
Application Type	Original Application
STN	125512/0
CBER Received Date	November 25, 2013
PDUFA Goal Date	October 24, 2014
Division / Office	DHCR /OBRR
Priority Review	Yes
Reviewer Name(s)	Lisa M. Faulcon
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Baxter Healthcare Corporation
Established Name	Antihemophilic Factor (Recombinant), Porcine Sequence
(Proposed) Trade Name	OBIZUR
Pharmacologic Class	Antihemophilic Agent
Formulation(s), including Adjuvants, etc	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder in single-use vials of 500 international units per vial
Dosing Regimen	Initial dose of 200 units per kg
Indication(s) and Intended Population(s)	Treatment of bleeding episodes in adults with acquired hemophilia A OBIZUR is not indicated for the treatment of von Willebrand Disease.
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AE	Adverse Event
AHA	Acquired Hemophilia A
APCC	Activated Prothrombin Complex Concentrate
BLA	Biologics License Application
BHK	Baby Hamster Kidney
BIMO	Bioresearch Monitoring
BU	Bethesda Unit
CHA	Congenital Hemophilia A
DSMB	Data and Safety Monitoring Board
ICH	Intracranial Hemorrhage
Package Insert	PI
PICC	Peripherally Inserted Central Catheters
rFVIIa	Recombinant Factor VIIa
SAE	Serious Adverse Event
TPA	Tissue Plasminogen Activator

1. EXECUTIVE SUMMARY

Baxter Healthcare Corporation (Baxter) has submitted an original biologics license application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant), Porcine Sequence. The proprietary name of the US marketed product is OBIZUR. OBIZUR, a purified, recombinant porcine factor VIII (FVIII) glycoprotein produced in baby hamster kidney (BHK) cells, is indicated for the treatment of bleeding episodes in adults with acquired hemophilia A (AHA).

Clinical trials that provided the evidence for safety and efficacy of OBIZUR were conducted under IND 10695. To support licensure for the proposed indication, the clinical development program included: (1) an international, multicenter, open-label, prospective trial (OBI-1-301) where subjects with AHA due to auto-immune inhibitory antibodies to human factor VIII subjects 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 congenital hemophilia A (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 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 focused on the safety and efficacy trials for the treatment of serious bleeds 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.

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 that were enrolled in 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 surgeries, 1 retroperitoneal hemorrhage, and 1 periorbital bleeding event. 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 FVIII levels achieved. Subjects with a prior history of bleeding disorders other than AHA, anti-porcine factor VIII 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 sufficiently represents 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, 11 subjects (28%) received immunosuppressive therapy, 11 subjects (28%) previously received anti-hemorrhagic medications (e.g. rFVIIa, activated prothrombin-complex concentrate, tranexamic acid) and 8 subjects (28%) were previously treated for a 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 United Kingdom (4 subjects; 2 sites).

A total of 18 (62%) subjects completed the study. As expected, due to the fact that the enrolled subjects were critically ill and had significant co-morbidities, there were a large number of discontinuations. The status of one subject was unknown at the time of BLA submission. Ten 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)
- Lost to follow-up (one subject)

Regarding product efficacy, 28 subjects evaluable for efficacy had a positive response (using a pre-specified definition) to treatment for the initial bleeding episodes at 24 hours after dosing. 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 and 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%) were treated successfully. Of the 11 subjects who previously received anti-hemorrhagic therapies, 8 (73%) achieved treatment success.

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

- Subject -(b)(6)-: This 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 overwhelmingly 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 UTI. 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 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 was an 87 year-old Asian female who received OBIZUR to treat a gastrointestinal (GI) 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 was a 61 year-old White male who received OBIZUR to treat bleeding related to a planned hemicolectomy. This subject received OBIZUR prior to the bleeding event, which was considered a major protocol violation. At the 8- and 24-hour assessments, bleeding was evaluated as effective. On routine pharmacokinetic assessment 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 and 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 less than two weeks since the initial bleed, the bleeding event was considered not controlled. The subject died as a result of the intestinal hemorrhage.

The efficacy of OBIZUR to treat subsequent serious bleeding events could not be fully evaluated because only four subjects experience subsequent bleeding events (left knee hemarthrosis, ICH, retroperitoneal bleeding, and left hand bleed) during the trial. Two (50%) of these events (hemarthrosis and hand bleed) were treated successfully; an anti-

porcine inhibitor titer of 22 Bethesda Units likely contributed to the lack of efficacy observed for the subject with the retroperitoneal bleed. During the trial, two of the three ICH events (two as qualifying bleeds and one as a subsequent bleed) were unsuccessfully treated with OBIZUR; however, meaningful conclusions cannot be drawn since the number of ICH event treated are small and ICH can be associated with increased mortality.

The safety of OBIZUR was assessed in the pivotal trial using the following endpoints: frequency of adverse events, vital signs, clinical laboratory tests, and immunogenicity testing. Adverse events (AEs) were coded using MedDRA Version 13.1 and were analyzed based on the principle of treatment emergence during study treatment. Safety was also assessed for hypersensitivity reactions, thrombogenicity, and the development of inhibitors to porcine factor VIII. All safety analyses were based on the safety population, which included all subjects who received at least one dose of OBIZUR (n=29). There were seven deaths (sepsis, ICH (n=2), renal failure, systemic mycosis, cholangitis/sepsis, intestinal hemorrhage) reported during the trial, including five deaths that occurred during the study, and 2 subjects died after discontinuing from the study. None of the deaths were considered related to the product by this reviewer.

No serious adverse reactions were reported during the trial. No confirmed thromboembolic events that were 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 TPA that was considered possibly related to OBIZUR by this reviewer. Thrombosis was not confirmed by ultrasound or any other diagnostic imaging, but was suggested by patency of the PICC line after treatment with TPA. Clinically significant AEs that were related to abnormal laboratory values included hypofibrinogenemia in one subject that was considered possibly related to OBIZUR. No serious adverse reactions were reported during the trial.

A total of 264 AEs were reported in 27/29 (93%) of subjects. Most were mild (50%) or moderate (38%) in severity; 13 (5%) were considered life threatening. The most frequently reported AEs were constipation (12 subjects, 41%), diarrhea (7 subjects, 24%), hypokalemia (7 subjects, 24%), anemia (6 subjects, 21%) and peripheral edema (6 subjects, 21%). The most common adverse reaction observed in greater than 5% of subjects was the development of inhibitors to porcine factor VIII.

All subjects were monitored for inhibitory antibodies to OBIZUR Nijmegen modification of the Bethesda inhibitor assay and binding antibodies to BHK protein by validated electrochemiluminescent assay. A subject was considered to have developed an inhibitor if the titer was ≥ 0.6 Bethesda Units (BU)/mL. No patients developed *de novo* anti-BHK antibodies. Of the 29 subjects treated with OBIZUR, 5 (20%) developed anti-porcine factor VIII antibodies following exposure to OBIZUR. Nineteen of the 29 subjects were negative at baseline. Of the 10 subjects with detectable anti-porcine factor VIII antibodies at baseline, only 2 (20%) experienced an increase in titer.

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 bleed, antibodies to human FVIII, and OBI-1 inhibitory antibody titer ≤ 20 BU
- OBI-1-302: 1 subject with CHA (b)(6)-; a 46 year-old, 94 kg White male with a history of phimosis) who received four pre-and post-operative doses for circumcision. The overall surgical outcome was considered 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 adverse events or new bleeding noted.
- OBI-1-201: 9 subjects with CHA and inhibitors who had an active non-life and non-limb threatening bleed, antibodies to human FVIII, and OBI-1 inhibitory antibody titer ≤ 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. All SAEs were considered not related by this reviewer (see Table 9)

OBIZUR received orphan drug designation for the treatment and prevention of episodic bleeding in patients with inhibitor antibodies to human coagulation factor VIII; therefore STN BL 125512/0 is exempt from PREA.

Efficacy and safety clinical data for OBIZUR supported a favorable benefit/risk determination for the proposed indication of control and prevention of acute bleeding episodes in patients with AHA. Acquired hemophilia A is a rare bleeding disorder which is associated with development of autoantibodies that inhibit FVIII in the circulation, thus creating FVIII deficiency and preventing the blood clotting mechanism from working properly. People with acquired hemophilia A experience repeated episodes of potentially life-threatening bleeding into skin, muscles, soft tissues and mucous membranes. Treatment with bypassing agents (rFVIIa) has limitations because of the short half-life of rFVIIa. In addition, monitoring efficacy by means of standard measures of coagulation, such as prothrombin time or activated partial thromboplastin time, is not useful. OBIZUR provides an ability to monitor efficacy by standard measures, which is considered a major contribution to the improvement of patient care.

