects evaluated for efficacy (n = 28) had a positive response to treatment at 24 hours after dosing for the initial bleeding episode. No safety concerns were identified in the trial.

2. Background

AHA is a rare bleeding disorder caused by the development of autoantibodies to FVIII, thus creating FVIII deficiency and preventing normal hemostasis. The bleeding episodes in patients with AHA may be spontaneous and severe at presentation, and they may be life-threatening. The clinical manifestations of AHA include hemorrhages into the skin, muscles, soft tissues, or mucous membranes. AHA affects both males and females and is associated with significant morbidity and mortality.

The principle of using pFVIII is based on its low cross-reactivity with anti-human FVIII antibodies due to sequence variations between human and pFVIII in the A2 and C2 domains, the main targets of FVIII inhibitors. The cross-reactivity of inhibitory antibodies to human FVIII with pFVIII is estimated at 15% in patients with CHA, and is even lower in patients with AHA. Therefore, when administered to patients with AHA, pFVIII is less likely to be bound by inhibitory antibodies and can function in the coagulation cascade to promote hemostasis.

Plasma-derived pFVIII (marketed as Hyate:C under U.S. License 1609) has been licensed in the U.S. since 1980 to achieve hemostasis in patients with anti-human FVIII inhibitors. The commercial production of Hyate:C was discontinued in 2005 due to problems with sourcing suitable porcine plasma. Therefore, OBIZUR may address the clinical need for a FVIII-based product for use in patients with AHA.

OBIZUR was developed under Investigational New Drug (IND) application, IND 10695, originally submitted by Ipsen (France). The ownership of the program was transferred from Ipsen to Inspiration Biopharmaceuticals, Inc. in 2010, and from Inspiration to Baxter in 2013. The product was granted Orphan Drug designation on 18 March 2004 for “the treatment and prevention of episodic bleeding in patients with inhibitor antibodies to human coagulation factor VIII”, and the Orphan Drug designation status was re-confirmed on 24 April 2013. IND 10695 was granted Fast Track designation on 24 October 2012 on the basis that the drug is intended to treat a serious disease and has the potential to address an unmet medical need.

Regulatory History

The application was submitted as a rolling BLA beginning with the Non-Clinical modules on 10 October 2013; followed by the CMC Quality and Facility modules on 8 November 2013; and finally the Clinical modules on 25 November 2013. The BLA was reviewed under the Priority Review schedule of the PDUFA V program.

During the review, FDA requested Baxter to tighten the in-process control limits of the manufacturing process, re-validate the lyophilization process, perform shipping validation, re-validate a number of analytical procedures, revise the Drug Product Specification, and perform additional stability studies. In response, Baxter submitted Amendment 17 in April 2014, which contained a substantial amount of new information. This submission was classified as a *Major Amendment*, and the action due date was extended to 25 October 2014.

The data contained in the BLA and its amendments support the consistency and robustness of the manufacturing process for OBIZUR. In addition, all the issues identified during the inspections of the facilities in -----(b)(4)----- satisfactorily addressed.

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----- (b)(4) -----
-----.

A batch of rpFVIII FBDS is defined as the material manufactured using -----
----- (b)(4) -----.

OBIZUR Drug Product (DP) is manufactured at the ----- (b)(4) -----
----- . The DP manufacturing process consists of the ----- (b)(4) -----
-----, sterile filtration --- (b)(4) ---, filling, lyophilization, and over-sealing. Labeling and
secondary packaging is performed at Baxter's facility in ----- (b)(4) -----.

Source Material Quality and Control

Cell Bank System

----- (b)(4) -----

Characterization of the master cell bank (MCB), WCB and End-of-Production (EOP) cells was performed in accordance with ICH Guideline Q5D: *Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological / Biological Product*, and included specification analyses for Sterility, Mycoplasma, Product Identity, and Cell Viability. Evaluation of the cell bank system for safety with regard to adventitious viruses was performed in accordance with ICH Guideline Q5A(R1): *Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* (detailed under Viral Safety).

Genetic characterization was performed in accordance with ICH Guideline Q5B: *Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products*. -----

----- (b)(4) -----

----- . The stability program for MCB and WCB is in place, and lifetime projections provide evidence of sufficient reserves of these source materials to maintain long-term manufacture of OBIZUR.

Other Raw Materials

manufacturing process, -----(b)(4)----- . The process was validated by production, at commercial scale and nominal operating conditions, of three consecutive DS Process Validation (PV) batches. All pre-defined acceptance criteria stated in the Protocol (for CPPs, hold times, IPC and release testing) were met, thus fulfilling the requirements for process validation.

The validation studies for the DP manufacturing process were performed at ----(b)(4)----- facility, the intended commercial contract facility, under a prospective process validation protocol. The original validation studies were designed for commercial scale, nominal operating conditions, and extended process times to confirm process consistency and robustness and were completed in 2012 with the manufacture of (b)(4) consecutive DP PV batches. An additional confirmatory DP PV batch was manufactured in 2013 to qualify the maximum lyophilizer load of filled vials. Process (CPPs) and quality (IPC tests) controls for DP PV lots complied with the prospectively defined acceptance criteria and the results of release testing were within specifications thus fulfilling the requirements for a successful process validation.

Based on the evaluation of the manufacturing and testing data for the Phase III clinical, process validation and post-validation batches of DS and DP, the manufacturing process for OBIZUR is found to be well controlled, adequately validated and consistent as evidenced by:

- Identification of CPPs and validation of their operating ranges;
- Identification of IPC and release tests and validation of their acceptance criteria;
- Robustness of the manufacturing process steps within the proven acceptable ranges;
- Extensive characterization of DS and DP batches, representative of different stages of process development, and their comparability;
- Satisfactory release data for over (b)(4) DS and over 25 DP batches (commercial scale), including IPC and release test results of all PV batches, that meet the pre-determined criteria for quality characteristics;
- Availability and adherence to SOPs as verified during the two pre-license inspections.

Final Drug Product: Composition and Presentation

OBIZUR is supplied as a white lyophilized powder in single-use vials that nominally contain 500 units per vial in 1-vial, 5-vial, and 10-vial package sizes. Each package contains an appropriate number of each of the following components correlating to the vial package size: single-use vial of OBIZUR, pre-filled syringe with 1 mL SWFI, and vial adapter with filter.

Each vial of OBIZUR is labeled with the actual rpFVIII activity expressed in units determined by a one-stage clotting assay, using an rpFVIII reference material calibrated against the World Health Organization (WHO) 8th International Standard for FVIII concentrate, which is of human origin.

OBIZUR is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with SWFI. The reconstituted product contains rpFVIII and the following components per mL: 8.8 mg sodium chloride, 0.04 mg Tris-base, 0.73 mg Tris-HCl, 1.47 mg tri-sodium citrate dehydrate, 0.15 mg calcium chloride dehydrate, 1.9 mg sucrose, and 0.05 mg polysorbate 80.

The identity and purity of rpFVIII were investigated using -----
----- (b)(4) -----
----- . These studies confirmed the ----- (b)(4) ----- of rpFVIII and its -----
----- (b)(4) -----
----- .

Functional Characterization

The biological function of rpFVIII is to enable the production of a fibrin clot via the intrinsic coagulation pathway where activated FVIII serves as a cofactor for activated Factor IX (FIXa) to activate Factor X (FX). The functional studies for rpFVIII included the assessment of the kinetics of its activation by thrombin, and binding to von Willebrand Factor (vWF). These studies demonstrated the thrombin cleavage pattern of rpFVIII to be consistent with the expected cleavage sites, and high affinity of rpFVIII for vWF at a ----- (b)(4) -----
----- .

