London, 23 July 2015
EMA/627966/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Obizur

International non-proprietary name: susoctocog alfa

Procedure No. EMEA/H/C/002792/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AEX	anion exchange
aPTT	activated partial thromboplastin time
AUC0-∞	area under the plasma concentration time curve from time 0 to infinity
AUCt	area under the plasma concentration time curve from time 0 to the last experimental point
AUCτ	area under the plasma concentration-time during a dosage interval
BHK	baby hamster kidney
CA	chromogenic assay
CBT	cuticle bleeding time
CFU	colony forming unit
CL	plasma clearance
Cmax	peak plasma level
DEAE	diethylaminoethanol
DP	drug product
dPBS	Dulbecccos phosphate buffered saline
FBDS	formulated bulk drug substance
GLP	Good Laboratory Practice
HP	high performance
IU	International Units
OBI-1	recombinant porcine factor VIII, B-domain deleted
OSCA	one stage coagulation assay
PETG	polyethylene terephthalate glycol
PS80	polysorbate 80
PSI	pound per square inch
RB	roller bottle
SD	standard deviation
SOP	standard operating procedure
t1/2	elimination half life
TBP	tributylphosphate
Tmax	time of peak plasma level
U	unit
Vdss	volume of distribution at steady state
WCB	working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Baxalta Innovations GmbH submitted on 30 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Obizur, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 July 2012.
Obizur was designated as an orphan medicinal product EU/3/10/784 on 20 September 2010. Obizur was designated as an orphan medicinal product in the following indication: Treatment of haemophilia A.

The applicant applied for the following indication:

Treatment of bleeding episodes in patients with acquired haemophilia A.

OBIZUR is indicated in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that susoctocog alfa was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0040/2012 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Marketing Authorisation under exceptional circumstances

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004 based on the following

claim: the applicant is unable to provide comprehensive clinical data on the efficacy and safety under normal conditions of use due to the rarity of the indication.

The applicant justified that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, due to the fact that:

- Acquired Haemophilia is a rare bleeding disorder
- Due to the extremely limited subject availability, it was not feasible to identify and recruit the minimum number of subjects recommended by the Note for Guidance on the clinical investigation of recombinant Factor VIII and IX products for the first PK study.

The applicant proposed a specific obligation in relation with article 14(8) of Regulation (EC) No 726/2004 by establishing a prospective non-interventional study to evaluate the safety and effectiveness of Obizur in real-life practice (EU) and a recombinant porcine sequence FVIII treatment registry (USA)

New active Substance status

The applicant requested the active substance susoctocog alfa contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 29 May 2009, 22 October 2009, 15 December 2011 and 19 December 2013. The Protocol Assistance pertained to quality and clinical aspects of the dossier.

Licensing status

Obizur has been given a Marketing Authorisation in United States on 23 October 2014 and Puerto Rico on 8 June 2015.

A new application was filed in the following countries: Canada, Colombia, Australia and Switzerland.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: Outi Mäki-Ikola

- The application was received by the EMA on 30 June 2014.
- The procedure started on 23 July 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2014.
- PRAC RMP advice and assessment overview adopted by PRAC on 6 November 2014.
- During the meeting on 20 November 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 February 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 March 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 10 April 2015.
- During the CHMP meeting on 23 April 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 June 2015, and requested a marketing authorisation under exceptional circumstances pursuant to article 22 of Directive 2001/83/EC.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues on 30 June 2015.
- During the meeting on 23 July 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Obizur.
- Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Obizur as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

2. Scientific discussion

2.1. Introduction

Acquired haemophilia is owing to the development of auto-antibodies directed against factor VIII: the resulting reduction in factor VIII activity is associated with a significant bleeding tendency. Bleeding may be spontaneous or in response to (often minimal) trauma. The classical form of haemophilia A is an x-linked (i.e. occurs in males) congenital bleeding tendency associated with a reduction in the factor VIII activity, where bleeding typically occurs into large joints.

Acquired haemophilia occurs in about 2 per million of the population, in all ethnic groups and with worldwide prevalence and is typically a disorder of middle age, occuring equally in both sexes. The pattern of bleeding seen in acquired haemophilia is distinct from that seen in the more common congenital form. Bleeding most commonly occurs into skin and soft tissues. Cases may present with, for example, compartment syndrome, haematuria, gastrointestinal bleeding and prolonged post-partum bleeding. The reported mortality rate is up to 20% (Kessler et al 2005).

About half of cases have an associated condition such as malignancy, auto-immune disease, pregnancy or present as an adverse reaction to certain medicines. In other cases, the condition is labelled as idiopathic. Elderly patients may be prescribed medications that can exacerbate the bleeding tendency in acquired haemophilia through inhibition of platelet function e.g. aspirin for cardiac disease.

The typical laboratory findings of acquired haemophilia are a prolonged activated partial thromboplastin time (APTT) and a low factor VIII. The thrombin and prothrombin times and the

platelet count and function are typically normal. Mixing studies may be used to demonstrate the presence of a time-dependent inhibitor of factor VIII, as described in the World Federation of Haemophilia laboratory manual: Diagnosis of Haemophilia and Other Bleeding Disorder (http://www1.wfh.org/publications/files/pdf-1283.pdf). The antibodies in acquired haemophilia are invariably directed towards factor VIII and not factor IX. The antibodies are usually polyclonal IgG4 antibodies (rarely IgM or IgA). Most antibodies bind to the 44-kD A2 domain and / or the 72-kD C2 domain of factor VIII and do not fix complement. There is a poor correlation between the measureable factor VIII level and bleeding severity in acquired haemophilia (in distinction to congenital haemophilia).

The objectives in treating patients with acquired haemophilia A are (i) to stop the acute bleed and (ii) to suppress inhibitor formation.

Exogenous human factor VIII is likely to be very rapidly inactivated by a significant titre of inhibitory antibody and so may lack efficacy, even at high doses. By-passing agents (that circumvent the normal factor VIII-dependent coagulation cascade and hence the effect of factor VIII inhibitors) such as activated prothrombin complex concentrate (aPCC) or activated recombinant factor VII (rFVII) may be used. Laboratory tests are not informative and so response to treatment must be assessed on clinical grounds.

There are published case reports of venous and arterial thrombosis associated with both by-passing agents. Exposure to activated prothrombin complex concentrate (which contains factor VIII) may lead to an increase in inhibitor titre of the recipient.

Immunosuppressive therapies such as steroids and cyclophosphamide are effective in eradicating factor VIII inhibitors in up to 70% of cases (about 1 in 5 patients will display a recurrence of the autoantibody).

Porcine clotting factor VIII (Hyate:C, purified from the plasma of pigs) was used to treat severe bleeding episodes in patients with haemophilia and who have antibodies to human clotting factor -from 1984 to 2004. Hyate:C was withdrawn due to concerns over exposure of human recipients to pig-derived infectious agents.

Obizur is a purified, recombinant, B-domain-deleted porcine factor VIII that is expressed by a genetically engineered baby hamster kidney cell line with a DNA construct coding for 1448 amino acids. The molecular weight of Obizur is approximately 175 kDa (based on the amino acid sequence).

The rationale for Obizur is that it is sufficiently similar to human factor VIII to have haemostatic effect in humans yet sufficiently different so as to be less susceptible to inactivation by circulating antibodies.

The Applicant applied for the following indication:

“Treatment of bleeding episodes in patients with acquired haemophilia A.

OBIZUR is indicated in adults.”

The final indication approved by CHMP is:

“Treatment of bleeding episodes in patients with acquired haemophilia caused by antibodies to Factor VIII.

OBIZUR is indicated in adults.”

The recommended initial dose is 200 U per kilogram bodyweight, given by intravenous injection.

Initial Phase

Type of Bleeding	Target Factor VIII Trough Activity (Units per dL or % of normal)	Initial Dose (Units per kg)	Subsequent Dose	Frequency and Duration of Subsequent Dosing
Mild and moderate superficial muscle / no neurovascular compromise and joint bleeding	> 50%	200	Titrate subsequent doses based on clinical response and to maintain target Factor VIII trough activity	Dose every 4 to 12 hours, frequency may be adjusted based on clinical response and measured Factor VIII activity
Major moderate to severe intramuscular, retroperitoneal, gastrointestinal, intracranial bleeding	> 80%			

Healing phase

Once bleeding has responded, usually within the first 24 hours, continue OBIZUR with a dose that maintains the trough FVIII activity at 30-40% until bleeding is controlled. The maximum blood FVIII activity must not exceed 200%.

The clinical development programme is based on safety and efficacy data from 28 subjects with AHA treated with OBIZUR in the phase 2/3 open-label clinical study OBI-1-301/OBI-1-301a (CSR OBI-1-301). The safety, haemostatic activity and pharmacokinetic profile of OBIZUR is supported by results of an open-label phase-2 study in patients with CHA with inhibitors (CSR OBI-1-201) and a randomized phase-1 study comparing OBIZUR with a plasma-derived porcine factor VIII (CSR OBI-1-101).

Scientific advice

General scientific advice on product development was given by the MHRA (UK) and MPE (SE) in October 2008, by the CHMP in May 2009 and by MEB (NL) in July 2009.

Protocol assistance was given by the CHMP in December 2011 (EMA/CHMP/SAWP/945059/2011) in which the company was advised to collect 'relatively dense pharmacokinetic profiles in individual subjects' and that, owing to the rarity of acquired haemophilia A, the 'concept of a single-arm, open label study in a limited number of patients' is agreed. 24hrs as the selected time for the primary efficacy endpoint was accepted. Regarding the use of the one stage coagulation assay for assigning potency, the Applicant was advised that since the chromogenic assay is not mandatory, the choice of assay should be supported by scientific data.

Follow-up protocol assistance was given by the CHMP in December 2013 (EMA/CHMP/SAWP/749449/2013) in which the company was advised to submit an application on the basis of 29 planned patients (to include 4 patients treated under an expanded access programme).

2.2. Quality aspects

2.2.1. Introduction

Susoctocog alfa (Recombinant Porcine Factor VIII, B-Domain Deleted) is a purified glycoprotein produced in baby hamster kidney (BHK) cells by recombinant DNA technology. Obizur is available as

powder in single-use vials containing 500 units (nominal) of coagulation factor VIII (FVIII; recombinant) per vial. One unit of susoctocog alfa is equivalent to the potency of factor VIII in one ml of normal human plasma. The finished product is a kit, which includes the drug product vial, the 1 ml pre-filled WFI syringe for reconstitution and the individual syringe vial adapter. The vial adapter consists of a 15 µm in-line filter and the puncture of the rubber stopper is achieved by means of the integral plastic spike.

Obizur is for intravenous use after reconstitution with water for injection (WFI).

2.2.2. Active Substance

General information

The molecular weight of Obizur (susoctocog alfa) is approximately 175 kDa (based on the amino acid sequence).

Susoctocog alfa is a heterodimer consisting of a heavy chain and light chain held together through non-covalent interactions consisting of approximately 1448 amino acids. Full length human and porcine factor VIII are composed of the domain structure A1-A2-B-A3-C1-C2. In susoctocog alfa, the porcine factor VIII B-domain, which is not known to be necessary for procoagulant activity, has been replaced with a twenty-four amino acid linker containing amino acids of the B domain adjacent to the C terminus of the heavy chain and amino acids of the B-domain adjacent to the N terminus of the light chain. Thus, the naturally occurring cleavage sites for the B-domain of factor VIII have been incorporated into the susoctocog alfa molecular construct. The susoctocog alfa structure also includes the original activation sequence of the molecule within the light chain, including a 40 amino acid activation peptide. The primary susoctocog alfa molecule contains intramolecular disulfide bonds, free sulfhydryls, sulfated tyrosine residues, and N-linked and O-linked glycosylation sites.

Manufacture, characterisation and process controls

Manufacturer

Information on the manufacturing sites and their responsibilities was provided.

Description of manufacturing process and process controls

Susoctocog alfa drug substance manufacturing process has been adequately described. Main steps are fermentation, recovery, purification and steps for virus inactivation and virus removal.

Briefly, the manufacturing of susoctocog alfa FBDS (Final Bulk Drug Substance) utilizes a roller bottle cell culture process for cell expansion and recombinant protein expression followed by a series of filtration and chromatographic steps to purify the product from process related impurities. The active substance manufacturing process includes as well two orthogonal viral removal/inactivation steps for clearance of potential virus particles.

A batch of FBDS is defined as deriving from a single vial of Working Cell Bank (WCB).

Control of materials

Information on compendial and non-compendial raw materials used in the active substance manufacturing process has been submitted.

The origin and the description of the coding sequences for the B-domain deleted porcine factor VIII construct as well as the cloning strategy for the expression construct were described.

The Applicant is using a concept of two-tiered cell banking system that consists of MCB and WCB. The source, history and manufacture of the BHK cells, MCB and WCB have been described and documented in detail according to ICHQ5B. Both MCB and WCB have been qualified and characterised by extensive testing for specified parameters. However, it is recommended that the Applicant further evaluates and thereby confirms the genetic stability of the BHK cells (see 2.2.6).

The establishment of a new WCB was described and the protocol to establish a new WCB can be accepted.

The storage and stability of the cell banks was established according to the ICH Q5D guideline.

Control of critical steps and intermediates

The application is not a QbD application, but a large number of critical steps were defined together with process parameters, in-process limits and consequences when these are out of range. While the list of critical steps was largely agreed with and accepted, a number of other concerns were raised with regard to the control of critical steps. These were resolved by the Applicant with the responses submitted. For non-conformance, the batch will be terminated unless there is a technical justification, supported by adequate validation. If the non-conformance batch is to be released, the review of the non-conformance will entail sufficient rigor to ensure that the quality of the product is unaffected.

Process validation

The active substance manufacturing process was validated conventionally. The results from these validation batches are deemed to be consistent.

Manufacturing process development

The development of the FBDS manufacturing process was carried out at two manufacturing sites. Changes to manufacturing processes, analytical methods and reference standards have occurred during the development. With the LoQ D120 the applicant was requested to provide a clear overview of the changes, including an impact analysis of their criticality and a clarification how comparability of different batches used in clinical trials has been ensured, if critical/major changes have taken place. Subsequently, summaries of changes in cell culture and purification process development were provided as well as a summary of changes in analytical methods.

The changes in reference standard were described as requested. According to the Applicant the only major changes which resulted in an effect on the potency testing results were associated with two reference standard lot numbers which were calibrated against the WHO 7th or WHO 8th International Standard. These effects were mitigated by implementation of a correction factor for the purposes of data comparison during stability. In addition, the Obizur product specifications were re-evaluated via change control to account for the known differences.

A more thorough table of summary of comparability data across manufacturing process phases for FBDS and FDP was presented in the response package. The analytical results of the batches supporting clinical studies of Obizur showed that the Obizur FBDS or FDP can be considered comparable throughout the phases with improved purity of the material produced in support of Phase 3 clinical studies.

Characterisation

Extensive characterisation of the rFVIII has been carried out including the molecular structure as well as process and product related impurities. The porcine derived FVIII coagulation factor has been shown having a similar biological effect as human factor VIII.

Specification

After revision during the evaluation procedure, the active substance specifications were considered adequately set and justified.

The specification for impurity was originally thought to be set too wide which allowed a high amount of this impurity per dose in the product. With the response to the D120 LoQ the applicant justified these higher limits by referring to the variability in the amount of the impurity in clinical trial batches. However, the current high levels of porcine rFVIII proposed to be dosed (200 U/Kg) may mean that a relatively high level of the impurity could be given to a patient with very low levels of circulating porcine rFVIII. Results from validation batches with substantially less content of this impurity than the mean obtained for the clinical batches indicate the possibility to produce batches with lower impurity content. The applicant has tightened the limits of this impurity and committed to review the impurity specifications once more process experience is gained (see 2.2.6).

Analytical methods

The FBDS is tested using a combination of compendial and non-compendial methods. The methods applied, their validation and their acceptance ranges were presented in the dossier.

Information on the potency assay is included in the Finished Product section under the heading Analytical methods (see below).

Reference materials

There is a comprehensive reference standard program and qualification in place for reference standards used within Obizur analyses. There is no international reference standard available for recombinant porcine factor VIII. Therefore, Obizur is labelled in units.

The primary reference standards were prepared from Obizur drug substance or drug product, depending on the reference standard use. Each in-house reference standard is qualified for use by meeting release test, comparison with previous reference standard, and through additional characterisation. The reference materials used by the applicant have been well characterised using additional analysis that is used for batch release.

Stability

The Applicant has studied the stability of the active substance properly according to ICH Q5C. The proposed FBDS shelf-life is approvable.

Comparability exercise for Active Substance

Reference is made to manufacturing process development.

New Active Substance Status

The active substance susoctocog alfa, a recombinant antihaemophilic factor VIII, porcine sequence, B-domain deleted is produced in Baby Hamster Kidney cells. From 1984 to 2004, a plasma-derived

porcine factor VIII product was licensed under the name of Hyate C. Susoctocog alfa, as recombinant product, was developed as an improvement in safety to this product.

Susoctocog alfa is a biological active substance not previously authorised as a medicinal product in the European Union. There is no essentially similar medicinal product authorised in the community or has previously been authorized as a medicinal product which is comparable in the manufacturing and safety of susoctocog alfa.

Based on the review of the data CHMP considered that the active substance susoctocog alfa contained in the medicinal product Obizur is to be qualified as a new active substance in itself.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The pharmaceutical form of Obizur 500 U is powder and solvent for solution for injection. There is only one dosage strength.

The container closure system has been satisfactorily described. Obizur 500 U is supplied in 3 ml type I borosilicate glass vials as lyophilisate for reconstitution with 1 ml sterile water for injections (WFI). The glass vial is closed with a 13 mm rubber stopper with an inert coating and sealed with a 13 mm aluminium overseal and tamper proof snap-off PP flip top. The drug product is intended to be marketed as a kit containing a prefilled syringe with WFI for reconstitution and an adapter as a medical device.

Table 4: Drug product composition

Ingredient	Reference
Susoctocog alfa	In-house
Polysorbate 80	NF/Ph. Eur.
Sodium chloride	USP/Ph. Eur.
Calcium chloride dihydrate	USP/Ph. Eur.
Sucrose	NF/Ph. Eur.
Tris base	USP/Ph. Eur.
Tris HCl	Biotech reagent grade
Trisodium citrate dihydrate	USP/Ph. Eur.

The pharmaceutical development has been adequately described. The quality of all excipients has been described and their presence in the final product justified through extensive formulation development

studies. The current formulation has been used in all clinical studies to date and is intended for commercial supply.

Manufacture of the product and process controls

Manufacturer

Information on manufacturers and their responsibilities was provided.

Description of manufacturing process, process controls and validation

The drug product (DP) manufacturing process has been sufficiently described. The batch formula has been presented.

The DP manufacturing process flow chart has been submitted. The Applicant has defined critical process steps and implemented critical control parameters and acceptance criteria which are considered reasonable. Regarding the control strategy the same concerns were raised as for the manufacturing process for the active substance and subsequently resolved by the Applicant (see above).

The process was validated conventionally with commercial batches. The validation results were consistent showing that the manufacturing process is well controlled.

Control of excipients

Most of the excipients are compendial and the quality is controlled according to the corresponding monographs.

Product specification

Overall, the drug product specifications are considered adequately set and justified.

Analytical methods

Analytical methods were described and validated.

The applicant investigated two methods for potency determination: the one stage coagulation assay (OSCA) and the chromogenic assay (CA). The use of the OSCA for potency labelling was considered acceptable based on the justification provided by the applicant and this would be in agreement with previous CHMP scientific advice. It is noted that the Ph. Eur monograph method for human rFVIII requires the use of the chromogenic rather than the OSCA, however, there is no requirement for porcine rFVIII.

The applicant investigated the effect of different commercially available aPPT reagents on the potency of Obizur reference standards in the OSCA (aPPT reagent with SiO2 activator and aPPT reagent with ellagic acid as activator). The potency results showed that the aPPT reagent with the SiO2 activator were lower than those obtained with the aPPT reagent with ellagic acid activator. Subsequently the applicant initiated a collaborative field study assessing the variability of Factor VIII activity assays for analysis of Obizur. 34 clinical and haemostasis laboratories measured the FVIII activity of Obizur at 3 different concentrations using OSCA assays with a variety of aPTT reagents, where 25 laboratories used SiO2 and 9 laboratories used ellagic acid as activator. Results showed that all laboratories produced similar results for Obizur within the 80-120% variability of the stated sample potency.

Reference materials

See above.

Stability of the product

Stability data support the shelf life claim in the SmPC. The proposed shelf life at 2-8 °C with light protection and storage after reconstitution at ambient temperature and light conditions is considered approvable.

Comparability exercise for finished medicinal drug product

There were few changes in one step of the drug product manufacturing process. Results showed that the pre- and post-change batches were comparable.

Adventitious agents

The Applicant has addressed both non-viral and viral contaminants. Overall the risk of TSE can be considered negligible.

