**SCIENTIFIC DISCUSSION**

**This module reflects the initial scientific discussion for the approval of Advate. For information on changes after approval please refer to module 8.**

## 1. Introduction

ADVATE is containing recombinant human antihaemophilic factor VIII (rFVIII; INN: octocog alfa), which is synthesised by a genetically engineered Chinese hamster ovary (CHO) cell line. The approved therapeutic indication is: "Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)". ADVATE does not contain von Willebrand factor in pharmacological doses and is therefore not indicated in von Willebrand's disease.

Antihaemophilic Factor VIII (FVIII) is the blood clotting factor deficient or absent in individuals with classic haemophilia A, an X-chromosome-linked bleeding disorder. The frequency of clinically severe bleeding correlates with the degree of FVIII deficiency. Replacement therapies for FVIII deficiency consist of either plasma-derived or recombinant FVIII concentrates. So far, the main advantage of recombinant products is the higher viral safety. The major complication in the treatment of haemophilia A is the occurrence of inhibitors against FVIII (neutralising antibodies) in about 30% of patients, usually within the first 100 exposure days. Patients with severe haemophilia A (FVIII levels < 1-2% of normal activity) are at a far higher risk to develop an inhibitor.

ADVATE is a modification of Recombinate, which was granted a positive opinion by the CPMP through the former Concertation procedure on 12 May 1993 and is now regulated through the mutual recognition procedure (NL/H/43/01-03). The drug substances for ADVATE and Recombinate are produced by the same genetically engineered Chinese hamster ovary (CHO) cell line. This cell line has been designed to co-express rFVIII and human von Willebrand factor (vWF). The latter is the transport protein of FVIII in plasma and stabilises rFVIII during cell culture, which results in an increase in the production yield of rFVIII. Recombinant vWF is separated from the drug substance during the purification processes of Recombinate and ADVATE.

For the manufacture of Recombinate, master cell bank (MCB), working cell banks (WCB) and the fermentation process were run under cell culture conditions adapted to the presence of animal-derived (bovine) proteins. The drug product of Recombinate is stabilised by human albumin.

In an attempt to increase product safety, ADVATE was developed by introduction of modifications to the fermentation, the purification process and the drug product formulation, which eliminated the requirements for human and animal-derived raw materials and excipients at all stages of the production process. In addition, the purification scheme was modified to introduce a solvent/detergent viral inactivation step. The product is formulated with a buffer of neutral pH consisting of salts (sodium chloride, calcium chloride), a disaccharide stabilizer (trehalose), a bulking agent (mannitol), buffer agents (Tris, histidine), vegetable-derived polysorbate 80 (surfactant) and a reducing agent (glutathione).

All initial physicochemical characterisation studies, as well as the non-clinical and early clinical development were performed with ADVATE lots produced at pilot scale at the production facilities in Vienna, Austria. In December 2000 production of ADVATE commercial scale lots commenced at a dedicated manufacturing facility in Neuchatel, Switzerland. According to the applicant, the manufacturing processes for the pilot- and commercial-scale drug substances are virtually identical, except that commercial-scale material is produced at a two-fold increase in cell culture volume and a four-fold increase in the downstream purification scale.

## 2. Chemical, pharmaceutical and biological aspects

**Composition**

ADVATE is a sterile, white to off-white, lyophilised powder for injection presented in four dosage forms (250 IU, 500 IU, 1000 IU, 1500 IU). The composition and concentration of excipients is the same for all strengths. Each dosage form is reconstituted with 5 ml water for injection. The powder for injection and solvent vials are supplied in the final package in combination with an application kit consisting of a needleless transfer device, a butterfly infusion set, 10 ml sterile syringe, alcohol swabs, bandages, one full prescription insert and patient leaflet.

The composition of the final drug product is as follows:

| **Drug substance:** | **Octocog alfa** | | | | |
|---|---|---|---|---|---|
| | IU/vial | | | | |
| **Nominal Potency:** | 250 | 500 | 1000 | 1500 | |
| **Excipients:** | mg/ml | | | | **Specification** |
| Trehalose | 8.0 | 8.0 | 8.0 | 8.0 | In-house specification |
| Histidine | 1.6 | 1.6 | 1.6 | 1.6 | Ph.Eur. |
| Tris | 1.2 | 1.2 | 1.2 | 1.2 | Ph.Eur. |
| Sodium Chloride | 5.3 | 5.3 | 5.3 | 5.3 | Ph.Eur. |
| Calcium Chloride | 0.2 | 0.2 | 0.2 | 0.2 | Ph.Eur. |
| Gluthatione (reduced) | 0.08 | 0.08 | 0.08 | 0.08 | In-house specification |
| Polysorbate-80 (vegetable derived) | 0.1 | 0.1 | 0.1 | 0.1 | Ph.Eur. |
| Mannitol | 32 | 32 | 32 | 32 | Ph.Eur. |
| **Diluent** | **Water for Injection** | | | | |
| | 5 ml | 5 ml | 5 ml | 5 ml | Ph.Eur. |

In addition, traces of host cell proteins and murine IgG, which derive from the fermentation and purification process, are found in the product.

The container closure system complies with the requirements of the Ph.Eur.. Functional studies like coring and bacterial barrier characteristics established the suitability of the container and closure. The lyophilised powder for injection is presented in 5 ml single-dose vials of neutral borosilicate Type I glass with Teflon coated chlorobutyl rubber stoppers. The solvent is presented in 10 ml Type I glass vials with chlorobutyl rubber stoppers. The medical devices are CE-marked and compatibility with ADVATE has been demonstrated.

**Drug substance**

*Description of Active Sustance*

Octocog alfa is a glycoprotein. The full length protein consists of 2332 amino acids with a molecular weight of approx. 280 kD before, and more than 300 kD after glycosylation. The amino acid sequence of rFVIII is similar to human Factor VIII, and posttranslational modifications are similar to those of the plasma-derived molecule. The single chain protein is rapidly processed in cell culture resulting in a heterodimer with an 80kD light chain deriving from the C-terminus, and a family of heavy chains with

molecular weights between 90 and 210 kD, including the 90 kD N-terminal sequence and varying amounts of the B-domain. In the B-domain, which is not required for the co-factor activity of FVIII, 19 of 25 potential N-linked glycosylation sites are located. The protein also contains 10-12 O-linked glycans. Evidence suggests, that all or most of the O-linked glycans reside in the B-domain.

*Gene construct, producer strain*
The production cell line for ADVATE (clone GD8/6) is derived from the same MCB (10A1C6) used for the production of Recombinate and was adapted to serum- and protein-free medium enriched with plant proteins and non-protein additives at the Baxter facility in Orth, Austria.

Source, history and generation of this original MCB are described. Briefly, in the first step an expression plasmid containing the FVIII cDNA was co-transfected into dihydrofolate reductase (DHFR)-deficient CHO cells (DUKX-B11) along with a plasmid expressing a DHFR-selectable marker to create the cell line 10A1. Methotrexate was then used to amplify FVIII expression. In the second step, the MAA decided to co-express vWF in the 10A1 cells along with FVIII in order to stabilize it. An expression plasmid containing sequences for the full-length vWF cDNA and an additional plasmid containing a selectable adenosine deaminase (ADA) marker were introduced into the 10A1 cell line by protoplast fusion. Adenosine and deoxycoformycin (dCF) were used to select for expression of vWF. Based on high levels of expression of both Factor VIII and vWF, a single clonal cell line (10A1C6) was chosen for production.

The development of cell line GD8/6 from the parent MCB 10A1C6 has been described in sufficient detail. Cells were adapted to serum and protein free culture medium, and a clone was chosen which displayed good growth characteristics, production of high FVIII and vWF activity, and similar FVIII banding patterns when compared to the original cell line. This clone was used to create the MCB 9710 for the production of ADVATE.

*Cell banks*
*1. Establishment of MCB/WCB, tests performed*
A classical two-tiered cell bank system with MCB and WCB has been set up at the Baxter facility in Hayward, USA. For production, WCB ampoules are shipped deep-frozen under validated conditions (temperature < - 90°C for max. 12 days) by air to the Neuchatel facility in Switzerland.

The MCB and WCB have been extensively tested for identity, growth and secretion characteristics, and adventitious agents with appropriate assays. Testing of the MCB for adventitious agents included a battery of tests for e.g. sterility (bacteria/funghi), mycoplasma, lytic viruses, in vitro tests for viruses (including bovine viruses), in vivo tests for viruses, and an assay for retroviruses. No adventitious agents were found.
Each WCB is tested for adventitious agents on a routinely basis including tests for sterility (bacteria/funghi), mycoplasma, lytic viruses, in vitro tests for viruses (including bovine viruses) and in vivo tests for viruses. Appropriate release specifications are set.

*Genetic stability of cell banks*
The genetic stability of the rFVIII sequences that have been integrated into the GD8/6 cells was assessed using a variety of tests. First, the integrity of the Factor VIII and vWF DNA sequences in the Master Cell Bank and the Post-Production Cell Bank were determined in order to verify that the coding sequences remain stable throughout the production process. Second, the structural integrity of the expression cassettes was examined using Southern blot methodology. Third, real-time quantitative PCR was used to determine the overall copy number of the inserted genes, and to confirm the genetic stability data from the Southern blots. The results from these studies indicate that roughly 25-100 copies of the rFVIII gene and a few copies of the vWF gene are integrated into the GD8/6 genome, and that these sequences are stable through at least 78 generations, well beyond the production limit of 65 generations.

***Fermentation and purification***

Drug substance batches at pilot scale for pivotal clinical trials were produced at the Baxter facility in Vienna, Austria and drug substance batches at commercial scale for the pivotal clinical trials and to be marketed were/will be produced at the Baxter facility in Neuchatel, Switzerland.

*Batch and scale definition*

One production campaign is defined as all drug substance batches derived from the same WCB vial(s) and continuous culture and consists of approximately 20 drug substance batches. One drug substance batch is defined as the batch resulting from one elution step of the immunoaffinity column. Usually, three harvests are loaded and purified to produce one batch of drug substance. One harvest is defined as the amount of cell suspension collected from the 2500 L bioreactors in a 24-hour period (1250 L per bioreactor per day). One drug substance batch is defined by a batch volume of 700 to 1400 ml, and a potency of 1250 IU/ml minimum and a specific activity of 4000 to 10000 IU/mg protei, respectively.

*Fermentation*

The cell culture process (from WCB vial to harvest) has been sufficiently described. In brief, the inoculum expansion process utilizes a batch/refeed process over approximately 20 generations. One or two WCB vials are inoculated and expanded in roller bottles. This inoculum is subsequently further expanded using three bioreactor steps of which the last one is a 2500 L bioreactor. The contents of the 2500 L tank are used to inoculate a second 2500 L bioreactor, and both are then used for production. The Applicant maintains a backup culture in one of the smaller bioreactors to re-inoculate the 2500 L tank if necessary.

For production, a continuous (chemostat) culture method with well-defined medium, which is free of human and animal derived proteins, is used. The continous culture is maintained up to 65 generations from thawing of the WCB vials. This means 60 days of continuous culture after the expansion phase. As the cells grow exponentially, rFVIII is produced and secreted into the medium.

Appropriate in process controls and limits are in place during expansion and continuous culture for a.o. cell density/viability/doubling time, pH, dissolved oxygen, and temperature. The culture is tested for mycoplasma, sterility, and adventitious agents at the end of the campaign. The harvest is tested specifically for the presence of MMV virus.

*Purification*

The purification process of rAHF-PFM is similar to the purification process for Recombinate. A new solvent/detergent step (1% Triton-X-100, 0.3% Polysorbate 80, 0.3% TNBP (tri-N-butyphosphate)) has been introduced which is specifically aimed at viral inactivation. The process is based on four key steps: i) immunoaffinity chromatography, ii) cation exchange chromatography, iii) solvent/detergent virus inactivation, and iv) anion exchange chromatography. These steps have been analysed and described in detail. Validation of the removal of impurities derived from the fermentation and purification process such as host cell proteins, host cell DNA and murine have been performed. Column lifetimes can be provisionally approved but regular updates are requested until final resin life times are set.

