This clinical study synopsis is provided for informational purposes only. It may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained across the entire product development.
2. **SYNOPSIS**

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<th>Name of Sponsor/Company:</th>
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<tbody>
<tr>
<td>Octagen Corporation *</td>
<td>(For national authority use only)</td>
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<tr>
<td>Name of Finished Product:</td>
<td>OBI-1</td>
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<tr>
<td>Name of Active Ingredient(s):</td>
<td>OBI-1 (B-Domain Deleted Recombinant Porcine FVIII)</td>
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**Title of study:** 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

**Investigators:**
Sixteen principal investigators at 16 study sites in Canada, the United States, Russia and South Africa.

**Study centre(s):**
Sixteen investigational sites in Canada, the United States, Russia and South Africa.

**Publication (reference):**
None

**Studied period (years):**
Date of first enrolment: 06-July-2005
Date of last visit completed: 26-September-2007

**Phase of development:**
II

**Objectives:**
The primary objective of the study was to evaluate the hemostatic activity of OBI-1 to control a bleeding episode in hemophilia A patients with inhibitors who were experiencing a non-life and/or non-limb threatening bleeding episode.
The secondary objectives of this study were to assess the:
- Safety of OBI-1;
- Serial anti-OBI-1 and anti-human factor VIII (FVIII) inhibitor antibody responses following therapeutic administration of OBI-1; and
- Pharmacokinetics of OBI-1 administered to control a bleeding episode.

**Methodology:**
This was a prospective, open-label, non-comparative study.

**Number of patients (planned and analysed):**
The hemostatic activity of OBI-1 was to be evaluated in a minimum of 24 bleeding episodes in a minimum of 12 patients. Twenty eight subjects were screened, 24 met eligibility requirements with 9 subjects comprising the intent-to-treat (ITT) population having a cumulative 25 bleeding episodes.

**Diagnosis and criteria for inclusion:**
- Age ≥ 12 years (for non-Russian Sites) and Age 18 years (for Russian Sites only);
- Clinical diagnosis of congenital hemophilia A with inhibitors to hFVIII;
- 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);

* The investigational medicinal product was acquired by Baxter Innovations GmbH in 2013 after completion of this clinical trial. On 01 May 2015 the sponsor's name was changed from Baxter to Baxalta.
Test product, dose and mode of administration, batch number:

OBI-1 (recombinant B-domain deleted porcine coagulation FVIII) was provided in sterile vials containing a nominal 500 units (U) FVIII activity/vial. Each vial was reconstituted with 1.0 mL water for Injection USP to a final nominal concentration of 500 U/mL. Three batches of study medication were used for treatment: Lot #004, #023 and #024. OBI-1 dose levels were: 50 U/kg (1st dose), 50 U/kg (2nd dose), 50 U/kg (3rd dose), 100 U/kg (4th dose), 100 U/kg (5th dose), 100 U/kg (6th dose), 150 U/kg (7th dose), and 150 U/kg (8th dose). Patients could not receive more than 1000 U/kg of OBI-1 within any 24-hour period.

All patients received a Loading Dose (see below), unless the patient had an inhibitor titer <0.8 BU against OBI-1.

The Loading Dose was determined by the formula provided in the Hyate:C labelling, using the patient’s most recent available inhibitor titer, body weight, and hematocrit.

**Loading Dose** = plasma volume x inhibitor titer (BU)

\[= \text{blood volume} \times (1 - \text{hematocrit}) \times \text{inhibitor titer}\]
**Name of Sponsor/Company:** Octagen Corporation  
**Name of Finished Product:** OBI-1  
**Name of Active Ingredient(s):** OBI-1 (B-Domain Deleted Recombinant Porcine fVIII)  

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where blood volume = body weight (kg) x 80 mL/kg, and where plasma volume = blood volume x (1 – hematocrit)  
Operationally, the formula for determining the Loading Dose therefore is:  
**Loading Dose = body weight (kg) x 80 mL/kg x (1-hematocrit) x inhibitor titer**  
By making clinical assessments of the patient’s signs and symptoms to determine whether the bleeding episode has been controlled, additional injections of OBI-1 were administered, until EITHER (1) the bleeding episode was controlled, (2) eight injections of OBI-1 were administered, (3) the patient received 1000 U/kg per 24 hours or (4) the investigator determined that OBI-1 had no effectiveness. Injections were given at least 6 hours apart.