The BHK cell line used for the production was well characterised. MCB, WCB and EPC have been characterised for the absence of contaminating viruses according to ICHQ5A.

A virus validation study was performed according to CPMP/BWP/268/95. The capability of process steps to reduce adventitious viruses has been adequately demonstrated using model viruses. The viruses for the clearance studies can be considered to represent a wide range of physico-chemical properties that demonstrate the ability of the system to eliminate the viruses in general. The viral clearance validation was considered acceptable.

Finished product – Solvent (Water for Injections)

The solvent is sterile Water for Injections (WfI) according to Ph. Eur., USP-NF, Ph. J. The WfI pre-filled syringes are manufactured and tested for compliance with the appropriate specifications.

The description of the WfI manufacturing process, in-process controls, validation data and specification are considered adequate. The stability studies were performed according to the ICH Q1A guideline. The claimed shelf-life for the sWFI pre-filled syringes when stored at 2°C to 30°C was confirmed with the stability data obtained.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In general, information on development, manufacture and control of the active substance and finished product has been presented in an acceptable manner. A number of other concerns were raised during the evaluation procedure which were satisfactorily resolved by the applicant with some points recommended for further development (see 2.2.6)

Overall, the data provided on the manufacturing and control of the active substance and finished product indicate consistency and uniformity of product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Appropriate measures to ensure TSE and viral safety of the product are in place. Therefore, the risk of contamination with TSE or viral agents is considered negligible.

Based on the review of the data CHMP considered that the active substance susoctocog alfa contained in the medicinal product Obizur is to be qualified as a new active substance in itself.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Obizur is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. It is recommended that the Applicant further evaluates and confirms the genetic stability of BHK cells.
2. In view of the high dosing regimen, it is recommended that the Applicant follows the amount of one impurity in future batches. The specifications should be reviewed according to the gained experience. If the manufacturing experience produces batches with low levels of this impurity, no further action by the company will be required. If the future batches produced show the same range of variability of the impurity that was seen in the clinical trial batches the company should consider investigating the source of this variability and adopt appropriate steps to reduce the variability in the levels of this impurity.

2.3. Non-clinical aspects

2.3.1. Introduction

Obizur is a B-domain deleted form of porcine factor VIII and is manufactured in a baby hamster kidney (BHK) derived cell line.

Primary pharmacodynamics studies comprised of *in vitro* binding to von Willebrand Factor and biological activity by chromogenic assay and *in vivo* testing in dog and mouse models. The pharmacokinetics of Obizur was investigated in the haemophilia A dog and cynomolgus monkey. The toxicology program included assessment of single dose toxicity in haemophilia A dogs and in the cynomolgus monkey, 28-days and 90-days repeat dose toxicity in cynomolgus monkeys, as well as two immunogenicity studies in haemophilic mice and in cynomolgus monkeys. The repeat dose toxicity studies were conducted in compliance with the GLP regulations. The single dose toxicity study in cynomolgus monkeys and the immunogenicity study were conducted under GLP, however no QA auditing of the laboratory analyses took place.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The in vitro functional characterisation studies for the Obizur molecule included an assessment of the kinetics of activation by thrombin and the binding affinity of Obizur to von Willebrand factor (vWF), as well as biological activity as determined by the chromogenic assay and one-stage coagulation assay. These studies are briefly outlined in this report and discussed in detail in the Quality section.

In vitro

Binding to von Willebrand Factor

In order to assess the interaction of Obizur with vWF, Obizur was incubated with vWF to generate bi-molecular complexes. Size exclusion chromatography (SEC) was used to separate bound complex from unbound Obizur and vWF, based on differences in molecular size. A titration technique using ratios of increasing amounts of OBI-1 to a fixed concentration of vWF was also employed. Using this titration technique, the profile of Obizur /vWF complex formation was determined from the SEC chromatograms. The data obtained supported the conclusion of published data (Lollar, 1987) that the stoichiometry of binding between Obizur with vWF was approximately 1:1 mole equivalent. This 1:1 stoichiometric ratio was observed for both the Obizur drug product (DP) and final batch drug substance (FBDS) batches tested.

Biological Activity by Chromogenic Assay:

The chromogenic assay (CA) for determining the potency of factor VIII is based on the indirect measure of the role of factor VIII in the activation of factor X. The chromogenic assay is the method used in the European Pharmacopoeia to measure human FVIII potency.

The rate of the conversion of factor X to factor Xa was measured as a change in optical density (OD) at 405 nm, resulting from the activated factor Xa converting a substrate releasing a coloured product (p-nitroaniline). Thus the OD at 405 nm was directly proportional to the amount of factor VIII activity in the sample.

The results of this assessment for 2 batches of Obizur DP and 2 batches of Obizur DS showed that Obizur was capable of reacting with thrombin and Factor IXa to catalyse the activation of Factor X. The

Obizur batches of FBDS tested demonstrated comparable Factor X activation near the target FBDS potency of 1100U/mL, as did Obizur batches of DP near the target DP potency of 500 U/mL.

Biological Activity by the One-Stage Coagulation Assay:

The one-stage coagulation assay (OSCA), used for determining the potency of Obizur, was based on its ability to shorten the prolonged coagulation time of factor VIII deficient plasma.

Obizur was first activated by thrombin, and then together with factor IXa activates factor X (to factor Xa) in the presence of calcium ions and phospholipids, thereby initiating the coagulation cascade (similar to the intrinsic pathway in the natural coagulation cascade). Factor Xa is then available to catalyse prothrombin to thrombin at a rate that is proportional to the Obizur activity in the sample. The coagulation was monitored at 660 nm as a function of turbidity. The time required to reach the total change in light intensity was defined as the coagulation time, and was proportional to the level of Obizur present in the sample tested.

The data obtained demonstrated the ability of Obizur to be activated by thrombin and react with Factor IXa to initiate the coagulation cascade, leading to clotting in Factor VIII-deficient plasma. The Obizur batches of formulated bulk drug substance tested demonstrated comparable clotting activity near the target potency of 1000 U/mL, as did Obizur batches of drug product near the target potency of 500 U/mL.

In vivo

Efficacy of Obizur in a Knock-out Mouse Haemophilia A Model

A study was conducted to determine the comparative efficacy of recombinant B-chain deleted porcine factor VIII (Obizur; Lot 214-01-001) and Hyate:C, a plasma-derived porcine factor VIII (previously marketed in the US but commercial production discontinued in 2004).

Male and female haemophilia A mice (strain E 16 mice), produced by targeted disruption of exon 16 in the factor VIII gene and backcrossed into a C57BL/6 background (Bi, 1995), were used to evaluate the efficacy of Obizur compared to Hyate:C (PCMU-101A). Survival/mortality at 24 hour following tail transection was the efficacy parameter monitored.

The ED_{50} values determined were 89 U/kg and 64 U/kg for Obizur and Hyate:C, respectively. The difference in results was not statistically significant.

Acute blood loss was found to equal body weight loss. At the time of death, untreated haemophilia A mice lost 5.0% of their initial body weight. Surviving mice treated with Obizur or Hyate:C or normal mice lost 2.9%, 2.7% and 3.4%, respectively, of their body weight at 2 hours which was significantly less than in the control hemophilia A mouse group.

Efficacy of Obizur in the Haemophilia A Dog Model

Other studies were conducted in a canine model of haemophilia A in which dogs had no circulating factor VIII activity (PCD-101). The dogs (n=2 to 4) were administered a single injection of either 3, 25, and 100 U/kg Obizur or Hyate:C in a cross over design with the subsequent injection of the other product approximately four days later. Animals were observed for adverse effects. Blood samples were taken at intervals up to 72 hours post dose and analysed for blood count (including platelet count), partial thromboplastin times, prothrombin times, clottable fibrinogen levels and fibrin degradation products. In the cuticle bleeding time (CBT) test, the cut cuticles of anaesthetised dogs were observed for up to 12 minutes and the CBT determined.

No adverse effects or behaviour were observed during the study. There were no significant changes in heart rate, respiratory rate or body temperature. Apart from a positive test for fibrin degradation products in a single dog, no haematologic toxicity was documented during the study

Obizur (3 to 100 U/kg) was effective at decreasing the CBT in seven of the nine evaluations. Obizur appeared to be more effective in correcting the bleeding tendency than Hyate:C.

Secondary pharmacodynamic studies

No specific secondary pharmacodynamic studies were conducted. Any secondary pharmacodynamic effects were assessed as part of the pharmacology and toxicology studies.

Safety pharmacology programme

The safety pharmacology of Obizur was assessed as part of the pharmacology and toxicology studies in the haemophilia A dog and the cynomolgus monkey.

Respiratory and cardiovascular

Heart rate and respiratory rate were assessed in haemophilia A dogs (n=6/sex/group) (PCD-101). No adverse effects were observed following intravenous injection of Obizur at doses of 3, 25 and 100 U/kg.

In a repeat dose toxicity study (PCM-101), cynomolgus monkeys (n=1/sex/group) were intravenously administered 100, 300, 600 and 1000 U/kg Obizur daily for 28 days with dose increases every 7 days. Body temperature, respiratory rate and blood pressure were measured at intervals up to Day 22 prior to dosing and at 1 and 4 hours post dose.

No significant changes in body temperature, heart rate, respiratory rate and blood pressure were observed in treated animals (in all dose groups) as compared to baseline.

In a repeat dose toxicity study in cynomolgus monkeys (n=6/sex/group) intravenously administered daily doses of 75, 225 and 750 U/kg (corresponding to actual doses of 82.5, 247.5 and 825 U/kg) or Hyate:C at 100 U/kg for 90 days, electrocardiograms (EGGs) were recorded from all animals pre-study and prior to dosing on Days 7, 28 and 90 (PCM-102).

No changes in the electrocardiographic evaluations were observed in the monkeys in all dose groups.

Pharmacodynamic drug interactions

The Applicant states that no studies on pharmacodynamic drug interaction were conducted because Obizur is applied as a monotherapy.

2.3.3. Pharmacokinetics

Methods of analysis

The one stage clotting assay and/or the chromogenic assay were used to determine factor VIII activity in the experimental animals. Prior to the initiation of the study in the haemophilia A dog, performance and reproducibility of the one stage clotting assay and the chromogenic assay were evaluated (PCD-101). The reference curves against which the test factor VIII levels were measured were either Hyate:C or Obizur for the quantitation of Hyate:C and Obizur, respectively. The Obizur and the Hyate:C reference material were measured against a plasma reference for factor VIII. These studies showed a value of 1.03 U/mL for Obizur and 0.96 U/mL for Hyate:C.

Values for factor VIII activity were higher for Obizur compared to Hyate:C at all doses and with both assays. The variability was generally lower when using the chromogenic assay (see Table 1). In the cynomolgus monkey (PCM-104, PCM-105) plasma concentrations of factor VIII were measured using the chromogenic assay. Plasma concentration of factor VIII in the 90 day toxicology study in the cynomolgus monkey was assessed using an one-stage clotting assay and a chromogenic assay (PCM-102).

Table 8. Assay Reproducibility with the One Stage Clotting Assays and Chromogenic Assay

	Assay Variability	
Compound	One stage clotting assay	Chromogenic assay
OBI-1	7-10%	2-3%
Hyate:C	8-13%	5-9%

Absorption

A study was conducted to compare the pharmacokinetics of Obizur and Hyate:C, in dogs with severe haemophilia A, following a single intravenous injection (PCD-101, 08/PKR/019).

Haemophilia A dogs (n=2 to 4) were administered Obizur or Hyate:C at three dose levels (3, 25 and 100 U/kg). Each dog was randomised to receive either Obizur first, followed by Hyate:C, or Hyate:C first followed by Obizur, within the respective dose level. Blood samples were collected before dosing and at intervals up to 72 hours post dose and analysed for factor VIII. A non-compartmental pharmacokinetic analysis of plasma factor VIII levels was performed individually for each dog. Plasma concentrations of factor VIII were corrected by subtracting the baseline factor VIII levels.

Plasma factor VIII values for Obizur were consistently higher than those obtained with equivalent doses of Hyate:C when measured either by the one stage clotting assay or the chromogenic assay. Considerable inter-animal variances in factor VIII values were noted at each of the three factor VIII doses.

Due to the small sample size, no statistical comparisons between pharmacokinetic parameters of Obizur and Hyate:C were performed. The AUC_{0-t} of both Obizur and Hyate:C increased with dose in a subproportional manner. Exposure to Obizur appeared higher than that to Hyate:C. The plasma CL and Vdss were lower for Obizur than for Hyate:C. No relevant differences were found between the half-lives of both compounds.

Table 9. Peak Values of Plasma fVIII Following Intravenous Injection of Obizur or Hyate:C to Haemophilia A Dogs

		One Stage Clotting Assay		Chromogenic Assay	
		Peak Values of Plasma Factor VIII (U/mL)			
Dose (U/kg)	Gender	OBI-1	Hyate:C	OBI-1	Hyate:C
3	F	0.05	0.04	0.191	0.091
	F	0.11	-	0.214	-
	M	0.21	0.14	0.223	0.082
25	F	1.08	0.60	1.413	0.427
	M	0.64	0.26	1.099	0.330
100	M	2.3	1.63	3.970	1.490
	M	5.13	2.26	6.530	1.494
	M	4.98	1.81	3.670	1.387
	F	5.24	2.11	3.740	1.328

Data are corrected for baseline factor VIII

Table 10. Pharmacokinetic Parameters of fVIII after Single Intravenous Administration of Obizur and Hyate:C to Haemophilia A Dogs

	OBI-1 (U/kg)			Hyate:C (U/kg)		
Parameter	3	25	100	3	25	100
AUC0-t (U.h/dL)	94 ±18	726, 1634	3204 ± 2532	11, 60	169, 358	1152 ± 511
$AUC_{0-\infty}$ (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	8.20, 9.10	33.0, 42.7	143 ± 5.64
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, 0.0364	0.049 ± 0.04	0.029, 0.136	0.059, 0.121	0.092 ± 0.034
Vdss (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, 9.07	9.257 ± 1.28

Data represent mean ± standard deviation when n≥3; Median and range for Tmax. When n=2, individual values are shown. PK parameters were calculated from the data obtained from the chromogenic assay.

A study was conducted to compare the pharmacokinetics of Obizur and Hyate:C, in the cynomolgus monkey following a single dose administration (PCM-104, 08/PKR/018). Experimentally non-naive cynomolgus monkeys were intravenously administered Obizur (49.5 or 77 U/kg) or Hyate:C (100 U/kg) (n=4 males/group). Blood samples were collected pre-dose and at 24 hours post-dose and analysed for factor VIII using a chromogenic assay. Plasma concentrations of factor VIII were corrected for baseline by subtracting that level from all subsequent samples. For the determination of pharmacokinetic parameters a non-compartmental pharmacokinetic analysis of plasma factor VIII levels was performed.

The plasma clearance of factor VIII following the intravenous administration of Obizur at dose levels of 49.5 and 77 U/kg (0.056 and 0.085 dL/h/kg) were lower than after intravenous administration of Hyate:C at dose level of 100 U/kg (0.107 and 1.09 dL/h/kg). Consequently the systemic exposure of Obizur after intravenous administration (944 and 1443 h·U/dL) at dose levels of 49.5 and 77 U/kg was higher than that obtained after administration of 100 U/kg Hyate:C (91.8 and 934·h·U/dL). Mean

plasma levels of factor VIII were comparable for the two doses of Obizur (see Table 11). Plasma levels of factor VIII were higher after administration of Obizur than after dosing with Hyate:C. This was attributed to the lower clearance of Obizur. Levels of Obizur remained above the basal values for 24 hours post dose.

Table 11. Pharmacokinetic Parameters of fVIII after a Single Intravenous Administration of Obizur and Hyate:C to Cynomolgus Monkeys

Test Article	OBI-1 (n=4)		Hyate:C (n=3)[#]
Dose (U/kg)	49.5	77	100
PK Parameters for baseline-corrected fVIII			
AUC $_{0\text{-}t}$ (U.h/dL)	826 ± 298	1011 ± 710	255 ± 213
AUC$_{0\text{-}\infty}$ (U.h/dL)	944 ± 276	1433 ± 1390	91.8, 934[a]
C$_{max}$ (U/dL)	107 ± 23	169 ± 32.2	78.7 ± 20.4
T$_{max}$ (h) *	0.98 (0.33-1.00)	0.33 (0.33-0.87)	0.7 (0.33-1.20)
CL (dL/kg)/h	0.056 ± 0.02	0.085 ± 0.05	0.107, 1.09[a]
Vdss (dL/kg)	0.576 ± 0.33	0.806 ± 0.26	1.54, 3.21[a]
t$_{1/2}$ (h)	6.71 ± 3.61	8.33 ± 5.09	1.32, 18.7[a]

*: tmax is described by the median and the range of values
#: Only PK parameters can be estimated in two of the three animals because one monkey did not have sufficient concentration values (individual values are shown)
a: this monkey shows an extrapolated AUC higher than 20 %

Distribution

No distribution studies have been performed with Obizur. The applicant stated that the volume of distribution at steady state (Vdss) values obtained from the absorption studies conducted in dogs and monkeys were comparable and approximate the blood volume/kg. Although no distribution study was conducted, the majority of Obizur administered was considered to be present in the circulating blood without distributing to other tissues or organs.

Metabolism

No metabolism studies have been submitted.

Excretion

No excretion studies have been submitted.

Pharmacokinetic drug interactions

No dedicated pharmacokinetic drug interaction studies have been submitted

Other pharmacokinetic studies

No other pharmacokinetic studies have been performed with Obizur.

2.3.4. Toxicology

The toxicology studies for Obizur included single dose toxicity studies in haemophilia A dogs and cynomolgus monkeys and repeat dose toxicity studies (up to 90 days) in cynomolgus monkeys. The

90-day repeat dose toxicity study was conducted in compliance with good laboratory practice (GLP) regulations. Hyate:C was used as a comparator. Pharmaco- and toxicokinetics were assessed in the single dose and 90-day repeat dose toxicity study. Local tolerance was assessed as part of repeat dose toxicity studies. Immunogenicity was evaluated in haemophilia A mice and cynomolgus monkeys.

Single dose toxicity

Dog

A study was conducted to compare the haemostatic efficacy, pharmacokinetics and tolerability of Obizur and Hyate:C, in a canine model of severe haemophilia administered a single intravenous injection (**PCD-101**). In a cross-over single dose study, Obizur and Hyate:C (at 3, 25 or 100 U/kg) were administered to dogs (n=6/sex/group) with congenital haemophilia.

General behaviour, heart rates, respiratory rates, body temperature and body weight were monitored post dose. The highest dose of 100 U/kg tested in this study corresponded to four times the minimal effective dose (25 U/kg) in this species.

No adverse effects or changes were detected in any of the parameters measured in any of the animals treated with up to 100 U/kg of either Obizur or Hyate:C.

Monkey

A study was conducted to compare the pharmacokinetics and tolerability of Obizur and Hyate:C in cynomolgus monkeys (PCM-104). Animals (n=4 males/group) were intravenously administered Obizur (49.5 or 77 U/kg) or Hyate:C (100 U/kg). The animals were observed for clinical signs, food consumption and body weight.

There were no clinical observations or changes in food consumption related to the administration of Obizur. One animal in the Hyate:C treatment group was reported to have had an allergic reaction and died. Following necropsy, the cause of this mortality remained inconclusive.

Repeat dose toxicity

28 day toxicity study: A study was conducted to determine the tolerability and potential immunogenicity of ascending doses of Obizur in cynomolgus monkeys when administered as once daily intravenous injections.

Two cynomolgus monkeys (1 male, 1 female) received daily intravenous injections (in the saphenous or cephalic veins) of Obizur for 28 days with dose levels increasing every seven days. Doses were increased from 100 to 300, 600 and 1000 U/kg.

Animals were observed for changes in clinical signs (including injection site observations), body weight and vital signs. Body weights were measured prior to the first dose (Day -1) and on Days 7, 14, 21 and 28. Vital signs were measured in the temporarily restrained non sedated animals. Measurements also included body temperature (rectal), respiratory rate, heart rate and blood pressure.

Blood samples for neutralising inhibitor antibody analysis were collected prior to dosing on Days 1, 8, 15, 22 and also on Day 29. The titer of factor VIII inhibitory antibodies was measured.

The Bethesda assay was not considered an accurate test for measuring the titer of factor VIII inhibitory antibodies due to the presence of circulating factor VIII levels. Therefore the factor VIII inhibitor antibody activity was determined using a mixing test. In this test a 1:1 mixture of the test plasma and porcine factor VIII product (Obizur) are incubated for 90 minutes and the residual activity of the mixture determined. Factor VIII activity was measured by the one stage clotting assay and the chromogenic assay.

Both animals survived the duration of the study. There were no clinical signs indicative of an adverse effect associated with the administration of Obizur. Slight bruising at injection sites was observed. The right cephalic injection site of the female animal was slightly swollen on Day 3 and had a slight sore during Days 12-13 and 15-16. No signs of inflammation were observed at the injection sites. There were no treatment-related changes in body weight and no effects on body temperature, respiration rate, blood pressure, mean arterial blood pressure and heart rate were observed.

