



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

Date: 20 August 2014

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Re: STN 125512\0

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Product: Antihemophilic Factor (Recombinant), B-Domain Deleted Porcine Factor VIII (OBI-1)

Subject: Original Biologics License Application – Pharmacovigilance Plan Review (Action Due Date 26Jul2014)

Sponsor: Baxter

1. INTRODUCTION

1.1 Product Information

OBI-1 is a porcine B-Domain Deleted recombinant Factor VIII (BDDrFVIII) product and is manufactured in baby hamster kidney (BHK) cells. The proposed indication for OBI-1 is the treatment and prevention of bleeding in adults with acquired hemophilia A (AHA) due to the autoimmune development of inhibitory antibodies to human FVIII. The product will be supplied as a white lyophilized powder in a single-dose glass vial containing 500 units per vial, which can be reconstituted using a 1 mL pre-filled syringe of sterile water for injection.

Of note, the product was named OBI-1 in development and three proposed proprietary names for the product – (b)(4)--, Obizur and (b)(4), are currently under review by FDA. For purposes of clarity this product will be referred to in this memorandum as OBI-1.

1.1.1 Porcine Factor VIII products

Like human FVIII, porcine FVIII activates factor IX in the coagulation cascade, resulting eventually in the development of a fibrin clot and thus promoting coagulation. Porcine FVIII has been of particular therapeutic interest for the following reasons. Patients with congenital hemophilia can develop inhibitory alloantibodies to human FVIII, which when bound to the exogenous FVIII product administered to the patient, limit the ability of the FVIII product to function in the coagulation cascade. Patients with AHA acquire this bleeding disorder as a result of the development of autoantibodies to endogenous FVIII which render the patients' own FVIII ineffective. Thus the management of bleeding in patients with congenital hemophilia who develop inhibitors and those with acquired hemophilia depends upon a therapeutic intervention which can negate or circumvent the effect of inhibitory FVIII antibodies. FVIII inhibitors most commonly bind to the A2 and C2 domains of the human FVIII molecule. Porcine A2 and C2 domains are 84% and 76% homologous with those of human FVIII, respectively.¹ As a result of the sequence variation between human and porcine FVIII, there is reduced cross-reactivity between inhibitors to human FVIII and porcine FVIII. The cross-reactivity of inhibitory antibodies to human FVIII with porcine FVIII is estimated at 15% in patients with congenital hemophilia, and approaches 0% in patients with AHA.² Thus because porcine FVIII lacks specific epitopes, it is less likely to be bound by inhibitory antibodies than human FVIII, and when administered to hemophiliacs with inhibitors or patients with AHA, porcine FVIII products can function in the coagulation cascade and promote hemostasis.

The first porcine FVIII product licensed in the US was a product derived from porcine plasma named Hyate:C. Regulatory approval was first granted to Ipsen Inc. in 1984 to market Hyate:C for the management of bleeding in patients with inhibitory antibodies against human FVIII.³ In 1996, batches of Hyate:C were found to contain small quantities of porcine parvovirus (PPV), a virus endemic to the pig population worldwide. Although PPV is not thought to be pathogenic in humans,⁴ the widespread nature of the virus made it difficult for Ipsen to obtain porcine plasma free of PPV and produce a final product that could meet the regulatory specification of being free from detectable virus. As a result, Ipsen chose to cease manufacture of Hyate:C in June 2004 -----(b)(4)-----

In 2002, Ipsen submitted an original Investigational New Drug application (IND) to the Food and Drug Administration (FDA) (10695) for the use of OBI-1 in the management of AHA. This IND resulted in the original Biologics License Application (BLA) for OBI-1 (125512\0) currently under review by FDA at this time. During the IND phase, Ipsen partnered with Inspiration BioPharmaceuticals Inc. in the development of OBI-1. In 2013 Baxter announced the acquisition of OBI-1 and related assets from Inspiration, including the acquisition of manufacturing operations from Ipsen.⁵ -----
----- (b)(4) -----

management of bleeding in patients with congenital hemophilia A who develop inhibitory antibodies. This second IND has yet to reach the BLA stage.

Of note, on 20Sep2010, Inspiration received orphan designation for this product from the European Commission.⁶ Sponsorship was transferred to Baxter in July of 2013. The product is not currently licensed in the European Union (EU).

1.1.2 Recombinant B-Domain Deleted Factor VIII products

The B-domain is a large central region of the FVIII glycoprotein which links two biologically active domains. In BDDrFVIII products, the B-domain is replaced with a short amino acid sequence that links the two biologically active 90-kd and 80-kd domains. An intact full length B-domain is thought to be non-essential for hemostatic effect as both recombinant and plasma-derived FVIII products lacking the B-domain have been shown to be effective in coagulation.⁷ Deletion of the B-domain reduces the size of the glycoprotein resulting in greater ease of manufacturing. In addition, it is thought that deletion of the B-domain confers greater stability on the smaller molecule, eliminating the need for human albumin as a stabilizer and thus reducing the risk of transmission of viral pathogens.⁸

There are currently three BDDrFVIII products approved by FDA – ReFacto, Xyntha and NovoEight. Wyeth improved on ReFacto – the first BDDrFVIII product approved by FDA – by eliminating human albumin from the manufacturing process and by using Chinese Hamster Ovary (CHO) cells grown in the absence of human or animal derivatives. This improved product was named Xyntha. Following Xyntha’s approval by the FDA, Wyeth reported their intention for Xyntha to replace ReFacto in the US market, while marketing a similar product ReFacto AF in Europe. Currently Xyntha is the only BDDrFVIII product marketed by Wyeth in the US. NovoEight, a BDDrFVIII product manufactured by Novo Nordisk, was recently licensed by the FDA on 15Oct2013 and is the second BDDrFVIII product marketed in the US. A third BDDrFVIII product named Eloctate was licensed by FDA on 6Jun2014. Eloctate is the only long-acting FVIII product licensed by FDA. Should OBI-1 be approved by FDA, it would be the fourth BDDrFVIII marketed in the US and the only porcine FVIII product on the US market.