The biological activity of rpFVIII was demonstrated by its ability to support FX activation in the chromogenic substrate (CS) assay and to promote blood clotting in FVIII-deficient plasma in the one-stage clotting (OC) assay. ----- (b)(4) -----
----- . Based on the data from (b)(4)
DP batches, the Applicant showed that the potency values of OBIZUR determined by the CS assay are generally lower than those by the OC assay, with an established OC/CS ratio of – (b)(4)- (further discussed under DP Specification).

Impurities

Product- and process-related impurities were identified and characterized in selected batches of - --(b)(4)-- DP that were studied in clinical trials. Removal of product- and process-related impurities by the manufacturing process was demonstrated during process development in -(b)(4)-- studies, and was confirmed during the validation of the commercial process. For each impurity, a risk assessment was performed in accordance with ICH Guideline Q9, and for all impurities, the final levels in --(b)(4)-- were confirmed to be safe in clinical studies.

As rpFVIII is produced from a BHK cell line, -----
----- (b)(4) -----
----- . The risk of immune response and hypersensitivity reactions to HCP is considered low because exposure to OBIZUR is expected to be short-term: OBIZUR will be used to treat immediate bleeding episodes with a typical two-week treatment period. Treatment-related antibodies against HCP were not detected in patients in the pivotal clinical trial.

----- (b)(4) -----
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Analytical Methods

Suitable analytical methods have been validated to support quality control testing throughout manufacture, final product release and stability monitoring. Clarifications were obtained through

requests of additional documentation and during the pre-license inspections of Baxter's -----
----(b)(4)----- facilities. The following issues were resolved in the course of the review.

In the validation of the -----(b)(4)-----, reproducibility was not adequately established due to the use of inappropriate acceptance criteria. The Applicant re-analyzed the data to calculate the relative standard deviation and confidence interval values, as recommended in ICH Guideline Q2R1 for determining reproducibility.

In the validation of the OC assay for FVIII potency, the assessment of accuracy, range and repeatability did not meet the requirements of ICH Guideline Q2R1 in that an insufficient number of concentrations and samples were used to cover the established range. In addition, the FDA was concerned about the use of the same material as standard and sample, and the qualification of the positive control. These concerns were satisfactorily addressed with a re-validation of the assay and the submission of comprehensive data demonstrating parallelism between dilution curves for references and samples.

The approach used in the validation of the OC assay also did not allow the assessment of intermediate precision in a statistically valid manner. The Applicant performed a re-validation of this parameter as recommended by FDA. The OC assay is now considered to be adequately validated and suitable for its intended use as a DP lot release test and as the DP potency assignment assay.

A number of deficiencies were identified in the validation of the CS assay for FVIII potency. Per FDA request, the method was re-validated, -----(b)(4)-----
------. However, the specification of the CS assay for DP release will be changed to "For Information Only" as discussed in the next section.

The deficiencies identified in the validation of assays for excipients were adequately resolved by providing supplemental validation reports, revised SOPs or re-evaluation of the data.

An acceptable reference standard qualification and maintenance program has been established. Two (b)(4) in-house product-specific primary reference standards have been qualified for routine analytical testing of commercial (b)(4)-- DP. The suitability of the primary potency reference standard was established in a collaborative study conducted in five laboratories, and its potency value was assigned against the WHO 8th International Standard for FVIII concentrate. This reference standard is used for the determination of (b)(4)-- DP potency by the OC and CS assays. The primary quantitative reference standard was qualified by meeting the acceptance criteria of the release specification and additional characterization, and is used for those parameters that are measured by -----(b)(4)----- analyses. A stability program for the standards is also in place.

Drug Product Release Specification

The specifications for DS and DP are established in accordance with ICH Guidelines Q6A and Q6B. The parameters are selected from critical quality attributes determined in the process development studies and risk assessments. Acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data. The manufacturing capability was assessed through analysis of release data for the Phase III clinical and process validation batches. The following substantive issues were resolved in the course of the review:

Potency by the CS assay: Although the CS method was re-validated, both the Applicant and the Agency identified issues related to the assay variability that appeared to be dependent on the chromogenic reagent kits and reference standards used. This variability requires further investigation. Since DP potency is assigned by the OC assay, the Applicant revised the DP Release Specification for FVIII Activity by the CS assay to “For Information Only”. Similarly, the OC/CS ratio will also be reported as “For Information Only”. The actual values of these two parameters will be reported in the *Certificate of Analysis*.

The final DP Release Specification in Table 2 is considered adequate to control the identity, purity, biological activity, and safety of OBIZUR.

TABLE 2: SPECIFICATION FOR DRUG PRODUCT

Attribute	Parameter	Method	Specification
Physical and Chemical	Appearance	Visual inspection ----- ----- (b)(4) -----	----- (b)(4) ----- ----- ----- (b)(4) ----- -----
	Residual Moisture	----- --- (b)(4) --- -----	--- (b)(4) ---
	Reconstitution Time	(b)(4)	--- (b)(4) ---
	(b)(4)	----- (b)(4) -----	--- (b)(4) ---
	----- (b)(4) -----	----- (b)(4) ----- -----	----- (b)(4) ----- -----
	Protein Concentration	--- (b)(4) ---	----- (b)(4) -----
Identity	Identity by --- (b)(4) ---	----- (b)(4) ----- -----	----- (b)(4) ----- -----
Purity and Heterogeneity	--- (b)(4) ---	--- (b)(4) ---	(b)(4)
	----- (b)(4) ----- -----	--- (b)(4) ---	(b)(4)
	--- (b)(4) ---	--- (b)(4) ---	(b)(4)
	--- (b)(4) ---	--- (b)(4) ---	--- (b)(4) ---
	--- (b)(4) ---	--- (b)(4) ---	--- (b)(4) ---
	--- (b)(4) ---	--- (b)(4) ---	--- (b)(4) ---
Potency	FVIII Activity Clotting	--- (b)(4) ---	----- (b)(4) -----
	Specific Activity, U/mg	Calculation based on OC assay and Protein Concentration	11000 to 18000 U/mg
	FVIII Activity Chromogenic	CS assay	For Information Only
	OC/CS Ratio	Calculation based on the OC and CS potency values	For Information Only
Impurities	--- (b)(4) ---	--- (b)(4) ---	(b)(4)
	--- (b)(4) ---	--- (b)(4) ---	(b)(4)
Safety	Sterility	----- (b)(4) -----	----- (b)(4) ----- --- (b)(4) -----
	Endotoxin	----- (b)(4) -----	--- (b)(4) -----
Excipients	Sodium	--- (b)(4) ----- -----	--- (b)(4) -----
	Calcium	--- (b)(4) ----- -----	--- (b)(4) -----
	Citrate	--- (b)(4) ----- -----	--- (b)(4) -----
	Chloride	--- (b)(4) ----- -----	--- (b)(4) -----
	Tris	(b)(4)	--- (b)(4) -----
	Sucrose	----- (b)(4) ----- -----	--- (b)(4) -----
	Polysorbate 80	----- (b)(4) -----	--- (b)(4) -----

Batch Analyses and In-Support Testing

The BLA contains results of release analyses of (b)(4) commercial-scale DS batches and 25 DP lots which include Phase III clinical, process validation and post-validation material. The results for all batches are within DS and DP release specifications.

The Laboratories of the Division of Biological Standards and Quality Control (DBSQC) in the Office of Compliance and Biologics Quality (OCBQ), CBER, FDA, performed in-support testing of the three PV batches of OBIZUR.

With the exception of the CS assay, all methods performed adequately, with all system suitability and assay validity criteria satisfied. The DBSQC results for the three DP lots tested were within the proposed specifications and comparable to the results reported by Baxter. The potency values measured by the CS assay were variable depending on the kit used for measurement, and did not meet the acceptance criteria on some occasions.