Recommendation:

Based on my review of the submitted data, OBIZUR appears safe and efficacious in patients with AHA. No post-marketing requirements are recommended for this product. An approval is recommended.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Acquired hemophilia A (AHA) is a rare, but potentially life-threatening, bleeding disorder caused by the development of autoantibodies (mostly of immunoglobulin G [IgG] subclasses 1 and 4) directed against coagulation factor VIII (FVIII). It occurs in approximately 0.2-1.0 case per 1 million persons per year.¹ Although approximately half of reported cases are idiopathic, several conditions are associated with this disorder including pregnancy, collagen, vascular, and other autoimmune disorders, inflammatory bowel disease, dermatologic disorders (e.g. psoriasis), diabetes, acute hepatitis B and C infections, allergic drug reactions, and malignancies (e.g. solid tumors and hematologic). The AHA patient population tends to be older (≥ 65 years of age) with significant co-morbidities.

The clinical manifestations include: hemorrhage into the skin, muscles, or soft tissues and mucous membranes, prolonged postpartum bleeding, excessive bleeding following surgery or trauma, and occasionally cerebral hemorrhage. Bleeding can occur spontaneously or after negligible or minor trauma. Severity of bleeding does not correlate with FVIII level or inhibitor titer and is not useful in predicting those patients who would have fatal bleeding or those who may not require hemostatic treatment. The reported mortality is between 7.9 and 22%, with most hemorrhagic deaths occurring within a few weeks of presentation. A meta-analysis of 249 patients with AHA found that three factors had an independent impact on overall survival and disease-free survival: related conditions, complete remission status, and age at diagnosis.² Survival was greatest in patients with postpartum inhibitors, in those who achieved complete remission, and in those who were younger than 65 years.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The objectives in treating AHA patients are to effectively control bleeding during acute bleeding episodes and to eradicate the autoimmune antibodies. Immunosuppressive therapy is used to eliminate the antibodies. Previously, from 1980 until it was no longer marketed in 2004, a plasma-derived porcine FVIII (HYATE:C) was used to treat patients with AHA. Currently, there are no approved replacement therapies for AHA with inhibitors. Bypassing agent, such as recombinant factor VIIa (rFVIIa) is approved for treatment of acute bleeds. A retrospective study of APCC use as first-line therapy in patients with AHA showed an overall complete response rate of 86% with a dosing regimen of 75 U/kg every 8-12 hours; the median number of doses required was 10.³

2.3 Safety and Efficacy of Pharmacologically Related Products

The development of activity-neutralizing antibodies (inhibitors), allergic reactions and pathogen transmission are the main safety concerns of treatment in subjects receiving FVIII products. The availability of recombinant FVIII products reduces the risk of pathogen transmission, but not inhibitor development. For FVIII products produced in

BHK cells, a potential risk exists of antibody development against BHK protein, and traces of hamster proteins may result in hypersensitivity reactions to this protein.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Obizur is not currently licensed in any other country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

October 2002	IND 10695 was submitted and subsequently placed on hold
March 2003	Clinical hold was lifted
March 2004	Orphan designation granted
September 2008	End-of-Phase 2 meeting held to discuss proposed phase 3 studies for congenital and acquired hemophilia
June 2010	Meeting to discuss the design and analysis of a pivotal clinical protocol, OBI-1-301
October 2012	Fast Track designation granted
October 2013	Pre-BLA meeting: FDA agrees minimum of 15 subjects may suffice to support the BLA submission
November 25, 2014	Application received with an interim analysis of 18 subjects
January 16, 2014	Filing Notification; Priority Review granted
May 28, 2014	Major Amendment Acknowledgment sent
August 8, 2014	Final Clinical Study Report submitted

2.6 Other Relevant Background Information

FVIII is a glycoprotein that circulates in an inactive form in complex with von Willebrand factor, which stabilizes FVIII and potentially helps to localize it to sites of vascular injury. Upon activation by thrombin, FVIII is activated and separates from von Willebrand factor. Activated factor VIII acts as a co-factor for activated factor IX and in the presence of calcium and phospholipids forms a complex that accelerates the conversion of factor X (FX) to activated FX (FXa). FXa then converts prothrombin into thrombin; thrombin converts fibrinogen into fibrin and a clot is formed. OBIZUR is designed to provide a FVIII that will function in the presence of inhibitors due to low cross-reactivity of human FVIII inhibitors and porcine FVIII. When administered in patients with acquired hemophilia A, OBIZUR temporarily replaces the inhibited endogenous FVIII that is needed for effective hemostasis.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. It was submitted electronically and formatted as an electronic Common Technical Document according to FDA guidance for electronic submission. This submission consisted of the five modules in the Common Technical Document structure.

3.2 Compliance with Good Clinical Practices and Submission Integrity

In order to assess compliance with good clinical practices and to verify the key submitted safety and efficacy data against source documents, a sampling of trial sites of the pivotal trial (OBI-1-301) was done. CBER Bioresearch Monitoring (BIMO) issued high-priority inspection assignments for two domestic sites and one Canadian site:

Table 1: Inspection Results

Trial Site Number	Trial Site	Location	Number of Subjects	Action
01	Tulane University	New Orleans, LA	4	NAI
02	Indiana Hemophilia and Thrombosis Center	Indianapolis, IA	4	VAI
40	Maisonneuve-Rosemont Hospital	Montreal, Canada	4	NAI

NAI = No Action Indicated VAI = Voluntary Action Indicated

The number of trial subjects enrolled and previous inspection history were among the factors used to select the inspected sites. The inspections focused on specific questions concerning the study protocol and the comparison of data submitted in the BLA to source documents. The BIMO inspections did not reveal any issues that would impact the data submitted in the BLA.

Applicant-identified Protocol Violations/Deviations

The inspection was based on data submitted with the original application: an interim analysis of 18 subjects who received at least once dose of OBIZUR for the treatment of acute bleeds. The applicant identified 16 protocol deviations that may affect safety or efficacy outcomes, including 12 procedural deviations related to assessments or samples not taken. In addition, four deviations related to entry criteria were noted:

1. Subject (b)(6)- participated in a clinical trial within 30 days of enrollment under the expanded access protocol.
2. Subject (b)(6)- was granted a waiver although the subject's platelet count was not consistent with a diagnosis of AHA; however, the results of the results of the aPTT mixing study and inhibitor testing are consistent with AHA.
3. Subject (b)(6)- received rFVIIa less than 3 hours before the initial dose of OBIZUR was given.
4. Subject (b)(6)- was granted an entry criteria waiver; the subject did not meet the aPTT and reduce FVIII activity inclusion criteria and therefore did not meet criteria for a diagnosis of AHA. The subject had a previous history of AHA with inhibitory levels of 5.1 to 10 Bethesda Units (BU).

The final study report reported deviations for 27/29 subjects. Two additional two deviations related to entry criteria occurred in two subjects:

1. Subject (b)(6)-: the qualifying bleeding episode (gastrointestinal bleed) was not documented as serious by the investigator
2. Subject (b)(6)-: the subject was previously taking antithrombotics and 3 half-lives had not yet elapsed when OBI-1 treatment was started.

Reviewer Comment: The outlined protocol violation/deviations did not undermine the quality of the trial data and the overall trial conclusions are not invalidated. Sensitivity analyses with data excluded from these subjects did not change the conclusions about the efficacy of the product.

3.3 Financial Disclosures

Financial certification and disclosure information (Form 3454) have been submitted for both US and Non-US sites. No questions about the integrity of the data were raised.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

OBIZUR is a purified recombinant porcine factor VIII, B-domain deleted glycoprotein that is expressed by a genetically engineered BHK cell line with a DNA construct coding for -----(b)(4)----- . The molecular weight of OBIZUR is approximately 165 kDa based on the amino acid sequence. The commercial product is a lyophilized powder available in single-use vials containing the labeled amount of FVIII activity, expressed in units per vial. Each vial contains nominally 500 units of FVIII (recombinant porcine sequence).

Table 2: Composition of OBIZUR

Ingredients	Composition after reconstitution in 1 mL of SWFI	Function	Reference to Standard
Active Substance:			
OBI-1	500 Units/mL (nominal)	Active	In-house Reference Standard
Excipients:			
Polysorbate 80	0.0535 mg/mL	(b) (4)	(b) (4)
Sodium chloride	8.765 mg/mL	(b) (4)	(b) (4)
Calcium chloride dihydrate	0.147 mg/mL	(b) (4)	(b) (4)
Sucrose	1.88 mg/mL	(b) (4)	(b) (4)
Tris Base	0.0445 mg/mL	(b) (4)	(b) (4)
Tris HCl	0.73 mg/mL	(b) (4)	(b) (4)
Tri-sodium citrate dihydrate	1.47 mg/mL	(b) (4)	(b) (4)
(b) (4)			

Table 3: Selected Specifications for OBIZUR

Test parameter	Analytical procedure	Acceptance criteria
Appearance	Visual inspection	White Cake (pre-reconstitution) Clear colorless solution (post-reconstitution)
(b)(4)	---(b)(4)-----	---(b)(4)---
Identity	---(b)(4)----- -----	---(b)(4)--
FVIII Potency	Chromogenic Assay One-stage Assay	---(b)(4)----- ---(b)(4)-----
Specific activity	One-stage Assay	---(b)(4)-----
---(b)(4)-----	---(b)(4)---	---(b)(4)-----

4.2 Assay Validation

The one-stage activated partial thromboplastin time assay (one-stage assay) and a two-stage chromogenic substrate assay (chromogenic assay) were used to determine FVIII a

plasma levels and incremental recovery (C_{max}/D) values. Both assays expressed the activity in international units; one IU of FVIII is equivalent to the amount of FVIII in one mL of normal human plasma. FVIII activity was generally higher using the one-stage assay, as compared to the chromogenic assay.