1.1.3 Proposed Product Indication – Acquired Hemophilia A (AHA)

The proposed indication for OBI-1 is for use in AHA. -----
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The current proposed indication – AHA, is a rare but often severe bleeding disorder caused by autoantibodies against FVIII. AHA occurs more frequently in the elderly and in association with malignancies, autoimmune disease, postpartum and following drug exposures – however about half of cases remain idiopathic.⁹ Unlike congenital hemophilia A where hemarthroses are among the most common bleeding events, hemorrhages in AHA more frequently involve soft tissue bleeding in muscle and skin. Treatment involves control of bleeding and treating the underlying condition when possible. Should OBI-1 be approved it would be the second product licensed in the US for management of AHA. NovoSeven is currently approved for multiple indications including the management of bleeding and perioperative care for patients with AHA. Multiple other products are used off-label for AHA including FVIII Inhibitor Bypassing Agents (FEIBA) and activated Prothrombin Complex Concentrates (aPCCs), as well as various steroids and chemotherapeutic immunosuppressants.⁹

When used for the proposed indication, Baxter proposes an initial dose of 200 units/kg of OBI-1 followed by titration of the dosing schedule based on FVIII recovery levels to maintain recommended target levels. In addition, the sponsor recommends monitoring of FVIII levels and clinical conditions every 3 hours in

the first 24 hours and thereafter based on clinical judgment to determine subsequent dosing and frequency.

1.2 Regulatory History

The original IND for OBI-1 was submitted to FDA by Ipsen and Inspiration, and was subsequently acquired by Baxter as described in section 1.1.1 above. Orphan designation (# 03-1814) was granted to Ipsen on 16Mar2004 by FDA, transferred to Inspiration in 2010, and then transferred to Baxter in 2013.

In 2012, while in the IND phase, OBI-1 received Fast Track designation from FDA for the proposed indication of management of AHA on the basis that the drug is intended to treat a serious disease and has the potential to fill an unmet medical need. For similar reasons, FDA has granted this BLA an 8 month priority review. The regulatory history of OBI-1 is summarized in Table 1 below.

Table 1. Regulatory History of OBI-1

Date	Event
2002	Ipsen submits an original IND (10695) to FDA for the use of OBI-1 in the management of bleeding in patients with AHA
2004	Orphan designation granted to Ipsen by FDA for OBI-1
2010	Ipsen and Inspiration enter into a partnership to develop OBI-1 and orphan designation is transferred to Inspiration
b(4)	-----b(4)----- -----
2012	IND 10695 receives fast track designation from FDA
2013	Baxter announces the acquisition of OBI-1 and related assets from Inspiration and Ipsen. Orphan designation is transferred to Baxter
2013	Baxter submits the original BLA 125512\0 for the use of OBI-1 in the management of AHA and the BLA is granted priority review by FDA

1.3 Objectives

This memorandum follows a request from the Office of Blood Research and Review (OBRR) for the Office of Biostatistics and Epidemiology (OBE) to review the available safety related data for OBI-1. As part of this comprehensive safety evaluation, the Pharmacovigilance Plan (PVP) submitted by the sponsor as part of the Risk Management Plan (RMP) for OBI-1 has been reviewed, as well as the additional materials listed in Table 2 below. A full set of references is provided in Section 6 below.

Table 2. Materials Reviewed

Document	Date	Source
OBI-1-101:Phase I Randomized, Parallel-Group, Blinded Comparison Study of Safety, Tolerance and PK of OBI-1 versus Hyate:C When Administered as a Single Intravenous Injection to Subjects with an Inhibitor Antibody to FVIII, in the Non-Bleeding State. Final Study Report.	26Jul2005	Ipsen
OBI-1-201:An Open-Label Study of the Hemostatic Activity, PK and Safety of OBI-1 When Administered by Intravenous Injection, to Control Non-Life and Non-Limb Threatening Bleeding Episodes in Congenital Hemophilia A Patients with an Inhibitor to Human FVIII. Final Study Report.	30May2008	Ipsen
Expanded Access to OBI-1 in the Treatment of Acquired Hemophilia A Due to Factor VIII inhibitory Auto-antibodies. Protocol Number OBI-1-301a.	02May2011	Inspiration
OBI-1-301/301a: Efficacy and Safety of OBI-1 in the Treatment of Acquired Hemophilia A Due to Factor VIII Inhibitory Auto-antibodies. Interim Study Report.	04Oct2013	Baxter
Investigator Brochure – Porcine Coagulation Factor VIII (Recombinant) (OBI-1) Edition 2.2	25Apr2013	Baxter

2. KNOWN SAFETY CONCERNS FOR PORCINE FVIII AND BDDrFVIII PRODUCTS

Should OBI-1 be approved by FDA, it would be the first recombinant porcine BDDrFVIII product licensed in the US. There is therefore little information available about the safety profile of this new subset of FVIII products. Safety information about OBI-1 submitted by Baxter in support of this BLA is reviewed in detail in section 4 below. Known safety concerns for porcine FVIII products and recombinant BDDrFVIII products are reviewed in sections 2.1 and 2.2 below respectively.

2.1 Known Safety Concerns for Porcine FVIII products

Hyate:C, the only porcine FVIII product previously licensed by FDA, was derived from porcine plasma and therefore carried a risk of transmission of infectious agents. In fact, Hyate:C is no longer produced due to concerns regarding transmission of PPV (Section 1.1.1). As OBI-1 is not derived from porcine plasma, the risk of transmission of porcine infectious agents is eliminated. However since the product is produced in -----(b)(4)-----, the risk of transmission of other infectious agents must still be considered.

The safety profile of Hyate:C was notable for two side effects – transfusion reactions and post infusion thrombocytopenia. Transfusion reactions were rare – estimated to occur following 3-7% of transfusions.² Risk factors include rapid infusion, bolus rather than continuous infusion and large doses. Post infusion thrombocytopenia is also thought to be dose related and is described as a slight drop in platelets of about 15% and usually of no clinical importance. The post infusion thrombocytopenia is thought to result from transient agglutination of platelets by porcine von Willebrand Factor (vWF) which co-precipitates out of porcine plasma during production of Hyate:C. Of note, since OBI-1 is not plasma derived, the concern for vWF mediated thrombocytopenia is minimal.

2.2 Known Safety Concerns for BDDrFVIII products

Known safety concerns for the entire class of FVIII products – particularly infectivity and immunogenicity – have led to changes in the manufacture of these products over time, culminating in the development of BDDrFVIII products, the newest subset of the class. This evolution in the manufacture of FVIII products is summarized in Table 3 below and the safety concerns of infectivity and immunogenicity are described in sections 2.2.1 and 2.2.2 below respectively.