The monkeys developed inhibitor antibodies to factor VIII after 14 days of dosing with Obizur at 100 and 300 U/kg.

90 day toxicity study: A study was conducted to determine the potential toxicity and immunogenicity of Obizur when administered by daily intravenous injection to cynomolgus monkeys for up to 90 days, compared to animals treated with Hyate:C (PCM-102).

Monkeys (6/sex/group) were intravenously administered 75, 225 and 750 U/kg Obizur (actual doses of 82.5, 247.5 and 825 U/kg) or 100 U/kg Hyate:C for up to 90 days and evaluated for changes in clinical signs and body weight. Electrocardiogram measurements were also taken (baseline, and prior to dosing on Days 1, 7, 28 and 90). Ophthalmic examinations were conducted prior to the study and at intervals up to Week 12.

Blood samples were taken pre-study and prior to the initiation of dosing on Days 7, 28, 56 and 90 and haematological parameters (serum chemistry, haematology, coagulation parameters) were evaluated.

In addition, blood samples were collected for toxicokinetic analysis prior to dosing and 1 and 6 hours post-dose on Days 1, 7, 28 and 90. Blood samples were also collected on Days 1, 7, 28 and 90 and analysed for factor VIII activities using stage clotting and chromogenic assays. Blood samples for neutralising inhibitor antibody analysis were collected prior to dosing on Days 1, 7, 28 and 90. A mixing study was used to measure levels of factor VIII inhibitory antibodies. Some animals were killed and necropsied on Days 8, 29 and 91. Urinalysis was conducted on samples collected by bladder aspiration at necropsy.

There were no changes in body weight, serum chemistry, electrocardiographic abnormalities or ophthalmic findings that were associated with the test or control articles.

Clinical signs observed were limited to intra-articular and soft tissue haemorrhages in four monkeys treated with Obizur, two monkeys dosed at 82.5 U/kg, one at the dose of 247.5 U/kg) and one at the dose of 825 U/kg. The findings of haemorrhage/haematoma at necropsy which coincided with haematology findings (decreases in the circulating red cell mass) and/or coagulation parameters changes (slight prolongation of aPTT from Day 28) in these animals were suggestive of bleeding in the tissues and/or an intra-articular bleed in one of the small joints of the foot. The Applicant stated that these non-dose-related clinical signs were not unexpected findings since the repeat injection of a porcine factor VIII recombinant such as OB1-1 in primates induced the production of anti-factor VIII antibodies, which can increase the risk of bleeding.

A dose-related decrease in aPTT values was observed in all animals that received Obizur or Hyate:C on Day 7. However, aPTT was prolonged by Day 28 in all Obizur and Hyate:C treatment groups.

An increase in factor VIII levels was seen at Days 1 and 7 one hour post-dose. On Day 7 baseline values for factor VIII were higher than on Day 1 for Obizur and Hyate:C treated animals, demonstrating an accumulating blood level of factor VIII. By Day 28 and Day 90, plasma factor VIII levels were markedly reduced in all monkeys (treated with either Obizur or Hyate:C) 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 haemophilia"

condition). A summary of inhibitor antibody findings is shown in Table 12. However, the values were not included in the final report of the study but presented as additional supportive data only.

Table 12. Inhibitor Antibody Bethesda titer (BU) generated against Factor VIII Product Administered in Cynomolgus Monkeys Treated Daily (OSCA)

	Day 28		Day 90	
	OBI-1 82.5 U/kg	**Hyate:C 100 U/kg**	**OBI-1 82.5 U/kg**	**Hyate:C 100 U/kg**
N	8	8	3	3
Mean	250	66	177	233
Standard deviation	276	61	71	77
Median	109.5	52.5	143	214

The inhibitor antibody titer generated in the Obizur -treated monkeys was equivalent to that observed in those monkeys treated with Hyate:C. This showed comparable reactivity of the neutralising inhibitor antibodies against Obizur and Hyate:C. These results are summarised in Table 13.

Table 13. Obizur 82.5U/kg-Treated Cynomolgus Monkeys: Inhibitor Antibody Bethesda Titer (BU) against Obizur and Cross-Reactive against Hyate:C (OSCA)

	Day 28		**Day 90**	
	Vs. OBI-1	**Vs. Hyate:C**	**Vs. OBI-1**	**Vs. Hyate:C**
Mean	249.5	212.8	177.3	120.0
Standard deviation	275.6	159.4	71.0	84.9
Median	109.5	163.5	143.0	74.0

Relative and absolute spleen weight were increased in the Hyate:C treatment group on Days 8, 29 and 91. This increase in spleen weight was consistent with the splenic lymphoid hyperplasia observed in the histopathology evaluation and was attributed to an Hyate:C associated immune response.

Glomerulopathy was found in both Obizur and Hyate:C treated animals. The incidence and severity of this finding tended to increase over time. The detection of anti-factor VIII antibodies in Obizur and Hyate:C supported the immunological basis (immune complex deposition) for the glomerulopathy.

Genotoxicity

No genotoxicity studies have been performed.

Carcinogenicity

No carcinogenicity studies have been submitted.

Reproduction Toxicity

No reproductive and developmental toxicity studies have been performed with Obizur.

Toxicokinetic data

An evaluation of plasma levels of factor VIII was conducted as part of a comparative immunogenicity toxicity conducted in cynomolgus monkeys (PCM-105, 08/PKR/017).

Male and female monkeys were administered eight intravenous injections, one injection every twelve hours for 4 days. Obizur was administered at dose levels of 40 and 100 U/kg; Hyate:C at a dose level

of 100 U/kg. Blood samples were taken prior to and up to 12 hours post injection and analysed for factor VIII using a chromogenic assay.

After intravenous administration of Obizur at dose levels of 40 and 100 U/kg and Hyate:C at dose levels of 100 U/kg, drug plasma levels were detectable until 12 hours post injection in all monkeys evaluated on Days 1 and 24.

Both Day 1 and Day 4 plasma levels of Obizur were greater than those of Hyate:C at equivalent doses. The pharmacokinetic parameters estimated at Day 4 when steady state was reached are summarised in Table 7.

The plasma clearance at steady state of factor VIII after repeated intravenous administration of Obizur was lower than after intravenous administration of Hyate:C. Consequently, the exposure of Obizur is higher than the exposure obtained after administration of the same dose of Hyate:C.

Table 14. Pharmacokinetic Parameters at Steady State (Day 4) for Baseline Corrected fVIII after Repeated Administration of Obizur or Hyate:C to Cynomolgus Monkeys

Test Article	OBI-1		Hyate:C
Gender (M/F)/No of Animals	M:2 /F:3	M:3 / F:2	M:3 / F:3
Dose (U/kg)	40	100	100
AUC_{τ} (U.h/dL)	835 ± 342	2743 ±1241	1372 ±507
C_{max} (U/dL)	131 ± 22.3	362 ± 90.5	210 ± 53.54
$C_{minimum}$ (U/dL)	23 ± 26.2	142 ± 95.0	40 ± 32.4
$C_{average}$	70 ± 28.5	229 ± 103	114 ± 42.3
CL (dL/kg)/h	0.067 ± 0.06	0.042 ± 0.02	0.085 ±0.04
V_{dss} (dL/kg)	0.575 ± 0.31	0.566 ± 0.09	1.038 ± 0.53
Peak trough fluctuation (%)[1]	214 ± 189	110 ± 45.9	161 ± 67.6

[1]Percentage difference between the levels at peak and trough.

In another comparative toxicity study, cynomolgus monkeys were intravenously administered 82.5, 247.5 and 825 U/kg Obizur or 100 U/kg Hyate:C or Obizur vehicle for up to 90 days (**PCM-102**). Blood samples were collected for toxicokinetic analysis prior to dosing, on Days 1, 7, 28 and 90. Factor VIII activity was assessed in plasma using a validated one-stage clotting assay and a validated chromogenic assay.

An increase in factor VIII levels was observed at Days 1 and 7 one hour post-dose. Baseline values of factor VIII were higher on Day 7 for both Obizur and Hyate:C treated animals, demonstrating accumulating blood levels of factor VIII. By Days 28 and 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.

- **Interspecies comparison**

A comparative assessment of the systemic exposure to Obizur in dogs (PCD-101, 08/PKR), monkeys (PCM-105, 08/PKR/017) and humans was conducted (see Table 8). Exposure values were higher in the haemophilia A dogs. The exposure in the monkeys and humans with haemophilia A intravenously administered Obizur were more comparable. The data provide support to the selection of cynomolgus monkey as the non-rodent animal species for the toxicology studies.

Table 15. Comparative Pharmacokinetic Parameters after one Single Dose Administration of Obizur in Dog, Monkey and Human

Species	Dose (U/kg)	Parameter[1]	
		C_{max} (U/dL)	AUC (U.h/dL)
Dog[2]	100	466 ± 162	3399 ± 2569
Monkey[3]	77	169 ± 32	1433 ± 1390
Human[4]	100	151 ± 32	1915 ± 591

[1] Mean and standard deviation.

Local Tolerance

The local tolerance of Obizur was assessed as part of the repeat dose toxicity studies where animals were intravenously administered Obizur. Daily intravenous administration of Obizur for up to 90 days, at dose levels up to 825 U/kg/day, or Hyate:C at 100 U/kg/day, was well tolerated locally by cynomolgus monkeys.

Other toxicity studies

Antigenicity

N/A

Immunotoxicity

Immunogenicity studies were conducted with Obizur in haemophilia A mice and cynomolgus monkeys. The factor VIII inhibitor antibody activity in the plasma of monkeys was determined using a mixing test. Factor VIII activity was measured by the one stage clotting assay and/or the chromogenic assay. The mixing assay was employed to determine the formation of inhibitory factor VIII antibodies in the cynomolgus monkey from repeat dose studies (PCM-101, PCM-102 and PCM-105). Assays were validated using a standard composed of human haemophilic plasma with the addition of the porcine factor VIII product being tested (PCM-101, PCM-102). Assays were performed under GLP guidelines.

Immunogenicity in the Haemophilia A mice pre-sensitised to recombinant human factor VIII

A study was conducted to determine the immunogenicity of Obizur in haemophilia A mice pre-sensitised to recombinant human factor VIII and to compare it to the immunogenicity of Hyate:C (PCMU-102).

Male and female haemophilia A mice (n=119 male and female), were intravenously administered 100 U/kg recombinant human factor VIII weekly for a total of five injections. Tail snip blood samples were collected one week after the fifth injection for the measurement of anti-human factor VIII antibodies by an enzyme-linked immunosorbent assay (ELISA).

At 16-21 weeks after the last injection of human factor VIII, mice tested positive for anti-factor VIII antibodies were randomised to receive 4 weekly injections of Obizur or Hyate:C at dose levels of 1, 10, 100 U/kg (n=16 to 17/group). Two weeks following the last injection of Obizur or Hyate:C, blood samples were taken to determine the levels of anti-human factor VIII antibodies, anti-Obizur antibodies and, anti-plasma derived factor VIII antibodies and anti-Hyate:C antibodies.

Inhibitory IgG antibodies were measured using a modified Bethesda assay in which human haemophilia A plasma was reconstituted with Obizur or Hyate:C, depending on which test material the animal received.

An increase in antibody titers (including both inhibitory and non-inhibitory antibodies) to Obizur porcine factor VIII or plasma derived porcine factor VIII antibodies was determined in plasma from the Obizur and Hyate:C treatment groups, respectively. For the Obizur mice, there was a statistically significant increase in antibody titers in the 100 U/kg group compared to the 1 U/kg and 10 U/kg groups. The difference between the 1 U/kg and the 10 U/kg groups was not significant. Similarly, for the Hyate:C-treated mice, there was a statistically significant increase in titers in the 100 U/kg group compared to 1 U/kg and 10 U/kg groups. Additionally, there was a statistically significant increase in the 10 U/kg group compared to the 1 U/kg group.

Measurement of inhibitory antibodies showed that in the Obizur mice there was a significant increase in the factor VIII titer in the 100 U/kg group compared to the 1 U/kg and the 10 U/kg groups. The difference between the 1 U/kg and the 10 U/kg groups was not significant. Similarly, in the Hyate:C mice, there was a significant increase in the factor VIII inhibitor titer in the 100 U/kg group compared to the 1 U/kg and 10 U/kg groups, but no significant difference between the 1 U/kg and 10 U/kg groups. No significant difference was detected between the Obizur and the Hyate:C groups in inhibitory antibody formation at 1, 10 or 100 U/kg.

There were several mice both in the Obizur and Hyate:C groups that developed anti-porcine factor VIII antibodies, but not inhibitory antibodies. In mice with positive Bethesda titers, there was a significant correlation between ELISA and Bethesda titers in both the Obizur and Hyate:C groups. In both the Obizur and Hyate:C groups, there was no significant correlation between the development of human factor VIII antibodies in the pre-sensitisation period and subsequent development of porcine factor VIII antibodies as detected by ELISA or Bethesda assay.

A dose escalation tolerability study of Obizur administered by intravenous injection to cynomolgus monkeys

The intravenous administration of Obizur by repeated daily intravenous injection at doses of 100, 300, 600 or 1000 U/kg (dose increments every 7 days) was well-tolerated in male and female cynomolgus monkeys (**PCM-101**). There were no clinical signs indicative of an adverse effect or changes in body weight or vital signs that were related to test article administration. Based on the results of this study, the apparent maximum tolerable dose of Obizur in monkeys was considered to be at least 1000 U/kg. After 14 days of administration of Obizur (7 days each of 100 and 300 U/kg) inhibitor antibodies to factor VIII, were detected.

A comparative immunogenicity study, up to 85 days duration, of Obizur versus Hyate:C administered by intravenous injection to cynomolgus monkeys

A study was conducted to compare the immunogenicity of Obizur and Hyate:C in cynomolgus monkeys (**PCM-105**). Cynomolgus monkeys (n=8/sex) were intravenously administered one injection every twelve hours of Obizur (at 40 or 100 U/kg) or Hyate:C (at 100 U/kg) for 4 days. Blood samples were collected for inhibitory antibody analyses on Days 1 (pre-dose), 8, 15, 29, 43, 57 and 85. The study was concluded when all monkeys demonstrated inhibitor titers below 20 Bethesda Unit (BU) and had stable or falling inhibitor antibody titers compared to the previous time point. The inhibitory factor VIII antibodies were determined using an anti-porcine factor VIII inhibitor Bethesda assay.

Monkeys in the 40 U/kg Obizur dose group did not develope anti-porcine factor VIII inhibitory antibodies and the group was therefore discontinued from the study at Day 43.

Only 2 of 5 monkeys from the Obizur and 2 of 6 Hyate:C animals treated at 100 U/kg developed inhibitor antibodies greater than 1 BU. There was no value greater than 20 BU. The study was terminated at Day 57. At this time point, the porcine titers were 8.5 and 2.2 BU in the Hyate:C group and 8.6 and 3.1 BU in the Obizur group.

Metabolites

N/A

Studies on impurities
Potential process-related impurities and the presence or absence in the Obizur drug substance were outlined and extensively characterized in the manufacturing process; evaluation of impurity clearance through the downstream processing steps of the commercial-scale manufacturing process is described. None of the impurities in Obizur FBDS were identified to be at levels posing a toxicological risk for patients.

2.3.5. Ecotoxicity / environmental risk assessment

An environmental risk assessment is not submitted as the product is exempted (See Section 2.3.6.).

2.3.6. Discussion on non-clinical aspects

Sucoctocog alfa is a B-domain deleted form of porcine factor VIII and is manufactured in a baby hamster kidney (BHK) derived cell line.

In vitro, the stoichiometry of binding between susoctocog alfa with vWF was approximately 1:1 mole equivalent.

Using the chromogenic assay, batches of OBI-1 DP and DS were shown to be capable of reacting with thrombin and Factor IXa to catalyse the activation of Factor X. Obizur batches of drug substance and drug product tested showed comparable Factor X activation near the target potency of 1100U/mL and 500 U/mL, respectively. Using the one-stage coagulation assay, susoctocog alfa was shown to be activated by thrombin and react with Factor IXa to initiate the coagulation cascade, leading to clotting in Factor VIII-deficient plasma. Batches of the drug substance and drug product showed clotting activity near the target potency of 1000 U/mL and 500 U/mL, respectively.

The administration of Obizur dose-dependently prevented blood loss in a murine model of haemophilia A. The efficacy was comparable to Hyate:C, a plasma derived porcine factor VIII. In a canine model of haemophilia A, susoctocog alfa in a dose range from 3 to 100 U/kg effectively decreased the bleeding tendency in the haemophilia A dog, as assessed by the CBT.

No specific secondary pharmacodynamic studies and on pharmacodynamic drug interaction were conducted; the programme for the preclinical safety and efficacy testing of susoctocog aims to assess a protein of known pharmacological action that has a comparable mode of activity to plasma-derived human FVIII (pd-FVIII). No specific safety pharmacology studies were conducted. This is acceptable as part of toxicity studies of up to 90 days, intravenous doses of up to 1000 U/kg/day had no adverse effects on the cardiovascular and respiratory parameters measured.

The cynomolgus monkey was selected as the non-rodent animal species for the toxicology studies based on the fact that no relevant differences in plasma clearance and volume of distribution were observed between monkeys and humans.

In haemophilia A dogs administered a single IV injection of Obizur at doses of 3, 25 and 100 U/kg, no adverse effects were observed. In monkeys, a single IV injection of OBI-1 at doses of 49.5 and 77 U/kg did not induce any adverse effects.

In monkeys, repeated daily intravenous injection of susoctocog alfa for 28 days at doses of 100, 300, 600 and 1000 U/kg (dose increments every 7 days) induced no clinical signs indicative of an adverse effect or changes in body weight and vital signs. After 14 days of administration of susoctocog alfa inhibitor antibodies to factor VIII, were detected.

A study was conducted to determine the potential toxicity and immunogenicity of susoctocog alfa when administered by daily intravenous injection to monkeys for up to 90 days, compared to animals treated with Hyate:C. Following daily intravenous administration of susoctocog alfa a slight dose -related reduction in aPTT was noted on Day 7. This was also observed in Hyate:C-treated animals. It was possible that this change reflected a slight augmentation of the intrinsic coagulation pathway by both factor VIII test articles, which is consistent with the pharmacologic nature of these agents. Clinical signs, changes in haematology and coagulation parameters (prolongation of aPTT, which may have contributed to the deep tissue bleeding) and/or gross necropsy findings observed after prolonged administration of susoctocog alfa were attributed to the formation of inhibitory antibodies to exogenous factor VIII that cross reacted with endogenous factor VIII. However, the incidence of clinical signs (intra-articular and soft tissue haemorrhage) and related changes indicating an 'acquired haemophilia' condition were low. The formation of inhibitory antibodies was detected in all animals treated with susoctocog alfa or Hyate:C. At necropsy, there were no gross or histological findings suggesting toxicity related to susoctocog alfa. Glomerulopathy observed following administration of susoctocog alfa and Hyate:C was not associated with any changes in plasma creatinine and urea and was considered most likely due to immune complex deposition. It was concluded that susoctocog alfa was well tolerated at doses up to 825 U/kg.

In a toxicokinetics study, following twice daily injections over 4 days of susoctocog alfa or Hyate:C to cynomolgus monkeys, exposure to susoctocog alfa at steady state appeared higher compared to those of Hyate:C.

In a 90-day toxicity study, increasing plasma factor VIII levels were determined after daily injections of susoctocog alfa up to day 7 in monkeys. The formation of inhibitory antibodies (which led to a decrease in circulating factor VIII), increase in aPTT and bleeding in tissues and joints, precluded the conduct of chronic toxicology studies beyond three months of administration.

In intravenous studies, the systemic exposure to susoctocog alfa was higher in the haemophilia A dogs than in humans with haemophilia A administered 100 U/kg and monkeys dosed 77 U/kg. The exposure in the monkeys and humans with haemophilia A intravenously administered susoctocog alfa were more comparable.

No genotoxicity or carcinogenicity studies have been performed as susoctocog alfa is a recombinant protein. According to ICH S6 guideline recommendations, the omission of studies on genotoxicity, carcinogenicity and reproductive and developmental toxicity is justified. In a 90 day toxicity study there was no histopathological evidence of treatment-related effects on reproductive organs. Animal reproduction studies have not been conducted with OBIZUR. Experience regarding the use of OBIZUR during pregnancy and breast-feeding is not available. Therefore, OBIZUR should be used during pregnancy and lactation only if clearly indicated. This information is included in section 4.6 of the SmPC and complies with the core SmPC wording for human plasma derived and recombinant coagulation factor VIII products (EMA/CHMP/BPWP/1619/1999 rev. 1); the lack of such studies is also stated under section 5.3.

In a local tolerance study in monkeys, susoctocog alfa was generally well tolerated following IV administration of up to 825 U/kg/day for 90 days.

