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.
## SYNOPSIS

**Name of Sponsor/Company:** Baxter Healthcare Corporation and Baxter Innovations GmbH *(For National Authority Use only)*  
**Name of Investigational Product (IP):** OBI-1  
**Name(s) of Active Ingredient(s):** B-domain deleted recombinant porcine factor VIII  
**CLINICAL CONDITION(S)/INDICATION(S):** Acquired hemophilia A (AHA)  
**PROTOCOL IDENTIFIER:** OBI-1-301/OBI-1 301a  
**PROTOCOL TITLE:** Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (OBI-1) in the Treatment of Acquired Hemophilia A Due to Autoimmune Anti-Factor VIII Inhibitory Antibodies  
**Short Title:** Efficacy and Safety of OBI-1 in AHA  
**STUDY PHASE:** Ph2/3  

**INVESTIGATORS AND STUDY SITE(S):**  
- M.D., USA  
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- M.D., USA  
- M.D., UK  
- M.D., UK  
- M.D., Canada  
- M.D., India  

* On 01 May 2015 sponsor’s name was changed from Baxter to Baxalta.
PUBLICATION (REFERENCE): Based on interim data from Study OBI-1-301/301a, 2 abstracts have been published in 2012\(^i\)\(^{, ii}\), 1 abstract in 2013\(^{iii}\) and 1 abstract and 1 article in 2014\(^{iv,v}\).

<table>
<thead>
<tr>
<th>STUDY PERIOD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation</strong></td>
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<tr>
<td><strong>Study Completion</strong></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>STUDY OBJECTIVES AND PURPOSE</th>
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<tbody>
<tr>
<td><strong>Study Purpose</strong></td>
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<tr>
<td>The purpose of this study was to investigate the safety and efficacy of OBI-1 for the treatment of serious bleeds in subjects with AHA aged 18 years or older and to gather pharmacokinetic data in those successfully treated subjects</td>
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<tr>
<td><strong>Primary Objective</strong></td>
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<tr>
<td>To evaluate the efficacy of OBI-1 for the treatment of serious bleeding events in subjects with AHA</td>
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<td><strong>Secondary Objective(s)</strong></td>
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<tr>
<td>1. Determine the proportion of serious bleeding events controlled with OBI-1 therapy</td>
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<td>2. Assess the efficacy of OBI-1 at designated time points after the initiation of therapy (percentage of bleeding events showing a response to therapy within specified time points after initiation of OBI-therapy)</td>
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<td>3. Determine the frequency, total dose, and total number of infusions of OBI-1 required to control all serious bleeding events</td>
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<td>4. Assess the correlation between response to OBI-1 therapy at specified assessment time points and eventual control of serious bleeding events</td>
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<td>5. Assess the correlation between the preinfusion anti–OBI-1 inhibitor titer, the total dose of OBI-1, the outcome at 24 hours and the eventual control of the bleeding event</td>
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<td>6. Assess the anti–OBI-1 inhibitor level before infusion, at specified time points during treatment, and at the end of the follow-up period at 90 days after final infusion</td>
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<td>7. Evaluate the safety of OBI-1</td>
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8. Assess drug exposure by using extensive (nonbleeding state) or sparse sampling (bleeding state), and a population PK approach (with sparse data) in subjects treated with OBI-1 therapy

**Tertiary Objective(s)**

Not Applicable

**STUDY DESIGN**

<table>
<thead>
<tr>
<th>Study Type/ Classification/Discipline</th>
<th>Efficacy, Safety, Pharmacokinetic</th>
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<tbody>
<tr>
<td>Control Type</td>
<td>Uncontrolled</td>
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<tr>
<td>Study Indication Type</td>
<td>Treatment</td>
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<td>Intervention model</td>
<td>Non-randomized</td>
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<td>Blinding/Masking</td>
<td>Open-label</td>
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<tr>
<td>Study Design</td>
<td>This was a Phase 2/3, multicenter, open label, single-cohort, prospective study to investigate the safety and efficacy of OBI-1 for the treatment of serious bleeds in subjects with AHA aged 18 years old or older. In addition, in those patients successfully treated with OBI-1, a Pharmacokinetic study was performed.</td>
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**CRITERIA FOR EVALUATION**

**Efficacy Endpoints**

**Primary Efficacy Endpoint**

- The proportion of serious bleeding episodes responsive to OBI-1 therapy at 24 hours after the initiation of treatment based on assessment of effectiveness and FVIII blood levels.

