



Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research



Pharmacology / Toxicology Primary Discipline Review

To: File (Original BLA 125512/0)

From: La’Nissa A. Brown, PhD, Pharmacologist, Division of Hematology Clinical Review (DHCR)/Office of Blood Research and Review (OBRR)

Through: Anne M. Pilaro, PhD, Supervisory Toxicologist, DHCR/OBRR

Subject: STN 125512/0 – Baxter’s Original Biological License Application (BLA) for Obizur (OBI-1), Antihemophilic Factor (Recombinant), Porcine Sequence

Indication: Treatment and prevention of bleeding episodes in adult patients with acquired hemophilia A (i.e., inhibitory antibodies to human Factor VIII)

This memorandum is the final primary review of the nonclinical program based on the pharmacology and toxicology data submitted in the Original Biological License Application (BLA) for Baxter’s OBI-1 (tradename Obizur), Antihemophilic Factor (Recombinant), Porcine Sequence. Obizur is indicated for the treatment and prevention of bleeding episodes in adult patients with acquired hemophilia A (i.e., inhibitory antibodies to human Factor VIII). From the toxicology/pharmacology reviewer’s perspective, this original BLA STN 125512/0 is recommended for approval.

I. Background

Inspiration Biopharmaceuticals and -----(b)(4)-----, initially developed Obizur (OBI-1), a recombinant porcine Factor VIII, beta-domain deleted, produced through recombinant DNA technology using a baby hamster kidney (BHK) cell-line. Obizur was developed for the treatment and prevention of bleeding episodes in adult patients with acquired hemophilia A. Baxter purchased OBI-1 from the previous Sponsors, and will be its manufacturer as well as the Applicant for the product in this BLA. OBI-1 will be administered to patients with acquired hemophilia A as a more effective means of replacement therapy than currently marketed Factor VIII (FVIII) products.

Hemophilia A is a recessive, sex-linked hereditary disease characterized by congenital FVIII deficiency, and is usually treated by replacement therapy with clotting Factor VIII. Although adverse events do occur from repeat FVIII use including thromboembolic events, anaphylactic (allergic) reactions, antibody formation and increased inhibitor titers, the longstanding use and efficacy of FVIII therapy substantiate its usefulness in the treatment of congenital hemophilia A.

By contrast, acquired hemophilia A is rare bleeding disorder, in which patients with normal FVIII expression spontaneously develop autoantibodies directed against coagulation FVIII. Historical data

demonstrate that FVIII replacement therapy is the most widely utilized and effective therapy to treat bleeding episodes and prevent the morbidities that occur in patients with acquired hemophilia A. Baxter has submitted data from clinical trials conducted in 18 patients (of a proposed 28, total) with acquired hemophilia that demonstrate safety and efficacy of OBI-1 in the treatment or prevention of bleeding episodes in this population, and is using those data as the basis for this BLA submission.

Related Files: IND 10695 –b(4)-----

II. Proposed Use and Doses

Obizur (OBI-1; rPFVIII) will be administered intravenously to adult patients with acquired hemophilia A (i.e., inhibitory antibodies to human Factor VIII [FVIII]), for the treatment and prevention of bleeding episodes. The dose will be determined by the treating physician based on each patient's FVIII levels after initial dosing, the severity of bleeding, and the patient's clinical condition. The recommended initial clinical dose is 200 U/kg, with subsequent doses titrated to maintain trough FVIII levels in an effective range.

III. Recommendations

Nonclinical studies to evaluate the general pharmacologic activity, pharmacokinetics, safety and toxicity of Obizur for the proposed indication were included in the BLA submission. This product is also indicated for an orphan drug designation.

Based on review of the submitted pharmacology/toxicology data, this original biological application STN 125512/0 is recommended for approval. The clinical trials completed using Obizur further support the intended use of this product. There were no nonclinical deficiencies identified in this submission, and there are no requests for any further nonclinical evaluations at this time. There are no outstanding issues from the nonclinical standpoint to prevent approval of this BLA.

IV. Summary Basis for Regulatory Action (SBRA) for Nonclinical Data

Official Summary Basis for Regulatory Action (SBRA)

4. Non-clinical Pharmacology/Toxicology

General Conclusions

Obizur (Antihemophilic Factor (Recombinant), Porcine Sequence) was determined to be safe for its intended use in the treatment and prevention of bleeding episodes in adult patients with acquired hemophilia A (inhibitory antibodies to human Factor VIII) based on nonclinical data from Good Laboratory Practices (GLP)-compliant and non-GLP studies, and on its clinical use both within and outside of the United States. The nonclinical program consisted of a series of studies to demonstrate the safety and effectiveness of rPFVIII in animals including hemophilic mice and dogs, and wild-type FVIII expressing ---b(4)----- monkeys.