**Duration of treatment:**  
Injections of OBI-1 were administered, until EITHER (1) the bleeding episode was controlled, (2) eight injections of OBI-1 had been administered, (3) the patient received 1000 U/kg per 24 hours or (4) the investigator determined that OBI-1 had no effectiveness. Injections were given at least 6 hours apart.

**Reference therapy, dose and mode of administration, batch number:**  
None

**Criteria for evaluation:**  
**Efficacy:** Activity data were summarized by subject and by bleed within subject. In cases where data were collected for each Treatment Dose, treatment data within bleed will be summarized. The overall summary was also provided. Summarized activity data included:  
- Success in controlling bleed (Yes/No);  
- Treatment success, controlling bleed within eight Treatment Doses (Yes/No);  
- Treatment success, controlling bleed within three Treatment Doses (Yes/No);  
- Number of Treatment Doses needed to control bleed (1, 2, …, 8 or bleed not controlled);  
- Inhibitory antibody titer (BU) after Loading Dose.

**Safety:**  
- Safety assessments performed in this study were standard and included: medical history, physical examination including body weight and vital signs, and laboratory tests;  
- Anti-hFVIII and anti-pFVIII inhibitory antibody titers were determined by the Nijmegen modification of the Bethesda assay (using standards for both hFVIII and pFVIII) at the Screening visit and defined intervals thereafter;  
- Samples for anti- BHK inhibitory antibody titers were collected at Screening, Day 28 (after each injection of study product), the 6-month visit, every 16 weeks thereafter, and at the end of the study.
**Pharmacokinetic:**
The blood sampling schedule and analysis were appropriate for characterizing the pharmacokinetics of OBI-1. Blood samples were to be taken just prior to the first treatment for a subject’s first bleed episode and 0.25, 0.5, 1, 3, 6, 9, 24, 32 and 48 hours after the first treatment.

**Statistical methods:**
The statistical methods are of a descriptive and explorative nature.
All data from all subjects collected during the study and all derived variables were included in the data listings.
Descriptive statistics of continuous variables included count(s), mean, standard deviation, median, minimum, and maximum. Tabulations of categorical variables included frequency and percentages.

**Summary - conclusions:**

**Efficacy results:**
- A total of 25 bleeds in 9 patients have been treated with OBI-1 and all bleeds were successfully controlled with eight or less injections of OBI-1;
- The median number of OBI-1 injections per bleeding episode was 1.0 (Range: 1 to 8);
- Across all bleeding episodes the median total dose of OBI-1 per bleeding episode was 224.1 U/kg (range: 50.0 to 1066.4 U/kg) and the median time from bleeding onset to treatment was 5.67 hours (Range: 1.5 to 20.00 hours);
- The median first Treatment Dose, including the Loading Dose, was 159 U/kg (Range: 50 to 576 U/kg) and resulted in a median increase of FVIII plasma level of 16 % (Range: 0.5 to 427%). Twenty of the 25 (80%) bleeds were controlled with one Treatment Dose (within 6 hours) of OBI-1;
- Anti-pFVIII titer values were increased following repeated OBI-1 injections in most subjects which lead to higher loading doses. However, in over half of the bleeding episodes, the titer value used to calculate the Loading Dose was different from the titer value at the time of the bleed. Where the titer at the time of the bleed was higher than the titer value used to calculate the Loading Dose only one Treatment Dose was sufficient to control the bleed;
- In this study OBI-1 was able to raise FVIII level to hemostatic levels as all bleeds were controlled even in the presence of high inhibitor levels showing the value of OBI-1 as a FVIII replacement therapy for patient with hemophilia A and inhibitors.

**PK Results**
- In four subjects without measurable anti-pFVIII antibodies at the start of the first treatment with OBI-1, mean recovery values obtained with the OSCA assay (1.66±1.34 (U/dL)/(U/kg)) were higher than the values obtained with the
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<td>chromogenic assay (0.95±0.47 (U/dL)/(U/kg)). Four subjects had measurable anti-OBI-1 antibodies at the start of the first treatment with OBI-1 and only a partial PK profile was available. In these subjects the mean recovery (Cmax/D) values were low (0.08±0.009 (U/dL)/(U/kg)) with the OSCA assay and 0.06±0.06 (U/dL)/(U/kg)) with the chromogenic assay as compared to the values obtained in the four subjects with anti-OBI-1 antibodies.</td>
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**Safety results:**

- The overall safety profile of OBI-1 demonstrates it is well tolerated by subjects enrolled in this study;
- Overall, only 18 AEs were categorized as treatment emergent;
- Two subjects reported AEs during the first bleeding episode that were possibly related to study drug;
- Three subjects suffered treatment emergent SAEs but none were related to study drug;
- No AE led to treatment interruption, discontinuation from study or death;
- Safety assessments: vital signs, laboratory values, medical history and physical examination were within normal parameters for this study and raised no safety concerns;
- Analyses of BHK antibody levels indicate that no subject produced detectable levels of antibodies against BHK at any time during the study.