**Secondary Efficacy Endpoints**

- The overall proportion of serious bleeding episodes successfully controlled with OBI-1 therapy, as assessed by the investigator.
- The proportion of bleeding episodes responsive to OBI-1 therapy at designated assessment time points after the initiation of therapy, as assessed by the investigator.
- Frequency, total dose, and total number of infusions of OBI-1 required to successfully control qualifying bleeding episodes.
- Correlation between response to OBI-1 therapy at specified time points and eventual control of serious bleeding episodes.
- Correlation between the pre-infusion anti-OBI-1 antibody titers, the total dose of OBI-1, the outcome at 24 hours and the eventual control of the bleeding episode.
- Drug exposure was determined by means of population PK analysis for the sparse -bleeding state-data, and compartmental analysis for the complete -non-bleeding state- data (estimated PK parameters: Clearance (Cl), Volume of distribution (Vd), area under the concentration-time curve (AUC) and Cmax/Dose).
Safety Endpoints
- TEAEs and serious adverse events (SAEs) throughout the study.
- Biochemistry, hematology, urinalyses and vital signs.
- Anti-human factor VIII antibody titer.
- Anti-OBI-1 antibody titer.
- Anti-host cell protein (BHK) antibody titer.

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION, AND BATCH NUMBER

Investigational Product(s) | Initial dose 200U/kg - additional doses at the discretion of the investigator based on FVIII activity level and clinical assessment of response to treatment (upper limit: 400 U/kg every 2 hours).
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Dosage form: injectable
Dosage frequency: at the discretion of the investigator, based on FVIII activity level and clinical assessment of response to treatment
Mode of Administration: IV
Batch number(s): Protocol 301a, C14953; C15839; E12859
Protocol 301, C09149; C14953; D20623; D30991; C08163; C13360; C15839; E10899; E12312; E13816; E21866; E14916; D33081; E04875; E05451; F02475; E01968; E08179

Placebo/ Control/ Comparator | Not Applicable
Duration of treatment: | The study duration for each subject was approximately 3 to 4 months for each qualifying bleeding event. This duration included 90 days follow-up after the final treatment with OBI-1. Subjects whose initial bleed was successfully treated with OBI-1 were eligible for retreatment with OBI-1 for subsequent qualifying bleeds while still active in the study (i.e., through final follow-up visit).

SUBJECT SELECTION

Planned | A maximum of 28 subjects
Analyzed | Safety Analysis Dataset (SAD, n = 29);
“Intent-To-Treat” population (ITT, n = 29);
“Per Protocol” population (PP, n = 23);
“Pharmacokinetic” population (PK, n = 9):
# DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

## Inclusion Criteria

1. Males or females ≥18 years of age
2. Written informed consent from subject, trusted person, or person who is legally authorized to sign on behalf of the subject (legal representative in United States), depending on local regulations
3. Subjects with acquired hemophilia with autoimmune inhibitory antibodies to human FVIII with a clinical diagnosis established by the following criteria:
   a) Prolonged activated partial thromboplastin time (aPTT)
   b) Prothrombin time ≤ upper limit of normal + 2 seconds and platelet count within normal range
   c) Abnormal aPTT mixing study (patient-normal control 1:1) consistent with a FVIII inhibitors
   d) Reduced FVIII activity level (below 10%)
4. Has a serious bleeding event, as documented by the investigator
5. Be willing and able to follow all instructions and attend all study visits
6. Subjects taking antithrombotics (such as clopidogrel, heparin or heparin analogue) may be included provided three half-lives of the agent have elapsed since the last dose of the agent.
7. Life expectancy, before the onset of the hemorrhagic episode, of at least 90 days
8. Subjects of reproductive age must use acceptable methods of contraception and if female, undergo pregnancy testing as part of the screening process.

## Exclusion Criteria

1. Hemodynamically unstable after blood transfusion, fluid resuscitation and pharmacologic or volume replacement pressor therapy
2. Has an established reason for bleeding that is not correctable
3. Bleeding event assessed likely to resolve on its own if left untreated
4. Anti–OBI-1 inhibitor that exceeds 20 BU (prospectively or retrospectively)
5. A subsequent bleeding event at the site of the initial qualifying bleeding event within 2 weeks after the final OBI-1 dose for the initial qualifying bleeding event, or a subsequent bleeding event at a different site than the initial qualifying bleeding event within 1 week after the final OBI-1 dose for the initial qualifying bleeding event will not be considered “new” qualifying bleeding event.
6. Prior history of bleeding disorder other than acquired hemophilia
7. Known major sensitivity (anaphylactoid reactions) to therapeutic products of porcine or hamster origin; examples include therapeutics of porcine origin (e.g., previously marketed porcine FVIII, Hyate:C®) and recombinant therapeutics prepared from hamster cells (e.g., Humira®, Advate®, and Enbrel®)
8. Use of hemophilia medication: activated recombinant factor VII within 3 hours before OBI 1 administration or activated prothrombin complex concentrate treatment within 6 hours before OBI 1 administration
9. Participation in any other clinical study within 30 days of the first OBI-1 treatment
10. Anticipated need for treatment or device during the study that may interfere with the evaluation of the safety or efficacy of OBI-1, or whose safety or efficacy may be affected by OBI-1
11. Is currently pregnant or breastfeeding, or planning to become pregnant or father a child during the study
STATISTICAL METHODS
The rate of positive response was presented with a two sided 95% Clopper-Pearson CI. PK parameters from the bleeding state were estimated by population PK modeling or when subject’s PK data were insufficient by a Bayesian approach, using the established OBI-1 population PK model. PK data from the non-bleeding state were analyzed using a compartmental analysis. Incidence of treatment emergent AEs (TEAEs) were summarized by system organ class, severity and relationship to OBI-1 treatment.