Pharmacological/Toxicological Findings

The Applicant (Baxter Inc.) has completed an extensive nonclinical program to demonstrate the safety and effectiveness of Obizur (Antihemophilic Factor (Recombinant), Porcine Sequence or *rPFVIII*). Based on data from GLP-compliant and non-GLP nonclinical studies, an adequate safety profile for rPFVIII has

been established to support its intended use in the treatment and prevention of bleeding episodes in adult patients with acquired hemophilia A (inhibitory antibodies to human factor VIII). Relevant animal models were employed including hemophilia A mice and dogs, and wild-type FVIII expressing mice and ---(b)(4)----- monkeys. To support the proposed clinical indications, the completed nonclinical program consisted of a series of studies to demonstrate the safety and effectiveness of rPFVIII in animals including: (a) safety pharmacology in hemophilia A mice and hemophilia A dogs, (b) proof of principle in hemophilia A mice and hemophilia A dogs, (c) acute toxicity in hemophilia A dogs and monkeys, (d) pharmacokinetics in monkeys and hemophilia A dogs, (e) repeat dose toxicity, with toxicokinetics, in mice and monkeys, (f) immunogenicity in hemophilia A mice and monkeys and (g) hemostatic activity of rPFVIII in hemophilia A mice and dogs..

Overall, the nonclinical safety profile of Obizur did not identify any unexpected findings or significant concerns; toxicities that were observed were due to exaggerated pharmacological effect of excess amounts of Coagulation Factor VIII, which are expected for products in this class. rPFVIII was tested acutely in animals at doses up to 1000 U/kg, (i.e., 5 times the intended starting perioperative clinical dose of 200 U/kg), without unexpected adverse events. Repeat-dose toxicity studies were completed with daily dosing of up to 1000 U/kg for up to 12 weeks (i.e., 13.3 times the intended, median prophylactic clinical dose of 75 U/kg) and the product was generally well-tolerated. Animal study results supported results from clinical trials investigating safety and efficacy of rPFVIII prophylaxis regimens. In animal studies, the exaggerated pharmacological effects of rPFVIII that were considered adverse included hypersensitivity, thrombogenic events and local reactions at the treatment site, and were reported after repeat dosing with rPFVIII doses 5-fold greater (i.e., 1000 U/kg rPFVIII) than the proposed clinical dose of 200 U/kg for use in the repeat dose setting. These findings were predictive for human use of the product, as confirmed by the adverse events reported in the clinical trial. Toxicokinetic profiles demonstrated a linear dose-dependent increase in the levels of porcine Factor VIII, followed by a time-dependent decrease in product levels. This profile was maintained until anti-product antibody formation occurred, resulting in decreased porcine Factor VIII activity. Although immunologic responses may occur in patients following repeated product administration and are a potential safety concern, the formation of anti-product antibodies in animals is not unexpected and is not predictive of an immunogenic response to rPFVIII in humans. There were no reports of neutralizing anti-Factor VIII antibodies or anaphylaxis in clinical trials of rPFVIII.

Based on the intended use of rPFVIII, nonclinical reproductive or developmental toxicity studies, long-term animal studies to evaluate carcinogenic potential, and studies to determine genotoxicity and effects of Obizur on fertility were neither required according to ICH guidelines nor performed. A toxicological risk assessment was completed on potential extractable and leachable impurities associated with the Obizur manufacturing process and container closure system. There were no concerns identified regarding these impurities, nor unexpected toxic effects that would require additional safety studies.

Recommendation: The results from the nonclinical program suggested that treatment of patients with acquired hemophilia A with Obizur will be reasonably safe for use for the labeled clinical indications. The Pharmacology/Toxicology Reviewer, La’Nissa A. Brown PhD, recommends that the Biological License Application (BLA) 125512/0 for Obizur be approved, based on the results from both the toxicological risk assessment, and the data from the nonclinical studies conducted by the Applicant.

IV. Nonclinical Labeling for the Package Insert (PI) for STN 125512/0

The label was revised to reflect current labeling guidelines and the relevant information for prescribing data based on nonclinical and clinical experience using Obizur.

Clean Revised Version of the Nonclinical Sections of the Label

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Obizur. It is also not known whether Obizur can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Obizur should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Obizur is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Obizur is administered in a nursing woman.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of Obizur or studies to determine the effects of Obizur on genotoxicity or fertility have not been performed.

Sections 12.3 Pharmacodynamics (nonclinical data only) and Section 13.2 Animal Toxicology and/or Pharmacology were removed.

FDA Revisions to Applicant's Label

Applicant's Language (Section edited):

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Obizur. It is not known whether Obizur can affect reproductive capacity or cause fetal harm when given to pregnant women. Administer Obizur to pregnant women only if clinically needed.

