

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

BLA 125512/0

Product: Recombinant porcine factor VIII, B-domain deleted (OBI-1)
Sponsor: Baxter Healthcare Corp
Indication: Treatment and prevention of bleeding episodes patients with acquired hemophilia A (AHA)
Date Received: November 25, 2013
Reviewer: Carl-Michael Staschen, M.D., Ph.D.
RPM: Thomas Maruna
Through: Iftekhar Mahmood, Ph.D. and Paul Mintz, M.D.

Introduction/Background

Acquired hemophilia A (AHA) is a rare (orphan) bleeding disorder resulting from the development of inhibitors (auto-antibodies) to human factor VIII, which creates a functional deficiency in procoagulant activity. Bleeding is often spontaneous or in response to minimal trauma. The AHA patient population tends to be elderly, most with significant co-morbidities that make treatment of the bleeding episode challenging. The objectives in treating AHA patients are (1) to stop the acute bleeding in the short term, and (2) to eradicate the autoimmune antibodies. Bleeding episodes in patients with AHA most often cannot be controlled or prevented with human factor VIII replacement.

Currently, treatment of AHA is focused on 1) eliminating human factor VIII inhibitors with immunosuppressive therapy, and 2) controlling the bleed with by-passing agents. OBI-1 offers an alternative to bypassing agents by providing a substitute for the inhibited native human factor VIII and restoring the factor VIII dependent coagulation cascade.

OBI-1 is a purified recombinant porcine factor VIII glycoprotein. In OBI-1, the B-domain normally present in naturally occurring porcine factor VIII has been replaced with a twenty-four amino acid linker. OBI-1 is expressed by a genetically engineered baby hamster kidney (BHK) cell line with a DNA construct coding for ---(b)(4)-----. The molecular weight of OBI-1 is approximately 165 kDa (based on the amino acid sequence). OBI-1 circulates as a heterodimer with only 2% in the single chain form, interacts with human von Willebrand factor and is activated by thrombin.

The company is seeking approval in the U.S. for the following indication:

Treatment and prevention of bleeding episodes in patients ---(b)(4)-- with acquired hemophilia A.

The following 3 submitted clinical study reports were reviewed by Clinical Pharmacology.

1. Study Title: A Phase I randomized, parallel-group, blinded comparison study of the safety, tolerance and pharmacokinetics of OBI-1 (B-domain deleted recombinant porcine FVIII) versus HYATE:C (porcine plasma derived FVIII) when administered as a single intravenous injection to subjects with an inhibitor antibody to FVIII, in the non-bleeding state. Study report OBI-1-101.

2. Study Title: an open-label study of the hemostatic activity, pharmacokinetics and safety of OBI-1 (B-domain deleted recombinant porcine FVIII), 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 report OBI-1-201.

3. Study Title: Efficacy and safety of B-domain deleted recombinant porcine factor VIII (OBI-1) in the treatment of acquired hemophilia a due to factor VIII inhibitory auto-antibodies. Interim study report OBI-1-301/OBI-1-301a.

1. Study Title: A Phase I randomized, parallel-group, blinded comparison study of the safety, tolerance and pharmacokinetics of OBI-1 (B-domain deleted recombinant porcine FVIII) versus HYATE:C (porcine plasma derived FVIII) when administered as a single intravenous injection to subjects with an inhibitor antibody to FVIII, in the non-bleeding state. (Study Report OBI-1-101).

Phase 1 Study Design and Objectives

Study OBI-1-101 was a Phase 1, parallel-group study comparing the safety and tolerability of OBI-1 versus HYATE:C when administered to congenital hemophilia A (CHA) subjects (> 12 yr) with inhibitors in a nonbleeding state and who had low or absent anti-porcine factor VIII antibody titers. A low titer was defined as an anti-porcine factor VIII titer of less than or equal to 0.80 Bethesda units (BU). Evaluable subjects randomized to receive 100 units/kg OBI-1 via intravenous infusion (duration about 15 min).

Nine of 24 planned subjects were enrolled and received study medication. Enrollment was discontinued early when HYATE:C was withdrawn from the market. The remainder of the review for this study will therefore focus on the results obtained with OBI-1 only.