Binding antibodies against BHK (host cell) protein were measured using a direct binding enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies against human FVIII (anti-human FVIII inhibitors) and porcine FVIII (anti-porcine FVIII inhibitors) were measured in a central lab using a Bethesda assay.

4.4 Clinical Pharmacology

Please see Dr. Carl-Michael Staschen's review memo for complete details.

4.4.1 Mechanism of Action

OBIZUR temporarily replaces the inhibited coagulation FVIII that is required for effective hemostasis.

4.5 Statistical

Please see Dr. Boris Zaslavsky's memo for a complete review.

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

4.6 Pharmacovigilance

Routine pharmacovigilance is recommended.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on a single open-label, prospective, Phase 2/3 trial to evaluate the safety, efficacy, and pharmacokinetics of OBIZUR for the treatment of serious bleeds in adults (≥ 18 years) with AHA due to autoantibodies to human FVIII (OBI-1-301) and its corresponding expanded access protocol (OBI-1-301a). In addition, safety data from the following trials were used for an integrated analysis of safety:

- OBI-1-302: Phase 3, prospective, non-randomized, open label trial of the efficacy and safety of OBIZUR to treat subjects with congenital hemophilia A (CHA) with inhibitors and with a history of inadequate response to bypassing agents
- OBI-1-201: Phase 2 prospective, open-label, non-comparative trial to assess the safety and hemostatic efficacy in subjects with CHA with inhibitors
- OBI-1-101: PK 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

Table 4: Review Responsibilities

Discipline Review	
Clinical Review	Lisa Faulcon
Clinical Pharmacology Review	Carl-Michael Staschen
Statistical Review	Boris Zaslavsky
Chemistry, Manufacturing and Controls Review	Natalya Ananyeva, Alexey Khrenov, Ze Peng
Pharmacology / Toxicology Review	La’Nissa A. Brown-Baker
Bioresearch Monitoring Review	Dennis Cato
Pharmacovigilance Review	Wambui Chege
Labeling Review	Loan Nguyen
Lot Release Coordination /In-Support Testing	Catherine Poole, Hyesuk Kong, Alfred Del Grosso, Qiao Bobo, Karen Campbell, Lokesh Bhattacharya, Grainne Tobin, Igor Bacik
Regulatory Project Manager	Thomas Maruna

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

5.3 Table of Studies/Clinical Trials

Table 5: Clinical Studies in the OBIZUR Clinical Development Program

Study Number	Phase	Study Status	Criteria	Dose Range and Frequency
OBI-1-301	2/3	Ongoing iCSR OBI-1-301/301a	AHA; age ≥ 18 y with serious bleeding episode	Initial OBI-1 dose, 200 U/kg
OBI-1-301a	3 expanded -access protocol	Ongoing iCSR OBI-1-301/301a	AHA; age ≥ 18 y with serious bleeding episode	Initial OBI-1 dose, 200 U/kg
OBI-1-302	3	Terminated by the sponsor after 1 subject was treated - not due to safety or lack of efficacy concerns	CHA with inhibitors; age ≥ 6 y with suboptimal response to bypassing agents; Anti-OBI-1 titer ≤ 10 BU	OBI-1 dose based on anti-OBI-1 titer: - Titer > 5 BU, initial dose 200 U/kg - Titer 2-5 BU, initial dose 150 U/kg - Titer < 2BU, initial dose 100 U/kg. - Life threatening situations with unknown anti-OBI-1 titer, initial dose 200 U/kg
OBI-1-201	2	Completed CSR OBI-1-201	CHA with inhibitors age > 12 y (non-russian sites); age ≥ 18 y (russian sites); Anti- OBI-1 titer ≤ 20 BU; with uncomplicated joint or soft tissue bleeding episode	Initial dose - for anti- OBI-1 titer > 0.8 BU, - determined according to the patient's inhibitor titer, body weight, and hematocrit. Treatment dose, 1st-3rd OBI-1 dose, 50 U/kg 4th-6th OBI-1 dose, 100 U/kg 7th-8th OBI-1 dose, 150 U/kg
OBI-1-101	1	Completed CSR OBI-1-101	AHA or CHA with inhibitors age ≥ 12 y in non-bleeding state Anti-factor VIII titer ≤ 20 BU	Single dose OBI-1 or comparator (HYATE.C), 100 U/kg

5.5 Literature Reviewed

1. Franchini M, Gandini G, Di Paolantonio T, Mariani G. Acquired hemophilia A: a concise review. *Am J Hematol.* Sep 2005;80(1):55-63.
2. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol.* Apr 2003;121(1):21-35.
3. Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. *Haemophilia.* Mar 2004;10(2):169-73.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 OBI-1-301/301a

6.1.1 Objectives

The primary objective was to evaluate the efficacy of OBIZUR for the treatment of serious bleeding events.

Secondary objectives included:

- Determine the proportion of serious bleeding events controlled with OBIZUR therapy
- Assess the efficacy of OBIZUR at designated time points after the initiation of OBIZUR therapy
- Determine the frequency, total dose, and total number of infusions of OBIZUR required to control all serious bleeding events
- Assess the anti-porcine FVIII (anti-OBI-1) inhibitor level during treatment follow-up
- Assess the correlations between the baseline anti-OBI-1 inhibitor titer, the total dose of OBIZUR, the control of the bleeding event
- Evaluate the safety of OBIZUR
- Assess drug exposure in subjects successfully treated with OBIZUR, using complete or sparse sample design and a population PK approach for the sparse data.

6.1.2 Design Overview

This is an ongoing international, multicenter, open-label, prospective, Phase 2/3 trial to evaluate the safety, efficacy, and pharmacokinetics of OBIZUR for the treatment of at least 28 serious bleeds in a minimum of 28 adults (≥ 18 years) with AHA due to autoantibodies to human FVIII. Serious bleeding events include:

- Bleeds that are a threat to a vital organ that could threaten life (e.g., intracranial bleed, or any site that could obstruct the airway)
- Bleeds that are a threat to a vital organ where life is not threatened but the organ function could be impaired (e.g., intraspinal bleed threatening the spinal cord and/or nerve conduction; a continual bleed into the kidney or bladder that could result in an obstructive uropathy, bleed in and around the eye)
- Bleeds requiring a blood transfusion to maintain the hemoglobin level at non-life-threatening or non-organ-threatening levels (e.g., post surgery, gastrointestinal, retro-peritoneal, thigh bleeds).
- Intramuscular bleeds where muscle viability and/or neurovascular integrity is significantly compromised or at risk of being compromised.
- Intra-articular bleeds impacting a major joint associated with severe pain, swelling and severe loss of joint mobility (reduced $>70\%$) or where a bleed could result in joint destruction (e.g., in and around the femoral head).

The initial Phase 2 portion of the trial was designed to assess dose-response to OBIZUR in subjects with AHA who presented with a serious bleeding event. The Data and Safety Monitoring Board (DSMB) determined that the approach to dosing was appropriate and satisfactory responses were observed; therefore, the trial continued into the Phase 3 portion.

Due to the significant morbidity and mortality associated with an AHA patient's failure to respond to current therapies, trial OBI-1-301 was extended in agreement with the FDA under expanded access (Title 21 of the Code of Federal Regulations, Section 312, Subpart I), under Protocol OBI-1-301a.

The trial duration for each subject was approximately 3 to 4 months for each qualifying bleeding event, which included 90 days of follow-up after the final treatment with OBIZUR.

Reviewer Comment: The design of the trial is sufficient to support the proposed indication.