In male and female haemophilia A mice intravenously administered 100 U/kg recombinant human factor VIII weekly for a total of five injections, inhibitory antibodies to porcine factor VIII were detected in both the susoctocog alfa -treated mice and Hyate:C-treated mice. No significant difference in inhibitory antibody formation was detected between the Obizur and the Hyate:C-treated groups (dosed at 1, 10 or 100 U/kg). In both the susoctocog alfa and Hyate:C-treated groups, there was no correlation between the development of human factor VIII antibodies and subsequent development of porcine factor VIII antibodies as detected by ELISA or Bethesda assay. This suggests that haemophilia A mice might recognise different T cell epitopes and/or B cell epitopes in human and porcine factor VIII.

Monkeys administered susoctocog alfa 40 U/kg by IV injection did not develop anti-porcine factor VIII inhibitory antibodies. There was no difference observed in the incidence or duration of the inhibitor antibodies in monkeys administered susoctocog alfa or Hyate:C at the 100 U/kg dose level. Recombinant porcine factor VIII, susoctocog alfa, was not shown to be more immunogenic than Hyate:C in this study.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity. However, in repeated dose toxicity studies, the incidence and severity of glomerulopathy observed in monkeys intravenously administered OBIZUR at doses of 75, 225 and 750 U/kg/day tended to increase over time.
According to the “Guideline on the environmental risk assessment of medical products for human use” substances like amino acids, peptides, proteins, carbohydrates and lipids are exempted from the guideline since they are unlikely to result in significant risk to the environment, Obizur is thereby exempted, consequently, an environmental risk assessment is not required.

2.3.7. Conclusion on the non-clinical aspects

The type and amount of non-clinical studies fulfil the requirements to support marketing authorization of Obizur.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

A tabular overview of clinical studies is shown in table 2:

Table 2. Listing of Clinical Studies in the OBI-1 Clinical Development Program				
Study Number	**Phase**	**Study Status**	**Criteria**	**Dose Range and Frequency**
OBI-1-301	2/3	Completed CSR OBI-1-301/301a	AHA; age ≥ 18 y with serious bleeding episode	Initial OBI-1 dose, 200 U/kg Further dosing based on clinical assessments and factor VII levels
OBI-1-301a	3 expanded -access protocol	Completed CSR OBI-1-301/301a	AHA; age ≥ 18 y with serious bleeding episode	Initial OBI-1 dose, 200 U/kg Further dosing based on clinical assessments and factor VII levels
OBI-1-302	3	Terminated by the sponsor after 1 subject was treated - not due to safety or lack of efficacy concerns	CHA with inhibitors; age ≥ 6 y with suboptimal response to by-passing agents; Anti-OBI-1 titer ≤ 10 BU	OBI-1 dose based on anti-OBI-1 titer: - Titer > 5 BU, initial dose 200 U/kg - Titer 2-5 BU, initial dose 150 U/kg - Titer < 2BU, initial dose 100 U/kg. - Life threatening situations with unknown anti-OBI-1 titer, initial dose 200 U/kg
OBI-1-201	2	Completed CSR OBI-1-201	CHA with inhibitors age > 12 y (non-russian sites); age ≥ 18 y (russian sites); Anti- OBI-1 titer ≤ 20 BU; with uncomplicated joint or soft tissue bleeding episode	Initial dose - for anti- OBI-1 titer > 0.8 BU, - determined according to the patient's inhibitor titer, body weight, and hematocrit. Treatment dose, 1st-3rd OBI-1 dose, 50 U/kg 4th-6th OBI-1 dose, 100 U/kg 7th-8th OBI-1 dose, 150 U/kg
OBI-1-101	1	Completed CSR OBI-1-101	AHA or CHA with inhibitors age ≥ 12 y in non-bleeding state Anti-factor VIII titer ≤ 20 BU	Single dose OBI-1 or comparator (HYATE:C), 100 U/kg

2.4.2. Pharmacokinetics

Study OBI-1-301 was an open-label study evaluating Obizur in 28 subjects with acquired haemophilia (subjects had autoimmune inhibitory antibodies to human factor VIII). 6 subjects in study OBI-1-301 consented to a pharmacokinetic sub-study.

The pharmacokinetics of Obizur were to be assessed during the bleeding state by sparse pharmacokinetic analysis but this could not be done because not enough samples were obtained.

Samples were collected during a non-bleeding state for pharmacokinetic analysis. For consenting subjects, serial blood samples were obtained after the final dose at the following time points: before dose, 15 to 20 minutes after dose, 1, 3, 6, 12, 18, and 24 hours after dose.

Blood samples were analysed by central laboratories.

- **Pharmacokinetic data analysis**

A routine non-compartmental analysis was used to estimate half-life and the trapezoidal rule was used to determine AUC, plasma clearance and volume of distribution. Generally, all samples in the log-linear terminal elimination phase were used in the determination of $t_{1/2}$, except if they were the C_{max} samples. For each subject, the following were determined: $t_{1/2}$, T_{max}, A_{max}, AUC from Time 0 to last measurement, AUC from Time 0 extrapolated to infinity, clearance and the volume of distribution at steady state.

Individual and summary final dose pharmacokinetic parameters from the chromogenic and one-stage factor VIII activity assays (baseline-corrected values) are presented in the following table:

Table 1.
Individual and Summarized Final Dose PK Parameter Values for Factor VIII Activity 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/%)
	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	4.90	26.6
	7,540	90	3.5	0.45	107	663	668	11.29	57.4
	9720	207	3.0	0.50	60	161	213	35.41	145.7
	10000	133	7.0	1.25	222	2148	2675	1.87	21.0
Summary Parameters		N	5	5	5	5	5	5	5
		Mean	3.3	0.44	108	599	691	11.80	53.8
		SD	0.4	0.04	37	459	418	13.44	52.9
One-Stage 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/%)
	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
	9720	207	1.8	0.50	53	122	135	56.06	135.3
	10000	133	4.2	0.75	178	1583	1686	2.97	21.0
Summary Parameters		N	5	5	5	5	5	5	5
		Mean	3.5	0.44	81	423	500	18.07	65.1
		SD	1.0	0.04	26	340	325	21.78	45.1

Source: OBI-1-301 fCSR Appendix 16.2.12.
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; PK = pharmacokinetic; $t_{1/2}$ = terminal half-life; T_{max} = time of maximum observed % activity; V_{ss} = volume of distribution at steady state.
[a] These parameters were generated by using the data from the repeated assay
[b] These data are not included in the summary statistics.

Pharmacokinetic data of study OBI-1-301/301a were re-calculated using data without baseline correction. The re-calculated PK-data for factor VIII activity after administration of the final dose of OBIZUR to 5 subjects with acquired haemophilia are presented in the table below. Subjects were in a non-bleeding state. Factor VIII activity was measured by the one-stage clotting assay.

Table 17: Individual pharmacokinetic data

Subject	Dose (U)	Dose (U/kg)	Baseline hFVIII activity (%)	t1/2 (h)	Tmax (h)	Amax (%)	AUC0-t (%·t)	AUC0-∞ (%·t)
1	5000	76.7	89	17	0.42	213	3124	4988
2	2934	30.0	18	4.6	0.42	100	694	712
3	7540	144.2	3	5.3	0.45	74	473	492
4	9720	206.8	0	1.8	0.50	53	122	135
5	10000	133.3	N/A	4.2	0.75	178	1583	1686
			N	5	5	5	5	5
			Mean	6.6	0.51	124	1199	1603
			SD	6.0	0.14	69	1204	1978

Amax = maximum observed % activity; AUC0-t = area under the concentration-time curve from time 0 to the last measurable concentration; AUC0-∞ = area under the concentration-time curve from time 0 extrapolated to infinity; t1/2 = terminal half-life; Tmax = time of maximum observed % activity, N/A = not available.

The mean half-life of Obizur in nine evaluable subjects in the bleeding state was (about) 10hrs (range 2.6 to 28.6hrs).

Additional pharmacokinetic data

Pharmacokinetic data are also submitted from studies OBI-1-201 and OBI-1-101.

Study OBI-1-201

Study OBI-1-201 was a multicentre, open-label, non-comparative study assessing the haemostatic activity, the safety, the immunogenicity and the pharmacokinetics of Obizur in subjects with congenital haemophilia A and inhibitors to factor VIII experiencing non–life-threatening or non– limb-threatening bleeds.

9 subjects were enrolled.

Subjects received Obizur, up to 1,000 units/kg/day, as follows:

- Initial dose, second dose, third dose: 50 units/kg
- Fourth dose, fifth dose, sixth dose: 100 units/kg
- Seventh dose, eighth dose: 150 units/kg

The rate of infusion was 1mL/min (increased to 2mL/min if infusion-related events were not observed). Obizur doses were no less than 6 hours apart. Treatment was given until the bleeding episode was controlled or 8 injections had been administered or the subject had received 1000U/kg/24hrs or the investigator deemed that Obizur was not effective.

Clinical assessments of the patient's signs and symptoms determined whether the bleeding episode had been controlled or whether additional doses of Obizur were administered.

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.

Only 1 subject had pharmacokinetic data available for all time points after a single injection, results shown below:

Summary of Pharmacokinetics Values (FVIII activity) after a Single Injection of OBI-1 to Subject 1504 with Anti-pFVIII Antibody Titer <0.8 BU/mL		
Parameter (Units)	**One-Stage Clotting Assay**	**Chromogenic Assay**
Cmax (units/dL)	89	54
Cmax/D (units/dL)/(units/kg)	1.78	1.08
AUC_t (h·units/mL)	989	683
$AUC_{\infty/D}$ (h·units/mL)	19.8	13.7
AUC	1,016	710
CL (mL/h)	467	669
CL (mL/h/kg)	4.92	7.04
Vz. (L)	6.00	9.49
Vss. (L/kg)	0.06	0.10
$T_{1/2\lambda z}$ (h)	9.27	10.10
MRT	12.8	14.18

In addition, 3 subjects without measurable anti–porcine factor VIII antibodies at screening had limited data collected for the calculation of PK parameters. Five subjects had measurable anti–porcine factor VIII antibodies at the start of the first treatment with rpFVIII. In four of these subjects a partial PK profile was available. These subjects received further treatment six hours after the first rpFVIII treatment dose administration, therefore only Cmax, tmax and AUC0-6h could be calculated. Table 3 provides the calculated PK-parameters normalized by the administered dose for these 8 subjects.

Table 18. Summary of PK Parameters (FVIII acivity) after a Single Injection of rpFVIII for Subjects with Complete and Partial PK Data (mean±sd).

Subjects with Anti-pFVIII·Titer·<0.8·BU/ml·(N=4)			
Parameter	**Units**	**OSCA·(n=4)**	**Chromogenic·(n=4)**
C_{max}/D·	(U/dL)/(U/kg)	1.77±1.22	0.95±0.47
t_{max} (mean and range)	h	0.25·(0.25-0.50)	0.50·(0.25-3.00)
AUC_{0-6h}/D·-		5.67±2.7	3.82±1.50
Subjects with Anti-pFVIII·Titer·>0.8·BU/ml·(N=4)			
Parameter	**Units**	**OSCA·(n=4)**	**Chromogenic·(n=4)**

Subjects with Anti-pFVIII Titer < 0.8 BU/ml (N = 4)			
C_{max}/D	(U/dL)/(U/kg)	0.8±0.09	0.06±0.06
t_{max} (mean and range)	h	0.25 (0.25-0.50)	0.63 (0.25-3.00)
AUC_{0-6h}/D		0.24±0.31	0.18±0.20

Study OBI-1-101

Study OBI-1-101 was a Phase 1, parallel-group study comparing the safety and tolerability of Obizur versus Hyate:C when administered to subjects with congenital haemophilia A with inhibitors in a non-bleeding state and who had low or absent anti–porcine factor VIII antibody titres.

9 subjects were enrolled (enrolment was discontinued early when Hyate:C was withdrawn from the market).

The Obizur pharmacokinetic population included 3 subjects who had an anti–porcine factor VIII inhibitory antibody titre <0.80 BU and sufficient measurable factor VIII activity levels after receipt of 100 units/kg of study product to allow calculation of pharmacokinetic values. There were also 3 subjects in the HYATE:C population.

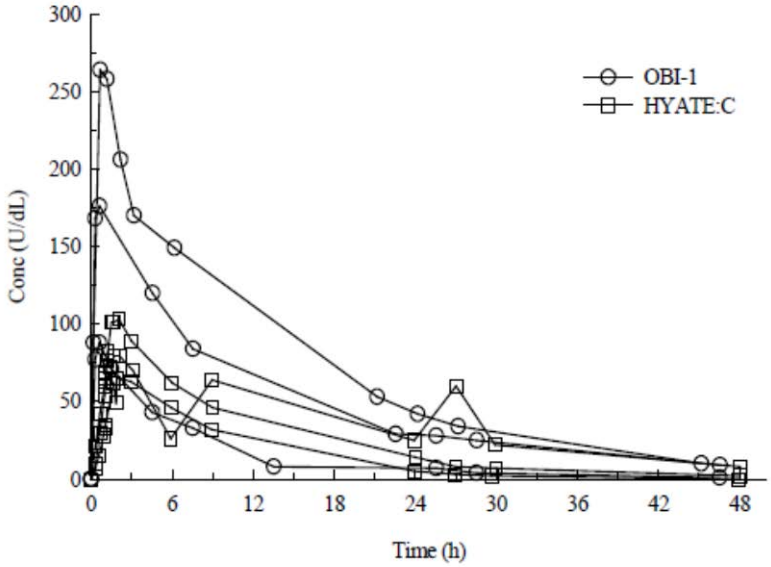
Subjects were randomized to receive on Day 1, while in the non-bleeding state either:

- a single dose of 100 U/kg Hyate:C (administered at 3mL/min) or placebo
- placebo or a single dose of 100 U/kg OBI-1 (administered at 1mL/min)

Each subject received only one study product in addition to the administration of placebo.

A baseline sample for factor VIII activity was collected immediately before study product administration. Subsequent collections for measurement of drug concentrations were taken at the following time points, with the start of dosing being Time 0: 20, 40, 60, 65, 75, 85, 105 and 125 minutes and then at 3, 6, 9, 24, 27, 30 and 48 hours after dose.
The following plots show time courses of both Obizur and Hyate:C as measured by the one-stage clotting assay:

Figure 1. Individual subject plasma concentrations of FVIII after intravenous administration of OBI-1 or HYATE:C (one-stage clotting assay)



Drug exposure measured by AUC and recovery were approximately twice as high with Obizur than with Hyate:C at the same dosage.

However, Obizur could be administered 5-6 times more rapidly than Hyate:C owing to the much higher concentration of factor VIII. As a result, the shape of the time-concentration curve after administration of the same 100-U/kg dose of each product differed, making it appear as though OBI-1 had an even higher recovery than Hyate:C.

Individual pharmacokinetic values for each subject are also shown in the following table:

Treatment	Assay method	C_{max} (U/dL)	T_{max} (h)	AUC0-t (h.U/mL)	AUC0-∞ (h.U/mL)	$T^{1/2}$ (h)	CL (mL/h)	Vz (L)
Obizur	One-stage	176	0.63	2,287	2,436	11.5	267.7	4.44
		88	0.62	669	684	10.4	973.1	14.66
		264	0.68	3,293	3,437	10.0	395.7	5.71
	Chromogenic	152	0.30	2,111	2,184	10.0	305.0	4.40
		119	0.62	1,099	1,237	19.0	538.5	14.79
		182	0.68	2,241	2,324	9.6	585.2	8.08
Hyate:C	One-stage	65	1.93	701	716	5.3	771.0	5.91
		103	2.08	1,194	1,218	8.6	649.1	8.03
		79	1.72	1,639	---[1]	---[1]	---[1]	---[1]

Treatment	Assay method	C_{max} (U/dL)	T_{max} (h)	AUC0-t (h.U/mL)	AUC0-∞ (h.U/mL)	$T^{1/2}$ (h)	CL (mL/h)	Vz (L)
	Chromogenic	37	1.85	409	436	6.2	1,265.3	11.30
		63	1.50	525	555	6.8	1,425.7	13.96
		58	1.10	1,188	1,321	15.4	431.5	9.57

---[1:] Parameter could not be estimated

Owing to limited data, formal statistical analysis of the differences in Cmax and AUC was not possible.

Special populations

Table 19. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	7	9	3
Non Controlled trials	n/A	n/A	n/A

2.4.3. Pharmacodynamics

Mechanism of action

No pharmacodynamic studies on the mechanism of action were submitted.

Primary and Secondary pharmacology

Obizur (factor VIII) activity was measured in clinical studies 101, 201 and 301. Dedicated pharmacodynamic studies were not submitted.

2.4.4. Discussion on clinical pharmacology

Susoctocog alfa is a recombinant, B-domain deleted, porcine sequence Factor VIII. Immediately after release into the circulation, human Factor VIII binds to von Willebrand factor (vWF). The Factor VIII/von Willebrand factor complex consists of two molecules (Factor VIII and von Willebrand factor) with different physiological functions. Activated Factor VIII acts as a co-factor for activated Factor IX, accelerating the conversion of Factor X to activated Factor X, which ultimately converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. The omission of pharmacodynamic studies on the mechanism of action of Obizur is justified as susoctocog is a protein of known pharmacological action that has a comparable mode of activity to plasma-derived human FVIII (pd-FVIII).

The omission of pharmacodynamic studies on the mechanism of action is justified as susoctocog is a protein of known pharmacological action that has a comparable mode of activity to plasma-derived human FVIII (pd-FVIII).

Studies OBI-1-101 and OBI-1-201 with congenital haemophilia A patients suggest that the half-life of Obizur is (about) 10hrs. Visual inspection of results of AHA patients in study OBI-1-301/301a whilst in the bleeding state also suggests that the half-life of Obizur is (about) 10hrs. Plasma FVIII activities were measured by the one stage clotting assay on a Sysmex CA-6000 analyser and calibrated with human plasma-derived FVIII. In order to more fully validate the assay, the Applicant has agreed to provide further validation data for the OSCA assay using a Sysmex CA-7000 analyser and Obizur as the test analyte.

Only 5 subjects in study OBI-1-301 returned adequate results for a pharmacokinetic analysis whilst haematologically stable. The half-life of Obizur in these patients in non-bleeding state was (about) 3.5hrs which was considerably shorter than in studies OBI-1-101 and OBI-1-201. Results of clearance and steady state volume of distribution in these 4 patients varied markedly and were also different from those reported in studies OBI-1-101 and OBI-1-201. It is suggested that the short half-life in acquired haemophilia A patients may be due to high-affinity autoantibodies against human FVIII which may cross-react with porcine FVIII. It is acknowledged that the number of patients available to be studied is small in this rare condition and that further investigation of this issue would be difficult. The PK-data in study OBI-1-301 was biased by the baseline endogenous FVIII levels and the baseline-corrected PK-data underestimates the half-life, AUC and other parameters. Of note, the mean half-life of Obizur in nine evaluable subjects in the bleeding state was (about) 10hrs (range 2.6 to 28.6hrs).

There is no international standard for possible ADA measurements the assay for neutralising antibodies has been partly validated, but the accuracy due to the missing standard is questioned and is not in line with the Guideline on bioanalytical method validation (EMA/CHMP/EWP/192217/2009).

Furthermore, the method for detection of inhibitory antibodies needs further validation. Validation of the Bethesda assay was performed by use of a monoclonal anti-FVIII antibody against human FVIII, representing the positive test sample in the validation experiments and data from analysis of this antibody analyzed at various concentrations were used to assess precision and lower limit of quantification of the assay, further information or characterisation data on this control has not been provided. Considering possible differences between anti-human FVIII antibodies and anti-porcine-Obizur antibodies, it is difficult to make any conclusions about the validity of the ADA assays in place. Overall, current approach allows only identification of inhibiting ADAs. A recommendation is made to the Applicant to continue work on the validation of specific porcine ADA assays.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of Obizur has not raised any particular concerns.

The CHMP considers the following recommendations for future continuous development in pharmacology:

1. The Applicant should continue/complete the validation of the OSCA by performing additional validation experiments at Sanquin using Obizur as test analyte to confirm that the OSCA provides valid activity data also for that protein.
   The company should continue to monitor the OSCA assay for potential sources of variability, e.g. new equipment and reagents and should consider periodically repeating the study where spiked plasma samples with Obizur are assayed by many different hospital laboratories to confirm the robustness of the OSCA assay when used with Obizur.

2. As there are no screening or confirmatory assays in place to detect possible anti-drug antibodies, and as the method detecting inhibitory antibodies against Obizur is validated using only human plasma-derived FVIII, the company could consider carrying out further work for establishing and validating specific porcine ADA-assays.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dedicated dose response studies were submitted.

