Application Type	BLA
STN	125512
CBER Received Date	Nov 25, 2013
PDUFA Goal Date	Jul 25, 2014
Division / Office	OBE/DB
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Priority Review	8 months
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Review Completion Date / Stamped Date	
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Applicant	Baxter Healthcare Corp.
Established Name	Recombinant Porcine Factor VIII, B-Domain Deleted (OBI-1)
(Proposed) Trade Name	OBIZUR
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Infusions
Dosing Regimen	200 U/kg
Indication(s) and Intended Population(s)	Treatment and prevention of bleeding episodes in patients with acquired inhibitory antibodies to human factor VIII (i.e., acquired hemophilia patients)

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GLOSSARY

Abbreviation	Definition
AE	adverse event
AHA	acquired hemophilia A
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
AST	aspartate aminotransferase
Baxter	Baxter Healthcare/Baxter Innovations GmbH
BHK	baby hamster kidney
BLA	biologics license application
BU	Bethesda Unit
CHA	congenital hemophilia A
CI	confidence interval

CSR	clinical study report
DSMB	Data and Safety Monitoring Board
hFVIII	human factor VIII
H(1)	Alternative hypothesis
iCSR	intermediate clinical study report
IMP	investigational medicinal product
ITT	intent-to-treat
NA	not applicable
PK	pharmacokinetic
SAE	serious adverse event
TEAE	treatment-emergent adverse event

1. EXECUTIVE SUMMARY

This biologics license application (BLA) is for the use of OBI-1 in the treatment and prevention of bleeding episodes in patients with acquired hemophilia A (AHA). OBI-1 is a recombinant B-domain deleted porcine Factor VIII. Licensure is sought based on final results of 18 subjects with AHA who have completed treatment with OBI-1 in the ongoing phase 2/3 open-label clinical study. The efficacy of OBI-1 has also been evaluated for the control of bleeds in subjects with AHA (Study-OBI-1-301), in an extended-access study, as well as in subjects with congenital hemophilia A (CHA) with inhibitors.

The efficacy of OBI-1 to control serious bleeds in subjects with AHA was assessed primarily by the response to treatment after 24 hours (as determined both clinically and by factor VIII (FVIII) levels achieved), and secondarily by the frequency, total dose, number of infusions of OBI-1 and length of time required to achieve hemostasis. The treatment was considered clinically beneficial if the lower bound of the two-sided 95% CI for the positive response rate is greater than 50%. All 18 subjects presenting with a serious ("qualifying") bleed and treated with an initial dose of 200 U/kg had a positive response to treatment at 24 hours (two-sided 95% CI: 81.5%, 100%). Eventual successful treatment of the qualifying bleeds was reported by the investigator in 15 of 18 subjects after treatment with OBI-1. This assessment was performed at the time of final treatment dose or progression to healing phase dosing.

OBI-1 was safe and well tolerated for the treatment of serious bleeds in subjects with AHA. There were no serious adverse reactions, and no thrombotic events occurred.

According to the original statistical plan, it was planned to enroll 28 subjects. The sponsor requested approval of the product based on the results for 18 subjects. This could be considered as an unplanned interim analysis which may result in Type I error inflation. The sponsor would need a total of 19 responses to treatment after 24 hours out of the initially planned 28 to show that the lower confidence limit of the rate of positive

responses is greater than 50%. Study OBI-1-301 continues to enroll subjects and collect data to meet the original goal of 28 subjects. All additional data will be confirmatory to the data presented in this study. There were no statistical issues in this trial.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

AHA is a rare (orphan) bleeding disorder resulting from the development of inhibitors (autoantibodies) to human factor VIII (hFVIII), which creates a functional deficiency in procoagulant activity. The clinical manifestations are frequently severe, anatomically diverse, with a mortality rate that approaches 20%. Bleeding is often spontaneous or in response to minimal trauma.