Table 3. Summary Timeline of Historical Evolution to BDDrFVIII ^{6, 7, 10, 11}

Date	Event	
1960s	Plasma-derived FVIII concentrates become commercially available.	
1980s	HIV epidemic results in viral contamination of plasma-derived products and widespread infection of more than half of all hemophiliacs with HIV. ¹⁰	
1990s	Recombinant FVIII products become commercially available and are a popular alternative to plasma-derived concentrates due to the reduced risk of viral transmission. Each generation of recombinant products aims to further reduce the risk of viral transmission as follows:	
	Generation:	Recombinant product produced in hamster cells, use human albumin as a stabilizer
	Generation:	Recombinant product produced in hamster cells, eliminate human albumin as a stabilizer utilizing sterile laboratory-produced stabilizers such as a combination of sucrose and one or more amino acids
	Generation:	Recombinant product produced in cells which are cultured in the absence of human and animal proteins, utilize sterile laboratory-produced stabilizers such as a combination of one or more sugars, amino acids and /or peptides.
2000s	The first BDDrFVIII product ReFacto is licensed by FDA in 2000 – the greater stability of the smaller molecule eliminates the need for human albumin as a stabilizer. Xyntha and NovoEight are licensed in 2008 and 2013. Eloctate – a fourth BDDrFVIII is currently under review by FDA	

2.2.1 Transmission of infectious pathogens

Successive generations of FVIII products have sought to reduce the risk of transmission of viral pathogens by moving from plasma-derived to recombinant products and by minimizing the use of human or animal proteins in the manufacturing process (Table 3).

As with other recombinant products, BDDrFVIII products seek to offer a lower risk of transmission of viral pathogens than plasma-derived products. Unlike Xyntha, NovoEight and Eloctate which are generation products, OBI-1 will be a generation BDDrFVIII product – that is, a recombinant product manufactured in BHK cells which are grown in medium -----(b)(4)----- but avoiding the use of additional animal or human derived proteins in the final product, by using sucrose, polysorbate 80 and calcium chloride as stabilizers instead. The manufacture of OBI-1 includes dedicated viral removal or inactivation steps to reduce the risk of transmission of infectious pathogens.

2.2.2 Immunogenicity – FVIII inhibitors and Antibodies to non-human proteins

Published studies sponsored by Wyeth have evaluated the currently licensed Wyeth BDDrFVIII products for immunogenicity with regard to the development of both FVIII inhibitors and antibodies to non-human proteins. In addition, NovoNordisk and Biogen Idec have provided information regarding immunogenicity for NovoEight and Eloctate respectively. These findings are summarized in sections 2.2.2 (a) and 2.2.2 (b) below.

2.2.2 (a) FVIII inhibitors

The development of FVIII inhibitors has long been recognized as a safety concern for the class of FVIII products. While the etiology of the development of inhibitors to FVIII by patients with congenital hemophilia A has not been fully elucidated, it is thought to result from a host alloimmune response to infusions of FVIII.

Deletion of the B-domain results in a novel peptide sequence not found in plasma-derived FVIII. Early concerns that this novel sequence might function as an antigenic epitope and provoke increased production of antibodies to the BDDrFVIII molecule have not been borne out in clinical studies. An open-label observational study of Wyeth's licensed BDDrFVIII products followed 113 severe congenital hemophiliacs who were previously treated patients (PTPs) for a period ranging from 12 months up to 5 years and found an incidence of inhibitor formation of 0.9% following the use of BDDrFVIII products, consistent with that reported for full-length recombinant and plasma derived FVIII products.¹² A similar study evaluated previously untreated patients (PUPs). In an open-label multicenter study, 101 PUPS received prophylactic and/or treatment doses of BDDrFVIII products for a period ranging from 50 exposure days (ED) up to 5 years. Thirty-two percent of patients developed inhibitors, a rate comparable to that seen with full-length recombinant products.¹³

Prelicensure studies submitted by NovoNordisk in support of licensure for NovoEight, were similarly reassuring. Of 214 PTPs, only 1 study subject was found to have a single low titer inhibitor test.¹⁴ The study subject was negative for inhibitors on repeat testing and had no clinical evidence of bleeding. Similarly, prelicensure studies of Biogen Idec's product Eloctate identified only 1 out of 153 study subjects with a single low titer inhibitor test which was negative on repeat testing and resulted in no clinical evidence of bleeding.¹⁵ Evaluation of inhibitor development in PUPs receiving these products are planned by both companies and will occur in the postmarketing phase.

2.2.2 (b) Antibodies to non-human proteins

Another more recent safety concern has been the detection of antibodies to non-human proteins in subjects treated with recombinant biologics. It appears for instance, that even minor amounts of CHO proteins in the final formulation of therapeutics can potentially stimulate an immune response. The

clinical significance of the presence of these antibodies is unclear. It has however been suggested that any regions of these mammalian proteins that are homologous to human sequences may stimulate an immune response resulting in inhibition of the active pharmaceutical ingredient and perhaps diminish both the safety and efficacy of the final recombinant product.¹⁶

In an open-label observational study of 94 PTPs who received Xyntha, none tested positive for the presence of antibodies to CHO proteins.¹⁷ Of the 214 subjects in NovoEight's prelicensure trials, 4 patients seroconverted from negative to positive for CHO antibodies following exposure to NovoEight.¹³ However, there do not appear to be shared clinical findings among these 4 subjects to suggest a common syndrome attributable to *de novo* seroconversion from negative to positive for these antibodies. Like Xyntha and NovoEight, OBI-1 is produced in a hamster cell line. While it is clear that patients who receive this subset of FVIII products can develop antibodies to hamster proteins, the frequency of seroconversions seems to be rare and of unclear clinical significance.

In summary, the available published literature suggests that when evaluated for the known safety concerns for the class of FVIII products, such as risk of infection and immunogenicity, BDDrFVIII products have a safety profile comparable to or better than that of other products in the class.

3. PHARMACOVIGILANCE PLAN

3.1 Clinical Safety Database

The overall clinical development program submitted by Baxter for OBI-1 consists of a total of four clinical trials (Table 4). Of these four trials, two have been completed in the pre-licensure phase – OBI-1-101 and OBI-1-201 – and final study reports have been submitted to FDA in support of this BLA. Baxter has also submitted the interim study report for the Pivotal Trial which includes data from two studies – OBI-1-301 and OBI-1-301a. The two studies have identical protocols, however OBI-1-301a is an expanded access study intended to allow patients who cannot physically reach any of the OBI-1-301 study sites, but would otherwise be eligible for protocol OBI-1-301, to have emergency access to the study drug. The fourth study OBI-1-302 was terminated by the sponsor after a single study subject was treated. OBI-1 was used to support a surgical procedure in this subject and was reported to be effective in this subject for control of bleeding during and after the surgical procedure. During the treatment of the subject in study OBI-1-302, no clinically significant adverse safety issues were identified.¹⁸ Baxter reports that study termination was not due to safety or efficacy concerns. Of note, the study population matches the current proposed indication in only one of the four studies – the Pivotal trial. The study reports for OBI-1-101, OBI-1-201 and OBI-1-301/301a have been submitted. These are reviewed in detail in sections 3.1.1, 3.1.2, and 3.1.3 below, respectively.