FDA Revision: Section 8.1 was modified to reflect labeling guidelines as per 21 CFR 201.57.

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Obizur. It is also not known whether Obizur can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Obizur should be given to a pregnant woman only if clearly needed.

Justification: Revised the language to be consistent with that provided in the CFR to describe the Pregnancy Category C designation for Obizur.

Applicant's Language (Section edited):

8.3 Nursing Mothers

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if Obizur is administered to nursing mothers. Use only if clinically needed.

FDA Revision: Section 8.3

8.3 Nursing Mothers

It is not known whether Obizur is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Obizur is administered in a nursing woman.

Justification: Revised the language to be consistent with that provided in the CFR to describe the risks of use of Obizur in nursing mothers.

Applicant's Language (Removed the entire Section 12.3, below):

12.3 Pharmacodynamics

Nonclinical studies with Obizur demonstrated hemostatic activity by dose-related control of bleeding using two animal models of hemophilia A. A single intravenous administration of Obizur in hemophilia A dogs shortened the cuticle bleeding time at doses of 25 or 100 units per kg. In the knock out mouse model of hemophilia A, Obizur produced 50% survival following a standardized tail snip hemorrhagic insult at an effective dose of 89 units per kg.

FDA Revision: Section 12.3

FDA Revision: Language immediately related to nonclinical data under the header for Section 12.3 was removed.

Justification: Removed nonclinical data in Section 12.3 due to redundancy with the clinical findings. The pharmacodynamic findings in animals are not essential for describing the clinical pharmacology; the Obizur product was evaluated for pharmacodynamic activity in clinical trials and the results and safety profile are appropriately described in the clinical sections of the label.

13. NONCLINICAL TOXICOLOGY

Applicant's Language (Section edited):

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies on the carcinogenic potential, reproductive and developmental toxicity, and genotoxic potential of the components of Obizur have not been performed.

FDA Revision: Section 13.1

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of Obizur or studies to determine the effects of Obizur on genotoxicity or fertility have not been performed.

Justification: Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility section was edited to convey important information that was omitted by the Applicant (i.e., an assessment of carcinogenic risk was performed, although in vivo animal carcinogenicity testing was not conducted), and needed to be added to the label.

Applicant's Language (Removed the entire Section 13.2, below):

13.2 Animal Toxicology and/or Pharmacology

Non-clinical safety pharmacology was assessed in the hemophilia A dog and in repeat dose toxicity studies in the ---(b)(4)---- monkey. In the hemophilia A dog, administration of Obizur did not affect heart rate or blood pressure. Correspondingly, in the ---(b)(4)---- monkey no effects on heart rate, respiratory rate, blood pressure and electrocardiograms were measured following repeat administration of Obizur up to dose levels of 825 or 1000 units per kg.

Repeat dose administration of Obizur at doses up to 825 units per kg over 90 days was well-tolerated in --(b)(4)---- monkeys.

FDA Revision: Language immediately under the header for Section 13.2 was removed.

Justification: Removed entire Section 13.2 due to redundancy. The product testing and findings in animals are not essential for clinical prescribing information; the Obizur product was evaluated in clinical trials and the results and safety profile are appropriately described in the clinical sections of the label.

V. General Comments

- Animal studies for carcinogenicity and fertility have not been conducted. These studies are not considered necessary for approval as per the ICH S6(R1) guidance, because Obizur is a recombinant, human protein and is not expected to directly interact with or damage DNA.
- There were no reproductive toxicity or teratogenicity studies conducted in animals using Obizur. These studies are not considered necessary for approval, because hemophilia A affects only male patients, and Obizur will not likely be used in pregnant women.
- There were no specific toxicity concerns identified for this product regarding impurities or unexpected toxic effects.
- There is clinical experience using this product, including in 18 patients (of the proposed 28 patients) in the clinical trials conducted to date. Clinical data and post-marketing data will be used in lieu of requesting additional nonclinical studies to support and corroborate the safety profile of Obizur for BLA licensure.