The eluate of the anion exchange chromatography represents the drug substance, which is frozen and stored at –80 °C.

*Monoclonal antibody*

The most important step with regards to selectivity and purification factor during the manufacture of ADVATE is the use of a monoclonal antibody (MAb) for immuno affinity purification. The monoclonal antibody F8.1 is produced at the Baxter facility in Hayward, CA, USA and is also used for the purification of the already licensed rFVIII product Recombinate as well as the plasma-derived FVIII product Hemofil. However, cell banks of the monoclonal antibody used in the rAHF-PFM purification process have been adapted to serum and protein free medium. This antibody recognises an epitope on the rFVIII heavy chain, which can be further localised to the 43 kDa fragment after thrombin digestion of rAHF-PFM. The monoclonal antibody is manufactured under the concept of a two-tiered cell bank system in which the MCB is used to generate the WCB. Characterisation of the cells banks follows the current guidelines and results are satisfactory. Data from a postproduction cell

bank assure stability of expression. Starting from the MCB a plasma /albumin free medium is used for the production of the monoclonal antibody. The unprocessed bulk is tested for viral and bacterial contamination. Purification of the MAb includes a protein A affinity chromatography. Removal of protein A has been validated. Control methods and routine release specifications for the uncoupled Anti-FVIII MAb and the Anti-FVIII coupled MAb resin are acceptable. Currently there are three lots of the uncoupled antibody on stability study and stability data for two lots over three months have been provided and this storage time can be approved at present. Three lots of the immuno affinity resin have been put on stability. At present data from 1 lot for 36 months, one lot for 18 months and one lot for 3 months. A shelf life of the resin of 18 months can be approved. The MAb appears to be suitable for use in the manufacture of ADVATE with respect to safety and functional aspects.

*Control of critical steps and intermediates*
The manufacturing process of the drug substance is monitored by adequate in-process controlls.

*Process validation*
Extensive process validation was performed at the commercial scale production facility in Neuchatel and designed to validate routine process and scale in both manufacturing Suites A and B. A battery of biochemical and biophysical methods for characterisation studies was employed. Evaluation of validation data indicated that the inoculum, buildup, cell culture, and purification process are capable of consistently producing drug substance in Suite A and B with comparable results, which meet pre-determined specifications. In addition, it was demonstrated that drug substance produced at the beginning, middle and end of an extended production campaign are physico-chemically comparable. All process and product impurities were effectively removed to levels below the pre-determined limits. Therefore, the process and the equipment used for commercial manufacturing of drug substance in Suite A and B are considered validated.

*Drug substance characterisation*
An extensive comparability exercise including data on the characterisation of the drug substance was submitted. The first objective of the comparability studies was to demonstrate comparability between ADVATE pilot scale lots and Recombinate lots prior to initiation of clinical trials. Since the application for ADVATE is a full and unabridged application, these data were considered as supportive information only. The second objective was to show comparability between ADVATE pilot and ADVATE commercial scale lots used in pivotal clinical studies.
Characterisation of the drug substance was performed by appropriate methods allowing an assessment of the protein primary structure, post-translational modifications (sulfatation, glycosylation), secondary structure, tertiary structure, protein heterogeneity, and protein integrity, process- and product-related impurities, as well as functional properties related to the interaction of FVIII with vWF, thrombin, and FIXa. With regard to all of the biochemical and biophysical data mentioned above, the applicant demonstrated that rAHF-PFM produced at both pilot and commercial scales is comparable to each other. This observation is in agreement with results obtained in the pivotal clinical trial comparing ADVATE pilot and commercial scale batches.
In order to corroborate the monosaccharide test results, the MAA will submit monosaccharide analysis data from a represenatative number of ADVATE pilot and ADVATE commercial scale batches including results on CHO cell-derived Neu-5Gc, which is an immunogen in humans.

*Specification of drug substance*
The drug substance is appropriately controlled. The specifications for the drug substance have been justified and tightened based on the current history of manufacture. These limits are acceptable. The choice of control methods (e.g. potency, rAHF immunoblot, specific activity, oligosaccharides, host cell protein, murine monoclonal antibody, von Willebrand factor, bioburden) has been justified. A specification for potency has been introduced. The test for oligosaccharides is performed on each batch. With regards to quantification of N-linked oligosaccharides the MAA is currently working on the validation of this method. It is intended to file a variation to change the oligosaccharide testing. The applicant is asked to commit to introduce a SE-HPLC (size exclusion high pressure liquid chromatography) and to develop an RP-HPLC (reverse phase high pressure liquid chromatography) method for drug substance release in order to improve detection of unwanted degradation and aggregation products. SEC (size exclusion chromatography) will be used as stability indicating

parameter fordrug substance. The western blotting should be replaced by a SDS-PAGE with silver staining because of superiority in detection of impurities not bearing an epitope for the polyclonal antibodies.

*Batch to batch consistency*
Three lots rAHF-PFM produced at different times during commercial scale manufacturing in Suite A and B were analyzed using a battery of biochemical and biophysical methods for proteinchemical and functional characterisation. Regarding all data submitted, the production of recombinant human FVIII by serum- and protein-free CHO fermentation technology (rAHF-PFM) at commercial scale is highly consistent throughout the entire duration of the fermentation process. Therefore, it can be expected that drug substance lots resulting from commercial production in Suite A and B will show very similar behavior *in vivo* as well, independent of the time of manufacture and the production site within the production phase.

*Stability of drug substance*
Baxter has initiated stability studies to determine the shelf life of the drug substance. Appropriate stability parameters have been selected. For 1 production campaign with 35 lots 12-month data are availlable, for 4 other campaigns with 15 lots 6- month data are presented. Current stability data are provided for storage conditions (-80°C) and accelerated conditions of -25 °C or -40°C, respectively. Studies are ongoing and more complete stability data will be generated post-approval. The stability data cover a shelf life of 18 months, which do not raise any concerns. A drug substance shelf life of 12 months is approved at this time.

The chemical composition of the bottle, screw cap and seal for storage of drug substance are provided and the material qualification and product compatibility were demonstrated. In real-time stability studies the container was found suitable for storage of drug substance for up to 18 month at –80 °C.

**Other ingredients**
Excipients are of Ph.Eur. quality with the exception of trehalose and gluthatione (reduced). Both are controlled by in-house specifications and meet the limits for residual solvents required by the ICH guidelnie Q3C.

**Product development and drug product**
*Product development*
The main objective was to develop a stable, pharmaceutically acceptable formulation without the addition of human albumin as stabiliser. The pharmaceutical development is described in detail with regard to the effect of changes in the composition of buffering substances, bulking agents, stabilisers and antioxidants on the recovery and stability of ADVATE during manufacture and long term stability. The choices as well as the limits of the excipients have been justified. The final, optmised formulation is pH neutral and contains polysorbate 80 (surfactant, vegetable-derived), sodium chloride and calcium chloride (salts), trehalose (disaccharide stabiliser), mannitol (bulking agent), Tris and histidine (buffers), and gluthadione (reducing agent).

*Clinical trial formulations vs intended market formulation*
The same batch formula has been used for production of pilot and commercial scale batches used in the pivotal clinical trials.

*Manufacturing process*
Formulation, lyophilization and finishing operations are performed at Baxter AG Vienna, Austria. Labelling and packaging are performed at Baxter SA Lessines, Belgium. It is stated that dedicated equipment will be used for the production of ADVATE.

The manufacturing process is typical for a protein parenteral product. Briefly, frozen drug substance is thawed (water bath set point 20 °C), pooled (at 2 – 8 °C) and subsequently formulated by dilution with two buffers: normalisation buffer and potency dilution buffer. Initial dilution is performed with normalisation buffer (about 120% of target potency) and afterwards diluted with potency dilution buffer to about 100% of the target potency. After sterile filtration the final bulk is filled into 6 ml glass

vials. For all potencies the same fill volume (2.12 g/ml) is applied. Freeze-drying, stoppering and crimping are the final steps to yield drug product. Hoding times were adjusted as supported by studies. A prospective validation study will be performed in order to implement maximum process times and to re-establish maximum times for process holding. The MAA is currently evaluating the need for potency determination as an in-process control for the manufacture of the drug product prior to filling.

*Drug product specifications*
The final drug product is adequately controlled using validated methods, which are suitable to control the consistency and quality of the drug product. The panel of tests methods includes the determination of e.g. potency, specific activity, aggregates, solubility, identity and purity, endotoxins and glutathione (total and reduced) and others. The limits have been sufficiently justified. The release specification for rFVIII potency has been changed to 80% to 120% of the nominal potency reflecting the requirements of the Ph.Eur. monograph for plasma-derived FVIII products. The applicant changed the potency method from the former used one stage clotting to the chromogenic method, which is in agreement with Ph. Eur. The in-house standard used for potency has been calibrated against the Mega 1 and WHO 6 international standard applying the one stage clotting as well as the chromogenic method. As the single results are close together for all determinations, the assigned potency of the In-house standard is the mean of these determinations. Based on current experience with the filling process of 3 consistency batches of the 250 IU/vial strength and 3 batches of 1500 IU/vial, the process of targeting nominal potency has very much improved. Nevertheless, it is noteworthy, that all 6 lots exhibited a lower actual than nominal potency.

*Validation*
Originally, three consecutive batches of 250 IU/vial were manufactured for consistency. The MAA ammended the process validation of the drug product manufacture by i) a retrospective process validation including one lot of 500 IU, one lot of 1000 IU and 3 lots of 1500 IU per vial and ii) a prospective validation including one lot of 500 IU, one lot of 1000 IU and 3 lots of 1500 IU per vial. All lots were required to meet product release specifications. Both studies showed that the process parameters for buffer preparation (normalisation and potency dilution buffer), formulation, sterile filtration; filling and freeze-drying complied with the respective requirements of the batch master record. Additional extensive testing was performed in both studies to evaluate product consistency and uniformity. Parameters tested were: potency, appearance of lyophilised cake and reconstituted product, solubility, residual moisture, absence of factor VIII aggregates. Aggregates were not tested for retrospective validation. Drug product results were found within the limits of the drug product specification. In summary, the MAA provided a prospective and a retrospective study for validation of the manufacture of the drug product. The provided study reports demonstrate consistency and uniformity of manufacture.

*Batch analyses*
All batch release tests have been transferred to EU sites. The release specifications were validated with batch analysis data from three qualification batches.

*Virus validation studies*
The fermentation processes of the rAHF-PFM and the anti-Factor VIII MAb 9801 are carried out with serum /protein-free media. This minimises a possible contamination for adventitious viruses. The cells used for production of rAHF-PFM have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB or WCB for rAHF-PFMA monoclonal antibody MAb 9801 is used for the purification of rAHF-PFM. Virus safety of this antibody has been sufficiently demonstrated by cell bank characterisation and validation of the MAb production process. Therefore, there are no concerns for the use of the MAb 9801 in the production process of ADVATE.

The most important step in the purification of rAHF-PFM is the S/D-treatment. The robustness and effectiveness of this step for the inactivation of enveloped viruses has been demonstrated. In addition, the purification steps of ADVATE also contribute to the virus safety. However, effectiveness of the immunoaffinity chromatography is virus specific and has only a very low effectiveness for removal of non-enveloped viruses (e.g. MVM). The other chromatographic steps further contribute virus specific but only to a low extent. Therefore, the overall inactivation/removal capacity of the ADVATE process

for non-enveloped viruses is limited. However, this is accepted considering that the production is performed in protein-free medium and that the MCB and WCB have been extensively investigated. Furthermore, routine virus screening for viruses including MVM is routinely performed at the end of the fermentation runs.

*TSE compliance*
Compliance with the TSE Guideline has been widely demonstrated. MCB and WCB, which are free from TSE-risk substances, have been established. The active drug substance is produced in a protein-free culture medium. All amino acids contained in the cell culture media are from non-animal origin.