Table 4. Study Subjects Enrolled in Prelicensure Studies of OBI-1

	OBI-1-101	OBI-1-201	OBI-1-301/301a	OBI-1-302
Study Type	Phase 1	Phase 2	Phase 2/3	Phase 3
Study Population	Congenital Hemophilia A with Inhibitors	Congenital Hemophilia A with Inhibitors	Acquired Hemophilia A	Congenital Hemophilia with Inhibitors
Study Status	Completed	Completed	Ongoing/Closed	Terminated
Study Description	PK and tolerability of OBI-1 vs Hyate:C	Safety, efficacy and PK of OBI-1	Pivotal/Expanded Access	Safety, efficacy and PK of OBI-1
Study Subjects (n)	4	9	18	1

3.1.1 Safety related data from Phase 1 trial OBI-1-101: OBI-1 vs Hyate:C

The pre-licensure Phase 1 trial OBI-101 has been completed by the sponsor. The final study report and published literature resulting from this study have been reviewed.¹ Safety related data from this study is summarized in Table 5 below.

Table 5. Summary of Phase 1 trial OBI-1-101: OBI-1 vs Hyate:C

Study Title:	Phase I Randomized, Parallel-Group, Blinded Comparison Study of the Safety, Tolerance and PK of OBI-1 vs Hyate:C When Administered as a Single Intravenous Injection to Subjects with an Inhibitor Antibody to FVIII, in the Non-Bleeding State				
Study Design:	Multicenter, randomized, blinded, parallel group comparison trial. Study subjects were randomized to receive a single dose of either Hyate:C followed by placebo or placebo followed by OBI-1 on Day 1 and were followed through Day 29 or longer as required by any medically significant laboratory value that had not returned to baseline.				
Eligibility criteria:	Individuals aged ≥ 12 yo in a non-bleeding state with congenital hemophilia A and a history of human anti-FVIII inhibitor antibody of any measurable value, and a low cross-reacting porcine anti-FVIII antibody titer of ≤ 20 BU				
Study Status:	Complete				
Study Objectives:	Objective:	• To compare the safety and tolerability of OBI-1 vs Hyate:C			
	Objective:	• To compare PK profile of OBI-1 with Hyate:C.			
Safety related endpoints:	<ul style="list-style-type: none"> • Medical history, physical examination, vital signs and laboratory tests were obtained each study day • Immune tolerance was assessed by measurement of antibody titers to human FVIII, OBI-1 and Hyate:C 				
Study Population (n=4):	Randomized to receive:	Age (y)	Race	Weight (kg)	Previous Hyate:C?
	Hyate:C				
	1	15	Black	55.3	N
	2	41	White	90.5	N
	3	44	White	81.0	N
	4	41	Black	57.0	Y
	5	36	White	83.6	N
	OBI-1				
	6	32	White	65.2	Y
	7	57	White	66.4	N
8	15	Black	68.6	N	
9	24	White	138.3	N	
Study Results:	VS, Lab, PE monitoring	No subject had a clinically significant change from baseline			
	AE monitoring	2 infusion related AEs reported both of which resolved – 1 report of chest heaviness and hypotension during Hyate:C infusion, and 1 report of chest pain during infusion of placebo			
	Immunogenicity	No apparent difference between the two study products in terms of immunogenicity			
Conclusion:	The authors conclude that OBI-1 is safe and well tolerated among hemophiliacs with inhibitors who receive the drug				

Immunogenicity results reported for this study were studied closely and are summarized in Table 6 below. All 9 study subjects were tested for antibodies to Hyate:C, OBI-1 and human FVIII both prior to receipt of the study drug and at day 29 of follow up.

Table 6. Anti-FVIII inhibitor titers at baseline and 29 days after receiving OBI-1 or Hyate:C.

Study Drug Received	Study Subject	Prior exposure to Hyate:C?	FVIII Inhibitor titers (BU/mL)					
			Anti-Hyate:C		Anti-OBI-1		Anti-human FVIII	
			Day 0	Day 29	Day 0	Day 29	Day 0	Day 29
Hyate:C	1	N	<0.8	3.5	1.0	8.0	0.9	9.9
	2	N	6.5	58.5	13.1	112.0	21.5	180.0
	3	N	<0.8	2.1	<0.8	2.2	20.3	52.8
	4	Y	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8
	5	N	10.7	15.0	14.6	24.3	21.6	25.9
OBI-1	6	Y	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8
	7	N	4.9	40.3	10.6	49.9	31.6	153.0
	8	N	<0.8	<0.8	<0.8	<0.8	7.4	8.7
	9	N	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8

On day 0, prior to receipt of the study drug, 4 of the 9 study subjects tested positive for antibodies to Hyate:C, OBI-1 or both (shaded gray in Table 3 above), and 5 did not. Of the 4 study subjects who tested positive for anti-porcine FVIII products prior to receipt of the study drug, none had received Hyate:C in the past suggesting that the positive serologies are not attributable to past exposure to Hyate:C, but rather to prior possible exposure to other porcine products. In addition, all 4 had an increase in both anti-Hyate:C and anti-OBI-1 antibodies at day 29 of follow up even though 2 were randomized to receive Hyate:C and 2 received OBI-1. This finding may be a reflection of the similarity in molecular structure of the two products and may indicate some cross reactivity in the assays used to measure antibodies to the two porcine FVIII products.

Of the 5 study subjects who tested negative for anti-porcine FVIII products prior to receipt of the study drug (unshaded in Table 2), 4 remained negative at day 29 of follow up and 1 seroconverted (study subject 3), with a low positive titer for both Hyate:C (2.1 BU) and OBI-1 (2.2 BU) on the last day of follow up. This study subject also had a significant increase in anti-human FVIII titers by day 29 of follow up. Cross reactivity among all three assays used to measure anti-FVIII titers may account for this finding.

3.1.1 Safety related data from Phase 2 trial OBI-1-201: Safety, Efficacy and PK of OBI-1

The pre-licensure Phase 2 trial OBI-201 has been completed by the sponsor. The final study report has been reviewed and safety related data from this study is summarized in Table 7 below.