The in-support testing confirmed the suitability of critical test methods for their intended use as release specification tests. Following the 22 August 2014 teleconference, Baxter changed the specification of the CS assay to “For Information Only”. -----(b)(4)-----

Stability Studies

The stability program for OBIZUR included studies under long-term storage (2 – 8°C) and accelerated ----(b)(4)----- conditions that were performed on DP lots representative of the intended commercial manufacturing process – (b)(4) primary stability lots, (b)(4) PV lots, (b)(4) supporting stability lots, and (b)(4) additional lots.

The stability data for DP PV lots in the original submission required re-evaluation to conform to the changes -----(b)(4)-----
----- . The stability data for the reconstituted product were not provided for the PV lots, and the Stability Protocol was found incomplete. Per FDA request, the Applicant provided up-to-date stability data, and revised the Stability Protocol.

The available stability data revealed no negative trends during the observed long-term storage period. The data support the proposed shelf-life of 24 months for OBIZUR final container when stored at 2 – 8°C (36 – 48°F). The photo-stability data indicate that OBIZUR is sensitive to extreme light, and that the package is able to protect the product from photo-degradation. Therefore, the product should be stored in the original carton to protect it from light.

Per FDA request, the data to demonstrate in-use stability of DP at release and after storage were submitted for the PV and primary stability lots. The data support the stability of the reconstituted product for up to three hours at ambient temperature. The storage conditions and handling of reconstituted OBIZUR are accurately described in the labeling.

Per FDA request, the Stability Protocol for DP was modified to add more frequent endotoxin and sterility testing, and container closure integrity testing. The final Stability Protocol has sufficient control of DP stability post-approval.

The stability data for DS are sufficient to support its shelf-life of ----(b)(4)----- . The established Stability Protocol is adequate to control DS stability post-approval.

Evaluation of Safety Regarding Adventitious Agents

Non-Viral Pathogen Safety

The safety with regard to non-viral adventitious agents such as bacteria, fungi, and mycoplasma is ensured through the control of bioburden in source materials, adherence to current good manufacturing practice, in-process control monitoring, validated sterile filtration and aseptic filling processes, and release and stability testing for sterility and endotoxin.

Viral Safety

Recombinant pFVIII is produced in a transfected BHK cell line. All cell banks (MCB and WCB) and EOP cells have been tested in accordance with ICH Guidelines Q5A(R1) and Q5D and demonstrated to be free of infectious viruses, mycoplasma, bacteria and fungi in both *in vitro* and *in vivo* tests-----

----- (b)(4)-----

----- (b)(4)-----

----- . Thus, the cell bank system is adequately controlled, and the viral safety of the cell culture is ensured for up to (b)(4) harvests used in the commercial production.

The risk of virus contamination is further mitigated by the inclusion of two dedicated viral clearance steps in the purification process: S/D treatment for virus inactivation and 15 nm nanofiltration for virus removal. -----

----- (b)(4)-----

----- . These model viruses represent a wide range of size and physico-chemical properties and the results support the effectiveness of the manufacturing process to clear viruses from OBIZUR.

b) Exemption from CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (8 December 1995), routine lot-by-lot release by CBER is not required for OBIZUR because it is a well-characterized recombinant product. The in-support testing by CBER confirmed suitability of critical quality-defining methods for their intended use as lot release specification tests. Exemption of OBIZUR from CBER Lot Release is justified.

c) Review of Manufacturing Facilities

The manufacture of -----(b)(4)----- is performed at the Baxter (b)(4) facility located in ----(b)(4)----- . The manufacture of OBIZUR DP is performed by a contract manufacturer, -----(b)(4)----- . Packaging and labeling of DP is performed at the Baxter -----(b)(4)----- facility located in (b)(4), ----- . The diluent is manufactured by -----(b)(4)-----

Baxter -----(b)(4)----- Facility

Baxter -----(b)(4)----- is used to manufacture OBIZUR DS. ---(b)(4)----- consists of the GMP manufacturing area, QC laboratories, warehouse, and office space. OBIZUR is the only product made at the Baxter (b)(4) facility. The pre-license inspection (discussed below) associated with this BLA was the first FDA inspection at the Baxter (b)(4) facility.

-----(b)(4)-----

-----(b)(4)-----

Baxter -----(b)(4)----- Facility

Packaging and labeling of the OBIZUR DP is performed at Baxter ----(b)(4)----- (part of Baxter (b)(4) facility) located in -----(b)(4)----- . This facility was last inspected by Team Biologics from -----(b)(4)-----, and the inspection was classified as VAI. The pre-license inspection of Baxter’s ---(b)(4)----- facility was waived per SOPP 8410.

-----(b)(4)-----

-----(b)(4)-----

-----(b)(4)-----

Inspection of the Manufacturing Facilities

CBER Pre-license Inspection of Bulk Drug Substance Manufacturing Facility

CBER conducted a pre-license inspection (PLI) at Baxter Health Corporation’s -----
-----(b)(4)-----.

The PLI of the Baxter (b)(4) facility covered the manufacturing process for the DS, which includes -----

-----(b)(4)-----

----- . The PLI covered Quality, Facility & Equipment, Materials Management, Production, Packaging & Labeling, and Laboratory Controls Systems with respect to the manufacture of OBIZUR DS. At the conclusion of the inspection, CBER issued Form FDA 483 with nine observations. Deficiencies were noted included qualification of the bulk DS container closure system;; deviation management; ; review and assessing validation

results for laboratory testing procedures; handling ----(b)(4)-----; record keeping for equipment use logs. In their 27 June and 24 August 2014 responses (Amendments 24 and 29), Baxter (b)(4) provided corrective actions implemented to address the 483 items. The corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

CBER Pre-license Inspection of Drug Product Manufacturing facility

CBER conducted a PLI at Baxter's contract manufacturer -----(b)(4)-----
-----.

The PLI of the ----(b)(4)----- facility covered the manufacturing process for OBIZUR DP, which includes ----(b)(4)----- sterile filtration of --(b)(4)--, aseptic filling, lyophilization, and over sealing of vials containing lyophilized DP. The PLI covered Quality, Facility & Equipment, Materials Management, Production, and Laboratory Controls Systems with respect to the manufacture of OBIZUR DP. At the conclusion of the inspection, CBER issued Form FDA 483 with six observations. Deficiencies were noted in the validation of the lyophilization process, environmental monitoring program, shipping validation, and equipment calibration. The corrective actions were received on 16 May 2014, 12 August 2014, 25 August 2014, 8 September 2014 and 19 September 2014 in Amendments: 20, 27, 29, 30 and 33 respectively, reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

d) Environmental Assessment

The BLA included a request for a categorical exclusion from an Environmental Assessment under 21 CFR § 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Recommendation

The manufacturing process for OBIZUR, Antihemophilic Factor (Recombinant), Porcine Sequence, is considered to be adequately validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of the commercial product that meets acceptable release specifications. The manufacturing process provides acceptable safety margins regarding adventitious agents. All inspectional issues were adequately addressed. The reviewers from the Division of Hematology Research and Review, OBRR, the Division of Manufacturing and Product Quality and the Division of Biological Standards and Quality Control, OCBQ, conclude that Baxter Healthcare Corporation has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of OBIZUR.