2.5.2. Main study

Study OBI-1-301/301a: Efficacy and safety of B-domain deleted recombinant porcine factor VIII (Obizur) in the treatment of acquired haemophilia A due to autoimmune anti-factor VIII inhibitory antibodies

This is a case series study, OBI-1-301 and an expanded access programme done agreed with the FDA, the OBI-1-301a study of 29 patients in total - summarised in the following table:

Table 2.
Listing of Clinical Studies in the OBI-1 Clinical Development Program

Study Number	Phase	Study Status	Criteria	Dose Range and Frequency
OBI-1-301	2/3	Completed CSR OBI-1-301/301a	AHA; age ≥ 18 y with serious bleeding episode	Initial OBI-1 dose, 200 U/kg Further dosing based on clinical assessments and factor VII levels
OBI-1-301a	3 expanded-access protocol	Completed CSR OBI-1-301/301a	AHA; age ≥ 18 y with serious bleeding episode	Initial OBI-1 dose, 200 U/kg Further dosing based on clinical assessments and factor VII levels

Study design: OBI-1-301/301a was an international, prospective, non-randomised, open-label, single cohort study that includes Obizur treatment of serious bleeds in subjects with acquired haemophilia A aged 18yrs and over. Also, a pharmacokinetic study was done in successfully treated subjects.

Dates of study: First subject in: 10th November 2010; Last subject out: 9th October 2013

The study was administered centrally at Baxter Healthcare Corporation (Westlake Village, CA, USA) where the trial master file is maintained.

Methods

- **Study participants**

Inclusion criteria

A clinical diagnosis of acquired haemophilia A, age ≥18 years of age and presenting with a serious bleeding episode. Life expectancy of at least 90 days prior to bleed.

Laboratory tests consistent with diagnosis:

- prolonged activated partial thromboplastin time (aPTT)
- prothrombin time (PT) ≤(upper limit normal + 2 seconds) and platelet count within normal range
- abnormal aPTT mixing study consistent with a factor VIII inhibitor
- factor VIII activity level below 10%

Exclusion criteria

Haemodynamic instability (after volume replacement)

Bleeding episode likely to resolve on its own if left untreated.

Anti- Obizur inhibitor that exceeds 20 Bethesda Units (prospectively or retrospectively)

Re-bleed at qualifying bleeding site within 2 weeks (or 1 week at non-qualifying site) will not be regarded as 'new' episodes

Reason for bleeding that is not correctable

The following concomitant medications were not permitted during this study:

- Haemophilia medication (rFVIIa within 3 hours or aPCC within 6 hours of OBI-1 administration
- Haemophilia medication other than OBI-1 at any time during the study unless required for use as rescue medication after failure/study withdrawal.

- **Treatments**

Selection of doses: dosing was based on results of the phase 1 & 2 studies.

If potential participants were in a non- bleeding state (i.e. has a pre-established diagnosis of acquired haemophilia) then they were pre-qualified for study eligibility and only enrolled at the time a serious bleeding episode occurred.

All eligible subjects were assigned to the treatment group.

Initial dose: 200U/kg Obizur dose was infused intravenously at a rate of 1 to 2 mL/min.

The decision to administer additional Obizur doses was made by the investigator based on an assessment of the subject's clinical response to treatment and FVIII activity trough levels.

Treatment phase

FVIII levels were assessed approximately every 2 to 3 hours for the first 24 hours.

The decision to administer additional Obizur doses was made by the investigator based on the subject's FVIII activity trough levels (>80% for bleeding episode of particular concern, >50% for all other serious bleeds) and clinical status.

- Severe intramuscular and joint bleeds: target trough FVIII activity levels ≥50%
- Retroperitoneal, gastrointestinal, intracranial bleeds: target trough FVIII activity levels ≥80%

When FVIII activity levels were not optimal, repeat infusions could be carried out at shorter intervals and / or higher doses but the dose of Obizur administered were not to exceed 400 U/kg every 2 hours (4800 U/kg/24 hours) and blood levels of FVIII activity not to exceed 200% (U/dL).

If consecutive FVIII activity levels indicated a decline of ≤10% in 4 hours, the interval between sampling could be increased to every 4-6 hours

If FVIII activity levels remained ≥50% even after administration of two or more additional doses of Obizur after the initial Obizur infusion, and the clinical response observed was not positive, the decision to discontinue Obizur therapy and switch to an alternative therapy had to be considered by the investigator.

If FVIII activity levels ≥50% were obtained, but no positive clinical response was observed, consideration were given to the need for additional interventions (such as surgery) to address uncontrolled bleeding that was not associated with the acquired anti-FVIII inhibitor.

Obizur treatment continued until either bleeding was successfully controlled or Obizur treatment was discontinued due to lack of efficacy as judged by the investigator or until the subject withdrew from the study.

- Non-target bleeding sites

  Non-target bleeding sites were evaluated at the same time as the target bleeding site according to the schedule of assessments but were not included in the efficacy assessment of the target bleeding site(s).

- New bleeding sites not present at study entry

  New bleeding sites also occurred that were not present at study entry: they were recorded as adverse events. For subjects who had positive responses to OBI-1, subsequent serious bleeding episodes (treated as in-patient) were eligible for treatment with OBI-1 but were not considered as qualifying bleeding episodes for the purposes of primary efficacy analysis.

- Re-occurrence of bleed at target site

  Bleeding that occurred at the same site of the qualifying bleed after initially successful haemostasis, and prior to 2 weeks following the last OBI-1 dose, was considered a continuation of the same bleeding episode. These were recorded as adverse events.

Healing phase

Once a subject's initial bleed was successfully controlled with Obizur, he/she could receive further therapy with OBI-1 to allow healing to take place with the dose designed to maintain the required trough levels (30-40%) and a maximum blood level not to exceed 200% (U/dL).

- All bleed types, target trough FVIII activity 30-40%
- The maximum blood FVIII activity level was not to exceed 200%

FVIII levels and clinical status were monitored at least every 24 hours during the healing phase until the healing process was completed as determined by the investigator.

Compliance was ensured by Obizur being administered by the investigator and assessed by vial count, documented in the case report file.

The independent data safety monitoring board monitored dosing.

Follow-up phase

Subjects were followed for 90 (±7) days after the final Obizur dose.

If a subsequent bleeding event was experienced during the follow-up period requiring treatment, the subject was followed for the 90 (±7) days after the final Obizur dose for treatment of the subsequent bleeding event.

Subsequent bleeding events were eligible for treatment with Obizur if the primary bleed was considered successfully treated.

Inhibitor titres to both human and porcine FVIII were collected at each follow-up visit (days 14, 28, 60 and 90 post-treatment).

Pharmacokinetic study

Agreement to participate in the pharmacokinetic part of the study was not mandatory for study participation.

Where possible, a final dose was provided and samples were obtained according to the following schedule relative to the final Obizur infusion and at 15-20 min, 1, 3, 6, 12, 18 and 24hrs post infusion.

Pharmacokinetic data was also acquired during the healing phase after the bleeding was controlled and the subject health status was stable.

Medications not permitted:

- Haemophilia medication (rFVIIa within 3 hours or aPCC within 6 hours prior to Obizur administration)
- Haemophilia medication other than Obizur at any time during the study unless required for use as rescue medication.

- **Assays**

Central laboratories were used for the protocol-required laboratory tests anti–human FVIII and anti–Obizur antibody titres, FVIII activity levels anti-BHK cell antibodies. Local laboratories were used for the following protocol-required laboratory tests FVIII activity levels, anti–human FVIII and anti– Obizur antibody titres.

Assays for FVIII activity were done using the one-stage and the chromogenic assays at the central and local laboratories. Anti-human FVIII and anti- Obizur inhibitor titres were determined by the Nijmegen modification of the Bethesda assay.

Measurements aimed to guide dosing were performed at the investigator's local laboratory. Local laboratories were pre-qualified for ability to provide these services prior to study participation.

To confirm local laboratory results, a central reference laboratory determined FVIII activity level, anti-human FVIII and anti- Obizur inhibitor titres on samples collected prior to Obizur treatment and at the follow up visits (14 ±3 days, 28 ±3 days, 60 ±5 days and 90 ±7 days).

Anti-baby hamster kidney antibody titres were determined at the central laboratory in samples collected prior to treatment and at the final visit.

- **Objectives**

Primary objective

The primary objective of studies OBI-1-301 and OBI-1-301a were to evaluate the efficacy of Obizur for the treatment of serious bleeding events in subjects with acquired haemophilia A.

Secondary objectives

The secondary objectives were to:

- Assess the efficacy of Obizur at designated time points after the initiation of therapy
- Determine the frequency, total dose and total number of infusions of Obizur required to control all serious bleeding events
- Assess the correlation between response to Obizur therapy at specified assessment time points and eventual control of serious bleeding events
- Assess the correlation between the pre-infusion anti– Obizur inhibitor titre, the total dose of Obizur, the outcome at 24 hours and the eventual control of the bleeding event
- Assess the anti– Obizur 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
- Evaluate the safety of Obizur
- Assess drug exposure by using extensive (non-bleeding state) or sparse sampling (bleeding state), and a population pharmacokinetic approach (with sparse data) in subjects treated with OBI-1 therapy

Outcomes/endpoints

Primary Efficacy Endpoint: the proportion of serious bleeding episodes responsive to Obizur 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 Obizur therapy, as assessed by the investigator.
- The proportion of bleeding episodes responsive to Obizur 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 Obizur required to successfully control qualifying bleeding episodes.
- Correlation between response to Obizur therapy at specified time points and eventual control of serious bleeding episodes.
- Correlation between the pre-infusion anti- Obizur antibody titres, the total dose of Obizur, the outcome at 24 hours and the eventual control of the bleeding episode.
- Drug exposure was determined by means of population pharmacokinetic analysis for the sparse-bleeding state-data, and compartmental analysis for the complete-non- bleeding state-data.

Safety Endpoints

The safety of Obizur was assessed from the following:

- Treatment-emergent adverse events and serious adverse events throughout the study
- Vital signs
- Routine laboratory testing
- Anti-human factor VIII antibody titre
- Anti- Obizur antibody titre

- Anti-host cell protein antibody titre

Incidence of treatment emergent adverse events were summarised by system organ class, severity and relationship to Obizur treatment.

Primary Efficacy Assessment

Prior to amendment 3, protocols OBI-1-301 and OBI-1-301a used a "three-point" scale of the investigator's assessment, as shown:

Table 9-1
Investigator Assessment of Response to OBI-1: Three-Point Scale

Assessment of Efficacy	Control of Bleeding	Clinical Assessment	Factor VIII Levels	Response
Effective	Bleeding stopped or significantly reduced	Clinical control	≥50%	Positive
Partially effective	Bleeding reduced but continuing	Clinical stabilization or improvement, or alternative reason for bleeding	≥20%	Positive
Not effective	Bleeding continuing or worsening	Not clinically stable	<20%	Negative

Note: If a clinical assessment was positive with below-target FVIII levels, the clinical assessment determined the response.

A four-point scale of the investigator's assessment was implemented when protocol OBI-1-301 Amendment 3.0 came into effect, as shown:

Table 9-2
Investigator Assessment of Response to OBI-1: Four-Point Scale

Assessment of efficacy	Control of bleeding	Clinical Assessment	Factor VIII levels	Response
Effective	bleeding stopped	clinical control	≥50%	positive
Partially effective	bleeding reduced	clinical stabilization or improvement or alternative reason for bleeding	≥ 20%	positive
Poorly effective[a]	bleeding slightly reduced or unchanged	not clinically stable	<50%	negative
Not effective	bleeding worsening	Clinically deteriorating	<20%	negative

Note: If a clinical assessment was positive with below-target FVIII levels, the clinical assessment determined the response.
[a] This assessment level was used in Study OBI-1-301 after Study Protocol-OBI-1-301, Amendment 3.0 was in effect. It was never used in Study OBI-1-301a.

In both scales, a positive response was defined as effective or partially effective control of bleeding. Because the definition of a positive response was identical for the three- and four-point scales, data from the two scales was combined for statistical analysis of the number of subjects with a positive bleeding response to Obizur therapy.

Secondary Efficacy Assessments

Assessment of FVIII activity level

Assessment of FVIII activity level was conducted at least every 2-3 hours for the first 24 hours after the initial dose of Obizur except where slow decline in activity was documented.

Following the first 24 hours, FVIII activity measurements were conducted with each subsequent dose of Obizur throughout treatment and at a minimum of once every 24 hours if dosing was less frequent than daily.

Exposure to OBI-1

Total dose, total number of Obizur infusions and the exact time of each infusion were recorded.

Assessment of response to Obizur treatment

Assessment of response to Obizur treatment was performed after each dose of OBI-1 or at least every 8 hours after the initial dose of Obizur for the first 24 hours using the 3- or 4-point scale, as described.

Between Day 1 and Day 5 of treatment, the response to Obizur was assessed after each Obizur dose or at least every 12 hours. Subsequent assessments were conducted at each dose or at least every 24 hours thereafter until after the last Obizur treatment dose or withdrawal.

Timing of assessments was relative to the administration of the first dose of Obizur until the resolution of the bleeding episode, failure of therapy was concluded or withdrawal of the subject.

A serious bleeding episode was considered as successfully controlled if the investigator checked "Completed OBI-1 therapy as treatment success" from the electronic case report form.

Assessment of control of bleeding

The tools used to assess the control of bleeding depended upon the site of bleeding and included:

- obvious blood loss
- haematology results
- blood transfusion and blood component requirements
- physical or technological examination of the bleeding site
- imaging studies to assess the size of the bleeding site where this cannot be assessed by visually

Sample size

The study included 28 bleeding episodes in 28 unique subjects.

The sample size estimate was based on showing that the lower 95% confidence interval for the response rate in this population was greater than a pre-specified limit derived from a literature review of studies in subjects with acquired haemophilia treated with plasma-derived porcine FVIII, rFVIIa and aPCC for serious but not-life threatening bleeding episodes and who showed efficacy rates from 55% to 90% within 24 to 72 hours after initiation of therapy.

Benefit for treatment with Obizur was concluded if the lower bound of the 95% confidence interval for the response rate was greater than 50% which required that the actual sample response rate was in excess of about 70%.

Assuming a positive response rate (i.e. response defined as effective or partially effective control of bleeding at 24 hours) of 80% in the cohort of 28, a baseline low response rate of 50% and a two-sided

alpha of 0.05, a study of 28 bleeding events would have in excess of 90% power to test the null hypothesis that the response rate equalled 50% against the alternative hypothesis that the response rate was greater than 50%.

- **Randomisation**

The study was non-randomised. All eligible subjects were assigned to the treatment group.

Only subjects with successful treatment of a serious bleed with Obizur were involved in the pharmacokinetic study.

- **Blinding**

This was an open-label study.

- **Statistical methods**

The rate of positive response was presented with a two sided 95% Clopper-Pearson confidence interval.

Pharmacokinetic variables from the bleeding state were estimated by population pharmacokinetic modelling or when subject's pharmacokinetic data were insufficient by a Bayesian approach using the established Obizur population pharmacokinetic model.

Pharmacokinetic data from the non-bleeding state were analysed using a compartmental analysis.

The "Intent-To-Treat" population (n = 29) consists of all eligible subjects who enrolled in the trial, were dosed and for whom any post-screening data are available.

The "Per Protocol" population (n = 23) consists of all subjects from the "Intent-To-Treat" population who met all inclusion/exclusion criteria.

The "Pharmacokinetic" population (n = 9) consists of all subjects in the "Intent-To-Treat" population who consented to blood sampling for FVIII activity level measurements by the central reference laboratory.

For the purposes of statistical analysis the "three-point" or "four-point" response assessment was converted to a binary response (positive or negative) based on clinical judgment and achieved FVIII levels. A positive response was defined as the investigator's assessment that Obizur was effective or partially effective on both the three-point and four-point scales:

- Effective response: bleeding stopped, with clinical stabilization and FVIII levels of 50% or higher
- Partially effective: bleeding improved, with clinical stabilization and FVIII levels of 20% or higher.
- Handling of Dropouts or Missing Data
- Because of the variable duration of treatment, some subjects did not have equivalent time points collected. In this case, data were only analysed at each time point for subjects who had that assessment performed.

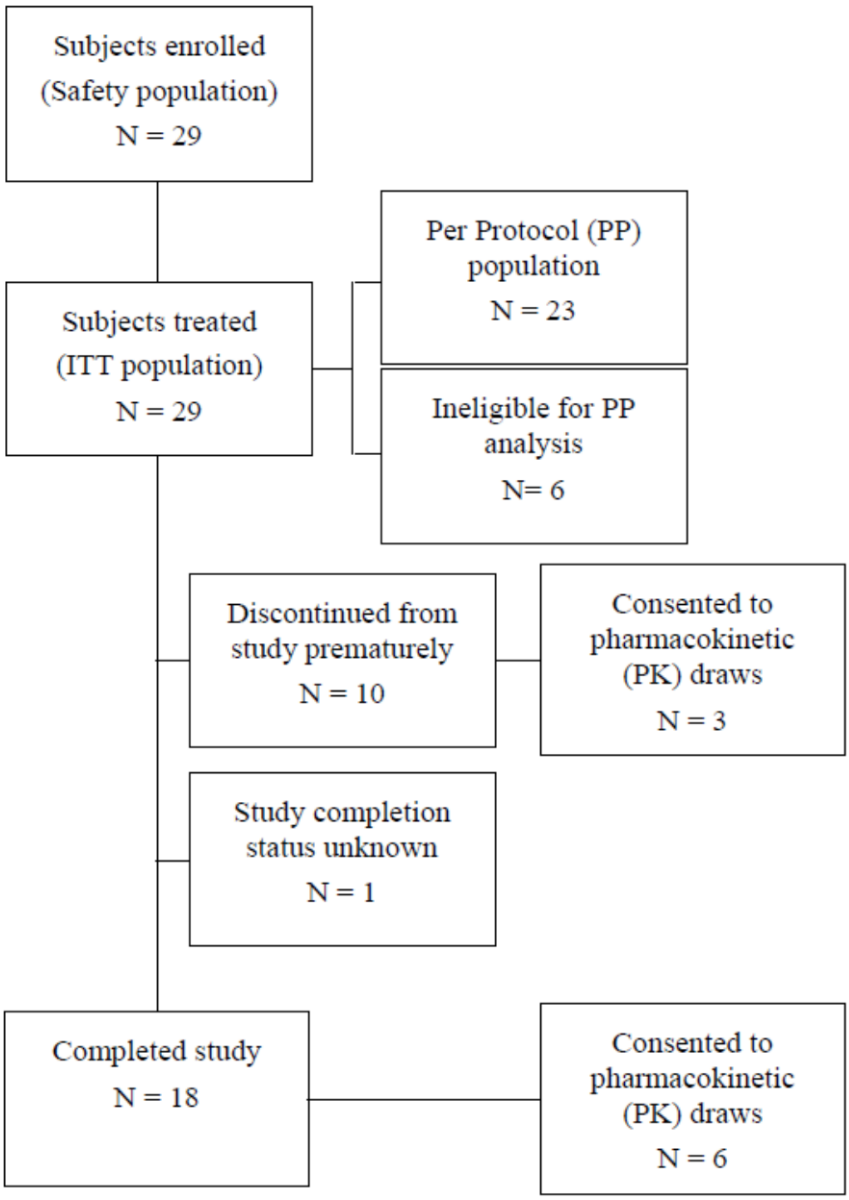
- Eligible subjects who withdrew from treatment at an earlier time point were assumed to be non-responders at the subsequent time points. No subjects were replaced.
- Subjects who received clinical trial material but had an anti– Obizur titre of more than 20 Bethesda Units within 24 hours after the initial Obizur dose were considered ineligible.
- Ineligible subjects could be continued to be treated but were not included in the analysis of the efficacy endpoints.
- Efficacy analyses were performed by using the ITT population including only eligible subjects.
- Subjects who had haemostatic response and stopped treatment because the bleeding was controlled, were assumed to be responders at subsequent time points. For analyses using the safety population, there was no imputation of missing endpoint values.
- Dates and times were not imputed unless needed for a calculation, in which case the most conservative (worst-case) date and time was used. In the case of determining baseline values, the last measurement before dosing was used.

Results

- **Participant flow**

29 subjects were enrolled and all were treated with Obizur. 18 subjects completed the study. 9 subjects consented to blood being taken at the final dose for a pharmacokinetic study, as shown in the diagram below:

Figure 1
Subject Enrollment and disposition for Study OBI-1-301 and 301a



Discontinuations

10 subjects discontinued the study (all 10 were included in the Safety and “Per Protocol” analyses):

- 4 because of adverse events
- 1 subject was lost to follow-up
- 1 because of lack of efficacy (continuous or recurrent bleed)
- 1 developed inhibitors to Obizur
- 1 subject had a ‘terminal status’
- 1 subject died
- 1 subject discontinued because of non-compliance

Reasons for discontinuation for the subjects who discontinued because of adverse events were: "technical problems" during third dose, (patient died shortly afterwards with intracranial haemorrhage); reason not explicitly stated but mental status changes developed on 9th day, treated with psychotropic medication and intracranial haemorrhage detected on day leading to death; detection of anti- Obizur titre of 8 Bethesda units on day 7 (although subject had responded to Obizur treatment) – subsequent death due to intestinal haemorrhage; development of anti- Obizur antibodies; subject known to have chronic renal failure deteriorated and died on day 14.