**Stability of the Product**
Fifteen batches of ADVATE have been included into ongoing stability studies. Up to 30 months data are available at present, however, the majority of data cover 18 or 24 months. The study report does not evaluate pilot and commercial scale batches separately. A shelf life of two years at a storage temperature of 2-8°C appears to be justified whereas the claim of the MAA for a 2 months storage at room temperature during the 2 years can not be granted because of the lack of real-time, real-condition data. To confirm the stability of the ADVATE FDP during storage, three lots of the 1500 IU presentation manufactured in 2002 have been added to the stability program. In addition, the MAA commits to adding three 250 IU lots, one 500 IU lot and one 1000 IU lot targeted at the nominal potency to the ongoing stability program to bracket the potency range. In order to support storage at different temperatures a temperature cycling study will be initiated with one lot of each potency. Vials of rAHF-PFM FDP will be stored at 2°C – 8°C for a minimum of 18 months. After 18 months of storage the samples will be moved to storage at +30°C for the remaining six months of the expected shelf life. After finalisation of the study the MAA will file a variation for approval of storage at different temperatures.

**GMP compliance**
All manufacturing sites are GMP compliant. A GMP certificate in compliance with the MRA agreement with Switzerland covers the manufacturing site of the drug substance in Neuchatel. The MAA will adapt the clean room classification from class D to class C for the buffer and media preparation area at its Neuchatel manufacturing site in order to comply in all aspects with EU GMP requirements.

**Discussion on chemical, pharmaceutical and biological aspects**
The newly developed, protein-free fermentation process and the modified purification process are sufficiently described and adequately monitored by in-process controls. Extensive validation of the manufacturing process for the drug substance at commercial scale demonstrated the production of drug substance of consistent and comparable quality in both designated manufacturing suites. The drug substance has been extensively characterised showing the comparability of pilot scale and commercial scale lots by using state of art techniques. Virus safety with regard to enveloped viruses was demonstrated. Compliance with the TSE guideline has widely been shown. The final drug product is formulated in a protein-free buffer containing trehalose as stabiliser and is adequately controlled using validated methods.
In summary, on the basis of the data provided and the agreed follow-up measures, the quality of the product is satisfactory for the granting of a marketing Authorisation.

## 3. Toxico-pharmacological aspects

Octocog alfa is the drug substance of Recombinate a medicinal product already authorised and marketed in the EU.

The non-clinical development strategy was to demonstrate the comparability of rAHF-PFM to Recombinate rAHF. Comparing the physicochemical, pharmacodynamic, pharmacokinetic, and toxicological profiles of Recombinate rAHF and rAHF-PFM accomplished this.

**Pharmacodynamics**

- *In vivo* studies

Study 98008-PT-012: The haemostatic efficacy of Recombinate and rAHF-PFM (here the three candidate formulations) were compared in the exon 16 knockout haemophilic mice. Haemostatic efficacy was evaluated in terms of ability to stop bleeding and to raise plasma Factor VIII levels. The formulation candidates included base excipients (10 mM *HEPES*, 10 mM Tris-HCl, 90 mM sodium chloride, 0.012% polysorbate 80, 0.08 mg/ml reduced glutathione and 1.6 mM calcium chloride) plus pairs of bulking/stabilising agents consisting of mannitol and arginine, glycine and trehalose, or mannitol and trehalose, all at final concentrations of 3.2% and 0.8%, respectively.

Study 98008-PT-019: evaluated the selected formulation for rAHF-PFM (with mannitol / trehalose as the bulking / stabilising agents and with 10 mM histidine instead of HEPES).

Haemophilic mice (5/sex/group) each received a single intravenous administration of Recombinate, 150 IU/kg or rAHF-PFM, 150 IU/kg, or an equivalent volume of the corresponding formulation vehicles (controls). The mice were then anesthetized and their tails transected approximately 20 mm from the tip. Blood from the transected tails was collected over 20 minutes beginning 30 minutes post-dosing and the volume of blood loss as a function of time was analysed.

Results obtained from both studies were similar. The mean blood loss observed in the rAHF-PFM and Recombinate rAHF treatment groups over the 20 minutes observation period was comparable (160 – 258 µl), and significantly lower than the formulation vehicle control groups (i.e., 499 – 609 µl for Study 98008 -PT-012 and 363 – 393 µl for Study 98008-PT-019). Statistical analysis of the data demonstrated that infusions of Recombinate rAHF and the candidate rAHF-PFM formulations resulted in comparable restoration of haemostasis. Measurement of factor VIII activity in the plasmas of these haemophilic mice was performed in separate groups of animals (3/sex/group). The results showed that factor VIII activity in the rAHF-PFM infused animals and Recombinate rAHF infused animals were comparable and significantly higher than in the control groups.

Study 98002-PT-018. Studies conducted as part of the non-clinical development for Recombinate rAHF showed equivalent efficacy of Recombinate rAHF drug substance and Hemofil T (pAHF).

The addition of rAHF-PFM may restore homeostasis in these animals, but no comparison was made with wild-type animals. In addition, it is not clear whether the choice of a specific vehicle is based on these pharmacodynamic data or on toxicity data. However, since the clinical use will be based on clinical criteria (e.g. reduction of bleeding episodes) further testing in mice will not provide additional information on the product.

In conclusion, a knockout mouse model was used in the pharmacodynamic studies. The haemostatic efficacy of Recombinate rAHF and rAHF-PFM were compared. Both compounds were evaluated for their ability to stop bleeding and raise plasma Factor VIII levels (Reports 98008-PT-012 and 98008-PT-019). Statistical comparisons of the data demonstrated that Recombinate rAHF and the candidate rAHF-PFM formulations tested exhibited comparable restoration of hemostasis. However, the lack of statistical differences is likely due to the small number of animals that leads to a high variance of the outcome making the results difficult to analyse quantitatively. Although the slope of the activity in time of all products tested (with different vehicles) in study 98008-PT-012 is similar, the variance does not allow any further conclusion (e.g. about the relative potency). However, based on the overlap of activity the PFM product has an activity approximately similar to Recombinate.

- General and safety pharmacology programme

No studies were performed to evaluate the safety pharmacology of rAHF-PFM. However, two studies were conducted with Recombinate rAHF to evaluate the safety pharmacology *in vivo* and *in vitro*. The *in vivo* studies were performed in mice, rats and dogs.

Study 98002-PT-014: The effects of Recombinate rAHF on the respiratory and cardiovascular systems were evaluated in dogs. The results of this study suggested that Recombinate rAHF had no effects on normal functioning of the respiratory or circulatory stems in beagles under the conditions of this study.

Study 98002-PT-016: Recombinate rAHF had no effect on the general behaviour, central and autonomic nervous, cardiovascular, and respiratory systems, nor did it affect smooth muscles, the digestive system, renal function, locomotors activity or body temperature.

Study 98002-PT-020: No toxic effects on the animal's heart, or respiratory rate or rectal temperature were observed for a period up to 120 minutes after infusion.

- Conclusion

In conclusion, the pharmacodynamic ability to stop bleeding of rAHF-PFM was demonstrated in a haemophilic mouse model. The effects were quite similar to those of the predecessor Recombinate.

**Pharmacokinetics**

Two additional pharmacokinetic studies, which focussed on the comparability of the pharmacokinetic profile of Recombinate rAHF and rAHF-PFM in a rat model (plasma of male SD rats) were conducted. The pharmacokinetic profile of rAHF-PFM was studied using the three rAHF-PFM candidate formulations in comparison to Recombinate.

The pharmacokinetic profiles for three rAHF-PFM candidate formulations (test article, candidate formulation were with HEPES and not with histidine as later used in the selected formulation) and Recombinate were compared in a rat model (studies 98008-PT-010 and 98008-PT-031).

Male Sprague-Dawley rats (15-17/group) received an intravenous bolus of 400 IU/kg of either Recombinate or rAHF-PFM. A series of blood samples were collected prior to and after 5, 15, 30, 90, 180, 300 and 420 minutes post injection of the products. A final blood sample was collected from all animals at 24 hours post injection. Human Factor VIII activity in the rat plasma samples was quantified using a monoclonal antibody capture/chromogenic substrate assay specific for human Factor VIII. The mean values for AUC, half-life, retention time, and clearance rate for each group of test animals were estimated from the plasma Factor VIII activity assay results.

The lack of statistically significant differences for any of the aforementioned pharmacokinetic parameters demonstrates that rAHF-PFM and Recombinate have comparable pharmacokinetic profiles.

| Formulation | n | AUC (IU/h/ml) | t ½ (h) | MRT (h) | CL (ml/h/kg) |
|---|---|---|---|---|---|
| **Recombinate** | **17** | **5.90 ± 1.50** | **1.54 ± 0.33** | **1.85 ± 1.08** | **71.9 ± 17.7** |
| **rAHF-PFM:** | | | | | |
| **Glycine/trehalose** | **17** | **5.81 ± 1.65** | **1.64 ± 0.53** | **1.98 ± 1.23** | **76.3 ± 45.8** |
| **Mannitol/arginine** | **16** | **6.51 ± 1.88** | **1.50 ± 0.30** | **1.77 ± 0.96** | **65.9 ± 18.1** |
| **Mannitol/trehalose*** | **15** | **6.75 ± 1.65** | **1.55 ± 0.47** | **2.44 ± 1.20** | **63.3 ± 19.0** |

***later selected formulation***

A conclusion concerning the bioequivalence of Recombinate rAHF and the rAHF-PFM formulations cannot be drawn from this study since this study was not conducted with crossover design. In addition, the fact that no statistical significant differences between several pharmacokinetic parameters were observed may be biased by the high variability of the observed AUC and $t_{1/2}$ values. These data only suggest that the pharmacokinetic behaviour (AUC, $t_{1/2}$, mean residence time and clearance rate) of the tested formulations is approximately similar in the species used in the study (rats). No additional animal studies are considered necessary, since bioequivalence has to be established in clinical studies.

Absorption, distribution, metabolism and excretion were not studied with rAHF-PFM reference was made to previous studies performed with Recombinate. The results are summarised below:

*Distribution:* $^{125}$I-octocog alfa (Recombinate formulation) was distributed mostly into organs and tissues highly vascularised (Study 98002 -PT-007). The thyroid gland showed the highest concentrations of $^{125}$I -Recombinate. The highest octocog alfa concentrations were observed in the following organs (in decreasing order of observed concentrations): the spleen, stomach, liver, lung, kidney and heart. A minimal amount was detected in the skeletal muscle and brain. One minute after the infusion, 65% of total infused $^{125}$I –octocog alfa (dpm/ml) were present in the blood. After five

minutes following the infusion, the distribution of $^{125}I$ –octocog alfa was 50% blood and at 24 hours, the only detectable $^{125}I$ –octocog alfa was present in the thyroid.

*Metabolism:* Octocog alfa is catabolised by proteases in the plasma and liver. Eight hours after the administration, about one-third of radioactivity in the plasma was present in metabolites. As previously mentioned, 24 hours after the infusion, significant distribution was observed only in the thyroid.

*Excretion:* The relative distribution of the metabolites of $^{125}I$ -radiolabelled octocog alfa excreted in the urine, bile and faeces was studied in rats. Octocog alfa was primarily excreted in the urine. During the first 48 hours after administration, approximately 63%, 23% and 1% of the total radioactivity was recovered in the urine, bile and faeces, respectively. By 72 hours after administration, approximately 83% and 7% of the administered radioactivity was recovered in the urine and faeces, respectively.

The amount of animal pharmacokinetic investigations as well as the choice of methods is considered appropriate since factor VIII is an endogenous human protein with a relatively simple metabolic pathway. These results did not reveal any unexpected findings.

**Toxicology**

The purpose of the rAHF-PFM development program was to demonstrate comparability with Recombinate rAHF.