VI. List of Nonclinical Studies in STN BLA 125512/0

- 1. Study Report PCD-101:** Cross-over Comparative Study of the Efficacy and Pharmacokinetics of OBI-1 (B domain-deleted Recombinant Porcine Coagulation Factor VIII) and Plasma Derived Porcine Factor VIII (Hyate:C®) in a Canine Model of Hemophilia A
- 2. Study Report PCMU-101A:** Comparative Efficacy of Recombinant B-chain Deleted Porcine FVIII-OBI-1 and Hyate:C® in Hemophilia A Mice
- 3. Study Report PCM-104:** A Comparative pharmacokinetic Study of OBI-1 (B domain-deleted Recombinant Porcine Coagulation Factor VIII) and Plasma Derived Porcine Factor VIII (Hyate:C®) administered by Intravenous Injection to ---(b)(4)---- Monkeys

4. **Study Report PCM-102:** A Comparative 90-Day Toxicity Study of OBI-1 (B domain-deleted Recombinant Porcine Coagulation Factor VIII) and Hyate: C® (Plasma Derived Porcine Factor VIII) administered by Daily Intravenous Injection in ---(b)(4)----- Monkeys
5. **Study Report PCM-101:** A Dose-Escalation Tolerability Study of OBI-1 (B domain-deleted Recombinant Porcine Coagulation Factor VIII) Administered by Intravenous injection to ---(b)(4)----- Monkeys
6. **Study Report PCM-105:** A Comparative Immunogenicity Study, Up to 85 Days Administration of OBI-1 (B domain-deleted Recombinant Porcine Coagulation Factor VIII) Administered by Intravenous injection to ---(b)(4)----- Monkeys
7. **Study Report PCMU-102:** Comparative Immunogenicity of Recombinant B-chain Deleted Porcine FVIII-OBI-1 and Hyate:C® in Hemophilia A Mice Pre-sensitized to human Factor VIII

VII. Summary of Nonclinical Studies in STN BLA 125512/0

In summary:

PEL (pharmacologically effective level) = 1 U/kg

tSF (tentative safety factor) = approximately 5-fold over the NOAEL for the prophylaxis regimen proposed, using the clinical dose of 200 U/kg Obizur

NOAEL = 750 U/kg for repeat dose regimen and acute dosing regimen

Animal Model	Study purpose	Study Design	Observations
Mice	Repeat Dose Toxicity	4x's/wk., 1, 10, 100 U/kg	OBI-1 vs. Hyate similar response
Monkey	PK	Repeated Dose and PK n=60/5 gr.'s, 82, 450, 820 U/kg OBI-1 for 90 days	OBI was well tolerated with comparable pharmacokinetic properties to Hyate
Hemophilia A Dogs	Single Dose Toxicity	Cross over study, tolerance, PK	OBI-1 vs. Hyate:C similar properties
Hemophilia A Mice	Efficacy	Tail Clip at 10, 48, 76, 120, 190 U/kg doses	OBI-1 vs. Hyate:C similar properties & efficacy
Hemophilia A Mice	Immunogenicity	ELISA, 4x's/wk., 1, 10, 100 U/kg	OBI-1 Well tolerated
Monkeys	Immunogenicity	40 or 100 OBI-1 U/kg/dose or Hyate:C® at 100 U/kg/dose 85 Days	OBI-1 vs. Hyate:C well tolerated
Monkeys	Repeat Dose Toxicity	7-day at 100, 300, 600 & 1000 U/kg w/ NSC	OBI-1 vs. Hyate:C well tolerated

Monkeys	Repeat Dose Toxicity	90-Day at 1000 U/kg	OBI-1 vs. Hyate:C well tolerated
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There were no reproductive toxicity, genotoxicity or chronic/carcinogenicity studies conducted with OBI-1 as they are unwarranted, based on previous experience with currently marketed FVIII replacement products (according to Applicant) and on guidance provided by ICH S6(R1).

Hyate:C® is a plasma-derived porcine FVIII comparator that was withdrawn by FDA from the US market in 2005, due to lack of source material to make the product.

Study Report PCD-101: Cross-over Comparative Study of the Efficacy and Pharmacokinetics of OBI-1 (B domain deleted Recombinant Porcine Coagulation Factor VIII) and Plasma Derived Porcine Factor VIII (Hyate:C®) in a Canine Model of Hemophilia A

The aim of this study was to evaluate the efficacy and pharmacokinetics of OBI-1 rPFVIII (Lot 214-01-001) in congenital hemophilia A dogs using the cuticle bleeding time (CBT) model. The comparator Hyate:C® was administered in a cross-over manner to compare results in each animal. Hemophilic dogs were dosed intravenously with 3 µg/kg (n=3), 25 µg/kg (n=2), 100 µg/kg (n=4) OBI-1 or Hyate:C® in a total of 6 dogs. Efficacy was tested using the cuticle bleeding model, based on time to hemostasis from the initiation of cuticle bleeding. The following observations were monitored during this study: heart rate, respiration, body temperature, weight, overt toxicity, clotting activity (aPTT and whole blood clotting time [WBCT]), prothrombin time, fibrinogen, functional FVIII activity (one-stage and chromogenic assays) and fibrin degradation product (FDP; using the -----(b)(4)-----), complete blood count. Dosing with OBI-1 at 25 and 100 U/kg demonstrated a hemostatic effect by shortening the CBT in all treated dogs. The prolonged CBT was shortened by an average of 6.6 minutes in dogs dosed with OBI-1 in the dose range from 3 to 100 U/kg. Clinical observations, mortality, and behavior were monitored throughout the study. There were no adverse effects reported.