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

An application requesting orphan drug designation for OBI-1 for the treatment and prevention of episodic bleeding in subjects with inhibitor antibodies to hFVIII was submitted to FDA on November 14, 2003. The orphan designation was granted to Ipsen on March 16, 2004, then transferred to Inspiration Biopharmaceuticals, Inc. in March 2010, and then transferred to Baxter Healthcare Corporation in April 2013. OBI-1 received Fast Track designation from FDA in AHA on October 25, 2012 on the basis that the drug is intended to treat a serious disease and has a potential to fill an unmet medical need. Priority review for this BLA was granted on December 3, 2013. On December 10, 2013, Baxter withdrew the FDA approved proprietary name ---(b)(4)--- and requested review of new proprietary names OBIZUR (primary) and (b)(4) (alternate).

A Type B End-of-Phase 2 meeting was held with the Office of Blood Research and Review (September 4, 2008). At this meeting, Ipsen and FDA discussed elements of the proposed Phase 3 studies for congenital and acquired hemophilia A. On June 25, 2010, a Type C meeting was held between the FDA and Inspiration regarding the design and analysis of a pivotal clinical protocol, OBI-1-301, for the treatment of serious bleeding episodes in patients with AHA using OBI-1. On May 9, 2011, a Type C meeting was held between the FDA and Inspiration regarding the design and analysis of a pivotal clinical protocol, OBI-1-302, for the use of OBI-1 in the treatment of serious bleeding episodes in patients with CHA who have developed inhibitors to hFVIII.

Originally 28 subjects were planned for the Phase 3 portion of Study OBE-1-301 in order to have at least 28 qualifying bleeding events in at least 28 unique subjects for the entire study. At the pre-BLA meeting in October 2012, it was agreed that a minimum of 15 subjects may suffice to support the BLA for OBI-1 to treat bleeding episodes in patients with AHA.

2.6 Other Relevant Background Information

OBI-1 is a recombinant porcine factor VIII glycoprotein. In OBI-1, the B-domain normally present in naturally occurring porcine factor VIII has been replaced with a twenty-four amino acid linker. OBI-1 is being investigated for the treatment and

prevention of bleeding episodes in patients with AHA. OBI-1 was used in subjects with CHA with inhibitors to hFVIII to determine the appropriate dose in subjects with AHA.

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

5.1 Review Strategy

The applicant submitted data on all available trials, all of which were very small. These trials are mentioned in Table 1 below. Only OBI-1-301/301a study provides the data supporting current BLA submission. Therefore, the integrated review of efficacy and safety is not presented in this report.

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

The following documents were reviewed: 2.5 Clinical Overview, 2.7.3 Summary of Clinical Efficacy, 2.7.4 Summary of Clinical Safety, 2.7.6 Synopses of Individual Studies, 5.3.5.2 OBI-1-301 Study Report and OBI-1-301 Statistical Analysis Plan. All data sources are included in the applicant's eCTD submission located in the FDA/CBER Electronic Document Room (EDR):
--(b)(4)---

5.3 Table of Studies/Clinical Trials

The clinical development program for OBI-1 is summarized in Table 1. All studies were one arm, multicenter. This review evaluates only the data presented for the pivotal study OBI-1-301 and its extension, OBI-1-301a.

			Table 1Listing of Clinical Studies in the OBI-1 Clinical Development Program		
Study Number	**Phase**	**Study Status and Sample size**	**Criteria**	**Dose Range and Frequency**
OBI-1-301	2/3	Ongoing iCSR OBI-1-301/301a 15 subjects	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 3 subjects	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 1 subject	CHA with inhibitors; age ≥ 6 y with suboptimal response to by-passing 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 9 subjects enrolled; 7 completed	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
OBI-1-101	1	Completed CSR OBI-1-101 9 subjects	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

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Study OBI-1-301/301a.