6.1.3 Population

Inclusion Criteria

- Males or females ≥ 18 years of age
- Written informed consent from subject, trusted person or person who is legally authorized to sign on behalf of the subject (legal representative in United States), depending on local regulations
- Subjects with AHA with autoimmune inhibitors to human FVIII, with a clinical diagnosis established by the following criteria:
 - a) Prolonged activated partial thromboplastin time (aPTT)
 - b) Prothrombin time (PT) \leq upper limit of normal + 2 seconds and platelet count within normal range
 - c) Abnormal aPTT mixing study (patient-normal control 1:1) consistent with a FVIII inhibitor
 - d) Reduced FVIII activity level (below 10%)
- Has a serious bleeding event, as documented by the investigator
- Be willing and able to follow all instructions and attend all study visits
- Subjects taking antithrombotics (such as clopidogrel, heparin, or heparin analogue) may be included provided three half-lives have elapsed since the last dose of the agent
- Life expectancy of at least 90 days before the onset of the bleeding event
- Subjects of reproductive age must use acceptable methods of contraception and if female, undergo pregnancy testing as part of the screening process

Exclusion Criteria

- Hemodynamically unstable after blood transfusion, fluid resuscitation and pharmacologic or volume replacement pressor therapy
- Has an established reason for bleeding that is not correctable
- Bleeding event assessed likely to resolve on its own if left untreated
- Anti-OBI-1 inhibitor that exceeds 20 BU (prospectively or retrospectively)
- Subsequent bleeding event at the site of the initial qualifying bleeding event within 2 weeks after the final OBIZUR dose for the initial qualifying bleeding event, or subsequent bleeding event at a different site than the initial qualifying

- bleeding event within 1 week after the final OBIZUR dose for the initial qualifying bleeding event will not be considered new qualifying bleeding events
- History of bleeding disorder other than AHA.
 - Known major sensitivity (anaphylactoid reactions) to therapeutic products of porcine or hamster origin; examples include therapeutics of porcine origin (e.g., previously marketed porcine factor VIII, HYATE:C®) and recombinant therapeutics prepared from hamster cells (e.g., Humira®, Advate®, and Enbrel®)
 - Use of hemophilia medication: activated recombinant factor VII within 3 hours before OBIZUR administration, or activated prothrombin complex concentrate treatment within 6 hours before OBIZUR administration
 - Participation in any other clinical study within 30 days of the first OBIZUR treatment
 - Anticipated need for treatment or device during the study that may interfere with the evaluation of the safety or efficacy of OBIZUR, or whose safety or efficacy may be affected by OBIZUR
 - Is currently pregnant or breastfeeding, or planning to become pregnant or father a child during the study
 - Abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardize the subject's safety or the chance of obtaining satisfactory data needed to achieve the objectives of the study

6.1.4 Study Treatments or Agents Mandated by the Protocol

A fixed initial dose of 200 units per kg was administered, and was based on recommendations from the DSMB from the Phase 2 (OBI-1-201) trial that was conducted in subjects with CHA. The dose and frequency for further infusions were based on clinical judgment and measured FVIII levels achieved. Target FVIII levels were not to exceed 200%, and the dose was not to exceed 400 U/kg every 2 hours. The recommended target post-infusion trough FVIII level for severe bleeds (e.g., severe mucosal, intracranial, intra-abdominal, genitourinary, traumatic, postoperative) was at least 80% for the first 24 hours. For all other serious bleeding events (e.g. joint, muscle, soft tissue) in the first 24 hours and for all bleeding events after the first 24 hours, the target post-infusion and trough FVIII levels was $\geq 50\%$.

Subjects with positive responses to OBIZUR were eligible for treatment for subsequent bleeding events.

6.1.5 Directions for Use

OBIZUR is supplied in 3-mL glass vials containing 500 U (nominal) of OBIZUR as a white cake for reconstitution with 1 mL sterile water for injection. It is administered as an intravenous infusion at a rate of 1 to 2 mL/min.

Reviewer Comment: For an average adult with a weight of 70 kg, the initial dose of 200 U/kg will require the reconstitution of approximately 28 vials of OBIZUR. The critical steps in reconstitution of numerous vials may not be an issue for treatment

given during hospitalization. The review team considered requesting a use-related risk analysis to identify potential use errors (interacting with the device and/or labeling/Instruction For Use) that could result in patient harm, but decided against it since Baxter confirmed that this product will not be marketed to patients.

6.1.6 Sites and Centers

Subjects were enrolled at 12 sites in 4 countries: United States (8 sites, 16 subjects), Canada (1 site; 5 subjects), United Kingdom (2 sites; 4 subjects), and India (1 site; 4 subjects). A total of eight sites enrolled subjects under Protocol OBI-1-301 only and four additional sites enrolled subjects under the expanded-access protocol (OBI-1-301a).

6.1.7 Surveillance/Monitoring

In addition to an Institutional Review Boards/Independent Ethics Committee, the trial had an independent DSMB, comprised of experts in the field of hemophilia research and clinical care who are not actively recruiting subjects for clinical trials. As per protocol, after five unique subjects were enrolled and treated, the DSMB convened to assess the dosing and monitoring plan. The DSMB recommended continuing the trial as planned. Subsequent DSMB reviews occurred after nine subjects were enrolled and treated (25 January 2012) and a follow-up and update meeting (03 June 2013).

Safety monitoring was considered adequate by this reviewer, and included: physical examinations, and assessments of AEs, vital signs, and laboratory testing (hematology, biochemistry, coagulation factors and parameters). After the initial dose, FVIII levels were assessed approximately every 2 to 3 hours after the infusion for the first 24 hours. Subsequent levels were checked every 24 hours, at a minimum. Clinical assessments were conducted each time an OBIZUR dose was administered or every 8 hours, whichever was sooner, during the first 24 hours. The FVIII levels and anti-human FVIII/anti-OBI-1 antibody titers are determined locally and centrally.

Immunogenicity monitoring included assessments of neutralizing antibodies (inhibitors) against human FVIII and porcine FVIII at screening, every 5 days while on treatment, at the PK assessment of the last dose, and at Visit 2 (14 [\pm 3 days]), Visit 3 (28 [\pm 3 days]), Visit 4(60 [\pm 5 days]), and Visit 5 (90 [\pm 7 days]). The Bethesda assay was used to monitor for inhibitors. Binding antibodies against BHK proteins were measured at screening and Visit 5 using ELISA.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy outcome 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:

Table 6: Hemostatic Efficacy Rating Scale

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

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 determined the outcome.

In addition to response to treatment, the overall treatment success was determined as a secondary endpoint by the investigator based on the ability to discontinue or reduce the dose and/or dosing frequency of OBIZUR: (a) control of bleeding, and continued with OBI-1 treatment to promote healing; (b) control of bleeding, and discontinued OBI-1 treatment, or (c) bleed not controlled.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Five subjects were enrolled in the initial Phase 2 portion of the trial to assess dosing and response to OBIZUR. The trial was designed to allow for up to 23 additional subjects to be enrolled in the Phase 3 portion of the trial in order to have at least 28 qualifying bleeding events in at least 28 unique subjects for the entire trial. Based on the assumptions of a response rate of 80%, 50% as a baseline low response rate and a two-sided alpha of 0.05, a trial of 28 bleeding events would have 90% power to test the null hypothesis (H_0) that the response rate = 50%, against the alternative hypothesis (H_1) that the response rate > 50% (based on the exact test of this null hypothesis).

The statistical plan was modified for the analysis of the data from the 18 subjects that was included in the Intermediate Clinical Study Report. Summary statistics for the percentage of initial bleeding episodes responsive at 24 hours was presented along with the 95% Clopper-Pearson confidence interval. The p-value was determined from an exact approach because of the relatively small sample size. The one-sided exact binomial test with a 0.025 significance level was used. A response rate of about 71% was required, and statistical significance was to be declared if the exact one-sided p-value was less than 0.025.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

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 that were enrolled in pivotal trial OBI-1-301 and 4 subjects enrolled under the expanded access protocol OBI-1-301a. The indications for therapy were: 19 intramuscular or joint, 4 post-surgical, 2 intracranial, 2 surgeries, 1 retroperitoneal hemorrhage, and 1 periorbital bleeding event. 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. Only the initial qualifying bleeding event was analyzed for the primary efficacy outcome measurement.

6.1.10.1.1 Demographics

Of the 29 treated subjects, 19 (66%) were male and 10 (34%) were female. The majority of the subjects were White (62%); 6 (21%) were African-American, and 5 (17%) were Asian. The median age was 70 years (range 42-90 years), which sufficiently represents the broader population targeted by the proposed indication.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

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, 11 subjects (28%) received immunosuppressive therapy, 11 subjects (28%) previously received anti-hemorrhagic medications (e.g. rFVIIa, activated prothrombin-complex concentrate, tranexamic acid) and 8 subjects (28%) were previously treated for a bleeding episode with unspecified therapy.

6.1.10.1.3 Subject Disposition

As of the data lock point for the intermediate Clinical Study Report (6 June 2013), 18 (62%) subjects completed the study. As expected, due to the fact that the enrolled subjects were critically ill and had significant co-morbidities, there were a large number of discontinuations. Ten 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)
- Lost to follow-up (one subject)

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

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

All 28 subjects evaluable for efficacy had a positive response to treatment for the initial bleeding episodes at 24 hours after dosing.