This study was completed in the -----(b)(4)----- in June 2002. The study was not conducted under GLP compliance due to study model feasibility.

The second part of this study investigated the pharmacokinetics of OBI-1 rPFVIII versus the comparator Hyate:C® using samples from the efficacy study described above. This second part of the study was completed under GLP compliance at ---(b)(4)----- in April 2008.

Blood samples were taken from the central auricular artery at 0 h, 15 min, 30 min, 60 min, 2 h, 4 h, 6 h, 8 h, 24 h, 32.5 h, and 48 h after dosing to assess the rPFVIII pharmacokinetic profile. The following non-compartmental pharmacokinetic parameters were evaluated using the chromogenic assay: Maximum concentration (C_{max} [IU/mL]), Timepoint of the peak maximum concentration (T_{max} [h]), elimination rate constant half-life ($t_{1/2 \lambda_z}$ [%]), area under the curve from time 0 to last experimental point (AUC_t [h×IU/dL], area under the curve from time 0 to infinity $AUC(0-\infty)$ [h×U/dL]), plasma Clearance ($CL_{(0-48)}$ [mL/h] and $CL_{(0-\infty)}$ [mL/h]), and volume of distribution (V_{ss} [mL]). The FVIII: antigen level was also assessed from collected samples. The results of the pharmacokinetic study are listed in the table below.

The table below is courtesy of Lillicrap et. al., 2002.

Parameter	OBI-1			Hyate:C		
	3	25	100	3	25	100
$AUC_{0-\infty}$ (U.h/dL)	157 ± 49.97	762, 1950	3399 ± 2569	22.1, 104	206, 425	1220 ± 506

C_{max} (U/dL)	20.9 ± 1.65	110, 141	466 ± 162	8, 9.10	33.0, 42.7	143 ± 5.65
T_{max} (h)	0.27 (0.25-0.50)	0.25, 1.0	0.25 (0.23-0.40)	0.25, 0.25	0.25, 0.50	0.38 (0.25-0.50)
CL (dL/kg/h)	0.023 ± 0.01	0.014, 0.036	0.049 ± 0.04	0.029, 0.136	0.059, 0.121	0.092 ± 0.034
V_{d_{ss}} (dL/kg)	0.184 ± 0.02	0.276, 0.28	0.429 ± 0.19	0.359, 0.380	0.758, 0.872	1.048 ± 0.31
T_{1/2} (h)	5.874 ± 1.97	5.785, 13.58	8.409 ± 1.90	1.839, 8.677	5.077, 9.079	9.257 ± 1.28

Study Report PCMU-101A: Comparative Efficacy of Recombinant B-chain Deleted Porcine FVIII-OBI-1 and Hyate:C® in Hemophilia A Mice

The objective of the study was to evaluate the acute efficacy of Recombinant B-chain Deleted Porcine FVIII-OBI-1 in comparison to plasma derived porcine VIII Hyate:C® using the tail clip bleeding model in hemophilia A (FVIII-deficient; Hem A) mice. Hemophilia A mice (FVIII knock-out mice) were intravenously dosed with 10, 48, 76, 120, 190 U/kg OBI-1 or 10, 44, 69, 109 U/kg Hyate:C. Two control groups: -----(b)(4)----- wild-type mice were dosed intravenously with OBI-1, Hyate:C® or buffer (positive control groups). The ability to reduce blood loss after tail clip injury was evaluated in Hem A mice (n =7 /group) after a single intravenous administration of OBI-1 or Hyate:C®. A group of vehicle-treated (buffer) Hem A mice were used as negative controls (n = 7). The positive control groups were vehicle control WT mice treated with OBI-1 and Hyate:C®. FVIII variant treated groups (n = 7/gr.) underwent tail clip procedure. Remaining mice (n = 5/gr.) were used to collect plasma samples to verify FVIII plasma activity at the time of tail injury, and at 2, 3, 6, and 24 hours after dosing. The tail transection model was modified to obtain results from which the estimated dose producing 50% survival rate could be established for the treated groups. Survival rates increased in a dose dependent manner following treatment with FVIII variants. All negative control animals died within 24 hours, as expected from a significant blood loss. Following a standardized tail-snip hemorrhagic insult, an estimated ED₅₀ of 89 U/kg OBI-1 (95% confidence interval: 65-120 U/kg) produced 50% survival. The efficacy did not differ significantly from that of Hyate:C (ED₅₀ = 64 U/kg; 95% confidence interval: 34-87 U/kg). Results showed that OBI-1 and Hyate:C® prevent blood loss in a similar, dose-dependent manner after tail clip injury, suggesting that OBI-1 has similar potency to Hyate:C® in resolving acute bleeds.