 Due to the significant morbidity and mortality associated with an AHA patient's failure to respond to current therapies, the 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. Data from the expanded access subjects are included with the data from subjects enrolled under Protocol OBI-1-301 sites in an intermediate clinical study report. This study is ongoing.

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective: To evaluate the efficacy of OBI-1 for the treatment of serious bleeding events in subjects with AHA with autoimmune inhibitory antibodies to hFVIII.
Secondary Objectives:
1) To determine the proportion of serious bleeding events controlled with OBI-1 therapy
2) To assess the efficacy of OBI-1 at designated time points after the initiation of therapy
3) To determine the frequency, total dose, and total number of infusions of OBI-1 required to control all serious bleeding events
4) To assess the correlation between response to OBI-1 therapy at specified assessment time points and eventual control of serious bleeding events
5) To assess the correlations between the pre-infusion anti–OBI-1 inhibitor titer, the total dose of OBI-1, the outcome at 24 hours and the eventual control of the bleeding event
6) To assess the anti–OBI-1 inhibitor level before infusion, at specified time points during treatment, and at the end of the follow-up period at 90 days after final infusion
7) To evaluate the safety of OBI-1
8) To assess drug exposure by using a complete (non-bleeding state) or sparse (bleeding state) sampling design and population pharmacokinetic (PK) approach (for sparse data) in subjects successfully treated with OBI-1 therapy.

6.1.2 Design Overview

The study is an international, prospective, nonrandomized, open-label design that consists of treatment of serious bleeds in subjects with AHA. PK is studied in subjects successfully treated with OBI-1. A potential participant who is in a non-bleeding state (i.e., has a pre-established diagnosis of AHA) is prequalified for study eligibility; factor VIII (FVIII) level, anti–hFVIII antibody titer, and anti–OBI-1 antibody titer are determined. The anti-hFVIII titer must be known and the anti–OBI-1 titer must be less than or equal to 20 Bethesda units (BU) (i.e. titers known due to documentation of previous assessment) for a subject to be prequalified. Eligible prequalified subjects are only enrolled at the time a serious bleeding event occurs.

The study duration for each subject is approximately 3 to 4 months for each qualifying bleeding event. This duration includes 90 days follow-up after the final treatment with OBI-1. Subjects with a successful bleeding control treatment with OBI-1 are eligible for retreatment with OBI-1 for subsequent qualifying bleeds while still active in the study (i.e., through final follow-up visit).

The initial Phase 2 portion of the study (five subjects) was to assess dosing and response to OBI-1 in subjects with AHA who present with a serious bleeding event. Up to 23 additional subjects were planned for the Phase 3 portion of the study in order to have at least 28 qualifying bleeding events in at least 28 unique subjects for the entire study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

For each serious bleeding event, an initial dose of 200 U/kg of OBI-1 was administered. After the initial dose, a clinical assessment was made approximately 2 to 3 hours after infusion. The decision to administer an additional OBI-1 dose was made by the investigator on the basis of the subject's post infusion FVIII level, anti–OBI-1 titer if available, clinical status, and target FVIII levels.

6.1.6 Sites and Centers

Table 2 presents the number of sites initiated and subjects enrolled by country.

Table 2 Site and Subject Numbers by Country in Study OBI-1-301		
Country	**Number of Sites**	**Number of Subjects Enrolled**
United States	8 (3)[a]	8 (3)[a]
Canada	1	4
United Kingdom	4	2
India	1	1
Germany	1	0
Sweden	1	0
Hungary	1	0

[a]Parentheses contain numbers for Protocol OBI-1-301a sites. Protocol OBI-1-301a is only being carried out in the United States