- Single dose toxicity

With rAHF-PFM two single-dose studies were conducted, one in Sprague-Dawley rats and one in New Zealand White rabbits. Since the rAHF-PFM studies did not include Recombinate as a concurrent reference article, separate studies were conducted with Recombinate (and subsequently used as reference data). During the non-clinical development of Recombinate, single dose, toxicity studies were conducted in rats, ferrets and dogs. These results were similar as far as the design and the criteria used to assess the toxicity of the product are concerned. These studies are listed below:

*Study 98008-PT-16 (Single-Dose Toxicity Study of rAHF-PFM in Rats)*

Young adult Sprague-Dawley rats (5/sex/group) were given a single intravenous infusion of the selected rAHF-PFM formulation at one of three doses: 475, 1,900 or 4,750 IU/kg. For each dose, the rate of infusion was standardised at 2-3 ml/min. These animals were sacrificed on day 14 post-treatment. A negative control group of 5 rats/sex received 40 ml/kg of normal saline (maximum dose-equivalent volume). The key observations in this study included clinical signs of toxicity (once daily), changes in body weight (weekly), clinical pathology findings (day 14), and gross necropsy findings.

No treatment-related effects were observed at any dose level. There were no remarkable differences between the treatment and the saline control groups for any of the aforementioned key study observations. Thus, a single intravenous infusion of rAHF-PFM at doses up to 4,750 IU/kg did not produce any toxicologically significant treatment-related effects in rats.

*Study 98008- PT-017 (single-Dose Toxicity Study of rAHF-PFM in Rabbits)*

The study was conducted in New Zealand White rabbits (4/sex/group) that were given a single intravenous infusion of the selected rAHF-PFM formulation (same doses as those given in the previous study).

No treatment-related effects were observed at any dose. There were no remarkable differences in any of the key study parameters between the treatment and saline control groups.

*Study 98008-PT-022 (single-Dose Toxicity Study of Recombinate in Rats)*

The study was conducted in young adult Sprague-Dawley rats (5/sex/group) that were given a single intravenous infusion of Recombinate at a dose of either 950 or 2,400 IU/kg at rates of infusion of 1.4 to 2.0 ml/min.

Once again, no treatment-related effects were observed in any study group. There were no remarkable differences in any of the key study parameters between the treatment and control groups.

*Study 98008-PT-024 (single-Dose Toxicity Study of Recombinate in Rabbits)*

New Zealand white rabbits (4/sex/group) were given a single intravenous infusion of Recombinate rAHF at doses of 950 and 2,400 IU/kg. All infusions were administered at an approximate rate of 5 ml/min.

No treatment-related effects were observed in any study group. There were no remarkable differences between the treatment and control groups for any of the key study parameters.

*Study 98002-PT-001 through Study 98002-PT-009 (single-Dose Toxicity Studies of Recombinate in Rats, Ferrets and Dogs).*

During the development of Recombinate rAHF, eight studies were conducted to compare the acute toxicity of Recombinate and Hemofil-T. The species used for testing included rats, ferrets and dogs. The doses of Recombinate rAHF tested ranged from 100 IU/kg to 10,000 IU/kg. Toxicity was evaluated following intravenous, intraperitoneal or subcutaneous routes of administrations. Changes in the manufacturing site and processes prompted the performance of multiple acute toxicity studies, which compared drug from the three manufacturing sites where the test material was produced

The results showed that the acute toxicity profile of Recombinate rAHF was comparable to Hemofil T. No mortality was observed in any dose group or in any species. In rat and ferret studies that included Hemofil T as the reference article, there were no differences between the test and reference article groups in the type or frequency of clinical signs suggestive of toxicity, changes in body weights, clinical chemistry findings, gross necropsy and histopathologic findings. No dose-response relationship was observed among rAHF-treated groups.

In ferret studies (Study 98002-PT-004), the high-dose females on day 14 post-treatment showed a slight but statistically significant increase in the percentage of reticulocytes in their blood (1.08% $\pm$ 0.34) compared to the other groups (0.32 –0.37%). This finding was not observed in a corresponding group of male ferrets. All values were within the reference range and slightly lower than those observed pre-treatment (1.38 – 2.05%). There were no other changes in haematologic parameters noted. The interpretation of this finding was that it was not considered a treatment-related effect.

In dogs (Study 98002-PT-009), reddening of the skin was seen soon after dosing in all animals. In addition, females showed skin oedema in the head area. Dogs received 2,500 IU/kg rAHF showed a transient restlessness followed by a decrease in spontaneous activity. These signs disappeared within minutes to a few hours after dosing. Two hours post-dosing, a slight decrease in body temperature was seen in the mid-dose female and both dogs in the high dose group. The body temperature returned to normal by 4 hours post-dosing. No other abnormality was observed. Since this study did not include Hemofil T treated animals as a reference group, it was not possible to determine if there was any difference in acute toxicity between the latter and rAHF. However, the above-described adverse reactions that were observed in association with the administration of rAHF were minor and readily reversible.

No acute toxicity was observed in rat and rabbit studies where the maximal rAHF-PFM dose tested was twice that for Recombinate. Neither rAHF-PFM nor Recombinate was irritating to the veins or peri-venous tissue in rabbits. Repeat-dose toxicity studies of several candidates as well as the selected formulation vehicles and a literature review to research the safety of major excipients were undertaken.

- Repeated dose toxicity studies

Repeat-dose toxicity studies have not been performed with rAHF-PFM. The applicant provided data from repeated dose toxicity studies to evaluate the toxicity of the formulation vehicle for rAHF-PFM and studies upon the repeat dose toxicity of Recombinate, which had already been submitted in the marketing authorisation application for Recombinate.

- Studies conducted with the formulation vehicle for rAHF-PFM

Two 30 days repeated dose toxicity studies were conducted to evaluate the toxicity of the formulation vehicle for rAHF-PFM in rats and rabbits (Reports 98008-PT-029 and 98008-PT-030). The purpose of these studies was to identify potential toxicological effects or interactions among the formulation vehicle ingredients.

There was no mortality in any groups. The incidence of clinical and ophthalmic findings was similar for the treatment and control groups. There were no differences in food consumption, changes in body weights, haematology and clinical pathology parameters, and organ weights. Further, there was no difference in histological findings between the control and high dose groups. The low and mid dose groups and all the recovery groups were not examined histologically due to the lack of treatment-related effect in the high dose groups.

These results demonstrated that the safety profile of the formulation vehicle for rAHF-PFM in rats and rabbits was comparable to that of saline when given intravenously for 30 consecutive days at doses up to 40 mL/kg, the highest technically feasible dose.

- Studies conducted with rAHF

Repeated dose toxicity studies were conducted with rAHF (Recombinate) (Reports 98002-PT-010, -PT-015 and -PT-023), rats and monkeys were intravenously infused with Recombinate or Hemofil T daily for up to 28 days. In Recombinate treated-groups doses ranged from 250 to 1000 IU/kg/day in rats and 125 to 500 IU/kg/day in monkeys. Hemofil T doses were 1000 IU/kg and 500 IU/kg in rats and monkeys, respectively. Results of these studies showed that Recombinate and Hemofil T possessed almost identical toxicity profiles. There was no mortality in any of the study groups. There were no treatment-related effects regarding cage side observations, food consumption, body weight changes, ophthalmic, clinical pathology, haematology, findings, urinalysis, gross necropsy or histopathologic examinations. Compared with baseline, a statistically significant increase in activated partial thromboplastin time was observed in all study groups for both species. This increase was, comparable for Hemofil T and Recombinate study groups. Neutralising anti-Factor VIII antibodies were detected in all treatment groups.

Thirty days repeated dose toxicity studies in rats and rabbits with the selected formulation vehicle and a 30-days repeated dose toxicity study in male rats with earlier candidate formulation vehicles was conducted. No formulation vehicle-related toxicity was observed at the maximal feasible doses in rats and rabbits in any of these studies.

- Genotoxicity

No genotoxicity studies were conducted with rAHF-PFM. These studies were performed with Recombinate, i.e. Recombinate drug substance was evaluated *in vitro* and *in vivo* as part of the Recombinate development program. The mutagenic potential of Recombinate drug substance was evaluated for its ability to induce reverse gene mutations in bacteria in the presence and absence of S9 fraction (Ames Test, Study 98002-PT-011). The clastogenic potential of Recombinate drug substance was evaluated by investigating the induction of chromosomal aberrations in Chinese hamster ovary cells in the presence and absence of S9 fraction (Study 98002-PT-012). The clastogenic potential of Recombinate was also evaluated in vivo by testing its ability to induce micronuclei formation in bone marrow cells in mice (Study 98002-PT-013). In each of these test systems, Recombinate drug substance was found to be non-mutagenic and non-clastogenic.

- Carcinogenicity

Long-term studies in animals to evaluate carcinogenic potential have been performed neither for rAHF-PFM nor for Recombinate. Since factor VIII is an endogenous coagulation protein, it is not expected to be carcinogenic.

- Local tolerance

*Study 98008-PT-018 (tissue irritability Study of rAHF-PFM in Rabbits)*

Equal numbers of young adult New Zealand White rabbits were given the selected rAHF-PFM formulation either by intravenous injection at a volume of 10 ml (n=6 males) or perivascular injection at a volume of 0.2 ml (n=6 males). Normal saline (control) was given either intravenously or perivenously in equivalent volumes. For intravenous injections, 10 ml of the test article was injected into the left marginal ear vein while an equal volume of the control article was injected into the right marginal ear vein. For perivenous administration, 0.2 ml of the test article was injected into the subcutaneous tissue adjacent to the left marginal ear vein with the corresponding right ear serving as the control. The degree of irritation at and around the injection sites was scored macroscopically at 4, 24 and 72 hours post-dosing. Three rabbits per group were sacrificed at 24 and 72 hours post-treatment for evaluation of microscopic inflammation at the injection sites.

No treatment-related effects were observed, neither irritation nor inflammation was observed in any of the treatment groups. Thus, the selected rAHF-PFM formulation was considered non-irritating under the described test conditions.

Finally, one study evaluated the tissue irritability of Recombinate (Study 98008-PT-026).

No-treatment-related effects were observed microscopically at either 24 or 72 hours post-treatment. A few minimal to mild foci of dermal inflammation and/or haemorrhage were observed in the perivenous Recombinate treated ear sections. However, the mean overall microscopic scores were similar for the Recombinate and saline groups.

**Discussion on toxico-pharmacological aspects**

The purpose of the rAHF-PFM development program was to demonstrate comparability with Recombinate rAHF wherever possible.

Animal testing of rAHF-PFM was conducted in two phases. The first phase concentrated on the evaluation of candidate formulation vehicles and more specifically, the selection of a suitable bulking and stabilising agent. Three pairs of bulking/stabilising agents were evaluated. These combinations consisted of mannitol and trehalose, mannitol and arginine, and glycine and trehalose (each pair 3.2% [w/v, bulking] and 0.8% [w/v, stabilising], respectively). Pharmacology, pharmacokinetic and toxicology studies of rAHF-PFM were conducted with one or all of the aforementioned pairs of bulking/stabilising agents. Repeated dose toxicology was also done using bulking and stabilising agents plus excipients in the absence of rAHF-PFM. The bulking and stabilising agents that were ultimately chosen for further development were mannitol (bulking) and trehalose (stabilising). In the second phase, studies were conducted to compare the haemostatic efficacy, pharmacokinetics and acute toxicity profile of rAHF-PFM and Recombinate rAHF and to evaluate the repeated dose toxicity of the selected rAHF-PFM formulation vehicle.

No acute toxicity was observed in rat and rabbit studies where the maximal rAHF-PFM dose tested was twice as high than for Recombinate. Neither rAHF-PFM nor Recombinate was irritating to the veins or perivenous tissue in rabbits. Repeat-dose toxicity studies of several candidates as well as the selected formulation vehicles and a literature review to research the safety of major excipients were undertaken.

Thirty days repeated dose toxicity studies in rats and rabbits with the selected formulation vehicle and a 30 days repeated dose toxicity study in male rats with earlier candidate formulation vehicles were conducted. No formulation vehicle-related toxicity was observed at the maximal feasible doses in rats and rabbits in any of these studies.