Blood samples for measurement of drug concentrations were taken at predose, 20, 40, 60, 65, 75, 85, 105, and 125 minutes; and at 3, 6, 9, 24, 27, 30, and 48 hours after dose.

Factor VIII activity was determined by both the one-stage clotting and the chromogenic assay. One expert central laboratory was designated to analyze the PK samples and antibody titers. All pharmacokinetic calculations were performed using a noncompartment analysis (SAS for Windows Version 8.2 or higher).

Pharmacokinetic Results

The PK population included 3 subjects in the OBI-1 group, all who had an anti-porcine factor VIII inhibitory antibody titer < 0.80 BU/mL at Day 0 and Day 29 and sufficient measurable factor VIII activity levels after administration of an intravenous infusion (over 17 min) of 100 units/kg of study product to allow calculation of PK values. A summary of the PK parameters calculated from these three subjects is provided in Table 1.

Table 1

Summary of pharmacokinetic parameter estimates (FVIII activity) after a single dose of 100 U/kg OBI-1 in subjects with low anti-pFVIII titer (<0.8 BU). Data shown as arithmetic mean (SD).

Parameter	OBI-1 (N = 3)	
	OSCA	Chromogenic Assay
C _{max} [U/dL]	176.0 (88)	151.0 (31.5)
T _{max} [h]	0.6 (0.03)	0.5 (0.2)
AUC _{0-inf} [h·U/dL]	2186 (1393)	1915 (591)
T _{1/2} [h]	10.6 (0.8)	12.9 (5.3)
CL [mL/h]	545.5 (375.8)	476.3 (150.1)
V _z [L]	8.3 (5.6)	9.1 (5.3)
IVR [U/dL per U/kg]	1.76	1.51

OSCA = one stage clotting assay, C_{max} = maximum observed plasma concentration, T_{max} = time to C_{max}, AUC_{0-inf} = area under the concentration time curve extrapolated to infinity, T_{1/2} = plasma half-life, CL = total clearance, V_z = volume of distribution, IVR = incremental in-vivo recovery.

Overall, the PK parameter differences between the two assay methods appear not to be of clinical significance.

2. Study Title: an open-label study of the hemostatic activity, pharmacokinetics and safety of OBI-1 (B-domain deleted recombinant porcine FVIII), 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 Report OBI-1-201)

Phase 2 Study Design

Study OBI-1-201 was a multicenter, open-label, noncomparative study assessing the hemostatic activity, the safety, the immunogenicity, and the PK of OBI-1 in subjects (> 12 yr of age) with congenital hemophilia A (CHA) and inhibitors to factor VIII experiencing non-life-threatening or non-limb-threatening bleeds. Nine subjects experiencing 25 bleeding episodes were enrolled and treated with OBI-1.

Full PK data were available for only one subject at all time points, and therefore a complete pharmacokinetic profile was only obtained for this subject.

A baseline sample for factor VIII activity was collected, and subsequent collections for measurement of drug concentrations were taken at the following time points after the first treatment dose: 0.25, 0.5, 1, 3, 6, 9, 24, and 32 hours.

Factor VIII activity was determined by both the one-stage clotting and the chromogenic assay.

All pharmacokinetic calculations were performed using a noncompartment analysis (SAS for Windows Version 8.2 or higher).

Pharmacokinetic Results

Only one patient (Subject (b)(6)) had PK data available for all time points resulting in a complete PK profile. The PK parameters calculated for Subject (b)(6) are summarized in Table 1. The subject never developed quantifiable levels of either anti-pFVIII or anti-hFVII inhibitors during the course of observation.

Table 1

Summary of pharmacokinetic parameter estimates (FVIII activity) after a single dose of 50 U/kg OBI-1 to subject (b)(6) with anti-pFVIII titer (<0.8 BU/mL).

Parameter	OBI-1 (N = 1)	
	OSCA	Chromogenic Assay
C _{max} [U/dL]	89.0	54
AUC _{0-inf} [h·U/dL]	1016	710
T _{1/2} [h]	9.3	10.1
CL [mL/h]	467	669
V _{ss} [L]	6.0	9.5
IVR [U/dL per U/kg]	1.78	1.08

OSCA = one stage clotting assay, C_{max} = maximum observed plasma concentration, AUC_{0-inf} = area under the concentration time curve extrapolated to infinity, T_{1/2} = plasma half-life, CL = total clearance, V_{ss} = volume of distribution at steady-state, IVR = incremental in-vivo recovery.