Table 7. Summary of Phase 2 trial OBI-1-201: Safety, Efficacy and PK of OBI-1

Study Title:	An Open-Label Study of the Hemostatic Activity, PK and Safety of OBI-1 when Administered by Intravenous Injection, to Control Non-Life and Non-Limb Threatening Bleeding Episodes in Congenital Hemophilia A Patients with an Inhibitor to Human FVIII
Study Design:	This was a prospective, open-label, non-comparative study.
Eligibility criteria:	Age > 12 years (for non-Russian Sites) and Age 18 years (for Russian Sites only); • Clinical diagnosis of congenital hemophilia A with inhibitors to human FVIII;

	<ul style="list-style-type: none"> • Ineligible for treatment with human FVIII; • OBI-1 inhibitor antibody titer > 20 Bethesda Units (BU) at screening; • Uncomplicated joint or soft tissue bleed, or other non-life threatening or non-limb threatening bleeding episode (except at the Screening Visit); 	
Study Status:	Complete	
Study Objectives:	Objective:	<ul style="list-style-type: none"> • To evaluate the hemostatic activity of OBI-1
	Objective:	<ul style="list-style-type: none"> • To assess the safety of OBI-1, PK of OBI-1 and serial anti-OBI-1 and anti-human FVIII inhibitor antibody responses
Safety related endpoints:	<ul style="list-style-type: none"> • Medical history, PE, VS and laboratory tests • Monitoring of anti-BHK antibody titers and of inhibitory antibody titers to both human and porcine FVIII 	
Study Population (n=9)		(n)
	Study Subjects	
	Received OBI-1	9
	Completed study	7
	Withdrew	2
	Sex	
	M	9
	F	0
	Race	
	White	3
	Black	6
		Mean
	Age (y)	23.7
	Weight (kg)	64.72
Height (cm)	172.23	
Study Results:	VS, Lab, PE monitoring	<ul style="list-style-type: none"> • Within normal parameters for all study subjects
	AE monitoring	<ul style="list-style-type: none"> • 7 subjects reported 18 AEs of which 3 were SAEs reported by 3 subjects – groin pain, L knee hemarthrosis, R knee hemarthrosis • No AEs led to treatment interruption, discontinuation from study or death
	Immunogenicity	<ul style="list-style-type: none"> • 8 of 9 (89%) subjects developed anti-porcine FVIII antibodies following exposure to OBI-1 • High anti-porcine FVIII did not affect efficacy or increase AEs • 5 subjects had a higher anti-human FVIII inhibitor titer at the end of the study • No BHK antibody detected in any study subject
Conclusion:	OBI-1 was safely administered and well tolerated by all study subjects	

Immunogenicity data provided in this study was reviewed in greater detail and is summarized in Table 8 below. The three study subjects who received the highest cumulative dose of OBI-1 and had the greatest number of exposure days (shaded gray in Table 8), do not appear to have the largest increase in anti-porcine FVIII titers, suggesting that development of these antibodies may not be dose related.

Table 8. Immunogenicity data from Phase 2 trial OBI-1-201: Safety, efficacy and PK of OBI-1

Subject Number	Cumulative Dose (U/kg) +Loading Dose	Cumulative Dose (U)	Total Exposure (days)	Anti-porcine FVIII Titer (BU/mL)		Anti-human FVIII Titer (BU/mL)	
				Titer at Bleed	Last Known Measurement	Titer at 1st Bleed	Last Known Measurement
(b)(6)	150	9600	1	<0.8	2.4	<0.8	<0.8
(b)(6)	274	17380	2	<0.8	5.1	<0.8	4
(b)(6)	2260	137404	8	1.2	10.3	8.4	9.2
(b)(6)	1498	120852	4	1.1 and <0.8	8.5	3.8 and 0.9	8.4
(b)(6)	243	19168	1	6.2 and 2.2	22	14 and 9.8	51.9
(b)(6)	516	28312	3	<0.8	5.7	2.3	1.4
(b)(6)	2204	87471	4	4.2 and 4	6.8	5.3 and 5.5	1.7
(b)(6)	314	20724	1	5.6	13.2	15.7	16.7
(b)(6)	50	4750	1	<0.8	<0.8	<0.8	<0.8

3.1.3 Safety related data from Phase 2/3 trial OBI-1-301/301a: Pivotal Trial

The Phase 2/3 trial OBI-301/301a is currently ongoing. The interim study report has been reviewed and safety related data from this study is summarized in Table 9 below.

Table 9. Summary of Phase 2/3 trial OBI-1-301/301a: Pivotal Trial

Study Title:	Efficacy and Safety of OBI-1 in the Treatment of AHA Due to FVIII Inhibitory Auto-antibodies	
Study Design:	International, prospective, nonrandomized, open-label	
Eligibility criteria:	Males or females aged ≥18 years with a clinical diagnosis of AHA, a serious bleeding event and anti-OBI-1 titer is ≤20 BU.	
Study Duration:	10Nov2010 to current	
Study Status:	Ongoing	
Goal enrollment:	28	
Study Objectives:	<ul style="list-style-type: none"> • To evaluate the efficacy of OBI-1 for the treatment of serious bleeding events in subjects with AHA • To evaluate the safety of OBI-1 including anti-OBI-1 inhibitor monitoring • To assess the correlation between total dose, outcome and preinfusion anti-OBI-1 inhibitor titer • To determine the required dosage and proportion of bleeding events controlled with OBI-1 therapy • To assess the efficacy of OBI-1 at designated time points after the initiation of therapy • To assess drug exposure 	
Safety related endpoints:	PE, VS and lab monitoring including anti-human FVIII, anti-OBI-1 and anti-BHK antibody titers; AE monitoring	

Study Population (as of 6Jun2013; n=18)	Study Subjects (n)	
	Study Protocol:	
	OBI-1-301	15
	OBI-1-301a	3
Study Completion Status:		
	Completed	11
	Status not verified	1
	Early termination	6
Reason for early termination:		
	AEs (Death due to ICH, GI bleed, sepsis)	3
	Other (anti-OBI inhibitor, death due to renal failure)	2
	Lack of efficacy (secondary bleed)	1
Gender:		
	M	10
	F	8
Race:		
	White	12
	Black	5
	Asian	1
		Mean
	Age (y)	71
	Weight (kg)	73.96
	Height (cm)	168.6
Study Results:	PE, VS and lab monitoring	Abnormal hematology and chemistry laboratory results were observed in all subjects and were considered consistent with underlying comorbidities and unrelated to study drug.
	AE monitoring	5 deaths occurred and 4 were considered unrelated – 2 deaths due to bleeding, 2 due to infection, and 1 due to renal failure. 9 subjects reported 19 SAEs, of which 3 were considered related to OBI-1 by investigators – Pneumonia , Atrial fibrillation, ICH.
	Immunogenicity	1 subject was positive for anti-porcine FVIII antibodies and developed an increase in titer after OBI-1. 3 subjects seroconverted from negative at baseline for anti-porcine FVIII antibodies to positive after treatment. None of the subjects developed anti-BHK antibodies.
Conclusion:	The sponsor concludes that OBI-1 was safe and well tolerated, that the 3 SAEs considered related by investigators were actually unrelated to OBI-1.	