Study Report PCM-104: A Comparative Pharmacokinetic Study of OBI-1 (B domain-deleted Recombinant Porcine Coagulation Factor VIII) and Plasma Derived Porcine Factor VIII (Hyate:C®) administered by Intravenous Injection to ---(b)(4)----- Monkeys

The aim of this study was to evaluate the pharmacokinetic profile of OBI-1 (B domain-deleted Recombinant Porcine Coagulation Factor VIII) compared to Plasma Derived Porcine Factor VIII (Hyate:C®) in ---(b)(4)----- monkeys following acute, intravenous administration. Monkeys were randomized into three dose groups injected with OBI-1(n=4/group) at doses of 49.5 and 77 U/kg (Batch 214-01-001) or Hyate:C® (n=3/group) at a dose of 100 U/kg (Batches 688, 691 and 691), respectively. There were no control groups utilized in this study.

Blood samples were taken from the central auricular artery at 0 h, 0.33h, 0.66h, 1h, 3 h, 6 h, 9 h, 12 h, 18h and 24 h after dosing to assess the pharmacokinetic profile. The following pharmacokinetic parameters were evaluated: Maximum concentration (C_{max} [U/mL]), Timepoint of the maximum concentration (T_{max}[h]), elimination rate constant (λ_z[h⁻¹]), half-life (t_{1/2λz} [%]), area under the curve (AUC_t [h×U/dL] and AUC[h×U/dL]), Clearance (CL[dL/h]) and volume of distribution (V_{ss} [dL/kg]). The FVIII: antigen level was also assessed from collected samples. Clinical observations, mortality, and behavior were monitored throughout the study.

Parameter (unit of measurement)	OBI-1 49.5 U/kg	OBI-1 77 U/kg	Hyate:C® 100 U/kg*
T _{max} (h)	0.975	0.33	0.70
C _{max} (U/dL)	107+22.6	169+32.2	78.7+20.4
t _{1/2λz} (h ⁻¹)%	6.71+3.61	8.33+0.26	10.01
V _{ss} (dL/kg)	0.576+0.33	0.806+0.26	2.375
CL (dL/h)	0.056+0.02	0.085+0.05	1.35
AUC _t (h×U/dL)	826+298	1011+710	255+213
AUC (h×U/dL)	944+276	1443+1390	512.65

*Only two animals in Hyate:C® group could be assessed for PK parameters, due to insufficient concentration values from the third animal. Values charted are the mean values for the group. The group numbers were too small to detect significant differences in intergroup values\.

The results of the pharmacokinetic study demonstrated dose-dependent FVIII levels after dosing with OBI-1, and levels above baseline for all other FVIII derivatives. The group numbers were small, but the intergroup results were consistent for the parameters tested. These results suggest that OBI-1 should have similar PK activity in clinical trials as Hyate:C®. This study was completed April 2008 at ---(b)(4)-----, in EU GLP compliance.

Study Report PCM-102: A Comparative 90-Day Toxicity Study of OBI-1 (B domain-deleted Recombinant Porcine Coagulation Factor VIII) and Hyate: C® (Plasma Derived Porcine Factor VIII) administered by Daily Intravenous Injection in ---(b)(4)----- Monkeys

The aim of this study was to investigate the toxic effects of subchronic, repeated dosing with OBI-1 in the ---(b)(4)----- monkey model. ---(b)(4)----- monkeys (n = 6 M and 6 F/group) were dosed intravenously by bolus injection with OBI-1 (lot No. 214-01-00) at doses of 75, 225 or 750 U/kg/day for 90 days. Control groups were dosed with 100 IU/kg/day of Hyate:C (positive control; lots no. 641, 643, 645, 646, 647, 648, 650, 651, 653, 655, 658, 659, 662, 664, 665, 668, 669, 670, 671, 673, 675, 676, 677, 779 and 694A) or vehicle (OBI-1 vehicle buffer) by the same dosing regimen. There was no treatment-free recovery period, which is intended to examine the reversibility of any treatment-related toxicities, included in this study. The following parameters were monitored on-study to evaluate the potential toxicity of OBI-1 in monkeys: clinical observations, mortality, body weights, behavior, ophthalmic examinations, serum blood chemistry and hematology panels, WBCT, aPTT, PT, urinalysis, and necropsy including gross anatomic pathology, organ weights and histopathology, toxicokinetics (TK) at days 1, 7, 28, 56, and 90, and safety pharmacology parameters (i.e. central nervous system [CNS], cardiovascular system-blood pressure [CVS-BP], electrocardiograph [ECG], and respiratory endpoints).