Table 7: Listing of Non-target Bleeding Sites

Subject	Qualifying Bleed
(b)(6) (82 year-old White female with chronic kidney disease stage III, diverticulitis, pernicious anemia, hypertension; enrolled in OBI-1-301a)	2+ pitting edema in the right upper extremity and ecchymosis, required blood transfusions
(b)(6) (43 year-old African American male with renal insufficiency, sickle cell disease, hepatitis c; enrolled in OBI-1-301a)	Right forearm compartment syndrome
(b)(6) (90 year-old White male with hypertension, anemia, TIA, dementia; enrolled in OBI-1-301a)	Hematoma of the right shoulder, intramuscular bleed of the deltoid muscle with pain, swelling and severe loss of shoulder joint mobility.
(b)(6) (68 year-old White male with chronic obstructive lung disease, hypertension, neuropathy; enrolled in OBI-1-301a)	Right peri-orbital bleed
-(b)(6) (69 year-old, African American male with abdominal aortic aneurysm, coronary artery disease, hypertension, adrenal mass, thyromegaly, anemia, leukocytosis, thrombocytopenia)	Left upper arm intramuscular bleed
(b)(6) (66 year-old African American male with chronic obstructive lung disease, hypertension, congestive heart failure, sjogren's syndrome)	Dorsum of right hand bleed
(b)(6) (74 year-old African American female with anemia, hypertension, diabetes mellitus, coronary artery disease, pulmonary hypertension, chronic kidney disease)	Right lateral thigh incision bleeding s/p fasciotomy
(b)(6) (70 year-old African American female with atrial fibrillation, congestive heart failure, coronary artery disease, hypertension, diabetes mellitus, thrombocytopenia, anemia, obesity)	Bilateral subdural hematomas with bleeding from a subdural hematoma drain.
(b)(6) (66 year-old White male with congestive heart failure, rheumatoid	Right upper extremity, intramuscular bleeding and bleeding into the tissue

arthritis, diabetes, cerebral palsy, painful bruising, obesity)	surrounding the site of a peripherally inserted central catheter
(b)(6) (86 year-old White male with atrial fibrillation, hypertension, coronary artery disease, prostate cancer)	Left upper arm intramuscular bleed
(b)(6) (79 year-old White female with non-small cell lung carcinoma with brain metastasis, hypertension, coronary artery disease, myocardial infarction, diabetes, anemia, deep vein thrombosis)	Retroperitoneal hemorrhage with iliopsoas hematomas
(b)(6) (81 year-old White female with hypertension, hypothyroidism, cardiomegaly, bilateral artificial knees and left hip arthroplasty)	Right iliacus muscle hematoma
(b)(6) (81 year-old White male with hypertension, hypercholesterolemia, benign prostatic hypertrophy)	Right thigh hematoma
(b)(6) (61 year-old White male with diabetes mellitus, IgG Kappa multiple myeloma status post autologous stem cell transplant)	Right iliopsoas muscle and right iliacus
(b)(6) (87 year-old Asian female with hypertension, cirrhosis, thyroid cancer, dementia)	Melena; scheduled surgery
(b)(6) (84 year-old African American female with atrial fibrillation, congestive heart failure, hypertension, pacemaker)	Tongue and neck swelling
(b)(6) (70 year-old White male with ulcerative colitis, prostate cancer, history of myocardial infarction)	Right arm bleed
(b)(6) (61 year-old White male with cecal mass, liver metastasis, anemia)	Surgical hemicolectomy
(b)(6) (51 year-old White male with tonsillar squamous cell carcinoma, spinal cord lesion, and multiple lung nodules)	Bleeding at a newly inserted PEG tube, requiring transfusion to maintain hemoglobin level.
(b)(6) (63 year-old White male with throat cancer, retroperitoneal mass, tracheostomy, hypertension, alcohol dependency)	Bleeding from venipuncture site of failed PICC line insertion
(b)(6) (64 year-old White female with hypothyroidism, superficial venous thrombosis)	Left forearm and elbow hematoma
(b)(6) (79 year-old White female with hypertension, B12 deficiency, anemia, hypothyroidism)	Left knee hemarthrosis with the risk of joint destruction
(b)(6) (82 year-old White female with	Bleeding from the surgical site of an

abnormal coagulation, anemia, stage III chronic renal insufficiency, hypothyroidism, angioplasty)	emergency tracheostomy requiring a blood transfusion
(b)(6) (84 year-old White male with hypertension, chronic renal insufficiency, peripheral sensory neuropathy)	Limb threatening, large hematoma in the posterior compartment of the right thigh requiring a blood transfusion.
(b)(6) (54 year-old White male with hypertension, dyslipidemia, diabetes, hyponatremia)	Peri-articular bleed of the left ankle including the left foot, lower leg and extension tendon sheath
(b)(6) (51 year-old Asian male with hypertension, lympho-proliferative malignancy)	Intracranial subdural hematoma
(b)(6) (61 year-old Asian male with hypertension, diabetes mellitus, right foot ulcer)	Connective/soft tissue of lower limb including hip
(b)(6) (42 year-old Asian male with cholelithiasis and hematuria)	Connective/soft tissue of lower limb including hip
(b)(6) (76 year-old Asian male with diabetes, syncope)	connective/ soft tissue of lower limb including hip

Source: STN 125512/0; Appendix 16.2.4, Listing of Target Bleed

Reviewer’s Comment: Although data on 28 subjects are included in the efficacy analysis, five of these subjects had protocol deviations that could have impacted the results of the trial:

1. Subject (b)(6): participated in a clinical trial within 30 days of enrollment under the expanded access protocol.
2. Subject (b)(6): granted a waiver although the subject’s platelet count was not consistent with a diagnosis of AHA; however, the results of the results of the aPTT mixing study and inhibitor testing are consistent with AHA.
3. Subject (b)(6): received rFVIIa less than 3 hours before the initial dose of OBIZUR was given.
4. Subject (b)(6): the qualifying bleeding episode (gastrointestinal bleed) was not documented as serious by the investigator
5. Subject (b)(6): the subject was previously taking antithrombotics and 3 half-lives had not yet elapsed when OBI-1 treatment was started.

A sensitivity analysis excluding data from these subjects did not alter the primary trial results; 100% of the remaining 23/28 bleeds received a positive response; therefore the trial results and conclusions remain unchanged.

Also, it appears that three out of the four subjects -----(b)(6)----- enrolled at the site in India had the same qualifying bleed of ‘connective/soft tissue of lower limb including hip’. A review of the case report forms and subject narratives did not identify any concerning/questionable data.

6.1.11.2 Analyses of Secondary Endpoints

Successful Treatment of Serious Bleeds

In addition to response to treatment, the overall treatment success was determined by the investigator. After the 24 hour response assessment, eventual successful treatment of the initial qualifying bleeds at the time of final treatment dose or progression to healing phase dosing was reported in 24/28 subjects (86%) after treatment with OBIZUR. 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 eventual treatment success reported. Of the 11 subjects who previously received anti-hemorrhagic therapies, eight (73%) had eventual successful treatment. Among the subjects who did not achieve this successful response to treatment, there were no apparent similarities in total dose or demographic characteristics. No statistical analysis was done to evaluate any association between pre-infusion cross-reactivity of anti-porcine antibody titers and baseline FVIII inhibitors with successful control of bleeding.

Narratives for Bleeds Treated Unsuccessfully treated with OBIZUR

- **(b)(6):** This was a 74 year-old African American female with multiple comorbidities, including hypertension, pulmonary hypertension, chronic kidney disease, diabetes mellitus, anemia, and thrombocytopenia. The subject was negative for OBII- inhibitor at baseline. The primary qualifying bleed was a life threatening bleed from a right lateral thigh surgical incision from a fasciotomy to treat compartment syndrome. The subject also had two concurrent bleeding surgical sites of the left lateral and medial calves. The bleed for the qualifying event was evaluated as having a positive response of 'partially effective' to treatment at 24 hours. Bleeding was reduced and FVIII levels ranged from 0 to 240% during the first 24 hours after the first dose. Hgb levels changed from 8.1 g/dL at screening to 9.7 g/dL 4 days after the initial dose to 7.2 g/dL on the last visit. Anti-human FVIII level at baseline was 147 BU and declined to 65 BU at week 10 and 77 BU on the last visit. Hemostatic control was considered effective after 5 doses from 3 to 10 days after the first dose and FVIII \geq 50%. Response to OBIZUR was considered not effective after 2 doses at one and 11 days after the first dose. The subject was subsequently discontinued by the investigator because of lack of efficacy for control of a secondary bleeding event of persistent hematuria that developed approximately 3 weeks after the initial dose of OBIZUR was given. The subject was thought to have a urinary tract infection as a result of immunosuppressive therapy (oral corticosteroids and rituximab) and later died from sepsis. The subject had an anti-porcine inhibitor of 6 BU, which is slightly increased from 3 BU at baseline. This subject received the highest number of infusions (140 infusions over 24 days) and the highest total dose of OBIZUR (20,660 U/kg).