6.1.7 Surveillance/Monitoring

The Data and Safety Monitoring Board (DSMB) met to review safety data for studies OBI-1-301 and OBI-1-301a after five subjects were enrolled. The DSMB then met subsequently after nine subjects were enrolled and treated under the study protocols. A follow-up and update meeting of the DSMB occurred 04 June 2013. The DSMB was made aware of all SAEs and deaths and were provided all safety data for review. The DSMB recommended at each meeting that the study continue as the protocol indicated.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy outcome is the proportion of serious bleeding events responsive to OBI-1 therapy at 24 hours after the initiation of treatment using a well-defined, four-point ordinal scale. Although rated on a multiple-point scale, all bleeding assessment outcomes are binary (positive or negative) for the purposes of statistical analysis. A positive response is defined as an effective or partially effective bleeding response to OBI-1 therapy. The response to OBI-1 therapy is based on the investigator's assessment of bleeding and blood FVIII antibody titer above or less than 20 BU. Investigator assessment of response to OBI-1 is given in Table 3. If there appears to be inconsistency between the clinical assessment and the FVIII levels (e.g., clinical response with undetectable FVIII levels), the clinical assessment determines the outcome. Therefore, the clinical assessment is the primary endpoint. The treatment is considered clinically beneficial if the lower bound of the two-sided 95% CI for the positive response rate is greater than 50%.

Table 3. Investigator Assessment of Response to OBI-1				
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 alternate 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

After the 24 hour response assessment, the long-term success of OBI-1 therapy was determined as a secondary evaluation by the investigator if the OBI-1 treatment had successfully controlled this bleeding episode as either (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 and 13 additional subjects were enrolled in the Phase 3 portion of the study, yielding 18 subjects presented in the interim study report submitted in this application. According to the original statistical plan, it was planned to enroll 28 subjects. The sponsor requested approval of the product based on the results for 18 subjects. This could be considered as an unplanned interim analysis which may result in Type I error inflation. The sponsor would need at least 19 successful treatments out of the planned 28 to be sure that the lower confidence limit of the rate of positive responses is greater than 50%.

The main objectives for secondary assessments rely on bleed control evaluations and amount of drug product used correlated to these evaluations. Therefore, the outcome measures of these parameters are the secondary endpoints.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The ITT population is comprised of all subjects who received OBI-1 treatment, regardless of whether treatment was completed. Only initial qualifying bleeding events were analyzed for the primary efficacy outcome measurement. All safety analyses are based on the safety population, which constitutes all subjects who received at least one dose of OBI-1. The PK population includes all subjects in the ITT population who consented to PK draws and had FVIII levels measured at the central reference laboratory.

6.1.10.1.1 Demographics

The median age of subjects in studies OBI-1-301 and OBI-1-301a was 72 years (range 43 to 90 years). There were 8 female and 10 male subjects. The majority of subjects (66.7%) were Caucasian, followed in frequency by black or African American (27.8%).

Table 4. Demographic and Baseline Characteristics (ITT Population)

Parameter	OBI-1 (n = 18)
Age (years)	
N	18
Mean	71.0
Median	72.0
SD	13.33
Minimum, maximum	43, 90
Sex [n (%)]	
Male	10 (55.6)
Female	8 (44.4)
Race [n (%)]	
White/Caucasian	12 (66.7)
Black or African American	5 (27.8)
Asian	1 (5.6)
Hawaiian Native or other Pacific Islander	0

Source: Table 11-1 (page 77) of OBI-1-301 Study Report.

6.1.10.1.3 Subject Disposition

A summary of subject disposition is provided in Table 4. At the time of the intermediate data lock, 18 subjects were both enrolled and treated under Protocols OBI-1-301 and OBI-1-301a. All 18 subjects are included in the ITT and safety populations and all 18 subjects had analysis of the primary efficacy endpoint. One subject's completion of study status could not be verified from source data and six subjects were discontinued prematurely (did not complete the 90-day follow-up visit). Thus 11 subjects completed the study.