4. Non-Clinical Pharmacology/Toxicology

a) General Considerations

The nonclinical program consisted of a series of studies to demonstrate the safety and effectiveness of rpFVIII in animals including hemophilic mice and dogs, and wild-type FVIII expressing ---(b)(4)----- monkeys. To support the proposed clinical indications, the completed nonclinical program consisted of the following:

- (a) safety pharmacology in hemophilia A mice and hemophilia A dogs,
- (b) proof of principle in hemophilia A mice and hemophilia A dogs,
- (c) acute toxicity in hemophilia A dogs and in monkeys,
- (d) pharmacokinetics in monkeys and hemophilia A dogs,
- (e) repeat dose toxicity, with toxicokinetics, in mice and monkeys,
- (f) immunogenicity in hemophilia A mice and in monkeys and
- (g) hemostatic activity of rpFVIII in hemophilia A mice and hemophilia A dogs.

b) Pharmacological/Toxicological Findings

The Applicant has completed a nonclinical program including GLP-compliant and non-GLP nonclinical studies in relevant animal models. Models included hemophilia A mice and hemophilia A dogs, and wild-type FVIII expressing mice and ---(b)(4)----- monkeys. An adequate safety profile for rpFVIII has been established to support its intended use in the treatment of bleeding episodes in adult patients with AHA.

To support the proposed clinical indications, the completed nonclinical program consisted of a series of studies to demonstrate the safety and effectiveness of rpFVIII in animals including: (a) safety pharmacology in hemophilia A mice and hemophilia A dogs, (b) proof of principle in hemophilia A mice and hemophilia A dogs, (c) acute toxicity in hemophilia A dogs and in monkeys, (d) pharmacokinetics in monkeys and hemophilia A dogs, (e) repeat dose toxicity, with toxicokinetics, in mice and monkeys, (f) immunogenicity in hemophilia A mice and in monkeys and (g) hemostatic activity of rpFVIII in hemophilia A mice and hemophilia A dogs.

The proof-of-principle and pharmacologic activity of rpFVIII were demonstrated using two animal models of hemophilia A. In hemophilia A dogs, cuticle bleeding time was shortened in a dose-related manner following a single intravenous injection of 3, 25 or 100 U/kg rpFVIII. Similarly, dose-related improvements in survival were reported in hemophilia A (i.e., Factor VIII knock-out) mice following hemorrhagic insult (tail transection). A single intravenous dose of 89 U rpFVIII/kg body weight resulted in a 50% survival rate following the tail injury, as compared to 0% survival in hemophilic mice injected with the vehicle control. The effective doses of rpFVIII identified in the animal models were used to establish the proof-of-principle and dosing range for the initial clinical trial in AHA patients.

Overall, the nonclinical safety profile of OBIZUR did not identify any unexpected findings or significant concerns; toxicities that were observed were due to exaggerated pharmacological effect of excess amounts of Coagulation Factor VIII, which are expected for products in this class. Recombinant porcine FVIII was tested acutely in animals at doses up to 1000 U/kg, (i.e., 5 times the intended starting clinical dose of 200 U/kg), without unexpected adverse events (AEs). Repeat-dose toxicity studies were completed with daily dosing of up to 1000 U/kg for up to 12 weeks (i.e., 13.3 times the intended, median prophylactic clinical dose of 75 U/kg) and the product was well-tolerated.

In animal studies, the exaggerated pharmacological effects of rpFVIII that were considered adverse included thrombogenic events and local reactions at the treatment site, and were reported after repeat dosing with rpFVIII doses 5-fold greater (i.e., 1000 U/kg rpFVIII) than the proposed

clinical dose of 200 U/kg for use in the repeat dose setting. An additional toxicity reported in the animal studies was hypersensitivity at the injection sites, as evidenced by gross and histopathologic findings of inflammation, cellular infiltrates, swelling and bruising. Together, the adverse findings in the animal studies were expected based on species differences between the test animals and the porcine FVIII, and predictive for human use of the product, as confirmed by the AEs reported in the clinical trial. Toxicokinetic profiles demonstrated a linear dose-dependent increase in the levels of rpFVIII, followed by a time-dependent decrease in product levels. This profile was maintained until anti-product antibody formation occurred, resulting in decreased rpFVIII activity. Although immunologic responses may occur in patients following repeated product administration and are a potential safety concern, the formation of anti-product antibodies in animals is not unexpected and is not predictive of an immunogenic response to rpFVIII in humans. There were no reports of neutralizing anti-rpFVIII antibodies or anaphylaxis in clinical trials of rpFVIII.

Based on the intended use of rpFVIII, nonclinical reproductive or developmental toxicity studies, long-term animal studies to evaluate carcinogenic potential, and studies to determine genotoxicity and effects of OBIZUR on fertility were not performed. A toxicological risk assessment was completed on potential extractable and leachable impurities associated with the OBIZUR manufacturing process and container closure system. There were no concerns identified regarding these impurities, nor unexpected toxic effects that would require additional safety studies.

c) Recommendation

The safety profile and hemostatic activity of rpFVIII determined for OBIZUR in the nonclinical program, and the toxicological risk assessment are sufficient to support OBIZUR's proposed use for the treatment of bleeding episodes in patients with AHA.

5. Clinical Pharmacology

a) Mechanism of Action

When administered in patients with AHA, OBIZUR temporarily replaces the inhibited endogenous FVIII that is needed for effective hemostasis. Upon activation by thrombin, rpFVIIIa acts as a cofactor for activated FIX triggering a chain of biochemical reactions – activation of FX, which converts prothrombin into thrombin, and subsequent interaction of thrombin with fibrinogen results in the formation of the fibrin clot that stops the bleeding.

b) Pharmacodynamics

Patients with AHA have normal FVIII genes but develop autoantibodies against their own FVIII (i.e., inhibitors). These autoantibodies neutralize circulating human FVIII and create a functional deficiency of this procoagulant activity. AHA results in a prolonged clotting time as measured by the -----(b)(4)----- assay, a conventional *in vitro* test for biological activity of FVIII. rpFVIII replaces the neutralized endogenous FVIII and restores the ability to form a fibrin clot.

c) Pharmacokinetics

A formal pharmacokinetic (PK) study of OBIZUR in patients diagnosed with AHA has not been conducted.

A PK analysis of OBIZUR was conducted under Study OBI-1-101, a Phase I, parallel-group study comparing the safety and tolerability of OBIZUR versus HYATE:C when administered to CHA subjects (> 12 yr). Only 3 patients receiving a single dose of OBIZUR (100 units/kg) as a short intravenous infusion were included in data analysis (as the study was terminated due to non-availability of HYATE:C). The patients in the OBIZUR Group were in a non-bleeding state, had no detectable inhibitors and had low or absent anti-porcine FVIII antibody titers. Blood samples for PK analysis were taken up to 48 h post-dose and rpFVIII activity was measured by the one-stage clotting assay. The estimated relevant mean PK parameters and respective standard deviations (SD) are: terminal half-life ($T_{1/2}$) = 10.6 (0.8) hr, total clearance CL = 546 (376) mL/h, Vd = 8.3 (5.6) L, IVR = 1.76 U/dL per U/kg. However, given the small number of patients (N=3) available for a full PK analysis the results are not robust enough to allow for a general PK characterization of OBIZUR in patients diagnosed with CHA.

In the pivotal clinical study (OBI-1-301), a formal PK analysis of OBIZUR in patients with AHA (non-bleeding state) was not conducted as participation in PK was optional, and obtaining blood samples at adequate time-points was not feasible in the bleeding AHA patients.. The summary parameters from 3 patients indicate a maximal activity of OBIZUR between 17 and 28 minutes following the final dose, with a calculated mean $T_{1/2}$ between 3.6 and 4.0 hours after dosing. The analysis and interpretation of the PK parameters is confounded by inadequate blood sampling schedules (up to 24 h post-dose). As a result, the terminal drug elimination phase has not been sufficiently captured and a meaningful interpretation of the PK data is precluded. In addition, even with a correct sampling schedule and data analysis, the number of patients (N=3) available for the PK analysis would not be sufficient to allow a robust interpretation of the PK parameters.