**Conclusion:**

All bleeds were successfully controlled with OBI-1 treatment; 20/25 bleeds (80%) were controlled with one treatment dose with or without Loading Dose, 1/25 bleeds (4%) were controlled with two Treatment Doses, 2/25 bleeds (16%) were controlled with three Treatment Doses and 1/25 (4%) bleeds required 4 Treatment Doses and 1/25 (4%) bleeds required 8 Treatment Doses to control bleeding. Across all bleeding episodes the median total dose of OBI-1 per bleeding episode was 224.1 U/kg (range: 50.0 to 1066.4 U/kg). The median initial Treatment Dose (including the Loading Dose if applicable), was 159 U/kg (Range: 50 to 576 U/kg) and resulted in a median increase of FVIII plasma level of 16 % with the OSCA assay (Range: 0.5 to 427%) and a median increase of 17% with the chromogenic assay (Range: 0 to 248 %). Twenty of the 25 (80%) bleeds were controlled within 6 hours only requiring one Treatment Dose of OBI-1. For those 20 bleeds controlled with one Treatment Dose (including the Loading Dose if applicable), the median dose was 200.8 U/kg.

OBI-1 was well tolerated and of the reported AEs (n=61) only 18 were considered treatment emergent. Two subjects reported an AE that was possibly related to study drug. One AE of itching/purities during the first bleeding episode but without reaction during a
second OBI-1 treated bleeding episode. The second AE was a report of increased ALT and AST possibly associated with a confirmed Hepatitis C infection. The investigator confirmed that the blood sample was withdrawn before study drug administration. However the error was not corrected in the CRF. Three subjects suffered treatment emergent SAEs but none were considered related to study drug. No reported AE led to treatment interruption, discontinuation from the study or death. Eight out of nine (8/9, 89%) subjects developed anti-pFVIII antibodies following exposure to OBI-1 and in subjects receiving repeated OBI-1 treatment higher anti-pFVIII titers did not affect efficacy nor safety as no increase in AEs or bleeding episodes were reported in subjects with the highest titers. In two subjects the anti-hFVIII titer was lower at the end of the study than before the first OBI-1 treatment; in two subjects there was no change (<0.8 BU/ml) and in five subjects the anti-hFVIII titers at the end of the study were higher than the first pre-treatment value. In subjects without measurable anti-pFVIII titers at the start of the first treatment with OBI-1, mean FVIII recovery values were substantially higher than in subjects with measurable ant-pFVIII antibodies. Regardless of the observed anti-pFVIII titers at pre-treatment or the obtained FVIII recovery values after treatment initiation, all bleeding episodes were successfully controlled.

The Loading Dose was intended to neutralize the circulating inhibitors to allow a small treatment dose to be hemostatic. In the study the Loading Dose was calculated based on the last known anti-pFVIII titer. However, in 15 bleeds (60%) the actual titers at the time of the bleed were different from the last known value. For all bleeding episodes where the titer at the time of the bleed was higher than the last known value the bleed was successfully controlled with one Treatment Dose, with or without a Loading Dose of OBI-1. Utilizing a complex calculation of the Loading Dose, as applied in this protocol, does not appear to be clinically feasible since the anti-pFVIII assay takes at least 2 hours and is not available in all hemophilia centers. Given that treatment in acutely bleeding subjects needs to be initiated without delay, awaiting the titer obtained at the time of the bleed will not be in the best interest for most subjects, and will require a more practical loading dose approach.

From the results of this Phase II study, a fixed dose of 200 U/kg has been selected for further studies as it is expected to raise plasma FVIII level and achieve hemostasis in at least 80% of subjects even in the presence of inhibitors. This initial dose will be titrated up or down based on clinical response and FVIII levels.

Date of report: 30-May-2008