Safety related data including reports of deaths, and information on immunogenicity and AEs of interest were reviewed in detail and are summarized in sections 3.1.3.1, 3.1.3.2 and 3.1.3.3 below.

3.1.3.1 Deaths and SAE related to OBI-1 reported in OBI-1-301/301a – Pivotal trial

3.1.3.1 (a) - Deaths

A total of 5 deaths were reported and the AEs leading to death are summarized in Table 10 below. The AEs leading to death were considered unrelated to OBI-1 in 4 of the deaths and probably unrelated or remotely related to OBI-1 in one case – Intracranial Hemorrhage in subject -(b)(6)-.

Table 10. Summary of deaths reported in OBI-1-301/301a – Pivotal trial

Subject Number	Age (y)	Sex	AE leading to death (Preferred Term)	AE Duration (Days)
-(b)(6)-	74	Female	Sepsis	7
-(b)(6)-	70	Female	Haemorrhage intracranial	1
-(b)(6)-	86	Male	Renal failure	5
-(b)(6)-	79	Female	Systemic mycosis	8
-(b)(6)-	61	Male	Intestinal haemorrhage	2

-(b)(6)- - 74 yo Black female enrolled in Study OBI-1-301 after she presented with a qualifying bleed and required perioperative management for fasciotomy of R lateral thigh compartment syndrome. On 19Jun2012 she received the first dose of OBI-1. Response to therapy at 24 hours was considered partially effective and bleeding was reduced. Post-procedure the patient received daily infusions with initial improvement in hemoglobin. The subject experienced 1 AE of device occlusion after OBI-1 which was considered possibly related to the study drug and resolved. On 20Jul2012, she developed a UTI which progressed to urosepsis despite antibiotic therapy. She died on ----(b)(6)----, due to the event of sepsis which the investigator considered unrelated to therapy with OBI-1.

-(b)(6)- - 70 yo Black female enrolled in Study OBI-1-301 after she presented with AHA and a primary qualifying bleed of bilateral subdural hematomas from a subdural hematoma drain. The initial dose of OBI-1 therapy was administered on 19Aug2012. Response to OBI-1 at 24 hours was considered partially effective and bleeding was reduced. The subject subsequently received additional infusions but experienced intracranial hemorrhage 2 days after the first dose which resulted in interruption of study drug administration and ultimately the subject's death.

-(b)(6)- - 51 yo White female who was enrolled in Study OBI-1-301 after she presented with an intramuscular bleed and compartment syndrome in the upper left arm after placement of an IV line after surgery. The initial dose of OBI-1 on 13Jan2011 and response to OBI-1 at 24 hours and at subsequent assessments was considered effective. She continued to receive daily infusions but developed renal failure 11 days after the first dose and ultimately died.

-(b)(6)-- 79 year old White female enrolled in Study OBI-1-301 after she presented with retroperitoneal and iliopsoas hematomas. The first infusion of OBI-1 was administered on 30Aug2011 and response at 24 hours was considered effective. The subject continued to receive daily infusions with improvement in anemia. The subject experienced 3 SAEs, all with an onset 71 days after the initial dose and all considered not related to study drug. Pneumonia and a urinary tract infection were treated and resolved. A severe systemic mycosis infection resulted in the subject's death

-(b)(6)- - 61 yo Caucasian male with cecal mass and liver metastases enrolled in OBI-1-301 after he presented with a qualifying bleeding event after hemi-colectomy. The initial dose of OBI-1 was administered on 16Jan2012 and OBI-1 was continued over the next 8 days. Response to OBI-1 was judged to be effective, with bleeding stopped. On 23Jan2012 the subject had an anti-OBI-1 titer of 8 BU resulting in withdrawal from the study. OBI-1 was discontinued and he was placed on rescue therapy. The subject suffered a SAE of intestinal hemorrhage resulting in death after withdrawal from the study and subsequent treatment with FEIBA. This SAE was not considered related to study drug. The subject suffered a total of 5 non-SAEs after treatment including the development of anti-OBI-1 titer, elevated neutrophils, elevated white blood cells, infection of wound site, and jugular venous clot. All of these AEs

were mild or moderate in severity and all AE (with the exception of the development of anti-OBI-1 titer) were considered unrelated to the study drug.

3.1.3.1 (b) SAE that may be related to OBI-1

Study investigators considered a total of 3 SAE in 2 study subjects to be remotely related or probably unrelated to OBI-1 – Pneumonia, Atrial fibrillation and ICH (Table 11). The narrative for subject (b)(6) is reviewed in section 3.1.3.1 (a) above. The narrative for subject -(b)(6)- was also reviewed in detail and is summarized below.

Table 11. Summary of SAEs that may be related to OBI-1 reported in OBI-301/301a – Pivotal trial

Subject	Sex	Age (y)	SAE (Preferred Term)	Duration	Relationship	Intensity	Outcome
(b)(6)	M	66	Atrial fibrillation Pneumonia	Ongoing 6 days	Probably unrelated/remote Probably unrelated/remote	Mild Moderate	Ongoing Resolved
(b)(6)	F	70	Brain oedema Haemorrhage intracranial	2 days 1 day	Not related Probably unrelated/remote	Life- threatening Life- threatening	Resolved Death

(b)(6) - 66 yo Black male who presented with a qualifying bleed of the R hand with severe pain and limited range of motion received the initial dose of OBI-1 on 23Jan2012. Response to OBI-1 at the target bleed at 24 hours was considered effective and bleeding stopped. The subject received an additional dose days after the first dose due to a recurrent bleed of the right hand with improvement. 11 days after the first dose, he developed pneumonia which resolved with treatment and Atrial fibrillation which was treated but did not resolve. Both SAEs were considered remotely related or probably unrelated to OBI-1 by the study drug.

3.1.3.2 Safety related immunogenicity data in OBI-1-301/301a – Pivotal trial

3.1.3.2 (a) – Anti-porcine inhibitors

Of the 18 study subjects, 6 had detectable anti-porcine inhibitors at baseline and 12 did not. Of the 6 subjects positive for anti-porcine inhibitor titer at baseline, 3 had no detectable anti-porcine titer after dosing, 2 had a decrease in titer and 1 had an increase from 3 to 6 BU/ml. The narrative of the study subject with an increase in OBI-1 titer after dosing – subject (b)(6), has been reviewed in detail and summarized in section 3.1.3.1 above.