6. Clinical/Statistical

a) Clinical Program

Clinical safety and efficacy trials of OBIZUR were conducted under IND 10695. To support licensure for the proposed indication, the clinical development program included: (1) an uncontrolled, international, multicenter, open-label, prospective trial (OBI-1-301), where subjects with AHA due to auto-immune inhibitory antibodies to human FVIII received OBIZUR to treat a serious bleeding event, (2) an expanded access protocol based on trial OBI-1-301 (OBI-1-301a), (3) an open-label, non-randomized, prospective safety and efficacy trial in subjects with CHA with inhibitors and with a history of inadequate response to bypassing agents, which was terminated by the applicant after enrollment of one subject (OBI-1-302), (4) a completed open-label safety and efficacy trial in non-life and non-limb threatening bleeding episodes in subjects with CHA with inhibitors (OBI-1-201), and (5) a pharmacokinetic study of OBIZUR versus HYATE:C in adolescents and adults with CHA, with low or absent anti-porcine FVIII inhibitor antibody titers, in a non-bleeding state (OBI-1-101). This review focuses on the safety and efficacy trials for the treatment of serious bleeding episodes in adults (≥ 18 years) with AHA due

to autoantibodies to human FVIII (OBI-1-301 and OBI-1-301a). Data from the clinical trials conducted in subjects with CHA were reviewed for an integrated analysis of safety.

The primary efficacy outcome of the study OBI-1-301 was the proportion of serious bleeding events responsive to OBIZUR therapy at 24 hours after the initiation of treatment. Hemostatic efficacy was evaluated using a pre-defined four-point rating scale (see below)

A positive response was defined as an effective or partially effective assessment. In the case of an inconsistency between the clinical assessment and the FVIII levels, the clinical assessment was used to determine the outcome. Based on the assumption of a response rate of 80% and 50% as a baseline response rate, using a two-sided alpha of 0.05, a sample size of 28 bleeding events would have 90% power to test the null hypothesis (H_0) that the response rate = 50%, with the alternative hypothesis (H_1) that the response rate >50% (based on the exact test of this null hypothesis). The small sample size is justified because of the rarity of the disorder of acquired hemophilia A. The treatment would be considered clinically beneficial if the lower bound of the two-sided 95% CI for the positive response rate is greater than 50%.

A total of 29 adult subjects (≥ 18 years) with AHA were enrolled and received at least one dose of OBIZUR to treat a serious bleeding episode that required hospitalization, including 25 subjects who were enrolled in the pivotal trial OBI-1-301 and 4 subjects enrolled under the expanded access protocol OBI-1-301a. These bleeding events included 19 intramuscular or joint, 4 post-surgical, 2 intracranial, 2 surgical, 1 retroperitoneal, and 1 periorbital bleeding events. All subjects received an initial dose of 200 units per kg OBIZUR; the dose and frequency of additional doses were based on clinical judgment and measurement of FVIII levels achieved. Subjects with a prior history of bleeding disorders other than AHA, anti-porcine FVIII antibody titer > 20 Bethesda Units (BU), or in whom the bleeding episode was judged likely to resolve on its own were excluded. One subject was considered evaluable at study entry; however, it was later determined that this subject did not have AHA, leaving 28 subjects evaluable for efficacy.

Of the 29 treated subjects, 19 (66%) were male and 10 (34%) were female. The median age was 70 years (range 42-90 years), which reflects the broader population targeted by the proposed indication. The majority of enrolled subjects had a significant medical history of cardiovascular disorders (76%) and endocrine/metabolic disorders (69%). A total of 14 subjects (48%) had a previous history of AHA, at which time 11 subjects (28%) received immunosuppressive therapy, 11 subjects (28%) received anti-hemorrhagic medications (e.g., rFVIIa, activated prothrombin-complex concentrate, tranexamic acid) and 8 subjects (28%) were treated with unspecified therapy for a previous bleeding episode. The majority of the subjects were White (62%); 6 (21%) were African-American, and 5 (17%) were Asian. Enrolled subjects were from the United States (16 subjects; 14 sites), Canada (5 subjects; 1 site), India (4 subjects; 1 site) and the United Kingdom (4 subjects; 2 sites).

A total of 18 (62%) subjects completed the study. As expected, there was a large number of discontinuations due to the fact that the enrolled subjects were critically ill and had significant co-morbidities. Nine subjects were discontinued from the trial for the following reasons:

- Fatal intracranial hemorrhage (ICH; two subjects)
- Development of anti-porcine FVIII inhibitor (two subjects)
- Sepsis resulting in death (two subjects)
- Renal failure resulting in death (one subject)
- Lack of efficacy (one subject)

- Non-compliance (one subject)
- One subject was lost to follow-up for safety assessment but his initial qualifying bleed was included in efficacy analysis.

The status of one subject was unknown at the time of BLA submission.

Efficacy Analysis

The primary endpoint of hemostatic response at 24hrs was assessed by the study site investigator using a pre-specified rating scale (Table 3) that was based on clinical assessments and factor VIII activity levels achieved. An assessment of effective or partially effective was considered as a positive response.

Table 3: Hemostatic Efficacy Rating Scale

Assessment of efficacy	Control of bleeding	Clinical Assessment	Factor VIII levels	Response
Effective	bleeding stopped	clinical control	≥50%	positive
Partially effective	bleeding reduced	clinical stabilization or improvement; or alternative reason for bleeding	≥ 20%	positive
Poorly effective	bleeding slightly reduced or unchanged	not clinically stable	<50%	negative
Not effective	bleeding worsening	Clinically deteriorating	<20%	negative

All 28 subjects evaluable for efficacy had a positive response to treatment for the initial bleeding episodes at 24 hours after initiation of OBIZUR therapy. A positive response was observed in 19/20 subjects (95%) evaluated at 8 hours and all 18 subjects that were evaluated at 16 hours. The median dose per infusion to successfully treat the primary bleed was 133 units per kg with a median total dose of 1523 units per kg. In the initial 24 hour period subjects required a median of 3 infusions and a median dose of 200 U/kg. When treatment was required beyond 24 hours, a median of 10.5 infusions (median dose 100 U/kg) were given for a median of 6 days to control a bleeding episode. Of those subjects treated with OBIZUR as first-line therapy, defined as no immediate previous use of anti-hemorrhagic agents prior to the first OBIZUR treatment, 16/17 (94%) had treatment success reported. Of the 11 subjects who previously received anti-hemorrhagic therapies, eight had eventual successful treatment (73%).

In addition to response to treatment, the overall treatment success was determined by the investigator based on his/her ability to discontinue or reduce the dose and/or dosing frequency of OBIZUR (secondary endpoint). According to this measure of overall treatment success, a total of 24 of 28 (86%) subjects had successful treatment of the initial bleed (success criteria was not prespecified). Treatment success was not achieved in four subjects:

- Subject -(b)(6): This patient was a 74 year-old African American female who received OBIZUR to treat bleeding resulting from a fasciotomy of the thigh. Response to therapy at 24 hours was considered partially effective, bleeding was reduced, and Factor VIII levels were greater than 20% (range of 0 to 240% during the first 24 hours). The subject was on study for 24 days and received 140 infusions of OBIZUR before being discontinued by the investigator. A review of the hemostatic responses for this qualifying bleed revealed that the investigator’s assessment of efficacy was positive. Only two doses

at one and 11 days after the first dose were considered not effective. The subject experienced an AE of device occlusion that was considered possibly related to the study drug and an unrelated AE of urinary tract infection. She subsequently died from sepsis 31 days after the initial infusion of OBIZUR. The subject was negative for anti-porcine factor VIII inhibitor at baseline.