Protocol deviations

Protocol deviations were reported for 27 subjects during the study. Most deviations refer to missed blood (or urine) sample collections or inadequate samples, samples taken out of the specified window time or incorrect infusion rates.

Six subjects were granted waivers for entry into the study despite not meeting all of the eligibility criteria and were excluded from the “Per Protocol” analysis

- **Recruitment**

12 study sites participated in this study: 8 in the USA, 2 in the UK, 1 in Canada and 1 in India, as shown:

Table 11-3
Site and Subject Numbers by Country in Study OBI-1-301

Country	Number of Sites	Number of Subjects Enrolled
United States	10 (4)[a]	12 (4)[a]
Canada	1	5
United Kingdom	2	4
India	1	4

Source: OBI-1-301-list-patients-with-batches-2014may09

[a] Parentheses contain numbers for Protocol OBI-1-301a sites. Protocol OBI-1-301a was only carried out in the United States. Two sites enrolled subjects under bot protocol OBI-1-301 and expanded access OBI-1-301a

2 sites enrolled subject under protocol OBI-1-301 and expanded access protocol OBI-1-301a; 2 sites enrolled subjects under OBI-1-301a only.

Dates of study: First subject in: 10th November 2010; Last subject out: 9th October 2013

- **Conduct of the study**

12 study sites participated in this study. 2 sites enrolled subject under protocol OBI-1-301 and expanded access protocol OBI-1-301a; 2 sites enrolled subjects under OBI-1-301a only: 8 sites enrolled subjects under Protocol OBI-1-301 only.

1 site enrolled 5 subjects, 3 sites enrolled 4 subjects each, 1 site enrolled 3 subjects and 2 sites enrolled 2 subjects each. Five sites enrolled and treated a single subject each.

A study medical monitor was employed. Clinical research associates visited sites. Periodic site visits were scheduled within 2 weeks of a subject's first dose and after a subject completed the follow up period (or was discontinued). Data verification was performed for all key data according to company SOPs. Source document verification was performed by direct access to subjects' hospital and pharmacy records.

A data monitoring and safety board was convened with three clinicians with expertise in haematology and one biostatistician. The board was responsible for assuring patient safety and assessing safety data. The board met at intervals and on an incident basis regarding serious adverse events.

After the first 5 patients were enrolled and treated with Obizur, an interim analysis was done on summary data and reviewed by the company and data monitoring and safety board. The study would be stopped if 3 or more of the subject responses were considered to be negative.

Amendments

6 rounds of amendments were made between 14th July 2010 and 17th April 2013. Most of the amendments are clarifications. Of note: amendment 3.0 (12th February 2012) "*The scale used for the primary endpoint was changed from a three-point to a four-point ordinal scale with the inclusion of the assessment of "poorly controlled" bleeding*" and amendment 4.0 (17th April 2013) "*study sponsor was changed from Inspiration Biopharmaceuticals, Inc. to Baxter*". Reversion to a 4-point scale was done after receiving advice from the CHMP.

- **Baseline data**

Demographics

29 subjects enrolled (65.5% male, 34.5% female)

18 were White/Caucasian, 6 were Black or African American and 5 were Asian.

The median age was 70 years (range: 42-90 years).

The median weight was 74.1 kg (range: 47.0-106.1 kg) and the median height was 168.3 cm (range: 149-186 cm)

14 subjects had a previous history of acquired haemophilia A.

The time from first diagnosis of acquired haemophilia A was from 0 to 19 months.

One patient presented with an intracranial bleed entered into the study and received 405,000 units of Obizur over 21 infusions but who was shown not to have anti-factor VIII antibodies.

Another patient was also recorded as not having acquired haemophilia with inhibitors to factor VIII.

Bleedings in the presented 28 subjects were: bleeding into muscle or joints (20); bleeding after surgery (3) intra-cranial bleed (1); retroperitoneal bleed (1); peri-orbital bleed (1); prior to surgery i.e. Obizur administered as prophylaxis (2). All bleeds are described as 'limb- or life-threatening'.

27 subjects received concomitant immunosuppression during the course of study participation, 22 subjects had a significant medical history of cardiovascular disorders and 20 had endocrine / metabolic disorders; 11 subjects were reported as having received rFVIIa, aPCC or tranexamic acid prior to first treatment with Obizur. All dosing with Obizur was done on an inpatient basis and carried out by hospital staff. Compliance, expressed as a percentage of planned dose that was administered: the mean (SD) compliance for control of initial qualifying bleeding events was 99.83% (0.922).

- **Numbers analysed**

The "Intent-To-Treat" population (n = 29) consists of all eligible subjects who enrolled in the trial, were dosed and for whom any post-screening data are available.

The "Per Protocol" population (n = 23) consists of all subjects from the "Intent-To-Treat" population who met all inclusion/exclusion criteria.

The "Pharmacokinetic" population (n = 9) consists of all subjects in the "Intent-To-Treat" population who consented to blood sampling for FVIII activity level measurements by the central reference laboratory.

- **Outcomes and estimation**

Primary Efficacy Parameter

A positive response was defined as the investigator's assessment that Obizur was effective or partially effective on both the three-point and four-point scales.

All 29 subjects (100%, 95% CI:88.1-100) were judged by the investigators to have a positive response to Obizur at 24 hours after initiation of treatment, as shown in the following table:

14.1.2 Efficacy

Table 14.2.1.1
Responses of Initial Serious Bleeding Episodes at 24 Hours [1]
(ITT Population)

	Statistic	OBI-1 (N=29)
Total number of subjects with initial serious bleeding episodes	N	29
Positive response[2]	n (%)	29 (100.0)
Negative response	n (%)	0 (0.0)
	95% CI for positive response rate[3]	(88.1, 100)
	p-value[4]	<0.001

[1] Post 24 hour assessments will be used if 24 hour assessment is missing.
[2] A positive response is defined as effective or partially effective control of bleeding, as determined by the investigator by using
a 4-point rating scale. Percentages are based on the total number of subjects with all subsequent serious bleeding episodes.
[3] Clopper-Pearson confidence interval is presented.
[4] One-sided binomial exact test
Date: 13MAY2014 Data Source: adrp.sas7bdat Program Source: T_ADRP1.sas

A one-sided exact Binomial test was performed at the 2.5% level of statistical significance, and the p-value based on intention to treat population (and the per protocol population) was <0.001 (statistically significant evidence in support of response rate >50%).

No subjects were judged to have a negative response (poorly effective or not effective) to Obizur treatment at 24 hours after their initial dose.

The per protocol analysis is shown below:

Table 14.2.1.3
Responses of Initial Serious Bleeding Episodes at 24 Hours [1]
(Per Protocol Population)

	Statistic	OBI-1 (N=23)
Total number of subjects with initial serious bleeding episodes	N	23
Positive response[2]	n (%)	23 (100.0)
Negative response	n (%)	0 (0.0)
	95% CI for positive response rate[3]	(85.2, 100)
	p-value[4]	<0.001

[1] Post 24 hour assessments will be used if 24 hour assessment is missing.
[2] A positive response is defined as effective or partially effective control of bleeding, as determined by the investigator by using
a 4-point rating scale. Percentages are based on the total number of subjects with all subsequent serious bleeding episodes.
[3] Clopper-Pearson confidence interval is presented.
[4] One-sided binomial exact test
Date: 13MAY2014 Data Source: adrp.sas7bdat Program Source: T_ADRP1.sas

Secondary Efficacy Parameters

Treatment Success as Assessed by the Investigator

A serious bleeding episode was considered as successfully controlled if the investigator checked "Completed Obizur therapy as treatment success" from the electronic case record file. Percentages are based on the total number of subjects with initial serious bleeding episodes.

Qualifying bleeding events treated with Obizur were judged by the investigator to have been controlled successfully in 25/29 (86.2%) of subjects at the time of final treatment dosing or progression to healing phase dosing.

A summary is shown in the following table for the intention to treat population:

Table 14.2.2.1
Successful Control of Initial Serious Bleeding Episodes
(ITT Population)

	Statistic	OBI-1 (N=29)
Total number of subjects with initial serious bleeding episodes	N	29
Bleeding successfully controlled [1]	n (%)	25 (86.2)
Bleeding not successfully controlled [2]	n (%)	4 (13.8)
	95% CI for successful control rate[3]	(68.3, 96.1)
	p-value[4]	<0.001

eCRF = electronic case report form.
[1] A serious bleeding episode is considered as successfully controlled if the investigator checked "Completed OBI-1 therapy as treatment success" from the eCRF. Percentages are based on the total number of subjects with initial serious bleeding episodes.
[2] The subjects are 30104, 30105, 30601, and 32101 who discontinued study prematurely (see Listing 14.2.2.3).
[3] Clopper-Pearson confidence interval is presented.
[4] One-sided binomial exact test
Date: 13MAY2014 Data Source: adrp.sas7bdat Program Source: T_ADRP3.sas

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

"Treatment success" was not achieved in 4 qualifying bleeds in 4 unique subjects, as assessed by the investigator (all 4 subjects did have a positive response to Obizur therapy at their qualifying bleeding site at 24 hours).

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.

The per protocol analysis is shown below: the per protocol analysis (87% success) supports the intent-to-treat analysis (86% success).

Table 14.2.2.5
Successful Control of Initial Serious Bleeding Episodes
(Per Protocol Population)

	Statistic	OBI-1 (N=23)
Total number of subjects with initial serious bleeding episodes	N	23
Bleeding successfully controlled [1]	n (%)	20 (87.0)
Bleeding not successfully controlled [2]	n (%)	3 (13.0)
	95% CI for successful control rate[3]	(66.4, 97.2)
	p-value[4]	<0.001

eCRF = electronic case report form.
[1] A serious bleeding episode is considered as successfully controlled if the investigator checked "Completed OBI-1 therapy as treatment success" from the eCRF. Percentages are based on the total number of subjects with initial serious bleeding episodes.
[2] The subjects are 30104, 30105, and 32101 who discontinued study prematurely (see Listing 14.2.2.3).
[3] Clopper-Pearson confidence interval is presented.
[4] One-sided binomial exact test
Date: 13MAY2014 Data Source: adrp.sas7bdat Program Source: T_ADRP3.sas

Response to Obizur Treatment at Specific Time Points

Positive and negative bleeding responses to Obizur administration at specified time points after the initial Obizur dose are summarised for the intent-to-treat population in the following table:

Table 14.2.1.2
Responses of Initial Serious Bleeding Episodes by Time
(ITT Population)

Time/ Response	Statistic	OBI-1 (N=29)
Response at 8 hours (n=21)		
Positive[1]	n (%)	20 (95.2)
Negative	n (%)	1 (4.8)
	95% CI of positive response[2]	(76.2, 99.9)
Response at 16 hours (n=19)		
Positive[1]	n (%)	19 (100.0)
Negative	n (%)	0 (0.0)
	95% CI of positive response[2]	(82.4, 100)
Response at 24 hours (n=29)		
Positive[1]	n (%)	29 (100.0)
Negative	n (%)	0 (0.0)
	95% CI of positive response[2]	(88.1, 100)

Note: Report ends when there are less than 3 initial serious bleeding episodes or all subjects are responders.
[1] A positive response is defined as effective or partially effective control of bleeding, as determined by the investigator by using
a 4-point rating scale. Percentages are based on the total number of subjects with initial serious bleeding episodes.
[2] Clopper-Pearson confidence interval is presented.
Date: 13MAY2014 Data Source: adrp.sas7bdat Program Source: T_ADRP2.sas

Some subjects were not assessed at all time-points. Of the 21 subjects assessed at 8 hours after the initial dose, 20 (95.2%) subjects showed a positive response to Obizur treatment, 19/19 subjects showed a positive response at 16 hours after initial infusion.

Amount of Obizur Required to Control Bleeding

Following the initial single 200 U/kg dose of Obizur, the investigator was to determine the subsequent doses based on clinical status and maintaining target FVIII activity trough levels. After successful control of the bleed, based on clinical assessment, Obizur treatment was either stopped or continued at lower dose / frequency (healing phase). For subjects whose qualifying bleeding event was controlled, a summary of dose and number of infusions of Obizur until control of the qualifying bleed is shown in the following table

Table 14.2.2.4
Summary of Exposure and Compliance of Doses until Bleed Control for Subjects Who Successfully Controlled Initial Serious Bleeding Episodes
(ITT Population)

Parameter	Statistic	OBI-1 (N=25)
Total exposure per subject (U/kg)	n	25
	Mean	2683.2
	Median	1637.0
	SD	2928.61
	Min, Max	100,12194
Total number of infusions per subject	n	25
	Mean	15.4
	Median	13.0
	SD	12.64
	Min, Max	1,57
Average number of infusions per day	n	25
	Mean	2.10
	Median	2.10
	SD	1.109
	Min, Max	0.3,4.5
Compliance (%)	n	25
	Mean	99.83
	Median	100.00
	SD	0.985
	Min, Max	96.6,102.8

Note: Compliance is calculated as the total dose administered (U) divided by total dose planned (U).
Note: Includes doses of infusions used to treat intial bleed until control was acheived.
Date: 13MAY2014 Data Source: ADEX.sas7bdat Program Source: T_ADEX4.sas

For subjects whose qualifying bleeding event was controlled, a summary of dose and number of infusions of Obizur is shown in the following table for the entire duration of study participation:

Table 14.2.2.2
Summary of Exposure and Compliance of Doses of All Infusions for Subjects Who Successfully Controlled Initial Serious Bleeding Episodes
(ITT Population)

Parameter	Statistic	OBI-1 (N=25)
Total exposure per subject (U/kg)	n	25
	Mean	3146.0
	Median	1637.0
	SD	3275.73
	Min, Max	150,12194
Total number of infusions per subject	n	25
	Mean	20.2
	Median	14.0
	SD	18.55
	Min, Max	2,79
Average number of infusions per day	n	25
	Mean	1.82
	Median	1.76
	SD	0.998
	Min, Max	0.2,4.0
Compliance (%)	n	25
	Mean	99.84
	Median	100.00
	SD	0.980
	Min, Max	96.6,102.8

Note: Compliance is calculated as the total dose administered (U) divided by total dose planned (U).
Note: Includes doses of all infusions used to treat and heal the intial bleed.
Date: 13MAY2014 Data Source: ADEX.sas7bdat Program Source: T_ADEX3.sas

Response to OBI-1 Treatment at Specific Time Points Correlated with Control of the Bleeding Event

Overall, subjects who were assessed to have a positive response to *Obizur* treatment earlier than 24 hours after dosing initiation, achieved eventual control of the qualifying event (secondary outcome measure).

Effect of Pre-infusion Anti–susoctocog alfa Titres and Anti-hFVIII Titres on Control of Bleeding Events

The presence of anti–susoctocog alfa antibodies with titres above 20 BU was an exclusion criterion.

Of the 4 subjects in whom bleed control was not achieved, 3 had no detectable anti-Obizur antibodies (titre <0.6 BU) and the fourth had a positive low Obizur titre (3 BU).

Response to Obizur Treatment Non-target Bleeds

33 non-target bleeding events were reported in 17 subjects.

23/33 bleeds resolved within 2 days after first assessment of the bleeding event.

Response to Obizur Treatment for Subsequent Serious Bleeds

Three subjects experienced a serious bleeding event subsequent to the qualifying bleed that was treated with susoctocog alfa.

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.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: summary of efficacy for trial OBI-1-301/301a

<table>
<tr><td colspan="4">Title: Efficacy and safety of B-domain deleted recombinant porcine factor VIII (OBI-1) in the treatment of acquired haemophilia A due to autoimmune anti-factor VIII inhibitory antibodies</td></tr>
<tr><td>Study identifier</td><td colspan="3">OBI-1-301/301a</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">Open-label, non-randomised, non-controlled multi-centre, multinational</td></tr>
<tr><td>Duration of main phase:

Duration of Run-in phase:
Duration of Extension phase:</td><td colspan="2">Duration for each patient depended on clinical response
First subject in: 10th November 2010
Last subject out: 9th October 2013

not applicable
not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">That serious bleeding in subjects with acquired haemophilia will respond to treatment with Obizur within 24hrs of starting treatment.</td></tr>
<tr><td>Treatments groups</td><td colspan="3">A case series of 28 patients with acquired haemophilia and life and / or limb-threatening bleeding episodes

(one additional patient was treated but did not have acquired haemophilia)</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>24hr response</td><td>the proportion of serious bleeding episodes responsive to Obizur therapy at 24 hours after the initiation of treatment based on assessment of effectiveness and FVIII blood levels

A positive response was defined as the investigator’s assessment that Obizur was effective or partially effective on both the three-point and four-point scales.</td></tr>
</table>

	Secondary endpoints	Success	The overall proportion of serious bleeding episodes successfully controlled with Obizur therapy, as assessed by the investigator. A serious bleeding episode is considered as successfully controlled if the investigator checked “Completed OBI-1 therapy as treatment success” from the electronic case report form.
		Amount Obizur needed	Frequency, total dose and total number of infusions of Obizur required to successfully control qualifying bleeding episodes.
Database lock	Not stated by company		
Results and Analysis			
Analysis population	Intent to treat		
Descriptive statistics	Primary endpoint	All 29 subjects (100%, 95% CI:88.1-100) were judged by the investigators to have a positive response to Obizur at 24 hours after initiation of treatment	
	Secondary endpoints	Qualifying bleeding events treated with Obizur were judged by the investigator to have been controlled successfully in 25/29 (86.2%) of subjects at the time of final treatment dosing or progression to healing phase dosing.	
		Frequency, total dose and total number of infusions of Obizur required to successfully control qualifying bleeding episodes were particular to each patient and varied from 1 infusion up to 57 infusions.	

Analysis performed across trials (pooled analyses and meta-analysis)

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	7	9	3
Non Controlled Trials	N/A	N/A	N/A

Supportive studies

Study OBI-1-201

In this phase II study, nine subjects (aged from 14 to 34 years) with congenital hemophilia A with inhibitors to human rFVIII, who were experiencing a non-life- or non-limb-threatening bleeding episode, received rpFVIII. As this study refers to congenital haemophilia A, it is only discussed from point of view of establishing the dose regimen.

The dosing regimen included a loading dose (based on body weight, hematocrit and inhibitor titer) in subjects with measurable anti-rpFVIII antibody titers (but not in subjects without measurable antibody titers), followed by up to eight treatment doses of rpFVIII (50–150 U/kg) at intervals of up to 6 hours.The loading dose used in the main study OBI-1-301 was derived from study OBI-1-201 and calculated as: Loading Dose = body weight (kg) x 80 mL/kg x (1-hematocrit) x inhibitor titer.

An independent Data Safety Monitoring Committee (DSMC) recommended stopping the Phase II study after reviewing data on 25 bleeding episodes in nine subjects, concluding that data on three more subjects would not modify the conclusion that rpFVIII was effective in establishing hemostasis. (A total of 12 subjects was originally planned.)

The target of 24 bleeding episodes was exceeded by one bleeding episode, with nine subjects treated. All bleeding episodes were successfully controlled with rpFVIII; 20/25 (80%) bleeding episodes were controlled with one treatment dose plus the loading dose when applicable.

The median dose administered for these 20 bleeding episodes was 200.8 U/kg (including the loading dose if applicable). Factor VIII levels were measured before and 0.5 hours after each treatment dose of rpFVIII. For all bleeding episodes, the initial factor VIII level was negligible before the first dose. The median first treatment dose (including the loading dose if applicable) for the 25 bleeding episodes was 159 U/kg and resulted in a median factor VIII level of 16% thirty minutes after the initial dose of rpFVIII.

The DSMC indicated that the initial dose (loading dose + first treatment dose) did not equal the amount specified in the protocol as the inhibitor titers against rpFVIII were often unknown until after the subject was dosed and treated. The DSMC recommended a fixed initial dose of rpFVIII for future studies.

Population PK analysis of rpFVIII combining data obtained in both the Phase I and the Phase II study (one-stage coagulation assay) was planned but not eventually performed. This study is further discussed from under Clinical safety.

2.5.3. Discussion on clinical efficacy

This initial marketing authorisation application is based on one key phase 2/3 study (OBI-1-301 + OBI-1-301a), one supportive phase 2 study (OBI-1-201) and one phase 1 study (OBI-1-101, PK). The Applicant has added supportive efficacy data from the Study OBI-1-201 with nine subjects with congenital hemophilia A with anti-hFVIII-inhibitors, who were experiencing a non-life- or non-limb-threatening bleeding episode, as this study is intended in a different indication the results are only informative as a justification of the dose for the rpFVIII used.

Design and conduct of clinical studies

Study OBI-1-301/301a was an open-label, non-randomised, non-controlled, multi-centre, multinational study. The study design of the key phase 2/3 study is acceptable and follows the various CHMP Scientific advices.