The results are consistent with the PK analysis of the Phase 1 study.

3. Study Title (ongoing study): Efficacy and safety of B-domain deleted recombinant porcine factor VIII (OBI-1) in the treatment of acquired hemophilia a due to factor VIII inhibitory auto-antibodies. Interim study report OBI-1-301/OBI-1-301a.

Study design

OBI-1-301 is an ongoing, Phase 2/3, multicenter, prospective, open-label study evaluating OBI-1 in subjects with acquired hemophilia A (AHA) with autoimmune inhibitory antibodies to human factor VIII. Study OBI-1-301a is an expanded-access protocol based on the OBI-1-301 protocol and is intended for subjects who are eligible for treatment but are unable to enroll at an active study site.

For each serious bleeding event, an initial dose of 200 units/kg of OBI-1 was administered by infusion. For treatment of all bleeding events, a blood sample was obtained within 10 to 20 minutes after an OBI-1 dose to assess factor VIII activity levels, and clinical assessments are made at prescribed time points after dosing. The protocol recommended that up to 400 units/kg per dose of OBI-1 could be administered up to every 2 to 3 hours up to a maximum of 4800 units/kg/d. Also, blood levels of factor VIII should not exceed 200%. For subjects responding to treatment, dosing continues at least until the bleed was controlled.

The sponsor determined that the data were insufficient to support the proposed sparse sampling design in the bleeding state. For the final analysis of this study, it will be re-examined whether or not sufficient data exist to analyze bleeding state PK.

The PK profile of OBI-1 was assessed during a nonbleeding state via a complete PK analysis. For the complete PK analysis, the data were gathered during optional final dose serial blood collections. For consenting subjects, samples were obtained at the following time points: before dose, 15 to 20 minutes after dose, 1, 3, 6, 12, 18, and 24 hours after dose. Factor VIII activity was determined by both the one-stage clotting assay and the chromogenic assay. Central laboratories were designated to analyze the PK samples and antibody titers per prescribed assays. A noncompartmental analysis was used to estimate the relevant PK parameters after correction for baseline.

Pharmacokinetic Analysis

PK data were obtained from subjects (N = 3) in a non-bleeding state. Individual activity-time profiles are shown below for the chromogenic (Figure 1) and one-stage (Figure 2) Factor VIII assays. These profiles represent the final dose after a multiple-dose administration for each subject, and the time indicated is the time since the last dose. For the final dose PK analysis, the % relative factor VIII activity data from both the chromogenic and one-stage assays were presented as baseline-corrected values. The PK parameters from the chromogenic and one-stage clotting Factor VIII activity assays are presented in Table 1 and Table 2.

Figure 1. Baseline corrected activity (%) of Factor VIII using the chromogenic assay after administration of the final (PK) dose of OBI-1.