- Subject -(b)(6): This patient was a 70 year-old African American female who received OBIZUR to treat bilateral subdural hematomas. The subject received three doses over a two-day period. The 8- and 24-hour assessments were positive; however, the subject’s mental status worsened and at 26 hours after the initial dose of OBIZUR the family decided to withdraw medical care. Two hours after withdrawal from the trial, the subject died.
- Subject -(b)(6)-: This patient was an 87 year-old Asian female who received OBIZUR to treat a gastrointestinal bleed that was considered controlled at the time of discontinuation. The subject developed cholangitis and sepsis and medical care was withdrawn at the family’s request.
- Subject -(b)(6)-: This patient was a 61 year-old White male who received OBIZUR to treat bleeding related to a planned hemicolecotomy. This subject received OBIZUR prior to the bleeding event, which was considered a protocol violation. At the 8- and 24-hour assessments, bleeding was evaluated as effective. The subject was found to have a positive anti-porcine inhibitor titer of 8 BU and was subsequently discontinued from the trial before the assessment of successful control was completed. After discontinuation, he was placed on a FVIII bypassing agent. Within two weeks of the initial treatment, the subject suffered a serious bleeding event at the initial qualifying site. As per protocol, because it was fewer than two weeks since the initial bleed, the bleeding event was considered not controlled. The subject expired as a result of the intestinal hemorrhage.

Bioresearch Monitoring (BIMO) Inspections

BIMO inspections of three clinical study sites were performed in support of the BLA and were conducted in accordance with FDA’s Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The three selected sites represent 60 percent of all clinical study sites that enrolled subjects. The number of subjects selected for data verification and enrolled at the selected sites represents 80 percent of subjects enrolled in the pivotal study OBI-1-301.

Table 4: Inspection of clinical sites and outcome

Site Number	Study Site	Location	Number of Enrolled Subjects	Form FDA 483 Issued	Final Classification
01	Tulane University	New Orleans, Louisiana	4	No	NAI*
02	Indiana Hemophilia and Thrombosis Center	Indianapolis, Indiana	4	Yes	VAI*
40	Maisonneuve-Rosemont Hospital	Montreal, QC, Canada	4	No	NAI*

*NAI = No Action Indicated; VAI = Voluntary Action Indicated

A Form FDA 483 was issued at Site 02; objectionable conditions included a number of deviations from protocol adherence and IRB procedures, and data discrepancies between the

source documents and the data reported in the BLA. The inspections did not reveal significant problems that would impact the validity of the clinical data submitted in the BLA.

Efficacy Conclusion

The outcomes of the study support the efficacy of OBIZUR in treating serious bleeding events in patients with AHA with baseline anti-porcine factor VIII inhibitor titers less than 20 BU. However, there are insufficient data and too few subjects were enrolled to assess the efficacy of OBIZUR for specific bleeding events. The effectiveness of OBIZUR for the specific treatment of ICH is uncertain; neither of the two ICH cases enrolled in the OBIZUR study were treated successfully. It would be difficult to evaluate the success of OBIZUR in most cases of ICH due to the rapid nature of such hemorrhages and the high mortality rate due to the complications of vasogenic edema and herniation. Also because subjects with baseline anti-porcine factor VIII inhibitor titers greater than 20 BU were excluded from the trial, there are no effectiveness data for treatment of bleeding events in these subjects. These limitations of the efficacy study OBI-1-301 are due to the rarity of AHA and the difficulty and infeasibility of designing and conducting a larger, more diverse, randomized controlled study. Therefore the study design and efficacy data available are adequate for supporting the efficacy of OBIZUR but may not represent a more diverse population that might utilize this product after licensure. Postmarketing pharmacovigilance will improve the efficacy database and address remaining uncertainties.

b) Pediatrics

OBIZUR received Orphan Drug designation for “the treatment and prevention of episodic bleeding in patients with inhibitor antibodies to human coagulation factor VIII” on 18 March 2004, and the Orphan Drug designation status was re-confirmed on 24 April 2013. Therefore, the BLA is exempt from the Pediatric Research Equity Act (PREA) requirements.

c) Other Special Populations

Pregnancy Category C

Animal reproduction studies have not been conducted with OBIZUR. It is also not known whether OBIZUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Nursing Mothers

It is not known whether OBIZUR is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if OBIZUR is administered to nursing mothers.

Geriatric Use

Of the 28 subjects with AHA who were enrolled in studies OBI-1-301 and OBI-1-301 (OBI-1-301a), the average age was 70 years of age. Nineteen subjects were 65 years of age or older. While no differences were observed between geriatric and adult responses to OBIZUR, these findings are inconclusive given the small number of subjects enrolled in either group.

The recommendations for use of OBIZUR in specific populations are described in the Package Insert.

d) Overall Comparability Assessment

The current manufacturing processes for OBIZUR DS and DP were established at the late developmental stage and remained essentially unchanged. The DP used in nonclinical and Phase I and Phase II clinical studies was manufactured by -----(b)(4)-----, using DS manufactured by -----(b)(4)----- . Since then, the DS and DP manufacturing processes were transferred to the facilities in -----(b)(4)-----, respectively, where the Phase III clinical DP lots were manufactured. These sites are intended for commercial manufacture of OBIZUR.

The Applicant conducted comparability and characterization studies and provided sufficient data to demonstrate biochemical and functional comparability between OBIZUR batches used in the nonclinical and clinical studies and the commercial product. The material used in the Phase III clinical trials is representative of that manufactured by the commercial manufacturing process.

7. Safety

Safety Summary

The safety of OBIZUR was assessed using the following endpoints: frequency of AEs, vital signs, clinical laboratory tests, and immunogenicity testing. AEs were coded using MedDRA Version 13.1 and were analyzed based on the principle of treatment emergence during study treatment. All safety analyses are based on the safety population, which included all subjects who received at least one dose of OBIZUR (n=29). No confirmed thromboembolic events related to OBIZUR were reported. However, one subject -(b)(6)- had two instances of peripherally inserted central catheter (PICC) line occlusion that resolved after administration of tissue plasminogen activator (TPA). The latter occlusions were found to be possibly related to the administration of OBIZUR, although thrombosis was not confirmed by ultrasound or any other diagnostic imaging, but was suggested by patency of the PICC line after treatment with TPA.

There were seven unrelated deaths reporting during the trial, including five deaths that occurred during the study. Two subjects died after discontinuing from the study:

Table 5: Reported Deaths

Subject Number	Sex	Age (y)	Cause of death	AE Duration (days)
-(b)(6)-	Female	74	Sepsis	7
-(b)(6)-	Female	70	Intracranial hemorrhage	1
-(b)(6)-	Male	86	Renal failure	5
-(b)(6)-	Female	79	Systemic mycosis	8
-(b)(6)-	Female	87	Cholangitis/Sepsis	2
-(b)(6)-	Female	84	Intracranial hemorrhage	5
-(b)(6)-	Male	61	Intestinal hemorrhage	2

Adverse Reactions

A total of 264 AEs were reported in 27/29 (93%) of subjects. Most were mild (50%) or moderate (38%) in severity; of the 7% that were serious, 13 (5%) were considered life threatening. The most frequently reported AEs were: constipation (in 12/29 subjects), diarrhea (in 7/29 subjects), hypokalemia (in 7/29 subjects), anemia (in 6/29 subjects) and peripheral edema (in 6 subjects).

The most common adverse reaction (defined as an undesirable effect, reasonably associated with use of a drug, which may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence) observed in greater than 5% of subjects was the development of inhibitors to porcine FVIII. Clinically significant AEs that were related to abnormal laboratory values included hypofibrinogenemia in one subject that was considered possibly related to OBIZUR.

Serious Adverse Events (SAEs) are discussed below.