Twelve subjects had no detectable anti-porcine inhibitor titer at baseline. Of these 12 subjects, 7 remained negative after dosing, 2 had no additional measurements and 3 had an increase in titer. The narratives for the 3 subjects with *de novo* seroconversions from undetectable to positive for anti-porcine inhibitors after OBI-1 have been reviewed in detail. The narratives of 2 of these subjects – subjects ---(b)(6)----- are summarized in section 3.1.3.1 above. The narrative of subject (b)(6) – the third subject with *de novo* seroconversion from undetectable to positive for anti-porcine inhibitors – is summarized below:

(b)(6) - 51 yo Caucasian man with tonsillar squamous cell carcinoma with multiple lung nodules presented with a qualifying bleed following PEG tube placement. The initial dose of OBI-1 was administered on 25Feb2012 and continued through 05Mar2012. Assessments of response to OBI-1 24 hours after initial dose and following subsequent doses, were considered effective with bleeding stopped. The subject completed OBI-1therapy as a treatment success on 05Mar2012 but presented with a second bleed in the left psoas and received a second dose of OBI-1 on 14Mar2012 which was not effective. The subject’s anti-porcine inhibitor titers were undetectable at screen but he was found to have anti-OBI-1 titers of 22BU on 14Mar2012 and 87 on 19Mar2012. The development of a positive anti-OBI-1 titer resulted in discontinuation of the subject from the study. Of note, the subject’s anti-human FVIII levels

also increased from 24 BU at screening to 169 BU at termination. The development of anti-OBI-1 inhibitor was considered mild and definitely related to study drug.

3.1.3.2 (b) – Anti-BHK antibodies

A total of 16 subjects had anti-BHK antibodies tested at baseline and 13 subjects had follow-up samples drawn. A single subject had a positive result for anti-BHK prior to the first dose but tested negative 3 months later.

3.1.3.3 Other AEs of interest – Thrombotic events and Thrombocytopenia

Adverse events known to occur with currently available treatments for AHA such as NovoSeven and FEIBA include thrombotic events. Thrombocytopenia has been described with the porcine plasma derived product, Hyate:C.

3.1.3.3(a) Thrombotic events

A total of 3 study subjects experienced thrombotic events. Subject (b)(6) developed occlusion of a PICC line which was considered possibly related to the study drug and eventually resolved (section 3.1.3.1 above). Subject (b)(6) a patient with underlying malignancy, developed a jugular thrombus after being switched from OBI-1 to FEIBA (section 3.1.3.1 above). Subject (b)(6) is a 62 yo White man with HTN, uncontrolled DMII and coronary artery disease who had a TIA two weeks after starting OBI-1 for a right upper extremity hematoma. The TIA was considered unrelated to the study drug and resolved with treatment.

3.1.3.3(b) Thrombocytopenia

A single study subject (b)(6) developed moderate thrombocytopenia one day after starting the study drug. The thrombocytopenia resolved after discontinuing cyclophosphamide.

3.2 Pharmacovigilance Plan

Baxter has submitted a Pharmacovigilance Plan for OBI-1 which is summarized in Table 12 below. In addition to routine pharmacovigilance, Baxter proposes a registry to collect and assess data on the treatment, safety, and outcomes of subjects with AHA who receive OBI-1. The registry protocol has been reviewed and is summarized in section 3.2.1 below.

Table 12. Summary of Pharmacovigilance Plan for OBI-1

Safety Concern	Planned action(s)
Important Identified Risks	
Inhibitory antibodies to OBI-1	<ul style="list-style-type: none"> • Routine Pharmacovigilance • OBI-1 Treatment Registry
Important Potential Risks	
Hypersensitivity and allergic reactions	<ul style="list-style-type: none"> • Routine Pharmacovigilance • OBI-1 Treatment Registry
Lack of efficacy due to neutralizing inhibitory antibodies	<ul style="list-style-type: none"> • Routine Pharmacovigilance
Important Missing Information	
Use in subjects <18 years old	<ul style="list-style-type: none"> • Routine Pharmacovigilance
Use in pregnancy and lactation	<ul style="list-style-type: none"> • Routine Pharmacovigilance

3.2.1 Proposed OBI-1 Treatment Registry

The protocol for the Treatment Registry proposed by Baxter has been reviewed and is summarized in Table 13 below.

Table 13. Summary of Protocol of Planned OBI-1 Treatment Registry

Study Title:	OBI-1 (Recombinant Porcine Sequence FVIII) Treatment Registry; Protocol Number 241302	
Study Design:	Post-authorization, prospective, uncontrolled, non-interventional, multicenter study. Data will be collected over a period of 90 days follow up after the last OBI-1 treatment dose. Treatment regimen, frequency of laboratory and clinical assessment including measurement of anti-porcine FVIII antibodies and anti-human FVIII antibodies, will occur at the discretion of the treating physician. There will be no required predefined visits, medical tests, laboratory tests and/or procedures, or interventions during the Registry's duration	
Inclusion criteria:	<ul style="list-style-type: none"> Male or female subjects ≥ 18 yo with AHA who have been prescribed OBI-1 for the management of bleeding episodes as part of routine practice 	
Exclusion criteria:	<ul style="list-style-type: none"> Known anaphylactic reactions to the active substance, to any of the excipients, or to hamster protein Concomitant bleeding disorders other than AHA Participation in another clinical study involving an investigational product or device 	
Study Duration:	4 years	
Study Status:	To be launched December 2014	
1° Objectives:	<ul style="list-style-type: none"> Assess the safety of OBI-1 based on incidence of all serious AEs (SAEs) and related AEs 	
2° Objectives:	<ul style="list-style-type: none"> Describe effectiveness of OBI-1 in the treatment of bleeding episodes Determine dosing of OBI-1 required to control bleeding episodes Identify concomitant medications used during routine treatment with OBI-1 Identify presenting symptoms of AHA, patient co-morbidities, time to diagnosis, and time from diagnosis to first treatment with OBI-1 Describe the immunogenicity of OBI-1 during the course of treatment 	
Goal enrollment:	40	
Safety related endpoints:	<ul style="list-style-type: none"> Incidence and severity of both serious and therapy related non-serious AEs Incidence of <i>de novo</i> seroconversion from negative to positive for anti-porcine FVIII inhibitors (provided there is sufficient data collected as part of routine practice) 	
Estimated Milestones:	First subject in	December 2014
	Last subject out	December 2018
	Completion of Interim report	N/A
	Completion of Final report	June 2019

4. INTEGRATED RISK ASSESSMENT

4.1 Limitations of the Clinical Safety Database

4.1.1 Study population

The proposed indication for OBI-1 is for use in AHA. However, 3 of the 4 clinical trials in the clinical safety database were conducted in a different study population – congenital hemophiliacs with inhibitors (Table 4). Although bleeding is mediated by inhibitory antibodies in both populations, the two groups vary demographically with regard to age, gender and medical comorbidities. Patients with AHA are likely to be older and may have more comorbidities than congenital hemophiliacs.⁸ In addition, because hemophilia A is an X-linked disease, congenital hemophiliacs are almost exclusively male. By contrast, both males and females can be affected by AHA, with a larger number of women than men affected in the

20-40 age range due to pregnancy related AHA.⁸ For these reasons, it may be suboptimal to comingle safety data from these two populations. Of note, should congenital hemophiliacs be excluded from the clinical safety database, the total population of study subjects would drop by 44% from 32 to 18 study subjects, making an already small sample size even smaller and requiring even greater care in interpretation of the significance of the reported study results.