Reviewer's Comment: It is unclear if this bleed's assessment was influenced by the lack of efficacy for the subsequent bleed. A review of the hemostatic responses for the qualifying bleed (Appendix 16.2.6.1; pages 7-11; ADRP analysis dataset) revealed that the investigator's assessment of efficacy was

positive. Only 2/61 (3%) of the assessments was considered negative (not effective) and these were reported at one and eleven days after the first dose. Anti-FVIII level at baseline was 147 BU and declined to 65 BU at week 10 and 77 BU on the last visit.

- **(b)(6):** This was a 70 year-old African American female with multiple comorbidities, including congestive heart failure, atrial fibrillation, renal insufficiency, diabetes, morbid obesity, thrombocytopenia, and anemia. The primary qualifying bleed was bilateral subdural hematomas with bleeding from a subdural hematoma drain. The subject received three doses over a period of 2 days. At the 8- and 24-hour assessments, the bleed was evaluated as having a positive response of ‘partially effective’. 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 from the qualifying bleeding event of intracranial hemorrhage. The investigator’s assessment after the final dose (given approximately 26 hours after the first dose) was ‘not effective’.

Reviewer’s Comment: A review of the subject narrative revealed that the final dose was stopped prematurely due to “technical problems.” Based on the information submitted, it appears unlikely that completing the infusion of the third/final dose would have improved the outcome for this subject. I agree with the assessment of ‘not successful’ as it is clear that the initial improvement was not sustained. However, it is unclear to me that the fatal outcome would have been any different if another hemostatic agent (e.g. rFVIIa or aPCC) was used.

- **(b)(6):** This was an 87 year-old Asian female who received OBIZUR to treat a gastrointestinal (GI) 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.
- **-(b)(6):** This is a 61 year-old White male with a history of anemia and a cecal mass with liver metastases with a reported qualifying bleeding event of “hemicolectomy,” which is not a bleeding event. This subject received OBIZUR prior to the bleeding event. At the 8- and 24-hour assessments, bleeding was evaluated as having a positive response of ‘effective’. On routine PK assessment the subject was found to have a positive anti-OBI-1 antibody titer of 8 BU and was subsequently discontinued from the trial before the assessment of successful control was completed. The subject continued treatment with a FVIII inhibitor 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 less than two weeks since the initial bleed, the bleeding event was considered not controlled. The subject expired as a result of the intestinal hemorrhage.

Amount of OBIZUR Required to Control Bleeding (dose, number of infusions)

The amount of OBIZUR required to control bleeding was highly variable among subjects. For the 24/28 evaluable subjects who were treated successfully, the median dose per infusion to successfully treat the primary bleed was 133 units per kg and a median total dose of 1523 units per kg.

The Clinical Study Report reports on 25/29 subjects, which are included in the intent-to-treat population; the dose used to successfully control a bleeding event ranged from 100 to 12194 U/kg with a mean (SD) dose of 2,683 (2,928) U/kg and a median dose of 1,637 U/kg. Subjects received between one and 57 infusions, (median 13 infusions), and an average of two infusions per day (range 0.3 to 4.5 per day) to control the qualifying bleed. 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.

Reviewer Comment: The wide range of required doses and dosing frequency observed in this patient population likely reflects a number of contributing factors, including variability in individual response and size/location of the bleed. These findings support the proposed labeled dosing regimen of an initial fixed dose with subsequent dosing based on clinical response and FVIII levels.

Length of Time Required to Achieve Hemostasis

A positive response was observed in 19/20 subjects (95%) evaluated at 8 hours and all 18 subjects that were evaluated at 16 hours.

6.1.11.4 Dropouts and/or Discontinuations

Ten subjects were discontinued from the trial for the following reasons:

- Fatal intracranial hemorrhage -----(b)(6)-----
- Development of anti-porcine FVIII inhibitor -----(b)(6)-----
- Sepsis resulting in death -----(b)(6)-----
- Renal failure resulting in death (b)(6)
- Lack of efficacy for a secondary bleed (Subject (b)(6))
- Non-compliance (b)(6)
- Lost to follow-up (b)(6)

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

6.1.11.5 Exploratory and Post Hoc Analyses

Treatment of Non-target and Subsequent Bleeds

Non-target bleeds were defined as any bleed that occurred concurrently with or subsequent to the qualifying bleed; these bleeding events were not evaluated for the primary endpoint. A total of 33 nontarget bleeds occurred in 17 subjects, of which 23/33

(70%) resolved within two days of treatment of OBIZUR. At eight hours after initial dosing 40% of the evaluable non-target bleeds were resolved, 7% persisted but was improved, 46% remained unchanged and 7% had worsened.

Four subjects -----(b)(6)----- experienced a subsequent serious bleeding event:

- Subject (b)(6) received OBIZUR to treat a left knee hemarthrosis. No assessment was done at 24 hours; however, the bleed completely resolved.
- (b)(6) experienced an acute event of ICH after the qualifying bleed was successfully treated. The ICH was treated with rFVIIa and OBIZUR before the family withdrew medical care.
- Subject (b)(6) received one dose of OBIZUR for a subsequent serious bleeding event of retroperitoneal bleeding that was considered not effective. An assessment for anti-OBI-1 antibodies revealed a titer level of 22 BU; therefore, the subject was withdrawn from the trial.
- Subjects (b)(6) received OBIZUR to treat a left hand bleed that he sustained from an accidental fall from a chair. At 24 hours treatment was assessed as positive and the bleed was controlled.

In addition, Subject (b)(6) was withdrawn from the trial due to a lack of efficacy of the subsequent bleeding event of hematuria (see section 6.1.11.2). The subject had an anti-porcine inhibitor of 6 BU, which was slightly increased from 3 BU at baseline.

Reviewer Comment: The efficacy of OBIZUR in patients with anti-porcine inhibitor titers of >20 BU cannot be determined from these data. The Package Insert (PI) will include language to inform prescribers of this limitation of the data. In addition, there is insufficient data to assess the efficacy of OBIZUR to treat subsequent serious bleeding events since only three such events were treated in this trial, two (67%) of which was treated successfully. The PI will also advise prescribers to base treatment on clinical response, in addition to FVIII levels, and to consider alternative therapy if an adequate clinical response is not obtained.

6.1.12 Safety Analyses

6.1.12.1 Methods

Adverse events (AEs) are coded by using Medical Dictionary for Regulatory Activities (MedDRA), Version 13.1 and are analyzed based on the principle of treatment emergence on or after first infusion with the trial drug. All safety analyses are based on the safety population, which constitutes of all subjects who received at least one dose of OBIZUR (n=29).

6.1.12.2 Overview of Adverse Events

Exposure to OBIZUR

For the 29 subjects treated in trial OBI-1-301/301a, the median total exposure was 1842 U/kg (range 150-27,659). The median number of daily infusions per subject was 1.8 (range 0.2 to 5.6), and the median total number of infusions was 15 (range 2 to 140).

Treatment Emergent Adverse Events

Treatment-emergent AEs (TEAEs), herein after referred to as AEs, were defined as events with an onset date on or after the first infusion with OBIZUR, or conditions present prior to the first dose of trial treatment that worsened or becomes related to OBIZUR during the active phase of the trial.

No serious adverse reactions were reported during the trial.

A total of 264 AEs were reported in 27/29 (93%) of subjects. Most were mild (50%) or moderate (38%) in severity; 13 (5%) were considered life threatening. The most frequently reported AEs were constipation (12 subjects, 41%), diarrhea (7 subjects, 24%), hypokalemia (7 subjects, 24%), anemia (6 subjects, 21%) and peripheral edema (6 subjects, 21%). The most common adverse reaction observed in greater than 5% of subjects was the development of inhibitors to porcine factor VIII.

Severe AEs were reported in six subjects (21%) and included abdominal pain (n=2), constipation (n=2), hypocalcemia (n=2), and joint swelling (n=2).

Six mild/moderate AEs that were considered possibly related to OBIZUR by this reviewer occurred in four subjects (28%):

- Subject (b)(6) had mild tachycardia and intermittent hypotension. The hypotension and tachycardia occurred after the first dose was administered and was treated with a 1-liter normal saline bolus (resolved). There were no additional signs or symptoms that suggested that this may have been a hypersensitivity reaction. Mitigating factors include the fact that the subject was anemic with a hemoglobin of 7.6 g/dL and a hematocrit of 23.5%. The subject tolerated the subsequent (final) dose without incident.
- Subject (b)(6) had 2 instances of PICC line occlusion. The first report occurred approximately four days after the initial infusion, and the second occurred one week after the first report. The occlusion resolved with tissue plasminogen activator (TPA).
- Two subjects developed anti-OBI-1 inhibitors and were discontinued from treatment.