A literature review was conducted for each of the four major excipients included in the selected RAHF-PFM formulation: trehalose (Report SR06CT99142), mannitol (Report SR06CT99139), reduced glutathione (The Desaiah Report, 2001) and Tris (The Northup Report, 2000). Each of these excipients has been used in other intravenously administered drug products. A brief summary of these reviews is provided in the non-clinical written summary. These literature reviews raised no safety concerns regarding the proposed use of these excipients. In addition, no toxicological effects from these substances are expected.

Repeated dose toxicity, genotoxicity and safety pharmacology studies have not been conducted with rAHF-PFM. Extensive physicochemical comparability testing as well as the non-clinical comparison studies described herein indicate that the active drug ingredient in Recombinate rAHF and rAHF-PFM are virtually identical. Since repeated dose toxicity, genotoxicity and safety pharmacology of Recombinate drug substance have been adequately investigated in conjunction with the Recombinate rAHF development program, it was considered unnecessary to conduct these studies as part of the rAHF-PFM program.

In conclusion, the applicant provided results from two single dose and one tissue irritability studies. Repeated dose toxicity was tested as well, but only with the formulation vehicle. Supportive information has been provided from toxicological investigations with the predecessor Recombinate, i.e. studies upon single and repeat-dose toxicity, genotoxicity and local tolerance. In addition, the formulation candidates have also been evaluated in terms of single and repeat dose toxicity as well as local tolerance. All the presented investigations did not reveal any safety concerns.

## 4. Clinical aspects

The application is supported by data from four clinical studies, which enrolled a total of 131 patients with moderately severe to severe haemophilia A, 128 of whom were treated with rAHF-PFM.

An overview of the design, enrolment and formulation of rAHF-PFM (pilot or commercial) used in the pivotal study (069901), the continuation study (060102), supportive study in surgery (069902) and study (060101) in paediatric previously treated patients (PTPs) is summarised in the Table below. The design of all studies consists of an evaluation of pharmacokinetics (limited in study 069902), clinical efficacy and safety including immunogenicity of rAHF-PFM.

Along with other regulatory guidelines that may applicable to this Application, the evaluation of this dossier took into account the recommendations given in the Note for Guidance on the clinical investigation of recombinant factor VIII and IX products (CPMP/BPWG/1561/99) dated October 2000. The Applicant did not seek any scientific advice from the CPMP.

### Clinical pharmacology

*Pharmacodynamics*

- Mechanism of action

No pharmacodynamic studies in humans have been performed but the applicant refers to animal studies. This is acceptable due to the origin of factor VIII as an endogenous human protein and the high degree of comparability between findings in animal studies regarding ADVATE and Recombinate.

*Pharmacokinetics*

- General:

The pharmacokinetics of rAHF-PFM was evaluated in all four studies. The design of these studies is summarised in the table below.

**Clinical pharmacokinetic studies conducted with rAHF-PFM**

| Study number | Design and type of r-AHF-PFM | Enrolment |
|---|---|---|
| **069901 Pivotal** | Patients were randomised to Part 1 + 2, or to Part 2 + 3.<br><br>Part 1: Randomised crossover pharmacokinetic comparison of rAHF-PFM **pilot** and Recombinate.<br><br>*Part 2: Open-label, non-controlled, prophylactic treatment regimen for evaluation of the immunogenicity, safety and efficacy of rAHF-PFM pilot formulation during a period of at least 75 exposure days.*<br><br>Part 3: Randomised controlled, double-blind crossover pharmacokinetic comparison of rAHF-PFM pilot and rAHF-PFM **commercial formulations**. | n=111, 108 treated.<br>N=56, 54 treated.<br><br>*N=107 treated.*<br><br>N=55, 51 treated. |
| **060102 Continuation** (only for subjects who completed treatment of Part 1 and 2 of study 069901)<br><br>**Ongoing study** | Part 1: Single arm, open-label, controlled evaluation of the pharmacokinetics and safety of rAHF-PFM **commercial** after at least 75 exposure days of treatment with rAHF-PFM pilot in study 069901.<br><br>*Part 2: Open-label, non-controlled prophylactic or on-demand treatment regimen for the evaluation of the safety, immunogenicity, and haemostatic efficacy of rAHF-PFM **commercial**.* | N=19, 13 evaluable.<br><br>*N=27, 13 evaluable for efficacy, 27 for immunogenicity.* |
| **069902 Surgery**<br><br>**Ongoing study** | Multi-centre, prospective, open-label, non-controlled study of the safety and efficacy of rAHF-PFM in patients with severe or moderately severe haemophilia A who require a surgical, dental or other invasive procedure.<br>All patients were treated with rAHF-PFM **pilot.**<br>Minimums of 25 patients are planned. | N=10, 4 from study 069901 and 6 additional patients. |
| **060101 Paediatric PTPs < 6 years of age**<br><br>**Ongoing study** | Part 1: Open-label, non-controlled evaluation of the pharmacokinetics and short-term safety of rAHF-PFM **commercial**.<br><br>*Part 2: Open-label determination of the immunogenicity, haemostatic efficacy and safety of rAHF-PFM **commercial**. At least 50 exposure days according to a treatment regimen determined by the site investigator.*<br><br>A minimum of 50 patients are planned. | N=14, all treated.<br><br>*No available data.* |

*1. Description of the study 069901*

The *study 069901* is the pivotal and is divided into 3 parts.

The first part (part 1) was a randomised controlled crossover pharmacokinetic comparison of Recombinate and rAHF-PFM (pilot) with the objective of demonstrating bioequivalence based on $AUC_{(0-48)}$ and adjusted recovery, for these two products.

The second part (part 2) consisted of an open uncontrolled prophylactic treatment regimen for evaluation of safety (and in particular immunogenicity) and efficacy of rAHF-PFM pilot during a period of at least 75 exposure days.

The third part (part 3) was a randomised controlled double-blind crossover pharmacokinetic comparison of rAHF-PFM pilot and rAHF-PFM commercial with the objective of demonstrating bioequivalence, based on $AUC_{(0-48)}$ and adjusted recovery for the pilot scale and the commercial scale rAHF-PFM.

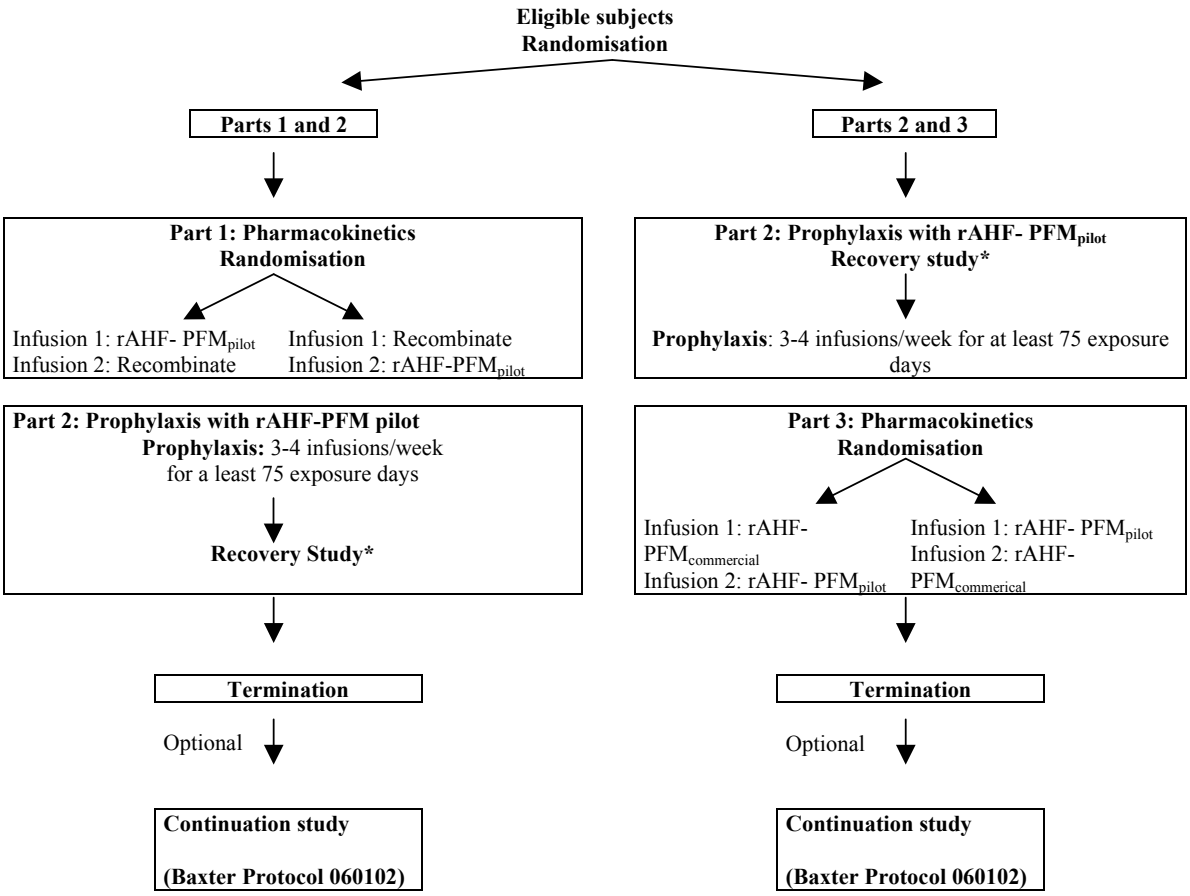
The main characteristics and criteria for inclusion were:

- Diagnosis of severe (baseline factor VIII ≤ 1%) or moderately severe (baseline factor VIII ≤ 2%) haemophilia A,
- History of at least 150 exposure days to all other factor VIII products,
- Age ≥ 10 years and weight > 35 kg,
- No detectable inhibitors to factor VIII in the local haemostasis laboratory at the investigative site at the time of enrolment,
- No history of factor VIII inhibitors > 1.0 BU,
- HIV-1 seronegative or, if HIV-1 seropositive, CD4+ lymphocyte count ≥ 400/$mm^3$,
- No known hypersensitivity to Recombinate,
- And a written informed consent.

The design of the pivotal study is depicted in the figure below.

Subjects randomised to Part 2 and 3 underwent an initial factor VIII recovery study, prior to initiating prophylactic treatment on Part 2, in order to provide initial abbreviated pharmacokinetic data for rAHF-PFM pilot. Upon completion of Part 2 (at least 75 exposure days), these subjects continued with pharmacokinetic assessment on Part 3.

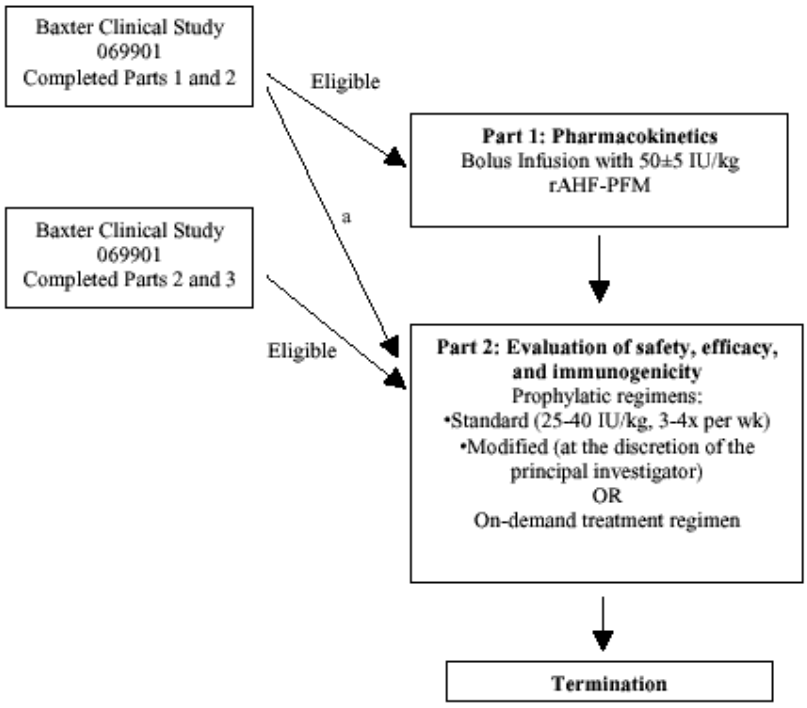
**Figure 1: Study design for pivotal study 069901**




* Subjects who completed treatment on Parts 1 and 2 could forego the recovery study if they enrolled on Baxter clinical 060102

*The continuation study 060102* is an open uncontrolled study with all subjects receiving rAHF-PFM commercial. Patients randomised to and who completed Parts 1 and 2 of the pivotal study were eligible to participate in a pharmacokinetic assessment in Part 1 of continuation study 060102. Part 2 of study 060102 is open for all patients who completed the pivotal study, received no factor VIII products other than rAHF-PFM upon completion of the pivotal study and developed no inhibitors to factor VIII during this study.