The sample size calculation for the overall population in the OBI-1-301 + OBI-1-301a is acceptable. Instead of minimum of 30 bleeding episodes in 30 different subjects as recommended by the CHMP, the number of subjects in the study was 29 which was reduced to a series of 28 patients with acquired haemophilia –as 1 patient did not have acquired haemophilia yet was entered into the study and consequently, the actual per protocol population was 22 (and not 23) subjects. A protocol assistance was given by the CHMP in December 2013 (EMA/CHMP/SAWP/749449 /2013) in which it was

acknowledged that the application would include 4 patients treated under an expanded access programme, as described.

The study population is representative of the European patients with AHA and the selection criteria of patients into OBI-1-301 + OBI-1-301a are acceptable.

The primary endpoint was “bleeding stopped/ improved, with clinical stabilization and FVIII levels of 20%/50% or higher” for the efficacy of rpFVIII for the treatment of serious bleeding episodes in subjects with acquired hemophilia which is appropriate for this kind of study, and is in line with the given CHMP scientific advice.

The study was done in hospital settings (hospitals named by the company are recognised as centres for management of haemophilia). Subjects were mostly elderly with extensive clinical histories.

2 subjects received Obizur for prophylaxis of bleeding during a surgical procedure. All others presented as a clinical emergency with bleeds that threatened life and / or limb. 14 subjects were known to have a clinical history of acquired haemophilia and 14 presented for the first time.

The initial dose of Obizur was 200U/kg infused intravenously at a rate of 1 to 2 mL/min. Variability in peak factor VIII activity levels in the first 24 hours was found. This suggests that it may be necessary to give a standard dose for initial treatment that leads to overdosing in some patients in order to ensure that all patients reach sufficient levels of factor VIII activity to treat the bleeding episode. The variability in peak factor VIII activity levels may be in part due to the cross-reactivity of the individual patient’s factor VIII antibodies with porcine factor. However, in the life-threatening, emergency situation of initial presentation, individual titration of posology will not be possible.

The decision to administer additional Obizur doses was made by the investigator based on an assessment of the subject’s clinical response to treatment and trough FVIII activity.

After an initial treatment phase to control bleeding, subjects entered into a healing phase during which Obizur was administered to maintain blood activity between 30 to 200%.

Given the rarity of the condition of acquired haemophilia and the emergency nature of the presentation of patients, the design and conduct of the study are considered acceptable.

The company was recommended to continue validation of the one stage clotting assay for factor VIII activity on a Sysmex CA-7000 instrument in post-approval (see also clinical pharmacology).

Efficacy data and additional analyses

The loading dose used in the main study OBI-1-301 was derived from study OBI-1-201. In this phase II trial subjects with congenital haemophilia and inhibitor to human FVIII were treated with pFVIII. The loading dose proved to be of limited value in that study. However, 20 bleeds out of 25 (80%) were controlled with one treatment dose (including the loading dose if applicable) with the median dose of 200.8 U/kg. Due to this finding the Applicant proposed this loading dose for the study OBI-1-301. The CHMP scientific advice regarding the initial fixed dose infusion of 200 U/kg of recombinant pFVIII was that the proposed strategy can be justified and acceptable.

All initial bleeding episodes had a positive response to treatment at 24 hours after initial dosing as assessed by the primary investigator. A positive response was one where bleeding had stopped or was reduced, with clinical improvement or with Factor VIII activity above a pre-specified target.

The primary clinical efficacy endpoint was the proportion of serious bleeding episodes responsive to Obizur therapy at 24 hours after the initiation of treatment based on assessment of clinical

effectiveness and FVIII blood activity. A positive response was defined as the investigator's assessment that Obizur was effective or partially effective on both 3-point and 4-point scales [the company has been requested to clarify why it chose to use a 3-point scale for some patients]. All subjects were judged by the investigators to have a positive response to Obizur at 24 hours after initiation of treatment. The primary efficacy endpoint was met in this study. In OBI-1-301 + OBI-1-301a: all 29 subjects had a positive response to recombinant pFVIII at 24 hours after initiation of treatment (100%, 95% CI:88.1-100).

A positive response was observed in 95% (19/20) of subjects evaluated at 8 hours and 100% (18/18) at 16 hours. In addition to response to treatment, the overall treatment success was determined by the investigator based on his/her ability to discontinue or reduce the dose and/or dosing frequency of OBIZUR. A total of 24/28 (86%) had successful control (resolution) of the initial bleeding episode. Of those subjects treated with OBIZUR as first-line therapy, defined as no immediate previous use of anti-haemorrhagic agents prior to the first OBIZUR treatment, 16/17 (94%) had eventual treatment success reported. Eleven subjects were reported to have received anti-haemorrhagic agents (eg. rFVIIa, activated prothrombin-complex concentrate, tranexamic acid) prior to first treatment with OBIZUR. Of these 11 subjects, eight had eventual successful treatment (73%).

The median dose per injection to successfully treat the primary bleed was 133 U/kg and the median total dose was 1523 U/kg for a median of 6 days. The median number of daily infusions per subject was 1.76 (range: 0.2 to 5.6). In the initial 24 hour period, the median total dose of 493 U/kg were utilized in the clinical study with a median of 3 infusions. When treatment was required beyond 24 hours, a median total dose of 1050 U/kg were utilized with a median of 10.5 infusions (median dose 100 U/kg) to control a bleeding episode.

Results from the secondary and other analyses were also in line with the primary efficacy endpoint.

Qualifying bleeding events treated with Obizur were judged by the investigator to have been controlled successfully in 25 subjects at the time of final treatment dosing or progression to healing-phase dosing. The response of patients was highly variable: 1 patient required only 3 infusions whilst another required 38.

The company has submitted a case series of 29 patients with acquired haemophilia to support the application. Currently advised posology is an initial dose of 200 U/kg. Also, in the first day of treatment, referred to as the 'initial phase' by the company, study OBI-1-301 submitted by the company recommended a trough factor VIII activity of >80% for moderate and severe bleeds and >50% factor VIII activity for mild bleeds.
Once bleeding had responded, usually within the first 24 hours, study OBI-1-301 protocol advised "a dose of Obizur that maintained the trough FVIII activity at 30-40% until bleeding is controlled. The maximum blood FVIII activity must not exceed 200%".
Hyate:C was porcine factor VIII, withdrawn from the marketplace in 2004 because of concerns of possible presence of transmissible agents. Hyate:C was indicated for "....bleeding in patients with inhibitory antibodies to human factor VIII:C....". The recommended starting dose of Hyate:C was 25-50U/kg (and up to 100U/kg in the presence of high antibody titre for anti-porcine factor VIII).
Phase 1 and 2 studies for Obizur have demonstrated similar pharmacokinetics of Obizur to Hyate:C.

Additional consultations with expert groups

The CHMP referred the posology discussion to the BPWP for the following reasons:

- In the first 24hrs of treatment, 7/29 patients had a peak factor VIII activity of 400-700%, 17/29 patients had a peak factor VIII activity of 200-400% and 5/29 patients had a peak factor VIII activity of <200%. There is concern that the factor VIII activities achieved are higher than required and that this may predispose to thrombo-embolic phenomena. The BPWP is requested to comment on the initial dosage and the factor VIII activities achieved.

BPWP considers that there is a need for this product in the treatment of bleeding episodes in patients with acquired haemophilia caused by antibodies to factor VIII. BPWP noted the variability seen in peak factor VIII activity levels in the first 24 hours. This suggests that it may be necessary to give a standard dose for initial treatment that leads to overdosing in some patients in order to ensure that all patients reach sufficient levels of factor VIII activity to treat the bleeding episode. The variability in peak factor VIII activity levels may be in part due to the cross-reactivity of the individual patient's factor VIII antibodies with porcine factor. However, in the life-threatening, emergency situation of initial presentation, individual titration of posology will not be possible. Nevertheless, there are safety concerns given the very high factor VIII activity levels seen in patients. Therefore, the SmPC should emphasise the limited experience with the recommended posology and the potential risk of thromboembolic ADRs. The elderly should be highlighted as particularly at risk. Further information on safety should be collected in the post-authorisation phase.

It does not seem possible at this stage to recommend use of a lower initial dosage since the clinical data is based on the posology proposed by the Company.

- After the first 24hrs and during the 'healing phase' of treatment, 1/29 patients had a peak factor VIII activity of 400-700%, 6/29 patients had a peak factor VIII activity of 200-400% and 22/29 patients had a peak factor VIII activity of <200%. The BPWP is requested to comment on the dosages advised in the 'healing phase'.

BPWP agreed with the proposal already made to the Company that lower dosages should be proposed in the 'healing phase' together with individual assessment by the treating physician. BPWP considered that it would be important to repeat FVIII activity measurements in the healing phase and adjust the dosage accordingly due to the risk of thromboembolic ADRs from high FVIII activity levels.

BPWP noted that if the product receives a positive opinion, it is likely to be under exceptional circumstances with annual review. BPWP considered this appropriate given the limited clinical data and the safety concerns.

The current posology would result in a 70kg subject being administered (about) 120 vials of Obizur over 24hrs. Concerns have been raised over the potential for incorrect counting of vials and over the amount of host cell protein that would be administered to patients (see RMP). The applicant received recommendation to develop an improved pharmaceutical strength/ formulation that would require less vials.

The Applicant will carry out a prospective, non-interventional study to evaluate the safety and effectiveness of Obizur in real life practice, including measurement of immunogenicity (levels of anti-pFVIII antibodies and any associated clinical manifestations) (see RMP).

Additional efficacy data needed in the context of a MA under exceptional circumstances

1. To collect and analyse immediate and long-term data on clinical efficacy and safety of all patients with acquired haemophilia and who are treated with Obizur, the MAH must conduct a surveillance programme/ registry according to an agreed protocol and for an indefinite time.

2.5.4. Conclusions on the clinical efficacy

Data submitted by the company suggest that Obizur bears clinical efficacy in the management of bleeding that is life and / or limb threatening in patients with acquired haemophilia. As it is difficult to assess the severity of the bleeding in a patient, the indication "Treatment of bleeding episodes in patients with acquired haemophilia caused by antibodies to Factor VIII" can be justified, while the clinician should balance the decision to treat a patient with the limited available data with the repeated use of Obizur.

Further experience of use of susoctocog alfa in the management of patients with acquired haemophilia will be obtained in a post-approval registry.
The company will pursue further validation of the one stage clotting assay for factor VIII activity post-approval.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a MA under exceptional circumstances:

- To collect and analyse immediate and long-term data on clinical efficacy and safety of all patients with acquired haemophilia and who are treated with Obizur, the MAH must conduct a surveillance programme/ registry according to an agreed protocol and for an indefinite time.

2.6. Clinical safety

Patient exposure
This application includes safety data from a total of 42 subjects exposed to Obizur between 15 April 2003 and 09 October 2013 in 3 clinical trials.

A summary of overall extent of exposure is shown in the following table:

Table 2.
Summary of Exposure to OBI-1 per Clinical Study

Dose	OBI-1-301	OBI-1-201	OBI-1-101
N	29	9	4
Total Exposure per Subject (Median U/kg)	1,842.0	224.1	100
Total Exposure per Subject (Median Days)	--	2	1
Total Number Infusions per Subject (Mean)	27.0	3.3	1

Source: OBI-1-101 CSR; OBI-1-201, Table 3; OBI-1-301, Table 14.1.5.1
--Not calculated for this study

Overall exposure in study OBI-1-301 is also shown in the following table:

Table 14.1.5.1
Summary of Overall Exposure and Compliance
(Safety Population)

Parameter	Statistic	OBI-1 (N=29)
Total exposure per subject (U/kg)	n	29
	Mean	4512.0
	Median	1842.0
	SD	6399.72
	Min, Max	150,27659
Total number of infusions per subject	n	29
	Mean	27.0
	Median	15.0
	SD	32.82
	Min, Max	2,140
Average number of infusions per day	n	29
	Mean	1.85
	Median	1.76
	SD	1.117
	Min, Max	0.2,5.6
Compliance (%)	n	29
	Mean	99.83
	Median	100.00
	SD	0.908
	Min, Max	96.6,102.8

Note: The dose(U/kg) for each infusion was calculated as planned dose(U/kg) times the proportion of planned volume actually infused.
If the planned or actual volume infused was not recorded, the dose(U) was calculated as the total dose(U)/weight.
If the total dose(U) was not recorded, the dose (U/kg) was calculated as the number of vials used * 500 / weight.
Note: Compliance is calculated as the total dose administered (U) divided by total dose planned (U).
Date: 13MAY2014 Data Source: ADEX.sas7bdat Program Source: T_ADEX1.sas

The dosing and overall exposure were highly variable because dose was based on factor VIII activity and clinical assessment. In addition to the 29 unique qualifying bleeding events, 3 serious bleeding events subsequent to the qualifying bleed that were treated with Obizur (data are included in the above table). The cumulative exposure to treat the qualifying bleed only was 1,637.0 U/kg (median, range: 100 to 20,660 U/kg).

Adverse events

Safety data are presented for 42 subjects treated with Obizur. The safety evaluation plans were similar across the clinical studies and included assessments of medical history and concomitant medications, physical examinations, clinical observations, clinical laboratory measurements, vital signs, blood coagulation tests, factor VIII activity, anti-human factor VIII antibody titres, anti-porcine factor VIII antibody titres, anti-baby hamster kidney cell antibody titres and evaluations of bleeding and adverse events.

In Study OBI-1-301 and its expanded access program, Study OBI-1-301a, non-qualifying and subsequent serious bleeding events not considered a continuation of the initial bleeding event were considered adverse events.

In Study OBI-1-301/301a, events were considered continuations of the initial bleed in the following circumstances:

- Bleeding that occurred at the site of the qualifying bleeding event after initially successful haemostasis and before 2 weeks after the last Obizur dose.
- Bleeding events that occurred at another anatomical site before 1 week after the last Obizur dose.

Clinical assessment of the bleed site followed the same parameters as were assessed for the initial bleeding events.

All subsequent serious bleeding events were recorded as adverse events.

All treatments, assessments and outcomes were fully documented for the subsequent bleeding events that were documented for the qualifying bleeding event.

The follow-up visit schedule was based on the final Obizur dose, regardless of whether for the qualifying bleed or a subsequent bleed.

A summary of the treatment emergent adverse events from each study is shown in the following table:

Table 4.
Summary of Treatment-Emergent Averse Events: Overview (Safety Population)

Study Number	OBI-1-301	OBI-1-201	OBI-1-101
N	29	9	4
Total number of TEAEs	264	18	10
Number (%) of subjects reporting:			
Any treatment-emergent adverse event	27 (93.1)	7 (78)	3 (75)
Any related treatment-emergent adverse event	6 (20.7)	2 (22)	0
Any severe adverse event	6 (20.7)	3 (33)	0
Any severe treatment-related adverse event	0	0	0
Any serious adverse event	13 (44.8)	3 (33)	0
Any adverse events leading to discontinuation of study drug	3 (10.3)	0	0
Adverse event leading to death	7 (24.1)	0	0

Source: OBI-1-101 CSR, Appendix IV, Listing 18; OBI-1-201 CSR, Table 10, Table 14.3.1.1, and Table 14.3.1.2, Appendix 16.2.7.1; OBI-1-301 CSR, Table 14.3.1.1

TEAE: treatment emergent adverse event

Safety data was not integrated owing to the differences in study populations, bleed state, severity and dosing regimen. Instead, safety data are summarised for each study.

Study OBI-1-301/301a

In Study OBI-1-301/301a, a total of 264 treatment emergent adverse events were reported by 27 of 29 subjects.

Most treatment emergent adverse events were mild (50.4%) or moderate (37.9%) in severity.

The most frequently reported mild treatment emergent adverse events included: constipation (2.7%), diarrhoea (2.3%) and oedema peripheral (2.3%), nausea (1.5%) and insomnia (1.9%).

The most frequently reported moderate treatment emergent adverse events included constipation (1.1%), pneumonia (1.1%), muscle haemorrhage (1.1%), hypertension (1.1%), hypokalaemia (3.0%), and pyrexia (1.5%).

Severe treatment emergent adverse events were reported in 6 subjects and included abdominal pain (0.8%), constipation (0.8%), hypocalcaemia (0.8%) and joint swelling (0.8%).

Relatedness of adverse events

7 non-serious treatment emergent adverse events considered by the investigator as related to Obizur were reported in 6 subjects.

Related treatment emergent adverse events were all mild or moderate in severity and all completely resolved except for one instance of a positive anti-porcine inhibitor which was ongoing as of study completion.

- One subject had mild hypotension and constipation which all completely resolved.
- One subject had 2 instances of central catheter line occlusion which completely resolved.
- One subject had a mild hypofibrinogenaemia which completely resolved.
- One subject experienced a mental status change.
- Two subjects developed anti-susoctocog alfaantibodies and were discontinued from treatment, however both subjects had a positive response to treatment at the 24 hour primary endpoint assessment.

The sponsor has reviewed the investigator-assessed related adverse events: the two incidences of anti-porcine inhibitors are considered related to susoctocog alfa treatment with all others unlikely related to susoctocog alfa treatment.

Information on blockage of in-dwelling venous catheters and pre-disposition towards thromboembolic disease in those with pre-existing cardiovascular disease and the elderly is proposed for the PI texts based on experience of raised factor VIII activities in these patient-groups.

Study OBI-1-201

Eighteen (18) adverse events were categorised as treatment emergent. The most frequently reported were haemorrhagic disorder and haemarthrosis: none led to treatment interruption or discontinuation from the study.

Study OBI-1-101

There were 10 adverse events, all considered unrelated to the current product. All adverse events resolved.

Serious adverse event / deaths / other significant events

Serious adverse events

Study OBI-1-301/301a

Thirty three (33) treatment emergent serious adverse events (including 8 treatment emergent serious adverse events leading to death) were reported in 13 (44.8%) subjects. Twenty eight (28) of the Treatment emergent serious adverse events were judged by the investigator to be unrelated to study drug and 5 were judged as probably not related / remotely related; all but one resolved during the study. The one subject who experienced an on-going treatment emergent serious adverse event was diagnosed with and received treatment for atrial fibrillation.

Pneumonia, reported in 3 (10.3%) subjects, was the most frequently reported treatment emergent serious adverse event followed by sepsis, reported in 2 (6.9%) subjects.

For studies OBI-1-301 and OBI-1-201 combined: the most common treatment emergent serious adverse events by system organ class were “infections and infestations” reported in 7 subjects (16.3%) followed by “musculoskeletal and connective tissue disorders” observed in subjects (14.0%) and “nervous system disorders” reported in 5 subjects (11.6%). No treatment emergent serious adverse events were considered related to Obizur treatment.

There were not any treatment emergent serious adverse events for Study OBI-1-101.

A summary of serious adverse events in Obizur studies is shown in the following table:

Table 7.
Cumulative Summary Tabulation of Serious Adverse Events from OBI-1 Clinical Trials

System Organ Class (SOC) Preferred Term	Number of subjects (percentage) N=43	
Cardiac disorders	**1**	**(2.3)**
Atrial fibrillation	1	(2.3)
Endocrine disorders	**1**	**(2.3)**
Dizziness	1	(2.3)
Gastrointestinal disorders	**2**	**(4.7)**
Intestinal haemorrhage	1	(2.3)
Oesophagitis	1	(2.3)
General disorders	**1**	**(2.3)**
Asthenia	1	(2.3)
Hepatobiliary disorders	**1**	**(2.3)**
Cholangitis	1	(2.3)
Immune system disorders	**1**	**(2.3)**
Anaphylactic reaction	1	(2.3)
Infections and infestations	**7**	**(16.3)**
Infection	1	(2.3)
Pneumonia	3	(7.0)
Sepsis	2	(4.7)
Urinary tract infection	1	(2.3)
Injury, poisoning, and procedural complications	**3**	**(7.0)**
Fall	1	(2.3)
Tracheostomy malfunction	1	(2.3)
Vascular pseudoaneurism	1	(2.3)
Musculoskeletal and connective tissue disorders	**6**	**(14.0)**
Arthralgia	1	(2.3)
Hematoma	2	(4.7)
Joint swelling	1	(2.3)
Musculoskeletal pain	1	(2.3)
Muscle haemorrhage	1	(2.3)
Nervous system disorders	**5**	**(11.6)**
Brain oedema	1	(2.3)
Haemorrhage intracranial	2	(4.7)
Grand mal convulsion	1	(2.3)
Transient ischemic attack	1	(2.3)
Renal and urinary disorders	**1**	**(2.3)**
Renal failure	1	(2.3)
Respiratory, thoracic, and mediastinal disorders	**1**	**(2.3)**
Respiratory failure	1	(2.3)
Skin and subcutaneous tissue disorders	**1**	**(2.3)**
Pruritus	1	(2.3)

Source: OBI-1 DSUR#3, version 2014May27

Deaths

Five (5) deaths occurred during study OBI-1-301 and 2 subjects died after discontinuing from the study.