The following organs were collected for necropsy (histopathology):

Adrenals - cortex and medulla

Brain - cerebellum, cerebrum, midbrain and medulla

Eyes - includes optic nerve

Gross Lesions

Head - with skull cap and nasal cavity

Heart - included aorta, auricular and ventricular regions

Injection Sites

Intestines - Large and small: Peyers patch, Sacculus rotundus, duodenum, jujenum, ileum, cecum/appendix, colon, rectum

Kidneys - included cortex, medulla and papilla regions

Liver - section from two main lobes (median and lf. Lateral)

Lymph nodes- mandibular, mesenteric, bronchial

Lungs - section from two major lobes, including bronchi

Mammary gland (female only)

Ovaries (without oviduct)

Optic nerve
Pancreas
Pharynx
Pituitary gland
Salivary gland-mandibular
Sciatic nerve
Seminal vesicle
Skeletal muscle (biceps femoris)
Skin with mammary
Spinal cord – thoracolumbar
Spleen
Stomach - included body and antrum
Testes
Thymus
Thyroid glands - with parathyroids
Tongue
Trachea
Urethra
Uterus (with cervix)
Urinary bladder
Vagina

There were no substantial clinical signs of toxicity reported that related to adverse events. Slight alterations in clinical observations were noted in this study, but none resulted in remarkable, statistically significant changes in outcome. There were signs of hypersensitivity and local irritation such as sneezing, and hemorrhage and irritation at the injection site noted following administration of OBI-1. At necropsy and on microscopic evaluation, hemorrhage was noted in several locations (i.e., genitalia, ears, limbs at restraint sites). These effects were dose-dependent, but were considered related to the exaggerated pharmacology of OBI-1 (i.e., thrombogenic effects).

The TK parameters evaluated included FVIII and antidrug antibodies (ADAs). Anti-porcine FVIII antibody titers were tested (by endpoint titer assessment [EPT]), and showed dose-dependent increases in both incidence and time-responses. There was a dose- and time-dependent increase in the formation of antibodies to exogenous (to monkeys) FVIII in all porcine FVIII-treated animals. The antibody formation (against FVIII) was expected given the duration of treatment with a porcine protein, and no abnormalities were noted due to antibody formation. Neutralizing antibodies to FVIII activity were not recorded in this study.

There was a dose-dependent increase in aPTT levels in all porcine FVIII-treated groups, and FVIII activity diminished as apparent effects and changes to toxicokinetics associated with antibody formation. There were no other pharmacodynamic parameters evaluated in this study.

This study was completed October 2002 at -----(b)(4)----- in compliance with the US FDA regulations and OECD GLP guidelines.

Study Report PCM-101: A Dose-Escalation Tolerability Study of OBI-1 (B domain deleted Recombinant Porcine Coagulation Factor VIII) Administered by Intravenous injection to ---(b)(4)---- Monkeys

The aim of this study was to determine the tolerability and potential immunogenicity of OBI-1 in ---(b)(4)---- monkeys following repeat intravenous injection. Naïve ---(b)(4)---- monkeys (n=2, 1M & 1F) were dosed daily by slow bolus intravenous injection with OBI-1, and the daily dose was increased every seventh day in the following increasing dose manner: 100, 300, 600 and 1000 U/kg/day, for one week at each dose level. The dosing regimen was intended to elicit an immunogenic response in animals,

based on the time and dose levels. Samples were taken for titer measurements on Days 1, 8, 15, 22 and 29 to determine antibody levels, if any. Clinical observations including overt toxicity and vital signs, CVS-BP, mortality, and behavior were monitored throughout the study.

There were no adverse events reported in this study. There was anti-FVIII antibody formation noted at day 7 that persisted throughout the study. Serologic testing demonstrated the development of inhibitor antibodies to Factor VIII that also cross-reacted with endogenous Factor VIII in both monkeys by Day 15, and persisted throughout the remainder of the study. Antibody titer levels were not reported in this study, and there was no inhibitor antibody development reported in this study. No other toxicologic changes were observed in any of the monkeys treated up to 1000 U/kg/dose. Although the presence of anti-Factor VIII antibodies is confounding, it appears that doses of rPFVIII up to 1000 U/kg/day were well tolerated in this dosing regimen. This study was completed May 2002 at -----(b)(4)----- under GLP compliance with the OECD guidelines.