SUMMARY – CONCLUSIONS
Efficacy Results:
The efficacy of OBI-1 to control serious bleeds in subjects with AHA was assessed in this study primarily by the response to treatment after 24 hours (as determined both clinically and by FVIII activity levels achieved), and secondarily by the frequency, total dose, number of infusions of OBI-1 and time required to achieve hemostasis.

Primary Efficacy Outcome:
All 29 subjects presenting with a serious (“qualifying”) bleed and treated with an initial dose of 200 U/kg had a descriptively positive response to treatment at 24 hours, which was defined as effective (bleeding stopped and ≥50% increase in FVIII) or partially effective (bleeding reduced and ≥20% increase in FVIII) control of the bleed. There is strong statistically significant evidence in support of response rate > 50%.

Secondary Efficacy Outcome(s):
There was a trend toward treatment response in less than 24 hours, as a positive treatment response was observed in most subjects by 8 or 16 hours after the initial OBI-1 infusion. There appears to be no impact of the type of bleed or baseline hFVIII inhibitor titer on treatment response in this time period.

The qualifying bleed was eventually successfully treated in 25 of 29 subjects under OBI-1 treatment, as assessed by the investigator. This assessment was performed at the time of final treatment dose or progression to healing phase dosing.

There was variability in dosing frequency, total dose, and the total number of infusions required to reach successful treatment outcome, which indicates that subject response to OBI-1 therapy is very individualized to patient clinical condition and type of bleed.

Among the 4 subjects who did not achieve “treatment success” (defined as control of qualifying bleeding event at the time of final treatment dosing), there were no apparent similarities in total dose, or demographic characteristics. Of note, these 4 subjects did show a positive response at 8, 16 and 24 hours after first infusion.

All 25 qualifying bleeds that achieved “treatment success”, had a positive response to treatment within the first 24 hours.

Bleeding events that were concurrent with or subsequent to the qualifying bleed (i.e. subsequent and non-target bleeds) were controlled in all but 2 subjects who died due to their co-morbidities.

Results of the efficacy evaluation in 29 subjects indicate that OBI-1 is effective in controlling serious bleeding episodes in subjects with AHA.
Safety Results:
OBI-1 was safe and well tolerated for the treatment of serious bleeds in subjects with AHA (N=29).

There were no serious adverse reactions, and no related thrombotic events occurred.

Five subjects had newly developed anti-pFVIII antibodies (inhibitors) after treatment (range: 0.6 - 108 BU at last follow-up visit). In 2 of these 5 subjects, inhibitor development was assessed as a related non-serious AE and the subjects were discontinued from the study. Of note, anti-pFVIII antibodies were also detected prior to infusion in 10 patients (range: 0.8 – 29 BU), yet all subjects had a positive response to treatment at the 24h assessment.

None of the subjects developed anti-BHK antibodies.

Other non-serious AEs related to treatment as assessed by the investigator were: hypotension and constipation in 1 subject; 2 instances of PICC line occlusion in 1 subject; hypofibrinogenemia in 1 subject; and mental status changes in 1 subject. All related TEAEs were mild or moderate in severity and all completely resolved except for one instance of a positive anti-porcine inhibitor which was ongoing at the time of subject study completion. Based on review of the investigator assessed related adverse events by the sponsor, the two incidences of anti-porcine inhibitors are considered related to OBI-1 treatment, with all others unlikely related to OBI-1 treatment.

Conclusion:
OBI-1 treatment is safe and well tolerated and shows a positive response for the treatment of bleeding events in subjects with AHA. Furthermore, because levels of FVIII activity can be monitored, individualized treatment courses can be tailored to account for individual responses to OBI-1 for efficacy and safety considerations, which provides an unmet need in the treatment of bleeds in AHA patients.

Treatment with OBI-1 has shown that it can be a safe and effective first-line therapy for subjects with AHA who have serious bleeding events.

Date of Report: 2014 MAY 27