Table 5. Summary of Subject Enrollment and Disposition	
Subject Status	**OBI-1 [n (%)]**
Subjects enrolled	18
Subjects included in ITT population[a]	18 (100.0)
Subjects included in safety population[b]	18 (100.0)
Subjects included in PK population[c]	4 (22.2)
Subjects completed study[d]	11 (61.1)
Subjects discontinued from study prematurely	6 (33.3)
Reasons for Early Termination	
Protocol violation	0
Adverse event	3 (16.7)
Withdrawal of consent	0
Lost to follow-up	0
Lack of efficacy	1 (5.6)
Other	2 (11.1)

Source: Table 14.1.1.

ITT = intent-to-treat; PK = pharmacokinetic.

[a]   The ITT population includes all eligible subjects who enrolled under the Protocol OBI-1-301 and Protocol OBI-1-301a and provides any post screening data.

[b]   The safety population includes all subjects who received at least one dose of OBI-1.

[c]   The PK population includes all subjects in the ITT population who consented to PK draws and had factor VIII levels measured at the central reference laboratory.

[d]   Eleven subjects have completed the study according to the protocol and for one subject (Subject (b)(6)--) study completion status could not be verified in the source data.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

All 18 qualifying bleeds had a positive response to OBI-1 treatment as assessed by the investigator at 24 hours after initial dosing. Therefore, the percentage of subjects meeting the primary efficacy endpoint was 100%. These data provide a two-sided Clopper-Pearson 95% CI of positive response rate between 81.5% and 100%.

6.1.11.2 Analyses of Secondary Endpoints

There was a trend toward control of bleeding in less than 24 hours, as a positive treatment response was observed in most bleeds by 8 or 16 hours after first infusion. The data are given in Table 6.

Table 6. Serious Bleeding Events that Are Responsive to OBI-1 Treatment at Specific Time points		
OBI-1 (n = 18)	**Eventual Control of Serious Bleeding[a]**	
	Yes	**No**
Response at 8 Hours (n = 15)[b,c]		
Positive [n (%)]	11 (73.3)	3 (20.0)
Negative [n (%)]	1 (6.7)	0 (0.0)
Response at 16 Hours (n = 16)[b,c]		
Positive [n (%)]	13 (81.3)	3 (18.8)
Negative [n (%)]	0 (0.0)	0 (0.0)
Response at 24 Hours (n = 18)[b]		
Positive [n (%)]	15 (83.3)	3 (16.7)
Negative [n (%)]	0 (0.0)	0 (0.0)

Source: Table 14.2.4

[a]   A serious bleeding event is considered as eventually controlled if the investigator checked "Completed OBI-1 therapy as treatment success" on the last dose electronic case report form page.

[b]   A positive response is defined as effective or partially effective control of bleeding,

[c]   n does not equal 18 because not all subjects were assessed at this time point

Fifteen of the 18 qualifying bleeding events were judged to be successfully controlled after treatment with OBI-1 at the completion of dosing (95% CI = 58.6% to 96.4%). Three subjects were not rated by the investigator as having eventual treatment success. There was variability in dosing frequency, total dose, and the total number of infusions required to reach successful treatment outcome, which indicates that subject response to OBI-1 therapy is very individualized to patient clinical condition and type of bleed. This variability in product use will need to be addressed by the clinical reviewer. Because all subjects responded by 24 hours, there was no evidence of an effect of the type of bleed or baseline hFVIII inhibitor titer on 24 hour treatment response.

6.1.11.3 Subpopulation Analyses

There were no apparent subgroup effects, including effects by age, race or sex.

6.1.11.4 Dropouts and/or Discontinuations

Six of the 18 subjects were discontinued from the study. Three of the six subjects were withdrawn from treatment by the investigator. These three subjects had all reached the assessment time point for the primary efficacy endpoints before their discontinuation and are included in the primary efficacy analysis.

6.1.12 Safety Analyses

Seventeen of the 18 subjects (94.4%) experienced a total of 154 treatment-emergent adverse events (TEAEs). Table 6 summarizes all TEAEs experienced by subjects in Study OBI-1-301 and Study OBI-1-301a.