**Figure 2: Study design for continuation study 060102**




[a] Subjects who completed Parts 1 and 2 of Baxter clinical study 069901 but did not have evaluable data were not eligible for Part 1 of Baxter study 060102 but were eligible for Part 2 of Baxter clinical study 060102.

Part 1 of study 060102 was designed to compare, in a single cohort of patients, pharmacokinetic parameters before and after at least 75 exposure days of treatment with rAHF-PFM pilot in Part 2 of the pivotal study 069901. This was achieved by comparing pharmacokinetic data from subjects treated with rAHF-PFM pilot in Part 1 of clinical study 069901 with pharmacokinetic data from the same subjects treated with rAHF-PFM commercial in Part 1 of study 060102. The primary efficacy variables were comparisons of $AUC_{(0-48)}$ and adjusted recovery. A minimum of 12 subjects was planned for this comparison to comply with the CPMP guideline.

- Infusion of the investigational medicinal product and sample collection

Parts 1 and 3 of the pivotal study were respectively a crossover pharmacokinetic comparison of Recombinate with rAHF-PFM pilot and of rAHF-PFM pilot with rAHF-PFM commercial. The first infusion was to be given at a dose of 50 ± 5 IU/kg. The second infusion was administered in a non-bleeding state after at least a 72-hour to 4-week washout period after the first pharmacokinetic infusion or after a prophylactic or therapeutic dose of Recombinate (Part 1) or rAHF-PFM (Part 3).

To undergo the recovery studies in the pivotal study, subjects had to be in a non-bleeding state and should not have received factor VIII for at least 72 hours prior to the infusion of rAHF-PFM pilot at a dose of 50 ± 5 IU/kg.

Eight lots of rAHF-PFM pilot were used in pivotal study 069901 and one lot of rAHF-PFM commercial in Part 3 of that study.

In Part 1 of the continuation study, administration of the rAHF-PFM required that the subject was not bleeding and had not received any factor VIII for at least 72 hours prior to the infusion. Eligible subjects were infused with rAHF-PFM commercial at a dose of 50 ± 5 IU/kg (identical to the dose in Part 1 of study 069901).

Five lots of rAHF-PFM commercial were used in study 060102. However, according to the Clinical Summary and the study protocol, all patients in Part 1 received the same lot of rAHF-PFM commercial.

*2. Primary endpoints/assays*

The highest concentration observed in the plasma following the administration of the dose ($C_{max}$,) plasma half-life, the area under the plasma concentration-time curve between 0 and 48h after the administration ($AUC_{(0-48)}$), the total area under the first moment-time curve (AUMC), the clearance (CL), the mean residence time (MRT) and the apparent volume of distribution under steady-state conditions based on product concentration in plasma ($V_{ss}$) and adjusted recovery were calculated using standard statistical methods.

*3. Statistical analysis*

The determination of bioequivalence between Recombinate and rAHF-PFM pilot in Part 1 and between rAHF-PFM pilot and rAHF-PFM commercial in Part 3 of the pivotal study utilised natural log-transformed AUC $_{(0-48)}$ and adjusted recovery. It was based on the calculation of the 90% confidence intervals for the difference in the log-transformed means for adjusted recovery and AUC. The results were analysed with an analysis of variance

The primary analysis of bioequivalence was a per protocol analysis. The per-protocol analysis data set was defined to be a subset of the intent-to-treat population and included, in the pivotal study, randomised subjects with no major protocol violations who: met all study entry criteria; received both study drug infusions for Part 1 or Part 3; were dosed according to the protocol, received the second infusion at a dose that was within 10% of the first infusion dose; had plasma factor VIII measurements at all assessment time points for both study drug infusions; did not develop a factor VIII inhibitor between infusion 1 and infusion 2 of Part 1 or Part 3; were not bleeding at the time of the pharmacokinetic infusion; received the second pharmacokinetic infusion at least 72 hours after the first pharmacokinetic infusion.

A descriptive evaluation was performed in the pivotal study of the secondary pharmacokinetic parameters (AUMC, half-life, CL, MRT, Vss, and Cmax) without a formal statistical comparison between the groups.

In the continuation study 060102 the comparisons of AUC $_{(0-48)}$ and adjusted recovery, before treatment and after at least 75 exposure days, were based on the calculation of the 95% confidence intervals for the mean difference in the log-transformed values. These confidence intervals were assessed against a zero difference. All secondary pharmacokinetic parameters (AUMC, half-life, CL, MRT, Vss, and Cmax) were reported using descriptive statistics.

**RESULTS**

*4. Study populations/accountability of patients*

A total of 111 patients from 23 investigative sites were enrolled in the pivotal study.

In *study 069901* 56 subjects were randomised to Part 1 and 2, 54 of whom were treated in Part 1. Fifty-one of the 54 patients treated in Part 1 met the criteria for inclusion in the intention-to-treat analysis and 30 met the criteria for the per-protocol analysis.

Fifty-five patients were randomised to Part 2 and 3, 51 of whom were treated in Part 3 and met the criteria for inclusion in the intention-to-treat analysis. Thirty-seven of the 51 patients treated in Part 3 met the criteria for inclusion in the per-protocol analysis.

Nineteen patients were enrolled in Part 1 of *study 060102*, 14 of whom had pharmacokinetic data collected. Thirteen out of 14 patients were included for the per-protocol pharmacokinetic analysis. All subjects enrolled in Part 1 had a baseline factor VIII < 1%.

In the *recovery studies*, among the 51 subjects who completed treatment in Parts 1 and 2 of the pivotal study, 34 were scheduled to enrol in the continuation study. Therefore, 17 patients had a factor VIII recovery determination at the completion of Part 2. Of the 55 subjects randomised to Parts 2 and 3 of the pivotal study, two subjects were missing factor VIII data for the recovery study. The remaining 53 subjects underwent the adjusted recovery evaluation at the beginning of Part 2.

*5. Results of pivotal study 069901 and continuation study 060102*

- Pharmacokinetics

The summary of the pharmacokinetic parameters in Part 1 and Part 3 are presented in the tables below.

In part 1 of the study, the difference between the observed means for the log-transformed $AUC_{(0-48)}$ (difference between rAHF-PFM pilot and Recombinate) was -0.001. The 90% CI [-0.04025; 0.03825] fell within the bioequivalence limits of [-0.223; 0.223].

The difference between the mean log-transformed adjusted recovery values (difference between rAHF-PFM pilot and Recombinate) was -0.0565 with a 90% CI of [-0.08926; 0.02374] which again fell within the bioequivalence limits of [-0.223; 0.223]. The intent-to treat analyses for both pharmacokinetic parameters gave similar results.

**Table 2: Summary of pharmacokinetic parameters in Part 1 of study 069901 (per protocol analysis)**

| | **Recombinate (n=30)** | | **rAHF-PFM pilot (n=30)** | |
|---|---|---|---|---|
| **Pharmacokinetic parameter** | **Mean** | **Range** | **Mean** | **Range** |
| AUC(0-48) (IU.h/dL) | 1515 | 970-2205 | 1533 | 876-2642 |
| Cmax (IU/dL) | 127 | 73-199 | 119 | 77-195 |
| Adjusted recovery (IU/dL per IU/kg) | 2.55 | 1.47-3.89 | 2.40 | 1.54-3.88 |
| Half-life (h) | 11.39 | 7.89 - 18.12 | 11.98 | 6.74 - 24.70 |
| MRT (h) | 20.41 | 10.53 - 43.86 | 22.83 | 9.80 - 66.66 |
| Vss (dL/kg) | 0.59 | 0.35 - 0.91 | 0.60 | 0.33 - 0.90 |
| CL (dL/kg.h) | 0.03 | 0.02 - 0.05 | 0.03 | 0.01 - 0.06 |
| AUMC ($IU.h^2/dL$) | 38343 | 10487 - 118065 | 52642 | 10527 - 283097 |

**Table 3: Summary of pharmacokinetic parameters in Part 3 of study 069901 (per protocol analysis)**

| | rAHF-PFM pilot (n=37) | | rAHF-PFM commercial (n=37) | |
|---|---|---|---|---|
| **Pharmacokinetic parameter** | Mean | Range | Mean | Range |
| AUC(0-48) (IU.h/dL) | 1544 | 856 - 2216 | 1494 | 767 - 2392 |
| Cmax (IU/dL) | 129 | 89 - 206 | 123 | 87 - 169 |
| Adjusted recovery (IU/dL per IU/kg) | 2.55 | 1.73 - 4.05 | 2.46 | 1.71 - 3.41 |
| Half-life (h) | 11.60 | 7.59 - 15.03 | 11.72 | 8.14 - 17.34 |
| MRT (h) | 20.39 | 11.23 - 33.69 | 20.96 | 12.18 - 41.04 |
| Vss (dL/kg) | 0.60 | 0.34 - 1.15 | 0.63 | 0.41 - 0.86 |
| CL (dL/kg.h) | 0.03 | 0.02 - 0.06 | 0.03 | 0.02 -0.06 |
| AUMC ($IU.h^2/dL$) | 38342 | 10004 - 92453 | 38573 | 10208 - 101434 |

In part 3 of the study, the difference between the means for the log-transformed $AUC_{(0-48)}$ (difference between rAHF-PFM commercial and rAHF-PFM pilot) was -0.030. The 90% CI [-0.06548; 0.00548] fell within the bioequivalence limits of [-0.223; 0.223].

The difference of the means of the log-transformed mean adjusted recovery values (difference between rAHF-PFM commercial and rAHF-PFM pilot) was -0.0325 with a 90% CI of [-0.06362; 0.00138] which again fell within the bioequivalence limits of [-0.223; 0.223]. The intent-to treat analyses for both pharmacokinetic parameters gave similar results.
Values of the secondary pharmacokinetic parameters were very similar among the three studied products.

- Comparison of pharmacokinetic data at onset and after at least 75 exposure days to treatment with rAHF-PFM

A summary of the pharmacokinetic parameters in the 13 patients included in the per-protocol pharmacokinetic analysis at the onset of treatment and after at least 75 exposure days with rAHF-PFM pilot is presented in Table 4.

**Table 4: Summary of pharmacokinetic parameters with rAHF-PFM in study 060102**

| | **Parameters at onset of treatment* (n=13)** | | **Parameters after at least 75 exposure days# (n=13)** | |
|---|---|---|---|---|
| **Pharmacokinetic parameter** | **Mean** | **Range** | **Mean** | **Range** |
| AUC(0-48) (IU.h/dL) | 1313 | 876 - 2314 | 1262 | 831 - 2731 |
| ln AUC(0-48)@ | 7.14 | 6.78 - 7.75 | 7.09 | 6.72 - 7.91 |
| Cmax (IU/dL) | 109 | 77 - 151 | 111 | 73 - 151 |
| Adjusted recovery (IU/dL per IU/kg) | 2.21 | 1.54 - 3.02 | 2.20 | 1.46 - 3.06 |
| Half-life (h) | 11.10 | 8.38 - 17.96 | 10.89 | 9.24 - 13.92 |
| MRT (h) | 19.17 | 9.80 - 40.56 | 18.14 | 9.39 - 29.82 |
| Vss (dL/kg) | 0.64 | 0.42 - 0.90 | 0.68 | 0.43 - 0.94 |
| CL (dL/kg.h) | 0.04 | 0.02 - 0.06 | 0.04 | 0.01 - 0.06 |
| AUMC ($IU.h^2/dL$) | 32990 | 10527 - 129569 | 28231 | 10065 - 100710 |

* rAHF-PFM pilot in Part 1 of study 069901
# rAHF-PFM commercial in Part 1 of study 060102
@ log transformed value of AUC(0-48)

The difference of the log-transformed mean values for $AUC_{(0-48)}$ (difference between rAHF-PFM commercial and rAHF-PFM pilot) was 0.546 and the 95% CI was [-0.031; 0.1405]. For adjusted recovery, the difference of the log-transformed mean values (difference between rAHF-PFM commercial and rAHF-PFM pilot) was 0.014. The 95% CI was [-0.068; 0.0958].