Study Report PCM-105: A Comparative Immunogenicity Study, Up to 85 Days Administration of OBI-1 (B domain deleted Recombinant Porcine Coagulation Factor VIII) Administered by Intravenous injection to ---(b)(4)--- Monkeys

The purpose of this study was to compare the immunogenicity of OBI-1 versus Hyate:C® in ---(b)(4)---- monkeys following repeat intravenous injections. ---(b)(4)----- monkeys (n=16/group) were intravenously dosed at 12 hour intervals with eight total injections of OBI-1 at doses of 40 or 100 U/kg/dose, or Hyate:C® at 100 U/kg/dose. This dosing regimen was intended to mimic the clinical setting. Samples for antibody measurement were taken on Days 1, 8, 15, 29, 43, and 57.

In summary, OBI-1 administered at 40 and 100 mg/kg/dose or HYATE:C® at 100 mg/kg/dose via intravenous bolus injection twice daily over 85 days were well tolerated, with no test article-related effects. This study was completed September 2007 at -----(b)(4)----- under GLP compliance with the US FDA and OECD.

Reviewer Comments: The results of antibody titres were recorded and given to Applicant but not reported in this study. The study was initially sanctioned by -----(b)(4)-----; then data transferred to Baxter Corporation. -----(b)(4)----- initially developed Obizur (OBI-1), Baxter purchased OBI-1 and its data from the previous Sponsors, and will be its manufacturer as well as the Applicant for the product in this BLA.

Study Report PCMU-102: Comparative Immunogenicity of Recombinant B-chain Deleted Porcine FVIII-OBI-1 and Hyate:C® in Hemophilia A Mice Pre-sensitized to human Factor VIII

This study was a sub-study of the 90-day repeat-dose toxicity study PCM-102, described above. The aim of this study was to evaluate the potential immunogenicity of OBI-1 compared to Hyate:C® in monkeys. ---(b)(4)---- monkeys (n=6/group) in a 90-day repeat dose toxicity study at daily doses of 82.5, 247.5 and 750-825 U/kg OBI-1 or OBI-1 vehicle, or 100 U/kg Hyate:C®. There was a rise in Factor VIII plasma levels at Day 1 and Day 7 one hour post-dosing of up to approximate 3000 U/dL. On Day 7, baseline values for Factor VIII were higher than on Day 1 in the OBI-1 and Hyate:C treated animals, demonstrating increasing trough levels of Factor VIII with repeated dosing. By Day 28 and Day 90, plasma Factor VIII levels were markedly reduced in all monkeys due to the development of anti-porcine Factor VIII inhibitor antibodies, which cross-reacted with the monkey's endogenous Factor VIII (and in some cases as described above, induced an 'acquired hemophilia' condition). Development of inhibitory anti-Factor VIII antibodies was shown following multiple injections of OBI-1. In the 90-day repeat dose toxicity study, the development of anti-porcine Factor VIII inhibitory antibodies significantly reduced plasma Factor VIII activity by Days 28 and 90, indicating a cross reactivity with the endogenous Factor

VIII. This study was completed October 2002 and was non-GLP compliant. Additionally, these results confirm cross-reactivity between monkey plasma and human factor VIII as can be expected in coagulation system testing in monkeys with human protein, indicating immune response to foreign materials (positive control for coagulation testing system).

OBI-1 Excipients Listing

Toxicological risk assessment analyses were completed on the excipients used to formulate the Obizur drug product, and the potential leachables and extractables associated with OBI-1 manufacturing and container closure systems. The results of analysis indicated that the levels of the leachables/extractables materials observed were within the range of specifications and at acceptable levels of potential leachable/extractable impurities were within range of the Applicant’s specifications, based on extensive clinical experience. Based on the results of both the toxicological risk assessment and the nonclinical studies conducted with the extractables/leachables from the components used in its manufacturing and storage, OBI-1 is approvable for licensure. Below is a line listing of excipients used as –(b)(4)– in

Component	Function	Strength	
		500 units/vial (nominal) after reconstitution	
		Quantity per unit	% w/w in Water for Injection (sWFI)
Recombinant Porcine FVIII-BDD	Active Ingredient	500 U (nominal)	0.010
Polysorbate 80	---(b)(4)-----	--(b)(4)----	--(b)(4)----
Sodium chloride	------(b)(4)-----	--(b)(4)----	--(b)(4)----
Calcium Chloride	---(b)(4)-----	--(b)(4)----	--(b)(4)----
Sucrose	------(b)(4)----- -----	--(b)(4)----	--(b)(4)----
Tris	---(b)(4)---	--(b)(4)----	--(b)(4)----
Tri-Sodium citrate	---(b)(4)-----	--(b)(4)----	--(b)(4)----
Water for Injection (sWFI)	---(b)(4)-----	--(b)(4)----	--(b)(4)----

rFPFVIII-BDD (500 U FVIII):

It appears that all of the excipients listed in the above table are present in the drug product at levels below the acceptable NOAELs, according to the toxicological risk assessment analysis.

Leachables and Extractables Analysis