Three (3) deaths were attributed to serious bleeding (2 intracranial haemorrhages, 1 intestinal), 2 deaths were attributed to infection, 1 death was attributed to infection and cholangitis and 1 death was attributed to renal failure. All deaths that were observed during or after the study were a result of subject's clinical condition which includes consequences of immunosuppressive therapy and co-morbidities. The treatment emergent serious adverse events leading to death were considered not related to the current product in 5 cases and probably not / remotely related to the current product in 2 cases of intracranial haemorrhage.

There were not any deaths in studies OBI-1-201 and OBI-1-101.

Laboratory findings

Haematology

Abnormal haematology laboratory results were observed in all subjects in Study OBI-1-301: these results were consistent with the subjects' underlying diseases and all resolved.

Clinical Chemistry

Abnormal clinical chemistry laboratory results were observed in all subjects in Study OBI-1-301 with no specific patterns of abnormal chemistry results.

Urinalysis

Overall, there were no significant abnormal urinalysis results or any specific patterns of abnormal urinalysis results in the clinical studies.

Immunological events

Anti OBI-1 antibodies

Presence of anti-Obizur antibodies with titres above 20BU was an exclusion criterion in Study OBI-1-301.

Ten (10) out of 28 eligible subjects had a detectable anti-Obizur inhibitor titre at baseline (range: 0.8-29 BU), yet all subjects had a positive response to treatment.

After dosing, 8 of these subjects had no detectable anti-porcine inhibitor titre (titre <0.6BU at the last reported result) and an increase in titre was observed in 2 subjects.

Eighteen (18) out of 28 eligible subjects did not have a detectable anti-Obizur inhibitor titre at baseline.

Twelve (120 of these subjects had no detectable anti-Obizur titre after dosing; 5 subjects had newly developed anti-porcine factor VIII antibodies (inhibitors) after treatment (range: 0.6-108 BU) and 1 subject had no post-treatment measurements.

In 2 of the 5 subjects with increased anti-porcine factor VIII antibodies levels, inhibitor development was assessed as a related non-serious adverse event and the subjects were discontinued from the study.

Anti-baby hamster kidney protein antibodies

Binding antibodies against baby hamster kidney protein were measured using a direct binding enzyme-linked immunosorbent assay. In Study OBI-1-301, 1 subject had a positive titre prior to treatment only; no anti-baby hamster kidney antibodies were detected in any subjects treated with OBI-1.

Safety in special populations

MedDRA Terms	**Age <65** number (percentage)	**Age 65-74 number (percentage)**	**Age 75-84 number (percentage)**	**Age 85+ number (percentage)**
Total AEs	59 (22.2)	75 (28.4)	73 (27.7)	57 (21.6)
Serious AEs – Total	2 (3.4)	8 (10.7)	11 (15.1)	12 (21.1)
- Fatal	1 (50.0)	3 (37.5)	2 (18.2)	1 (6.2)
- Hospitalization/prolong existing hospitalization	1 (50.0)	5 (62.5)	8 (72.7)	6 (50.0)
- Life-threatening	1 (50.0)	2 (25.0)	1 (9.1)	4 (33.3)
- Disability/incapacity	0	0 (0.0)	0 (0.0)	0 (0.0)
- Other (medically significant)	0	2 (25.0)	2 (18.2)	2 (16.7)
AE leading to drop-out	1 (1.7)	1 (1.3)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	3 (1.1)	6 (2.3)	3 (1.1)
Nervous system disorders	3 (1.1)	3 (1.1)	4 (1.5)	0 (0.0)
Accidents and injuries	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	1 (0.4)	4 (1.5)	1 (0.4)	1 (0.4)
Vascular disorders	3 (1.1)	2 (0.8)	5 (1.9)	2 (0.8)
Cerebrovascular disorders	0 (0.0)	2 (2.7)	1 (1.4)	0 (0.0)
Infections and infestations	4 (1.5)	15 (5.7)	12 (4.5)	4 (1.8)
Anticholinergic syndrome	1 (1.7)	5 (6.7)	2 (2.7)	0 (0.0)
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)
other AE appearing more frequently in older patients	N/A	N/A	N/A	N/A

Safety related to drug-drug interactions and other interactions

No interaction studies have been performed with Obizur

Discontinuation due to adverse events

In Study OBI-1-301 / OBI-1-301a, 3 (10.3%) patients experienced treatment emergent adverse events that resulted in withdrawal.

- Patient with intracranial bleeds was administered 3 infusions of the current product over 2 days. The third infusion had technical problems, factor VIII was assayed at 50%, there was a further intracranial bleed and infusions were stopped, the patient died shortly after.
- Patient with anti-human factor VIII antibodies at 26BU, presented with planned surgery for hemi-colectomy. This subject developed a positive anti–Obizur antibody titres of 8BU (in association with anti-human factor VIII antibodies now at 128BU) leading to discontinuation and starting rescue therapy with by-pass agents. The patient experienced an intestinal haemorrhage and died shortly afterwards.
- Patient presented with bleeding after a surgical procedure. Anti-human factor VIII antibodies were 24BU at screening. About 3 weeks after an initial bleed was treated, there was a second major bleed into the retroperitoneal space for which the subject was initially treated with Obizur but was found to have anti–Obizur antibody titres of22BU leading to discontinuation.

As a result of these discontinuations, a clarification was made to the Study Procedures Manual to indicate that anti-Obizur antibody titres were to be considered an adverse event but were not mandatory grounds for discontinuation from treatment with Obizur.

Overdose

The effects of higher than recommended doses of Obizur have not been characterised.

Pregnancy, Lactation, and Fertility

There are no adequate data from the use of Obizur in pregnant or lactating women. The effects of Obizur on fertility have not been established.

Effects on Ability to Drive and Use Machines

There is no information of the effects of Obizur on the ability to drive or operate an automobile or other heavy machinery.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The safety data reported by the company pertains mainly to study OBI-1-301/301a, the study of patients with acquired haemophilia. Study 301 was a non-comparator, non-placebo, non-randomised, open label, observational study. Patients enrolled in the study were mainly elderly and with many clinical pathologies present before exposure to study medication. Patients presented *in extremis* with haemorrhage that was a threat to limb and / or life.

The size of the patient database from study 301 is small (only 29 patients exposed to study medication in study 301, a case series report) but this may be understood in the context of a rare disease. Problems associated with the open label design should also be seen in this context.

There were not any unexpected signals detected by study 301. The company reports only the development of antibodies to Obizur as related to study medication. There were not any reports of anaphylaxis.

Obizur appears to be acceptably safe and well-tolerated both in the management of acute bleeding episodes of acquired haemophilia and in prophylaxis management prior to surgery.

From the safety database all the adverse reactions reported in clinical trials (Investigations; positive test for inhibitory antibodies against porcine Factor VIII;) have been included in the Summary of Product Characteristics section 4.8 as frequency: Common.

Inhibitory antibodies against porcine Factor VIII (measured using a modification of the Nijmegen variation of the Bethesda assay) were detected before and after exposure to OBIZUR. Inhibitor titres of up to 29 Bethesda units were recorded at baseline yet subjects responded positively to OBIZUR. It is recommended that treatment should be based on clinical judgement and not based on detection of inhibitory antibodies by the Bethesda assay.

OBIZUR is produced by recombinant DNA technology in baby hamster kidney cells. Antibodies to baby hamster kidney cell protein were not detected in subjects after exposure to OBIZUR.

High and sustained factor VIII activity in blood may predispose to thromboembolic events. Those with pre-existing cardiovascular disease and the elderly are at particular risk.

If a venous access is required, then risk of catheter site thrombosis should be considered.

Factor VIII activity determined by the chromogenic assay is generally lower than Factor VIII activity determined by the one-stage clotting assay. Measurement of Factor VIII activity must always be carried out using the same assay methodology on any one patient. The one-stage assay is recommended because it has been used in determination of the potency and the mean recovery rate of Obizur (see sections 4.2 and 5.2).

Furthermore it is described that Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) are possible and may progress to severe anaphylaxis (including shock) (see section 4.4).

The applicant will further investigate validation of laboratory assays of immunogenicity post-approval.

Additional safety data needed in the context of a MA under exceptional circumstances
As comprehensive data on the safety under normal conditions of use could not be generated, the CHMP considers the following specific obligation necessary to address the missing safety data in the context of a MA under exceptional circumstances:

- To collect and analyse immediate and long-term data on clinical efficacy and safety of all patients with acquired haemophilia and who are treated with Obizur, the MAH must conduct a surveillance programme/ registry according to an agreed protocol and for an indefinite time.

2.6.1. Conclusions on the clinical safety

The extent and nature of the available safety data, though limited, support a marketing authorisation for Obizur. Aspects of clinical safety that have given rise to concern such as the risk of thromboembolic events in response to raised factor VIII blood activity are addressed in the PI texts and risk management plan. Further information on clinical safety will be gained from a post-approval registry.

The CHMP has recommended that the company will complete validation of laboratory assays of immunogenicity post-approval.

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances:

- To collect and analyse immediate and long-term data on clinical safety of all patients with acquired haemophilia and who are treated with Obizur, the MAH must conduct a surveillance programme/ registry according to an agreed protocol and for an indefinite time.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.0 (dated 17 June 2014) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 1.0 (dated 10 July 2015) with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Inhibitory antibodies to OBIZUR
Important potential risks	Hypersensitivity and allergic reactions to the active substance, any of the excipients or to baby hamster kidney (BHK) protein Lack of efficacy due to neutralizing inhibitory antibodies against the product Thromboembolic events Catheter-related complications Dose dispensing errors
Missing information	No data on pregnant and lactating women or fertility Insufficient data on subject < 18 years of age Insufficient data on use of OBIZUR in patients with congenital haemophilia A with inhibitors (CHAWI)

Pharmacovigilance plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** **(planned, started)**	**Date for submission of interim or final reports (planned or actual)**
241501: Prospective, Non-Interventional Study to Evaluate the Safety and Effectiveness of OBIZUR in Real Life Practice (EU) (Category 2)	Describe the immune profile during treatment of bleeding episodes. Assess the safety and effectiveness of OBIZUR in the treatment of bleeding episodes.	-Inhibitory antibodies to OBIZUR -Hypersensitivity and allergic reactions to the active substance, any of the excipients or to baby hamster kidney (BHK) protein -No data on pregnant and lactating women or fertility -Insufficient data on off-label use of OBIZUR particularly in patients with congenital haemophilia A with inhibitors (CHAWI) -Thromboembolic events	Planned	Completion of final report: 6 months after last subject out (LSO)* *There is no pre-determined end date of this study
241302: Postmarketing noninterventional safety evaluation of OBIZUR in the	Describe the immune profile during treatment of bleeding episodes. Assess the safety	-Inhibitory antibodies to OBIZUR -Hypersensitivity and allergic	Planned	Completion of final report: Approximately 31 January 2020

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
treatment of bleeding episodes for patients with acquired hemophilia A (United States) (Category 3)	and effectiveness of OBIZUR in the treatment of bleeding episodes.	reactions to the active substance, any of the excipients or to baby hamster kidney (BHK) protein -Thromboembolic events		

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Inhibitory antibodies to OBIZUR	Proposed text in SmPC: Discussed in section 4.4, *Special warnings and precautions for use,* of the SmPC.	None proposed
Hypersensitivity and allergic reactions to the active substance, any of the excipients or to baby hamster kidney (BHK) protein	Proposed text in SmPC: Discussed in section 4.3, *Contraindications,* of the SmPC. Discussed in section 4.4, *Special warnings and precautions for use,* of the SmPC. Discussed in section 4.8, *Undesirable effects,* of the SmPC.	None proposed
Lack of efficacy due to neutralizing inhibitory antibodies against the product	Proposed text in SmPC: Discussed in section 4.4, *Special warnings and precautions for use,* of the SmPC.	None proposed
Thromboembolic events	Proposed text in SmPC: Discussed in section 4.4, *Special warnings and precautions for use,* of the SmPC.	None proposed
Catheter-related complications	Proposed text in SmPC: Discussed in section 4.4, *Special warnings and precautions for use,* of the SmPC.	None proposed
Dose dispensing errors	Proposed text in SmPC: Discussed in section 4.2, *Posology and method of administration,* of the SmPC.	Health care professional brochure including a detailed calculation of vials for a patient weighing for example 70 kg. An on-line video to further elaborate on the required calculation and administration of the drug.
No data on pregnant and lactating women or fertility	Proposed text in SmPC: Discussed in section 4.6, *Fertility, pregnancy and lactation,* of the SmPC.	None proposed
Insufficient data on subject < 18	Proposed text in SmPC:	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
years of age	Discussed in section 4.2, *Posology and method of administration,* under the section *Paediatric population* of the SmPC. Discussed in section 5.1, *Pharmacodynamic properties,* of the SmPC.	
Insufficient data on use of OBIZUR in patients with congenital haemophilia A with inhibitors (CHAWI)	Proposed text in SmPC: Discussed in section 4.2 of the SmPC*, Posology and method of administration*, in the subsection *Paediatric population*.	None proposed

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Obizur (susoctocog alfa) is included in the additional monitoring list as it is approved under exceptional circumstances.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In a prospective, non-randomised, open-label trial of 28 subjects, all initial bleeding episodes had a positive response to treatment at 24 hours after initial dosing as assessed by the primary investigator. In addition to response to treatment, the overall treatment success was determined by the investigator based on his/her ability to discontinue or reduce the dose and/or dosing frequency of OBIZUR. A total of 24/28 (86%) had successful control (resolution) of the initial bleeding episode. Of those subjects treated with OBIZUR as first-line therapy, defined as no immediate previous use of anti-haemorrhagic agents prior to the first OBIZUR treatment, 16/17 (94%) had eventual treatment success reported. Eleven subjects were reported to have received anti-haemorrhagic agents (eg. rFVIIa, activated prothrombin-complex concentrate, tranexamic acid) prior to first treatment with OBIZUR. Of these 11 subjects, eight had eventual successful treatment (73%).

Uncertainty in the knowledge about the beneficial effects.

The design of the study (open-label, single-cohort, non-randomised) and use of clinical judgement (as opposed to an objective measurement) to assess the primary endpoint (albeit coupled to a 3- or 4-point scale) are known to be susceptible to bias, however due to the rarity of the population and the nature of the condition, these weaknesses are acknowledged and moreover the magnitude of the effect is reassuring. Further data on clinical efficacy of all patients with acquired haemophilia and who are treated with Obizur, will be provided through the surveillance programme and registry according to an agreed protocol.

Risks

Unfavourable effects

Inhibitory antibodies against porcine Factor VIII were detected before and after exposure to OBIZUR. Inhibitor titres of up to 29 Bethesda units were recorded at baseline yet subjects responded positively to OBIZUR. It is recommended that treatment should be based on clinical judgement and not based on detection of inhibitory antibodies.

High and sustained Factor VIII activity in blood may predispose to thromboembolic events. Those with pre-existing cardiovascular disease and the elderly are at particular risk. Patients experiencing a thromboembolic event as a result of exposure to Obizur (or at least this cannot be excluded by data available) is suspected in 2 cases and has been addressed by appropriate warnings in section 4.4 of the SPC text.

Uncertainty in the knowledge about the unfavourable effects

The initial dose of 200 U/kg Obizur in some patients may lead to a high blood factor VIII activity, but as described is acceptable. Follow-on dosages are based on target factor VIII activities (it is recommended to assay factor VIII by the one stage clotting assay) and on clinical judgement.

It is not fully known how patients will respond immunologically to a second exposure to Obizur, though some patients in study OBI-1-301/301a were treated for second episodes of bleeding apparently with no concerns. Further aspects of immunogenicity will be pursued post-approval (see RMP).

Study 301 was a non-comparative, non-randomised, open label, observational study in an elderly population with many co-morbidities. It is considered that the design of the study and the nature of the population studied would hinder detection of adverse events unless the adverse events were striking in nature and / or commonly found.

Long-term data on clinical safety of all patients with acquired haemophilia and who are treated with Obizur, will be provided through the surveillance programme/ registry according to an agreed protocol.

There is concern that the large number of vials needed per infusion or per day may lead to mistakes in dosage administered. This will be addressed with appropriate educational material as agreed in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

Patients with acquired haemophilia and who present with bleeding that threatens life and / or limb are seriously ill and in need of urgent, specialist attention. The ability of susoctocog alfa to stop or reduce bleeding could potentially be life and limb saving and is of utmost importance.

The unfavourable effect of the development of inhibitory antibodies susoctocog alfa is of uncertain significance and has to be further investigated in the planned registry as part of on an ongoing safety evaluation. Any problems that may arise because of the large number of vials needed per infusion will be managed by suitable risk minimisation activity and even eliminated in the future as the company was recommended to consider developing an improved pharmaceutical formulation/ strength that would require less vials.

Benefit-risk balance

The ability of susoctocog to stop or reduce severe bleeding far outweighs the apparent development of inhibitory antibodies to the product, which were of uncertain significance in studies *in vivo* and will be studied further in post authorisation studies agreed.
Educational material will provide instructions to the user to help minimise the risk of medication associated with handling of the large number of vials that may be needed per infusion.

Discussion on the benefit-risk balance

Apart from the so-called by-passing agents, there are no medicinal products in the EU specifically intended for the treatment of acquired haemophilia, a rare condition which may result in potentially life-threatening bleeding problems.

Therefore, there is currently a clear unmet medical need for treatment of patients in terms of providing sufficient coagulation by means of a high-purity recombinant factor VIII drug product.

In the main clinical study all patients with serious bleeding episodes treated with Obizur responded positively at 24 hours after the initiation of susoctocog treatment. The absence of the potential to transmit porcine viruses or human blood-borne pathogens is of significance to patients. Measurable factor VIII activity levels permit guidance of dose and dose frequency after the initial susoctocog administration. These benefits outweigh the risk of potential hypersensitivity reactions and Obizur immunogenicity in patients with AHA. As the adverse effects of inhibitor formation and risk of thromboembolic events are well identified and expected, the benefit sufficiently outweighs the risks.

Management of patients is based on the assumption of continued bleeding: it is not known and cannot be anticipated if or when any one patient may spontaneously stop bleeding and moreover the severity of the bleeding may not be possible to be estimated prior to treatment initiation. On the other hand there is a lack of clinical information on the development of inhibitory antibodies to OBIZUR following repeated administration. Therefore, Obizur must only be administered when considered clinically necessary, as per physician's clinical judgement, this information is reflected in the SmPC. The benefit / risk balance may change over time in any one patient if that patient develops an immunological reaction to susoctocog alfa and requires repeated treatments for bleeding. Benefit may decline if neutralising antibodies are developed whilst risk will increase if sensitisation takes place. It is advised that a scheme is established to monitor clinical progress in patients who need repeated treatment for bleeds. A clinical registry of recipients will be undertaken to provide further information on clinical efficacy, safety and immunogenicity of Obizur.

Thus, the Applicant will carry out a prospective, non-interventional study to evaluate the safety and effectiveness of Obizur in real life practice, including measurement of immunogenicity (levels of anti-pFVIII antibodies and any associated clinical manifestations) (see RMP).

The company has applied for a MA under exceptional circumstances based on a case series of 28 patients treated with Obizur for the management of acquired haemophilia. The rarity of acquired haemophilia being an impediment for the applicant to provide comprehensive data justifies a licence to be granted under exceptional circumstances. Moreover there is a clear unmet medical need for a treatment specifically developed for acquired haemophilia.

The arguments put forward by the applicant to justify the criteria of a marketing authorisation under exceptional circumstances on the grounds of inability to provide comprehensive safety and efficacy data due to rarity of the indication –as set out in Part II.6 of Annex I to Directive 2001/83/EC such authorisation are acknowledged. In view of the above the CHMP concluded that a positive benefit/risk balance for Obizur has been established and recommends the grant of a marketing authorisation under exceptional circumstances subject to the obligations laid down in the annex II of the opinion. Continuation of the authorisation shall be linked to the annual reassessment of the specific conditions introduced.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Obizur in the treatment of bleeding episodes in adult patients with acquired haemophilia caused by antibodies to Factor VIII, is favourable and therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Obizur in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to minimize the risk of dose dispensing errors.

The MAH shall ensure that in each Member State where Obizur is marketed, all healthcare professionals who are expected to prescribe and dispense Obizur have access to/are provided with the following educational package:

- Physician educational material

The physician educational material should contain:

- The Summary of Product Characteristics
- The healthcare professionals training material

The healthcare professionals training material shall contain the following key elements:

- Health care professional brochure including a detailed calculation of number of vials for a patient weighing for example 70 kg

- An on-line video to further elaborate on the required calculation and administration of the drug

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
To collect and analyse immediate and long-term data on clinical efficacy and safety of all patients with acquired haemophilia and who are treated with Obizur, the MAH must conduct a surveillance programme/ registry according to an agreed protocol and for an indefinite time.	Annually within the annual reassessment

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that susoctocog alfa is qualified as a new active substance.