- Recovery studies (*Study 069902*)

The adjusted recovery data in these two groups are summarised in Table 5. No formal comparison was done between the data before and after treatment with rAHF-PFM pilot in Part 2.

**Table 5: Summary of adjusted factor VIII recoveries in Part 2 of study 069901**

| Randomised Group/Time point | Factor VIII recovery (IU/dL per IU/kg) | | | Factor VIII level (IU/dL) | | |
|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **Range** | **Mean** | **SD** | **Range** |
| **Parts 1 and 2 (n=17)** | | | | | | |
| 30 minutes | 2.35 | 0.44 | 1.71 - 3.18 | 121.3 | 22.5 | 83 - 160 |
| 1 hour | 2.18 | 0.49 | 1.04 - 3.05 | 112.8 | 26.2 | 49 - 157 |
| 3 hours | 1.71 | 0.34 | 1.34 - 2.57 | 88.9 | 19.0 | 65 - 133 |
| **Parts 2 and 3 (n=53)** | | | | | | |
| 30 minutes | 2.24 | 0.55 | 1.25 - 3.65 | 114 | 29.1 | 55 - 178 |
| 1 hour | 2.05 | 0.50 | 1.23 - 3.77 | 105.2 | 26.6 | 48 - 186 |
| 3 hours | 1.67 | 0.49 | 0.89 - 3.45 | 85.5 | 25.1 | 38 - 170 |
| **All (n=70)** | | | | | | |
| 30 minutes | 2.27 | 0.53 | 1.25 - 3.65 | 116.1 | 27.6 | 55 - 178 |
| 1 hour | 2.08 | 0.49 | 1.04 - 3.77 | 107.1 | 26.5 | 48 - 186 |
| 3 hours | 1.68 | 0.46 | 0.89 - 3.45 | 86.3 | 23.7 | 38 - 170 |

- Pharmacokinetic studies performed in patients who required a surgical, dental or other invasive procedure

*Study 069902* is a multi-centre prospective open-label uncontrolled study aimed at studying the safety and efficacy of rAHF-PFM in a minimum of 25 patients with severe or moderately severe haemophilia A (baseline factor VIII level ≤ 2%) who required a surgical, dental or other invasive procedure.

This interim study report includes data on 10 patients who were all treated with rAHF-PFM pilot. These patients received a loading dose ranging from 48.0 to 69.8 IU/kg. Post-infusion factor VIII levels were available in 9 patients. In all cases the target factor VIII level was met or exceeded and no additional loading doses of study drug were required in any of the patients.

All patients with available data post-infusion achieved the target levels of factor VIII, which is expected considering the loading doses of 48 to 69.8 IU/kg and an expected recovery of 2 IU/dL per IU/kg. One patient undergoing a dental extraction received 50.9 IU/kg of rAHF-PFM. The pre-infusion level factor VIII level of 2% only rose to 70% of normal in this patient. Haemostatic efficacy during and after dental extraction was excellent, however.

- Pharmacokinetic in children (*study 060101*)

Pharmacokinetics in paediatric patients was evaluated in *study 060101*. This is an ongoing open multi-centre uncontrolled study in patients with severe or moderately severe haemophilia A (baseline factor VIII ≤ 2%) younger than 6 years old. Other inclusion criteria were a history of at least 50 exposure days for all other factor VIII products, no detectable inhibitor to factor VIII, no history of a factor VIII

inhibitor at any time prior to screening, no inherited or acquired haemostatic defect other than haemophilia A, no known hypersensitivity to Recombinate, and written informed consent.

Part 1 of this study was a pharmacokinetic evaluation following a single infusion of 50 ± 5 IU/kg rAHF-PFM commercial in a non-bleeding state. Patients should not have received an infusion of factor VIII for at least 72 hours prior to the pharmacokinetic infusion.
The primary pharmacokinetic response variable was the terminal phase half-life of rAHF-PFM commercial.

One lot of rAHF-PFM commercial was used during the period covered by this interim report that includes data on 14 patients. All 14 patients were included in the intent-to-treat analysis. Five of the 14 patients were younger than 3 years of age and 9 were between 3 to 5 years of age. The mean ± SD weight was 17.6 ± 5.3 kg (range 10.8 to 27.2 kg) and the mean ± SD height 101.5 ± 15.4 cm (range 76 to 121cm). Thirteen subjects were Caucasian.

Eleven patients met the criteria for the per-protocol analysis. A summary of the pharmacokinetic parameters is provided in Table 6. A total of 50 subjects are to be enrolled in this study.

**Table 6: Summary of pharmacokinetic parameters in paediatric patients in study 060101**

| | **Intent-to-treat analysis (n=14)** | | | **Per-protocol analysis (n=11)** | | |
|---|---|---|---|---|---|---|
| **Pharmacokinetic parameter** | **Mean** | **SD** | **Range** | **Mean** | **SD** | **Range** |
| AUC(0-48) (IU.h/dL) | 1395 | 483 | 792 - 2285 | 1521 | 467 | 792 - 2285 |
| ln AUC(0-48)@ | 7.19 | 0.34 | 6.67 - 7.73 | 7.28 | 0.32 | 6.67 - 7.73 |
| Cmax (IU/dL) | 99 | 27 | 74 - 181 | 103 | 29 | 74 - 181 |
| Adjusted recovery (IU/dL per IU/kg) | 1.96 | 0.49 | 1.48 - 3.39 | 2.06 | 0.51 | 1.50 - 3.39 |
| Half-life (h) | 10.00 | 1.79 | 7.41 - 13.87 | 10.48 | 1.60 | 8.31 - 13.87 |
| MRT (h) | 16.73 | 4.49 | 9.43 - 24.35 | 18.03 | 3.75 | 12.77 - 24.35 |
| Vss (dL/kg) | 0.58 | 0.13 | 0.32 - 0.76 | 0.57 | 0.14 | 0.32 - 0.76 |
| CL (dL/kg.h) | 0.04 | 0.01 | 0.02 - 0.06 | 0.03 | 0.01 | 0.02 - 0.06 |
| AUMC ($IU.h^2/dL$) | 27176 | 15402 | 8379 - 67167 | 31270 | 14628 | 10692 - 67167 |

@ log transformed value of AUC(0-48)

- Conclusion

The applicant has submitted an application for rAHF-PFM comprising pharmacokinetic, clinical efficacy, and safety data required for a completely new product. The primary objective of the pivotal study was to demonstrate that rAHF-PFM is bioequivalent to the currently marketed Recombinate. Therefore, the applicant has followed a stepwise approach to align the clinical development and manufacturing strategies and constraints for rAHF-PFM. Firstly, a bioequivalence study was conducted with Recombinate and rAHF-PFM pilot in the Part 1 of the pivotal study. Secondly in Part 3 of the pivotal study a bioequivalence study was performed with rAHF-PFM pilot and rAHF-PFM commercial. The results based on $AUC_{(0-48)}$ and adjusted recovery, indicate, on the one hand, that Recombinate and rAHF-PFM pilot and, on the other hand, that rAHF-PFM pilot and rAHF-PFM commercial are bioequivalent. This stepwise approach is acceptable since the quality assessment of rAHF-PFM pilot and rAHF-PFM commercial has demonstrated comparability between these two products (see part II of this report).

In the meantime and following the submission of additional clinical data obtained with the commercial product (major clinical concern) a sufficient exposure (a sufficient) number of patients was obtained to assess the safety and efficacy and no further differences between pilot and commercial product have been observed.

In contradiction with the requirement in the Note for Guidance, that at least 3 lots should be employed in the pharmacokinetic trial, only one lot of rAHF-PFM commercial was used both in Part 3 of the pivotal study and in Part 1 of the continuation study. A total of 8 lots of rAHF-PFM pilot were used in the pivotal study Parts 1, 2 and 3. Data from at least three batches of rAHF-PFM commercial should be provided. Another open issue remains in form of pharmacokinetic data at the end of shelf life.

In conclusion the pharmacokinetic requirements described in the "Note For Guidance On The Clinical Investigation Of Recombinant Factor VIII and IX Products" CPMP/BPWG/1561/99 were fulfilled. The given data on pharmacokinetics for ADVATE show sufficient comparability with other authorised recombinant factor-VIII products. There also was shown equivalence of pharmacokinetics in humans between ADVATE and its predecessor Recombinate.

**Clinical efficacy**

Haemostatic efficacy of rAHF-PFM was evaluated in Part 2 of the pivotal study 069901, Part 2 of the continuation study 060102 and in supportive study 069902. Details on design, type of rAHF-PFM administered and numbers of enrolled patients in these studies are summarised in Table 1.

**Clinical studies conducted with rAHF-PFM**

| Study number | Design and type of r-AHF-PFM | Enrolment |
|---|---|---|
| **069901 Pivotal** | Patients were randomised to Part 1 + 2, or to Part 2 + 3.<br><br>*Part 1: Randomised crossover pharmacokinetic comparison of rAHF-PFM **pilot** and Recombinate.*<br><br>Part 2: Open-label, non-controlled, prophylactic treatment regimen for evaluation of the immunogenicity, safety and efficacy of rAHF-PFM pilot formulation during a period of at least 75 exposure days.<br><br>*Part 3: Randomised controlled, double-blind crossover pharmacokinetic comparison of rAHF-PFM pilot and rAHF-PFM **commercial formulations**.* | n=111, 108 treated.<br><br>N=56, 54 treated.<br><br>N=107 treated.<br><br>*N=55, 51 treated.* |
| **060102 Continuation** (only for subjects who completed treatment of Part 1 and 2 of study 069901)<br><br>**Ongoing study** | *Part 1: Single arm, open-label, controlled evaluation of the pharmacokinetics and safety of rAHF-PFM **commercial** after at least 75 exposure days of treatment with rAHF-PFM pilot in study 069901.*<br><br>Part 2: Open-label, non-controlled prophylactic or on-demand treatment regimen for the evaluation of the safety, immunogenicity, and haemostatic efficacy of rAHF-PFM **commercial**. | *N=19, 13 evaluable.*<br><br>N=27, 13 evaluable for efficacy, 27 for immunogenicity. |
| **069902 Surgery**<br><br>**Ongoing study** | Multi-centre, prospective, open-label, non-controlled study of the safety and efficacy of rAHF-PFM in patients with severe or moderately severe haemophilia A who require a surgical, dental or other invasive procedure.<br>All patients were treated with rAHF-PFM **pilot.**<br><br>A minimum of 25 patients are planned. | N=10, 4 from study 069901 and 6 additional patients. |
| **060101 Paediatric PTPs < 6 years of age** | *Part 1: Open-label, non-controlled evaluation of the pharmacokinetics and short-term safety of rAHF-PFM **commercial**.* | *N=14, all treated.* |

| | | |
|---|---|---|
| **Ongoing study** | Part 2: Open-label determination of the immunogenicity, haemostatic efficacy and safety of rAHF-PFM **commercial**. At least 50 exposure days according to a treatment regimen determined by the site investigator.<br><br>A minimum of 50 patients are planned. | No available data. |

*Main studies* (phase III = therapeutic confirmatory trials)

Part 2 of study 069901 consisted of an open uncontrolled prophylactic treatment regimen for the evaluation of immunogenicity, safety and efficacy of rAHF-PFM pilot during a period of at least 75 exposure days in previously treated haemophilia A patients.