Following a request from information from Baxter, the sponsor has acknowledged that the two study populations are distinct. The rationale for including data from all three studies is that the early Phase 1 and 2 studies were conducted in patients with congenital hemophilia, while the pivotal Phase 2/3 study was conducted in patients with AHA. Baxter has provided data across the entire clinical program in accordance with guidelines from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). However, Baxter intends that the package insert for OBI-1 should reflect only the experience with OBI-1 in the AHA population.

4.1.2 Estimates of Mortality

All-cause mortality in the OBI-1-301/301a Pivotal trial can be calculated as 5 of 18 or 28%. However, this estimate of all-cause mortality is likely confounded by the underlying serious comorbidities of the study subjects. Of the 5 deaths reported in the study, 4 were thought to be unrelated to OBI-1 and only 1 was thought to be remotely related or probably unrelated to the study drug (study subject (b)(6), section 3.1.3.1 above). Briefly, the subject developed intracranial hemorrhage (ICH) due to AHA, and initially responded to OBI-1 but eventually died due to the recurrence of ICH from the underlying disease. Thus none of the deaths in the study can be directly attributed to OBI-1, resulting in a relatively low estimate of mortality due to the study drug.

4.2 Assays used for Antibody Detection

4.2.1 Detection of Anti-porcine FVIII antibodies

Data submitted by the sponsor indicates that study subjects can test positive for anti-porcine FVIII antibodies despite no prior exposure to porcine FVIII (Table 6), suggesting that the assay used to detect anti-OBI-1 antibodies may not be specific to porcine FVIII. In addition, patients who develop an increase in anti-porcine FVIII antibodies, also develop an increase in anti-human FVIII antibodies and *vice versa* (Table 6). This finding may indicate cross-reactivity in the assays used to detect anti-porcine FVIII and those used to detect anti-human FVIII antibodies. The results of these assays should therefore be interpreted with caution and the assays used in these studies should be independently validated for accuracy and reproducibility.

Of note, the clinical significance of antibodies to porcine FVIII products remains unclear as no clinical syndrome common to study subjects who test positive has been described. The 3 study subjects who seroconverted from undetectable to positive for anti-porcine antibodies in the Pivotal trial do not appear to share similar adverse event profiles, underlying diagnoses or study outcomes (section 3.1.3.2).

4.2.2 Detection of Anti-human FVIII antibodies

Of note, the different kinetics of the autoantibodies to human FVIII in AHA may result in underestimation of antibody titers in these patients. The alloantibodies to human FVIII that develop in congenital hemophiliacs and the autoantibodies that develop in AHA follow different kinetics. Most inhibitors in congenital hemophilia follow Type 1 kinetics in that there is linear inactivation when the logarithm of the residual FVIII activity is plotted against plasma concentration. Alloantibodies completely neutralize FVIII when present in high concentrations. By contrast most autoantibodies follow Type 2 kinetics, meaning that they produce a nonlinear inactivation pattern and do not completely inactivate FVIII, even at the highest concentrations of inhibitor plasma. For this reason, the Bethesda assay which

quantifies the *in vitro* inhibitor titer, may underestimate the inhibitor potency of antibodies in AHA thus complicating therapeutic choices and monitoring.⁸

4.3 Limitations of Postmarketing Surveillance

In addition to routine surveillance, the sponsor proposes a Treatment Registry as part of the postmarketing surveillance of OBI-1 (Table 13). For patients enrolled in the Registry, the treatment regimen and the frequency of laboratory and clinical assessments will occur at the discretion of the treating physician. This unstructured approach to data collection may result in incomplete or inaccurate data. For example, one of the safety related endpoints in the Registry protocol is to determine the incidence and severity of both serious and therapy related non-serious AEs. If the frequency of assessment for AEs and the reporting of AEs is not mandatory, the calculation of the incidence of AEs may not be accurate.

The incidence of *de novo* seroconversion from negative to positive for anti-porcine FVIII inhibitors is also listed as a safety-related endpoint in the Registry protocol, provided there is sufficient data collected as part of routine practice. Since it is unclear that the assay to detect anti-porcine FVIII inhibitors is commercially available or that it will be made available to practitioners by the sponsor, the likelihood that testing for these inhibitors will occur as part of routine practice seems unlikely. If this is the case, the Registry is unlikely to meet this prespecified endpoint and may therefore provide limited information with regard to the incidence of development of anti-porcine FVIII inhibitors. Following an information request to the sponsor, Baxter reports that they have agreed to provide an OBI-1 substrate to clinical laboratories upon request in order to assay for porcine FVIII inhibitors. Baxter also notes that the assay methodology is the same as that used for the Bethesda assay which is routinely available in clinical practice and that no additional training of laboratory personnel is required.

While the limitations of the proposed Treatment Registry may result in limited information, it is important to note that any additional safety information provided by the registry is of value. Because OBI-1 is the first FVIII product indicated for management of AHA, and the only recombinant porcine FVIII product manufactured, there is little information available for this subset of products. In addition, while the Registry may not produce optimal results, it is also important to note that a structured study with a more rigorous protocol is unlikely to be feasible. Given the rarity and severity of AHA, the patient population is likely to be both small in number and severely ill. A mandatory requirement for frequent, precise and complete reporting, places an additional burden on physicians treating acutely ill patients, resulting in yet another barrier to study recruitment from an already small patient population. For these reasons, the proposed Registry may be an imperfect but adequate means of enhancing surveillance of OBI-1 and providing some additional safety related information for this new subset of products.

5. RECOMMENDATIONS

At this time OBE agrees with the planned activities listed in the PVP – routine pharmacovigilance as well as enhanced pharmacovigilance via the proposed Treatment Registry. In addition, at this time the available data do not suggest a safety concern that would necessitate either a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study.

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