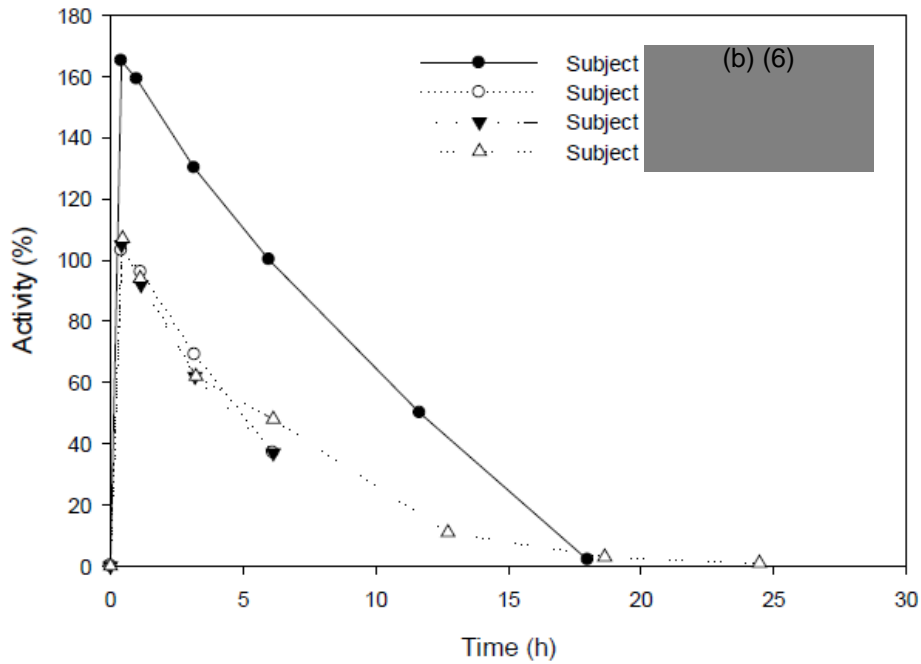


Figure 2. Baseline corrected activity (%) of Factor VIII using the one-stage assay after administration of the final (PK) dose of OBI-1.

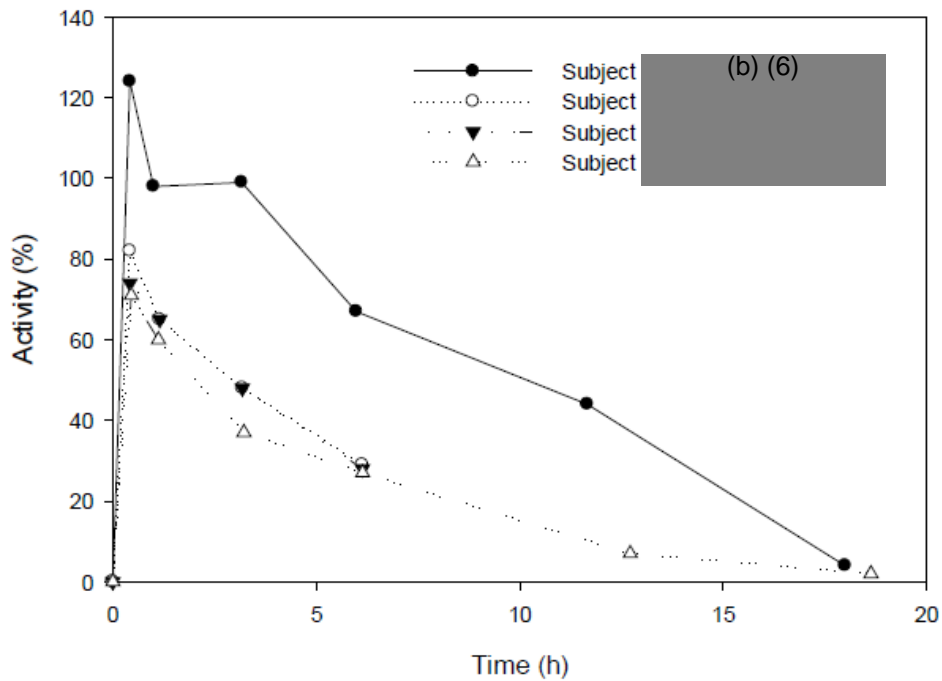


Table 1

Individual and summarized PK parameter values for Factor VIII baseline corrected data after administration of the final (PK) dose of OBI-1.

Chromogenic Assay									
Subject	Dose (units)	Dose (units/kg)	$t_{1/2}$ (h)	T_{max} (h)	A_{max} (%)	AUC_{0-t} (%·t)	$AUC_{0-\infty}$ (%·t)	CL (units/%·t)	V_{ss} (units/%)
(b) (6)	5,000	77	2.8	0.42	165	1,357	1,373	3.64	20.1
	2,934	30	3.6	0.42	103	418	613	4.78	24.7
	2,934	30	3.8	0.42	105	397	598	4.9	26.6
	7,540	90	3.5	0.45	107	663	668	11.29	57.4
Summary Parameters		N	4	4	4	4	4	4	4
		Mean	3.4	.43	120	709	813	6.15	32.2
		SD	0.4	0.02	30	449	375	3.47	17.0
One-Step Coagulation Assay									
Subject	Dose (units)	Dose (units/kg)	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (%)	AUC_{0-t} (%·t)	$AUC_{0-\infty}$ (%·t)	CL (units/%·t)	V_{ss} (units/%)
(b) (6)	5,000	77	3.8	0.42	124	1,005	1,042	4.8	30.7
	2,934	30	4.3	0.42	82	299	479	6.13	37.1
	2,934	30	4.1	0.42	74	293	460	6.38	37.3
	7,540	90	3.6	0.45	71	393	404	18.64	95.2
Summary Parameters		N	4	4	4	4	4	4	4
		Mean	4.0	0.43	88	498	596	8.99	50.1
		SD	0.3	0.02	25	341	299	6.47	30.2