Integrated Analysis of Safety

An integrated analysis of safety was conducted using data from the 43 subjects who were enrolled in clinical trials between April 15, 2003 and October 9, 2013 and received OBIZUR to treat a bleeding event, for perioperative management, or for pharmacokinetic assessment:

- OBI-1-301/301a: 29 subjects with AHA who had a serious active bleeding event, antibodies to human FVIII, and OBI-1 inhibitory antibody titer \leq 20 BU
- OBI-1-302: 1 subject with CHA (-(b)(6)-; a 46 year old, 94 kg Caucasian male with a history of phimosis) who received four pre-and post-operative doses for circumcision. The overall surgical outcome was considered to be excellent hemostatic control with no bleeding before and after surgery. There were no surgical complications after circumcision. The subject completed the study and no treatment related AEs or new bleeding were noted.
- OBI-1-201: 9 subjects with CHA and FVIII inhibitors who had an active non-life and non-limb threatening bleeding event, , and OBI-1 inhibitory antibody titer \leq 20 BU
- OBI-1-101: 4 non-bleeding subjects diagnosed with CHA with inhibitors to human FVIII

A review of the safety data from trials conducted in 14 subjects with CHA (OBI-1-302, OBI-1-201 and OBI-1-101) did not identify any new safety concerns.

In all trials conducted with OBIZUR, a total of 37 SAEs were reported in 16 subjects, included 33 reported in 13 subjects during OBI-1-301, and 4 reported in 3 subjects during OBI-1-201:

Table 6: Serious Adverse Events from Clinical Trials

Trial	Preferred Term	Severity	Relationship to Obizur
OBI-1-301	Asthenia	Mild	Not related (same subject for these 4 SAEs)
OBI-1-301	Dizziness		
OBI-1-301	Hematoma (right knee and chest)		
OBI-1-301	Hematoma (right chest)		
OBI-1-301	Atrial fibrillation	Mild	Not related
OBI-1-301	Pneumonia	Moderate	Not related (same subject for these 2 SAEs)
OBI-1-301	Sepsis	Life threatening	
OBI-1-301	Brain edema	Life threatening	Not related (same subject for these 2 SAEs)
OBI-1-301	Intracranial hemorrhage		
OBI-1-301	Transient ischemic attack	Moderate	Not related (same subject for these 3 SAEs)
OBI-1-301	Esophagitis		
OBI-1-301	Pneumonia		
OBI-1-301	Renal Failure	Life threatening	Not related
OBI-1-301	Pneumonia	Severe	Not related (same subject for these 3 SAEs)
OBI-1-301	Systemic mycosis	Life threatening	
OBI-1-301	Urinary Tract infection	Severe	
OBI-1-301	Gastrointestinal hemorrhage	Severe	Not related (same subject for these 11 SAEs) Not related
OBI-1-301	Arthralgia (left knee)	Moderate	
OBI-1-301	Arthralgia	Moderate	
OBI-1-301	Joint swelling (left knee)	Moderate	
OBI-1-301	Cholangitis	Severe	
OBI-1-301	Sepsis	Life threatening	
OBI-1-301	Arthralgia (left knee)	Severe	
OBI-1-301	Joint swelling (left knee)	Moderate	
OBI-1-301	Respiratory failure	Life threatening	
OBI-1-301	Anaphylactic reaction	Life threatening	
OBI-1-301	Hemarthrosis	Moderate	
OBI-1-301	Intracranial hemorrhage	Life threatening	Not related
OBI-1-301	Intestinal hemorrhage	Life threatening	Not related
OBI-1-301	Fall	Severe	Not related
OBI-1-301	Tracheostomy malfunction	Moderate	Not related (same subject for these 2 SAEs)
OBI-1-301	Vascular pseudoaneurysm		
OBI-1-301	Grand mal convulsion	Severe	Not related
OBI-1-201	Hemorrhagic disorder	Severe	Not related (same subject for these 2 SAEs)
OBI-1-201	Pharyngeal edema		
OBI-1-201	Hemarthrosis	Severe	Not related
OBI-1-201	Hemarthrosis	Severe	Not related

Selected Narratives:

- Atrial fibrillation occurred in a 66 year old African American male with a history of congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), tachycardia and Sjogren’s syndrome 11 days after the first dose of OBIZUR. The atrial fibrillation did not resolve and was considered probably not related to study drug.
- A hypoglycemic transient ischemic attack (TIA) was reported in a 66 year-old White male with a history of TIAs, hypertension, coronary artery disease, and poorly controlled

diabetes mellitus two weeks after receiving the first dose of OBIZUR. The TIA was considered unrelated to OBIZUR. Approximately 24 hours following the final dose of OBIZUR, the subject began to experience rapid onset right-sided weakness and facial tingling. He had a blood pressure of 176/84 mmHg, a heart rate of 85 bpm, an oxygen saturation of 95% on room air, and a blood sugar of 47 mg/dL. Electrocardiogram showed no significant findings; a CT scan was negative for acute changes.

- Renal failure developed in an 86 year-old White male with a history of renal insufficiency 11 days after the initial dose of OBIZUR. A nephrology consult was ordered and it was determined that the subject was fluid overloaded. No renal mass or obstruction was noted on ultrasound. The subject experienced respiratory distress during attempted insertion of a dialysis catheter, and was subsequently treated with supportive therapy. The subject died 15 days after the initial dose of OBIZUR of renal failure.
- Anaphylaxis and subsequent respiratory failure occurred in an 87 year-old Asian male following the administration of intravenous contrast for a CT study. The subject presented with signs and symptoms of cholangitis and was started on an antibiotic prior to receiving IV contrast. After the CT scan, the subject developed respiratory distress that was treated with a nebulizer. He then underwent an emergent endoscopic retrograde cholangiopancreatography for biliary decompression and stent replacement and developed septic shock. The subject died 106 days after the initial infusion as a result of the events of cholangitis and sepsis.
- Pharyngeal edema was noted in a 17 year-old male with CHA and inhibitor who presented with a three-day history of an upper respiratory tract infection and reports of increased throat swelling on the right side, dysphagia, pain and difficulty with speaking. CT showed no abscess and he was admitted to the intensive care unit for antibiotics, steroids and rFVIIa. The event resolved without incident.

Immunogenicity

All subjects were monitored for development of inhibitory antibodies to OBIZUR using the Nijmegen modification of the Bethesda inhibitor assay. A subject was considered to have developed an OBIZUR inhibitor if the titer was ≥ 0.6 Bethesda Units (BU)/mL. Of the 29 subjects treated with OBIZUR, 19 were negative at baseline for inhibitors to rpFVIII, and 5 (25%) developed anti-porcine factor VIII antibodies following exposure to OBIZUR. Of the 10 subjects with detectable anti-porcine factor VIII antibodies at baseline, 2 (20%) experienced an increase in titer. Development of inhibitor formation in 25% of the subjects who received OBIZUR is an expected event with a product of porcine sequence (when administered in humans).

All subjects were also monitored for development of binding antibodies to baby hamster kidney (BHK) protein by a validated electrochemiluminescent assay. No patients developed *de novo* anti-BHK antibodies.

Pharmacovigilance

The Division of Epidemiology of the Office of Biostatistics and Epidemiology agrees with the planned activities listed in the proposed Pharmacovigilance Plan: routine pharmacovigilance and enhanced pharmacovigilance via the proposed Treatment Registry. The proposed Treatment Registry (Protocol 241302) is a post-marketing, prospective, uncontrolled, non-interventional, multicenter study for the treatment of bleeding episodes for patients with AHA. The objectives

of the study include assessing the safety of OBIZUR and describing the effectiveness of the product when used for the proposed indication. The study is planned to be launched in December 2014, with study duration of 5 years.