6.1.12.3 Deaths

There were seven deaths (sepsis, ICH (n=2), renal failure, systemic mycosis, cholangitis/sepsis, intestinal hemorrhage) reported during the trial, including five deaths that occurred during the study, and 2 subjects died after discontinuing from the study. None of the deaths were considered related to the product by this reviewer:

Table 8: 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

Narratives of Deaths

- Subject (b)(6) developed persistent hematuria and signs of a urinary tract infection 22 days after the initial dose of OBIZUR. The subject was treated with antibiotics, but was diagnosed with sepsis 3 days later. The subject died of sepsis 31 days after the initial infusion of OBIZUR.
- Subject (b)(6) underwent a burr hole procedure to drain an intracranial hemorrhage and received treatment with rhFVIII and FEIBA bypass therapy prior to being enrolled under protocol OBI-1-301. Seven hours after the initial dose of OBIZUR the subject became confused and agitated and eventually became unresponsive. The family withdrew support, including OBIZUR treatment, 26 hours after the initial infusion of OBIZUR. The subject subsequently died 49 hours after the initial dose of OBIZUR of an intracranial hemorrhage.
- Subject (b)(6) had a history of renal insufficiency which was under control at the time of the initial dosing with OBIZUR. During the first 9 days of treatment the subject's creatinine levels were elevated but not life-threatening. Eleven days after the initial dose the subject's creatinine levels increased to life-threatening levels and experienced worsening edema. The creatinine levels increased over the next three days due to renal insufficiency. The subject died 15 days after the initial dose of OBIZUR of renal failure.
- Subject (b)(6) had a history of non-small cell lung carcinoma. Seventy-one days after the initial OBIZUR infusion the subject was started on antibiotics due to a urinary tract infection. The subject was admitted to the hospital emergency department the following day with an additional potential diagnosis of pneumonia. The subject died 79 days after the initial dose of OBIZUR. The cause of death was reported as non-small cell lung carcinoma. However, the investigator considered the event of systemic infection to be the fatal event.
- Subject (b)(6) had a history of enteritis, cirrhosis, hypothyroidism, and dementia who received OBIZUR to successfully treat a GI bleed. The subject subsequently developed cholangitis and sepsis during the follow-up phase of the study and medical care was withdrawn at the family's request.

- Subject (b)(6) had a history of atrial fibrillation and hypertension who was being treated with OBIZUR to control tongue and neck swelling (submandibular sialadenitis and possible intraglandular abscess without retropharyngeal abscess) when she developed persistent delirium that progressed to decreased responsiveness. A CT confirmed an intracranial hemorrhage, which was treated initially with rVIIa while OBIZUR was being prepared and subsequently with both medications. The family withdrew medical care and the subject died four days later.
- Subject (b)(6) was pre-enrolled under Protocol OBI-1-301 due to a planned hemicolnectomy due to metastatic colon carcinoma. The subject developed an anti-OBI-1 antibody titer 9 days after the initial infusion of OBIZUR. As a result the subject was discontinued from treatment with OBIZUR. The subject’s bleeding had stopped at the site of the initial qualifying bleeding event. Ten days after the initial infusion of OBIZUR, the subject experienced severe intestinal bleeding. The subject was given aPCC, but died shortly thereafter. The cause of death was listed as metastatic colon cancer, but the investigator considered the fatal even to be intestinal hemorrhage.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 33 serious adverse events (SAEs) were reported in 13 subjects (45%); all were considered not related to OBIZUR by this reviewer:

Table 9: Serious Adverse Events from Clinical Trials

Preferred Term	Severity	Relationship to OBIZUR
Asthenia	Mild	Not related (same subject for these 4 SAEs)
Dizziness		
Hematoma (right knee and chest)		
Hematoma (right chest)		
Atrial fibrillation	Mild	Not related
Pneumonia	Moderate	Not related (same subject for these 2 SAEs)
Sepsis	Life threatening	
Brain edema	Life threatening	Not related (same subject for these 2 SAEs)
Intracranial hemorrhage		
Transient ischemic attack		
Esophagitis	Moderate	Not related (same subject for these 3 SAEs)
Pneumonia		
Renal Failure	Life threatening	Not related
Pneumonia	Severe	Not related (same subject for these 3 SAEs)
Systemic mycosis	Life threatening	
Urinary Tract infection	Severe	
Gastrointestinal hemorrhage	Severe	
Arthralgia (left knee)	Moderate	Not related (same subject for these 11 SAEs) Not related
Arthralgia	Moderate	
Joint swelling (left knee)	Moderate	
Cholangitis	Severe	
Sepsis	Life threatening	
Arthralgia (left knee)	Severe	
Joint swelling (left knee)	Moderate	
Respiratory failure	Life threatening	
Anaphylactic reaction	Life threatening	

Preferred Term	Severity	Relationship to OBIZUR
Hemarthrosis	Moderate	
Intracranial hemorrhage	Life threatening	Not related
Intestinal hemorrhage	Life threatening	Not related
Fall	Severe	Not related
Tracheostomy malfunction	Moderate	Not related (same subject for these 2 SAEs)
Vascular pseudoaneurysm		
Grand mal convulsion	Severe	Not related

Selected Narratives for SAEs:

- 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 did not resolve and was considered probably not or remotely 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 that was unrelated to Obizur. Approximately 24 hours following the final dose of OBI-1, 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 cat scan was negative for acute changes.
- Renal failure developed in an 86 year-old White male with a history of Subject (b)(6) had 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. He experienced respiratory distress while attempting to have a catheter inserted for dialysis, and was subsequently treated with supportive therapy. The subject died 15 days after the initial dose of OBI-1 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.

6.1.12.5 Adverse Events of Special Interest (AESI)

Thromboembolic events:

No confirmed thromboembolic events were reported; however, one subject (b)(6) had two instances of PICC line occlusion that resolved after administration of TPA. The subject received additional medications intravenously.

Reviewer Comment: Thrombosis was not confirmed by ultrasound or any other diagnostic imaging, but was suggested by patency of the line after treatment with TPA. Although PICC lines are associated with an increased risk of venous thromboembolism, treatment with OBIZUR could have increased that risk.

Immunogenicity

All subjects were monitored for inhibitory antibodies to OBIZUR Nijmegen modification of the Bethesda inhibitor assay and binding antibodies to baby hamster kidney (BHK) protein by validated electrochemiluminescent assay. A subject was considered to have developed an inhibitor if the titer was ≥ 0.6 Bethesda Units (BU)/mL.

No patients developed *de novo* anti-BHK antibodies. Of the 29 subjects treated with OBIZUR, 5 (25%) developed persistent anti-porcine factor VIII antibodies following exposure to OBIZUR. Nineteen of the 29 subjects were negative at baseline. Of the 10 subjects with detectable anti-porcine factor VIII antibodies at baseline, 2 (20%) experienced an increase in titer.

Reviewer Comment: The development of antibodies to porcine FVIII is a recognized AE, as evidenced by data from use of Hyate:C; the utility of this treatment in the presence of high levels of porcine antibody is unclear. The risk of antibody formation is detailed in the PI.

6.1.12.6 Clinical Test Results

Clinically significantly abnormal laboratory values were observed in all subjects and were consistent with the subjects' underlying diseases. An abnormal laboratory value of hypocoagulable state (hypofibrinogenemia) was considered possibly related to treatment by the investigator; however, this reviewer assessed the relationship as not related as the hypofibrinogenemia persisted without treatment.

6.1.12.7 Dropouts and/or Discontinuations

Ten subjects were discontinued from the trial (see section 6.1.10.1.3 *Subject Disposition*)

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety concerns for this product are hypersensitivity and allergic reactions, thromboembolic events, and anti-porcine factor VII inhibitor development. The safety profile of OBIZUR is based on the analysis of safety data from 5 clinical studies.

- OBI-1-301 in subjects with AHA (completed)
- Expanded access protocol OBI-1-301a in subjects with AHA (on-going)
- OBI-1-302 in a subject with CHA (closed)
- OBI-1-201 in subjects with CHA (completed)
- OBI-1-101 in subjects with CHA (completed)

The safety evaluation plans were similar across the clinical studies and included assessments of medical history and concomitant medications, physical examinations, clinical observations, clinical laboratory measurements, vital signs, blood coagulation tests, FVIII levels, anti-human FVIII antibody titers, anti-porcine FVIII antibody titers, BHK cell antibody titers, anti- OBI-1 antibody titers and evaluations of bleeding and AEs.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate 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 bleed, 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 White male with a history of phimosis) who received four pre-and post-operative doses for circumcision. The overall surgical outcome was considered 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 adverse events or new bleeding noted.
- **OBI-1-201:** 9 subjects with CHA and inhibitors who had an active non-life and non-limb threatening bleed, antibodies to human FVIII, and OBI-1 inhibitory antibody titer \leq 20 BU
- **OBI-1-101:** 4 non-bleeding subjects diagnosed with CHA with inhibitors to human FVIII

8.2.3 Categorization of Adverse Events

AEs are coded by using Medical Dictionary for Regulatory Activities (MedDRA). All AEs were elicited by direct, non-leading questioning or were recorded if offered voluntarily by the subject. All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to OBI-1, were recorded in the AE fields of the case report form.