A_{max} = maximum observed % activity; AUC_{0-t} = area under the concentration-time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; CL = clearance; $t_{1/2}$ = terminal half-life; T_{max} = time of maximum observed % activity; and V_{ss} = volume of distribution at steady state.

*Subject 30203 had samples analyzed twice, and both profiles are included in the PK analysis.

For subject (b)(6)-- and subject (b)(6)-- no neutralizing anti-porcine FVIII antibody were detected during PK assessment. For subject (b)(6)-- antibody testing during PK assessment was not done.

The summary parameters indicate a maximal activity of OBI-1 between about 17 and 28 minutes following the final dose of OBI-1, with a mean $T_{1/2}$ of between 3.6 and 4.0 hours after dosing. The data are consistent with OBI-1 following first order elimination.

REVIEWER'S COMMENTS

- In general, the PK results of the clinical Phase 1 study and Phase 2 study are acceptable from a Clinical Pharmacology perspective. However, given the small number of patients (N=4) available for a full PK analysis the results are not robust enough to allow for a general PK characterization of OBI-1 in patients diagnosed with congenital hemophilia A.
- A formal PK analysis of OBI-1 during the ongoing pivotal clinical Phase 3 study in acquired hemophilia A patients (non-bleeding state) has not been conducted because participation was optional. However, the results and conclusions presented are not acceptable from a Clinical Pharmacology point of view. The analysis and interpretation of the PK parameters is severely confounded by a too short blood sampling schedule. As a result the terminal drug elimination phase has not been sufficiently captured. This, in turn, precludes a meaningful interpretation. However, even with a correct sampling schedule and correct data analysis, the number of patients (N=3) available for the PK analysis is not sufficient to allow a robust interpretation of the PK parameters.
- It should also be noted that the sponsor proposed a clinical indication for OBI-1 targeting acquired hemophilia A patients (AHA). It has not been conclusively demonstrated that OBI-1 has a comparable PK profile in patients diagnosed with AHA vs. patients diagnosed with CHA. Therefore PK results from the Phase 1 and Phase 2 studies (CHA patients) cannot be used in lieu of PK data from the Phase 3 study (AHA patients).

CLINICAL PHARMACOLOGY LABELING COMMENTS

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

<DRUG NAME> temporarily replaces the inhibited endogenous factor VIII that is needed for effective hemostasis in patients diagnosed with acquired hemophilia A (AHA).

12.2 Pharmacodynamics

The following deleted paragraph should be moved to the Nonclinical Section.

~~Nonclinical studies with <DRUG NAME> demonstrated hemostatic activity by dose-related control of bleeding using two animal models of hemophilia A. A single intravenous administration of <DRUG NAME> 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, <DRUG NAME> produced 50% survival following a standardized tail snip hemorrhagic insult at an effective dose of 89 units per kg.~~

Patients with acquired hemophilia A (AHA) have normal FVIII genes but develop autoantibodies against their own FVIII (i.e., inhibitors). These autoantibodies neutralize circulating human FVIII and create a functional deficiency of this procoagulant activity. AHA results in a prolonged clotting time as measured by the activated partial thromboplastin time (aPTT) assay, a conventional *in vitro* test for biological activity of FVIII.

The following Section 12.3. Pharmacokinetics should be added.

12.3 Pharmacokinetics

A formal pharmacokinetic study of OBI-1 in patients diagnosed with AHA has not been conducted.

RECOMMENDATION

A formal pharmacokinetic (PK) study with OBI-1 in acquired hemophilia A patients has not been performed. However, in this patient population the choice of an effective and safe dose of OBI-1 is based primarily on the clinical response in a symptomatic patient.

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