Table 7. Summary of Treatment Emergent Adverse Events (Safety Population)	
	OBI-1 (n = 18)
TEAEs[1]	
Total number of TEAEs	154
Number of subjects with TEAEs (%)	17 (94.4)
Number of subjects experiencing TEAEs by relationship to study drug (%)	
Related[b]	5 (27.8)
Not related	12 (66.7)
Number of subjects experiencing TEAEs by maximum intensity (%)	
Mild	5 (27.8)
Moderate	4 (22.2)
Severe	3 (16.7)
Life-threatening	5 (27.8)
Number of subjects with any TEAE leading to interruption or discontinuation of study drug	3 (16.7)
TESAEs[2]	
Total number of TESAEs	19
Number of subjects with any TESAE	9 (50.0)
Number of subjects experiencing TESAEs by strongest relationship to study drug (%)	
Related[b]	0
Not related	9 (100.0)
Number of subjects experiencing TESAEs by maximum intensity (%)	
Mild	1 (11.1)
Moderate	3 (33.3)
Severe	0
Life-threatening	5 (55.6)
Number of subjects experiencing TESAEs leading to interruption or discontinuation of study drug	1 (11.1)
Number of deaths (%)	
Total number of TEAEs leading to death	5
Number of subjects with any TEAE leading to death	5 (27.8)
Number of subjects with product related TEAE leading to death	0

Source: Table 14.3.1.1.
[1]TEAE = treatment-emergent adverse event; [2]TESAE = treatment-emergent serious adverse event.
[a]   Note: Adverse events are coded by using Medical Dictionary for Regulatory Activities, v13.1.
      TEAEs are adverse events that occur on or after first infusion with OBI-1 or adverse events that
      exist before the first infusion but then intensify afterwards.
[b]   Related TEAEs are those TEAEs reported as "definitely related," "probably related,"
      "possibly related" or have missing or unknown relationship to the study medication.
TEAEs are summarized by system organ class, preferred term, and severity in Table 14.3.1.6.

6.1.12.3 Deaths

Five deaths were reported: one death occurred during the study, and four subjects died after discontinuing from the study. None of the deaths were considered related to the study treatment by the sponsor.

6.1.12.4 Nonfatal Serious Adverse Events

Nineteen TESAEs were reported in nine subjects; one subject discontinued from the study because of a TESAE. All TESAEs were considered not related to OBI-1 treatment.

6.1.12.5 Adverse Events of Special Interest (AESI)

Safety was assessed in terms of adverse events including severe allergic reactions and thrombotic events, immunogenicity (inhibitory and total binding antibodies to factor VIII), clinically significant laboratory values (hematology and clinical chemistry) and vital signs. There were no serious adverse reactions, and no thrombotic events occurred. Three subjects developed anti-porcine FVIII antibodies (inhibitors). None of the subjects developed anti-BHK antibodies. Other non-serious AEs related to treatment as assessed by the investigator were: tachycardia, hypotension and constipation.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The sample size for the pivotal study was very small. The applicant enrolled 18 instead of originally planned 28 subjects to assess efficacy and safety. Clinical assessments were done at every 12 hours from 24 hours to 120 hours, every 24 hours after 120 hours, or with every dose until termination. All 18 subjects receiving OBI-1 for the treatment of a qualifying bleeding event were judged by the investigators to have a positive response to treatment at 24 hours after initiation of OBI-1 treatment (two-sided 95% CI: 81.5% to 100%). After the 24 hour response assessment, eventual successful treatment of the qualifying bleeds was reported by the investigator in 15 of 18 (83.3%) subjects after treatment with OBI-1. This assessment was performed at the time of final treatment dose or progression to healing phase dosing. Five deaths were not related to the study drug or to the development of anti–OBI-1 antibodies.

10.2 Conclusions and Recommendations

The pivotal study met the study success criteria.