8.4 Safety Results

8.4.1 Deaths

A total of 7 deaths were reported; all deaths occurred in trial OBI-1-301 and are discussed in section 6.12.3.

8.4.2 Nonfatal Serious Adverse Events

SAEs were reported for trials OBI-1-301 and OBI-1-201 only. In addition to the 33 SAEs reported in 13 subjects during trial OBI-1-301 that were discussed in section 6.2.12.4, an additional four SAEs were reported in 3 subjects for OBI-1-201: right

shoulder bleed and throat swelling in subject (b)(6) requiring hospitalization, left knee hemarthrosis requiring hospitalization in subject (b)(6), and right knee hemarthrosis requiring hospitalization in subject (b)(6). As per the protocol for OBI-1-201, any AE that resulted in hospitalization was considered an AE.

8.4.3 Study Dropouts/Discontinuations

A total of 12 subjects were withdrawn from clinical trials of OBIZUR, including 10 from Trial OBI-1-301 (discussed in section 6.1.12.7) and 2 subjects from OBI-1-201 who discontinued because of withdrawal of consent (n=1) and lack of compliance (n=1).

8.4.4 Common Adverse Events

In Trial OBI-1-301, a positive anti-porcine inhibitor test result was reported as an adverse event in 2 (11.1%) subjects, and was the most frequently reported TEAE considered related to OBI-1 by investigator assessment. The development of anti-porcine inhibitors is an expected AE based on previous experience with the plasma-derived Hyate:C product.

In Trial OBI-1-201, the most frequently reported TEAEs were hemorrhagic disorders (3 subjects; 33%) and hemarthrosis (2 subjects; 22%), which are expected in subjects with CHA.

In Trial OBI-1-101, mild bleeding (which is expected in subjects with CHA) was reported by 2 of the 4 subjects; all of which were considered unrelated to the study medication by this reviewer.

8.4.8 Adverse Events of Special Interest

No confirmed thrombotic events have occurred during the clinical development of OBIZUR. Since the product contains trace amounts of hamster proteins, allergic type hypersensitivity reactions (including anaphylaxis) may occur. No hypersensitivity reactions have been reported during any clinical trial; however, in trial OBI-1-201, subject (b)(6) had a related AE of itching that was mild in severity, did not require discontinuation of therapy, and was not reported with subsequent doses. One subject (b)(6) in trial OBI-1-301 had mild tachycardia and hypotension after the first infusion, but tolerated the subsequent infusion without incident.

8.5.8 Immunogenicity (Safety)

The immunogenicity of OBI-1 was assessed in all three OBIZUR clinical studies using a Bethesda assay based method. Of the 43 subjects treated with OBIZUR, 16 (37%) developed anti-porcine FVIII antibodies following exposure to OBIZUR. This includes 3/4 (75%) from OBI-1-101, 8/9 (89%) of subjects from OBI-1-201, and 5/29 (17%) subjects from OBI-1-301 who were negative at baseline. An additional three subjects enrolled in OBI-1-101 who received the comparator drug, HYATE: C also developed anti-porcine FVIII inhibitor titers. Anti-porcine FVIII titers remained high until the end of the study.

8.6 Safety Conclusions

The results of the integrated analysis of safety demonstrate the safety and tolerability of OBIZUR for the proposed indication of the control and prevention of bleeding episode in patients with acquired Hemophilia A.

9. ADDITIONAL CLINICAL ISSUES

9.1.3 Pediatric Use and PREA Considerations

This product has orphan designation for “the treatment and prevention of episodic bleeding in patients with inhibitor antibodies to human coagulation FVIII,” and therefore does not trigger PREA.

10. CONCLUSIONS

OBIZUR appears reasonably safe and likely to provide therapeutic benefit to patients with AHA. No reports of hypersensitivity/allergic reactions, confirmed thromboembolic events, or anti-BHK antibodies were reported in any clinical trial. The development of anti-porcine FVIII antibodies was a common adverse event that occurred with the porcine FVIII predecessor product. The initial dosing of 200 U/kg, with the target of maintaining FVIII levels of 50% or higher ($\geq 80\%$ for serious life-threatening bleeds) was sufficient to successfully achieve hemostasis in the treatment of initial acute bleeding episodes. There was insufficient evidence to assess the treatment of bleeds in subjects with anti-porcine titers >20 BU.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

11.2

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Acquired hemophilia A (AHA) is a rare, but potentially life-threatening, bleeding disorder caused by the development of autoantibodies directed against coagulation FVIII. The clinical manifestations include hemorrhage into the skin, muscles, or soft tissues and mucous membranes, prolonged postpartum bleeding, excessive bleeding following surgery or trauma, and occasionally cerebral hemorrhage. The objectives in treating AHA patients are to effectively control bleeding during acute bleeding episodes and to eradicate the autoimmune antibodies. 	<ul style="list-style-type: none"> AHA is a rare and potentially life-threatening disease
Unmet Medical Need	<ul style="list-style-type: none"> Currently, there are no approved replacement therapies for AHA with inhibitors. Bypassing agents, such as recombinant factor VIIa or an activated prothrombin complex concentrate, are used to treat acute bleeds, particularly in patients with high-titer (≥ 5 BU) inhibitors. Bypassing agents are associated with a risk of thrombotic adverse events, and do not have a useful mean of monitoring efficacy (e.g. standard measures of coagulation, such as prothrombin time or activated partial thromboplastin time). 	<ul style="list-style-type: none"> This product treats a serious condition and, if approved, would provide significant improvement in safety and effectiveness. The ability to monitor efficacy by standard measures is considered a major contribution to the improvement of patient care.
Clinical Benefit	<ul style="list-style-type: none"> Data on 28 acute, serious bleeding events in 28 subjects with AHA were obtained from subjects enrolled in Trial OBI-1-301/301a. All 28 bleeding events had a positive response to treatment at 24 hours 25/28 (86%) of bleeds were treated successfully 	<ul style="list-style-type: none"> Results of Trial OBI-1-301 demonstrate that OBIZUR is effective in treating serious bleeds. There was insufficient data submitted to assess the efficacy of this product to treat subsequent bleeds or to treat specific bleeds, such as ICH.
Risk	<ul style="list-style-type: none"> The risks of treatment with OBIZUR are allergic reactions, inhibitor development to porcine FVIII, and thrombogenicity. The development of anti-porcine antibodies may reduce the efficacy of this product to treat bleeds; however, the inhibitory antibodies against porcine FVIII were not associated with increased incidence of adverse events, and the maximum increase in titers was not related to dose. There were no reports of hypersensitivity reactions or confirmed thromboembolic events. 	<ul style="list-style-type: none"> All the evidence indicates that OBIZUR was well tolerated.
Risk Management	<ul style="list-style-type: none"> The potential risks are outlined in the package insert under Contraindications and Warnings and Precautions sections. The lack of data to demonstrate efficacy in patients with anti-OBI-1 titers of >20 BU is discussed in the package insert. Routine pharmacovigilance is proposed Additional pharmacovigilance actions include a recombinant porcine sequence FVIII treatment registry, as proposed by Baxter. 	<ul style="list-style-type: none"> The package insert and the current pharmacovigilance plan are adequate to manage the risks

Risk-Benefit Summary and 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 B.U. 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 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 a major contribution to the improvement of patient care.

Risk

The safety concerns for this product are hypersensitivity reactions and the development of inhibitors to porcine factor VIII. 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.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of this BLA. The manufacturing process for OBIZUR™ is validated and adequately controlled. Efficacy and safety clinical data for OBIZUR™ supported a favorable benefit/risk determination for the proposed indication of treatment and prevention of acute bleeding episodes in patients with acquired hemophilia A.

11.5 Labeling Review and Recommendations

The proposed proprietary name, OBIZUR, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective and determined to be acceptable. The package insert, carton and container labels submitted to BL STN 125512/0 are currently being reviewed.

11.6 Recommendations on Postmarketing Actions

The safety data reviewed do not substantiate a need for a post-marketing requirement (PMR) or REMS.

Postmarketing commitment study

Baxter Healthcare Corporation committed to collecting additional efficacy and safety data for 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 date: 31 March 2015

Study/trial completion date: 30 September 2019

Final Report Submission date: 31 January 2020