Safety Conclusion

The safety of OBIZUR has been adequately demonstrated for the proposed population and indications. The available data do not suggest a safety concern that would necessitate either a Risk Evaluation and Mitigation Strategy or a required post-marketing study. However, the clinical trials were small due to the rarity of the disease, therefore post marketing pharmacovigilance is necessary to continue to collect safety data. A post marketing Treatment Registry study will be conducted as post-marketing commitment (refer to section 11), to obtain additional safety and efficacy data.

8. Advisory Committee Meeting

The Division of Hematology Research and Review and the Division of Hematology Clinical Review in the Office of Blood Research and Review reviewed the information in this application and determined that referral to the Blood Products Advisory Committee prior to product approval was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- The new molecular entity provision (NME) does not apply to OBIZUR as it does not represent a novel product class. Recombinant FVIII products have been licensed in the U.S. since 1992 and have been used to control and prevent bleeding in hemophilia A patients. The first product in this class, RECOMBINATE, was approved by the FDA in 1992, and several full-length (KOGENATE FS, ADVATE) and B-domain-deleted (XYNTHA, Novoeight and ELOCTATE) FVIII products are currently licensed in the U.S.
- The mechanism of action of FVIII and its function in blood coagulation is well studied and understood. Upon activation by thrombin, FVIIIa acts as a cofactor for activated Factor IX, triggering a chain of biochemical reactions – activation of Factor X, which converts prothrombin into thrombin, and subsequent interaction of thrombin with fibrinogen resulting in the formation of a fibrin clot that potentially stops bleeding. When infused into a patient with hemophilia A, FVIII products temporarily replace the missing endogenous FVIII.
- OBIZUR shares approximately (b)(4) pair-wise homology with the B-domain deleted human FVIII. The amino acid composition of OBIZUR is consistent with that predicted from the cDNA sequence of the expression construct. The functional characteristics and hemostatic activity of OBIZUR are consistent with those of human FVIII products and enable the formation of a fibrin clot via the intrinsic coagulation pathway.
- The manufacturing process for OBIZUR includes two viral clearance steps – solvent/detergent treatment for virus inactivation and nanofiltration for virus removal – that meet the current requirements for assuring product safety with regard to adventitious viruses.

- The proposed indication for OBIZUR is similar to that of other U.S. licensed recombinant FVIII products for patients with hemophilia A, but focuses on the patient population with AHA.
- The design of the pivotal clinical study to evaluate the safety and efficacy of OBIZUR for treatment of AHA, a rare and life-threatening disorder, was adequate and the results of the studies did not raise any concerns. Evaluation of the safety data for OBIZUR (43 subjects) did not reveal any concerns. Development of inhibitors to OBIZUR is not a safety concern as it is an expected event with a product of porcine sequence. Additional safety data will be collected in a postmarket registry study.
- Review of information submitted in the BLA for OBIZUR did not raise any controversial issues or pose unanswered scientific questions which would have benefited from Advisory Committee discussion and recommendations.

9. Other Relevant Regulatory Issues

The notable issues raised in the course of the review are described in the respective sections of this document, and they have been satisfactorily resolved through information requests and teleconferences. There were no other relevant regulatory issues.

10. Labeling

Proprietary Name

The proposed proprietary name, OBIZUR, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective on 27 February 2014 and 22 September 2014. The proprietary name was determined to be acceptable.

Prescribing Information/Carton and Container Labels

The FDA comments regarding product labeling were conveyed on 3 and 24 September, and 7 and 15 October 2014. The final Full Prescribing Information (FPI) was submitted on 15 October 2014 and was determined to be acceptable. Carton and container labels submitted to the BLA on 9 October 2014 were considered acceptable.

A copy of FPI is attached.

11. Recommendation and Benefit/Risk Assessment

a) Recommended Regulatory Action

The CBER review committee recommends **APPROVAL** of this BLA. The manufacturing process for OBIZUR, Antihemophilic Factor (Recombinant), Porcine Sequence, is considered validated and adequately controlled. Efficacy and safety clinical data for OBIZUR support a

favorable benefit/risk determination for the proposed indication for the treatment of bleeding episodes in adults with AHA.

b) Benefit/Risk Assessment

AHA is a rare bleeding disorder associated with development of autoantibodies that inhibit FVIII in the circulation, thus causing an acquired FVIII deficiency and preventing the normal coagulation of blood. Patients with AHA experience repeated episodes of potentially life-threatening bleeding into the skin, muscles, soft tissues and mucous membranes. OBIZUR is designed to provide a FVIII that will function in the presence of inhibitors to endogenous human FVIII, due to low cross-reactivity of human FVIII inhibitors and porcine FVIII. When administered to patients with AHA, OBIZUR temporarily replaces the inhibited endogenous FVIII that is needed for effective hemostasis. OBIZUR is likely to be used acutely, and it is not expected that AHA patients will have long term exposure because of the likelihood of development of inhibitory antibodies against rpFVIII. Consequently, this diminishes the risk and consequences of rpFVIII inhibitor development.

Benefit

The efficacy of OBIZUR for the treatment of serious bleeding episodes in subjects with AHA and inhibitor titers ≤ 20 BU has been established in a prospective, open-label trial with 29 subjects enrolled. Of the 28 subjects evaluable for efficacy, all had a positive response (according to a pre-specified rating scale) to treatment for the initial bleeding episode at 24 hours after the initiation of treatment with OBIZUR, and a total of 24/28 (86%) had successful treatment of the initial bleed. OBIZUR, because of its low cross-reactivity with anti-human FVIII antibodies, is less likely to be bound by inhibitory antibodies of the AHA patients. Therefore, it functions like FVIII in the coagulation cascade to promote hemostasis and the clinical response can be monitored by standard laboratory measures. The ability to monitor efficacy by standard measures is considered an additional benefit.

Risk

The safety concerns for this product are hypersensitivity reactions and the development of inhibitors to porcine FVIII. Of the 29 subjects treated with OBIZUR, 8 (17%) newly developed anti-porcine FVIII antibodies following exposure to OBIZUR. Of the 10 subjects with detectable anti-porcine FVIII antibodies at baseline, 2 (20%) experienced an increase in titer. No subjects developed de novo anti-BHK antibodies. A single patient developed anaphylaxis, attributable to the infusion of a CT contrast agent, and was considered unrelated to treatment with OBIZUR. The ability to clearly define the risk for hypersensitivity reactions and inhibitor development is limited by the study size. The potential for these risks is discussed in the Warnings and Precautions section of the Package Insert. The risk is considered minimal, as OBIZUR will be used for the immediate treatment of bleeding and long-term exposure to the product is not likely. No serious AEs were found to be attributable to OBIZUR.

The benefits of OBIZUR outweigh the risks for the treatment of bleeding episodes in adults with AHA. In addition, the small number of subjects in the phase 3 trial precludes a subset or trend analysis according to age, sex, race or ethnicity.

c) Recommendation for Post Marketing Requirement Risk Management Activities

The available data do not suggest a safety concern that would necessitate either a Risk Evaluation and Mitigation Strategy (REMS) or a required post-marketing (PMR) study.

d) Recommendation for Post Marketing Activities

As stated in Amendment 044 dated 21 October 2014, Baxter commits to the following:

Baxter Healthcare Corporation commits to collecting additional safety and efficacy of OBIZUR in adults with acquired hemophilia A in the Treatment Registry study under Protocol 241302 “*A Non-Interventional Study of Safety and Effectiveness of Recombinant Porcine Sequence FVIII (OBIZUR) in the Treatment of Bleeding Episodes for Patients with Acquired Hemophilia A*”.

- Final Protocol submission: 31 March 2015
- Study/trial completion date: 30 September 2019
- Final Study Report submission date: 31 January 2020