Part 2 of study 060102 consists of an open uncontrolled prophylactic or on demand treatment regimen for evaluation of safety, immunogenicity and haemostatic efficacy of rAHF-PFM commercial in previously treated haemophilia A patients.

*1. Description of the study*

These studies were already described in the clinical pharmacokinetic part of the document. But in addition, in Part 2 of the pivotal study rAHF-PFM pilot was administered at a dose of 25-40 IU/kg infused 3-4 times/week. This prophylactic regimen was based on published data on haemophilia prophylaxis. New bleeding episodes were treated exclusively with rAHF-PFM pilot.

Part 2 of *study 060102* (continuation study) was open for all patients who completed the pivotal study, who received no other factor VIII products than rAHF-PFM upon completion of the pivotal study and developed no inhibitors to factor VIII during this study (Figure 2). All subjects received rAHF-PFM commercial according to a treatment regimen (i.e. standard prophylaxis [25-40 IU/kg infused 3-4 times/week], modified prophylaxis or on-demand) determined by the site investigator. New bleeding episodes are to be treated exclusively with rAHF-PFM commercial.

*2. Primary endpoints/assays*

Both in the pivotal and in the interim report of the continuation study the analysis of haemostatic efficacy is based on:

- The number of study drug infusions required to achieve adequate haemostasis for each new bleeding episode;
- The overall haemostatic response to treatment of new bleeding episodes with study drug on a scale of excellent, good, fair, or none, assessed by the subject (home treatment) or haemophilia centre (for hospital based treatment) following treatment of each bleed;

Additional haemostatic efficacy variables in the pivotal study were: the mean number of new bleeding episodes that occurred during the prophylactic regimen, the mean number of all bleeding episodes, including those secondary to trauma, per subject per month, the mean weight-adjusted dose administered for the treatment of each new bleeding episode and the mean number of new bleeding episodes occurring 0 to 24 hours and 24-48 hours after a prophylactic dose.

In the final study report of the continuation study additional parameters for determination of efficacy will be added such as the rate of new bleeding episodes per month and the number of new bleeding episodes occurring 0 to 24 hours and 24-48 hours after a prophylactic dose.

*3. Statistical analysis*

The sample size for Part 2 of the pivotal study was based on estimating the 95% confidence interval upper boundary of the risk of high responder inhibitor development. Based on the use of the Clopper-Pearson confidence interval and assuming that no more than one subject would develop a high

responder inhibitor, the required sample size to insure that the upper boundary of the 95% confidence interval for the risk of high responder inhibitor development was no greater than 6.7%, was calculated to be 81 subjects. The Sponsor planned to enrol at least 89 subjects. In actuality, 111 subjects were allowed to enrol based on their interest in the study.

For the continuation study the safety, immunogenicity and efficacy data were obtained from on at least 25 subjects with a minimum of 50 exposure days to rAHF-PFM commercial.
No further statistical analyses were performed in Parts 2 of the pivotal and continuation studies.

**RESULTS**

*4. Study populations/accountability of patients*

The disposition of study subjects in the pivotal study is shown in Table 7. A total of 103 patients completed Part 2, meaning that they continued therapy with rAHF-PFM pilot for at least 75 exposure days.

**Table 7: Disposition of study subjects in pivotal study 069901**

| **Populations** | **Number of subjects** | | |
|---|---|---|---|
| | **Randomised to Parts 1+2** | **Randomised to Parts 2+3** | **Total** |
| **Total randomised** | 56 | 55 | 111 |
| **Not treated** | 2 | 1 | 3* |
| **Total randomised and treated** | 54 | 54 | 108 |
| **Treated on Part 1** | 54 | NA | 54 |
| **Completed Part 1** | 53 | NA | 53# |
| **Treated on Part 2** | 53 | 54 | 107 |
| **Completed Part 2** | 51 | 52 | 103@ |
| **Treated on Part 3** | NA | 51 | 51** |
| **Completed Part 3** | NA | 51 | 51 |
| **Completed all Parts** | 51 | 51 | 102 |
| **Total discontinued** | 5 | 4 | 9 |
| **Reason for discontinuation** | | | |
| **AE** | 0 | 0 | 0 |
| **Consent withdrawn** | 3 | 0 | 3 |
| **Withdrawn by investigator** | 2 | 3 | 5 |
| **Lost-to-follow-up** | 0 | 0 | 0 |
| **Other** | 0 | 1 | 1 |

*One withdrew consent, one was erroneously identified as having a baseline factor VIII >2%, one was scheduled to receive an immuno-modulating drug (i.e. not meeting the inclusion/exclusion criteria).
# Subject withdrew consent
@ One withdrew consent, one was non-compliant, two had a history of factor VIII inhibitor > 1 BU
** Subject was non-compliant. This subject completed Part 2 but did not start Part 3.

*5. Results*

A summary of demographic characteristics and information on treatment regimens during the 6 months for all randomised patients with severe or moderately severe haemophilia A prior to enrolment in the pivotal study are presented in Tables 8 and 9, respectively. The vast majority of the patients (88%) used recombinant factor VIII products in the 6 months prior to enrolment in the pivotal study.

**Table 8: Summary of demographic characteristics for all randomised subjects in the pivotal study**

| Characteristics | Number of subjects (%) | Mean ± SD | Range |
|---|---|---|---|
| Age (years) | | | |
| 10-18 | 62 (56%) | | |
| > 18 | 49 (44%) | | |
| Race | | | |
| Caucasian | 103 (93%) | | |
| Black | 7 (6%) | | |
| Asian | 1 (1%) | | |
| Weight (kg) | 111 | 65.8 ± 16.7 | 32.2 - 108.0 |
| Height (cm) | 111 | 169.3 ± 13.0 | 135.0 - 191.0 |

**Table 9: Treatment regimens during the 6 months prior to study enrolment**

| Treatment characteristics | Number of subjects (%) | Mean ± SD | Range |
|---|---|---|---|
| Mode of therapy | | | |
| Prophylaxis exclusively | 47 (42%) | | |
| On-demand exclusively | 30 (27%) | | |
| Prophylaxis and on-demand | 34 (31%) | | |
| Total | 111 (100%) | | |
| Estimated total number of prophylactic infusions for 6 months prior to enrolment | 80 (72%)* | 60 ± 21 | 0-100 |
| For prophylaxis exclusively: typical number of infusions per week | | | |
| ≤ 2 infusions per week | 4 (9%) | | |
| 3-4 infusions per week | 43 (91%) | | |
| > 4 infusions per week | 0 (0%) | | |
| Total | 47 (42%) | | |
| Estimated total number of infusions for bleeding episodes within 6 months prior to enrolment | 111 (100%) | 14 ± 15 | 0 - 72 |
| Factor VIII products received during the 6 months prior to enrolment | | | |
| None | 1 (1%) | | |
| Subjects using one product only | 65 (59%) | | |
| Subjects using two or more products | 45 (40%) | | |

*Data unknown in one subject

As far as the compliance to the prophylactic treatment regimen during Part 2 of the pivotal study is concerned, 54 subjects (50%) received doses of study drug outside the range of 25-40 IU/kg for more than 20% of doses and 40 subjects (37%) received the investigational medicinal product less than 3 or greater than 4 times per week for more than 20% of the weeks on study. The number of patients who recived low doses of product (those who received doses < 25 IU/kg for more than 20% of the total prophylactic doses or infused less than 3 times a week) was calculated to be 37 subjects (35%).

Of the 108 patients who received at least one dose of study medication (any study part), 84 experienced one or more bleeding episodes during the study and were included in the analysis for haemostatic efficacy for the treatment of new bleeding episodes.

A total of 107 patients received at least one infusion of the investigational medicinal product during Part 2. Of these, 75 experienced one or more bleeding episodes during the first 75 exposure days and were included in the analysis of bleeding episodes by site and type, and in the frequency of bleeding 0 to 24 or 24 to 48 hours after a prophylactic infusion. The bleed rate analysis data set included all 107 subjects treated during Part 2.

A total of 526 new bleeding episodes occurred over the course of the pivotal study (all parts). Seventeen bleeding episodes occurred in Part 1. Fifteen bleeding episodes were treated with Recombinate and two episodes were treated inadvertently with rAHF-PFM pilot. During Part 2, 507 bleeding episodes occurred. One was treated inadvertently with Recombinate; the other 506 were treated with rAHF-PFM pilot. The two bleeding episodes that occurred during Part 3 were both treated with rAHF-PFM. Therefore, 510 bleeding episodes were treated with rAHF-PFM pilot and 16 were treated with Recombinate.

- Efficacy of rAHF-PFM pilot on haemostasis

Of these 510 bleeding episodes, 162 (31.8%) were spontaneous and 228 were trauma-related (44.7%). For the remaining 120 (24%) bleeding episodes the subject was unable to determine the aetiology. Regardless of the aetiology of the bleeding episodes, the majority of the bleeding sites were joints (273 out of 530 bleeding sites (52%)) and muscles and other soft tissues (173 out of 530 bleeding sites (33%)).

The overall haemostatic efficacy for rAHF-PFM pilot and the overall number of infusions required for the treatment of new bleeding episodes are shown in the Tables 10 and 11, respectively.

**Table 10: Overall haemostatic efficacy for rAHF-PFM pilot in the treatment of new bleeding episodes (study 069901)**

| | **N (%)** |
|---|---|
| Excellent/good | 439 (86) |
| Fair | 61 (12) |
| None | 1 (0) |
| Unknown | 9 (2) |
| Total | 510 (100) |

**Table 11: Overall number of infusions of rAHF-PFM pilot required for treatment of new bleeding episodes (study 069901)**

| **Number of infusions** | **N (%)** |
|---|---|
| 1 | 411 (81) |
| 2 | 62 (12) |
| 3 | 15 (3) |
| ≥ 4 | 22 (4) |
| Total | 510 (100) |

Efficacy according to outcome rating and number of study drug infusions was analysed for each type of bleeding (spontaneous, trauma-related, cause unknown) and these data reflected the overall outcome data. Ninety-five percent of all bleeding episodes that were rated excellent/good required 1 or 2 infusions of the investigational medicinal product. More than 2 infusions of rAHF-PFM were required in 5% of the 162 spontaneous episodes, 10% of the 228 trauma-related episodes, and 5% of the 120 episodes with unknown origin.

Overall outcome of bleeding in joints was regarded as excellent/good in 223/273 cases (82%), fair in 44 cases (16%), none in one case and unknown in 5 cases (2%). Overall outcome of bleeding in muscles and other soft tissues was regarded as excellent/good in 157/173 cases (91%), fair in 15 cases (9%) and unknown in 1cases.

Mean weight-adjusted doses of rAHF-PFM pilot required to treat a new bleeding episode (i.e. the sum of all infusions for a particular episode) are summarised in Table 12.

**Table 12: Total weight-adjusted dose (IU/kg) of rAHF-PFM pilot administered for the treatment of new bleeding episodes**

| Aetiology | Summary statistic | Value |
|---|---|---|
| **Spontaneous** | N | 162 |
| | Mean | 44.67 |
| | SD | 27.45 |
| | Range | 9.37 - 176.6 |
| **Secondary to trauma** | N | 228 |
| | Mean | 61.69 |
| | SD | 94.30 |
| | Range | 16.23 - 831.6 |
| **Unknown** | N | 120 |
| | Mean | 44.14 |
| | SD | 30.61 |
| | Range | 16.55 - 230.0 |
| **All** | N | 510 |
| | Mean | 52.15 |
| | SD | 67.06 |
| | Range | 9.37 - 831.6 |

- Ancillary analyses

The number of new bleeding episodes, the rate of bleeding episodes per subject per month, and the number of bleeding episodes that occurred within 24 or 24 to 48 hours of a prophylactic infusion of rAHF-PFM pilot were evaluated during the initial 75 exposure days when subjects received the protocol-prescribed prophylactic regimen.

A total of 274 bleedings occurred in 75 subjects during the initial 75 exposure days of prophylactic regimen in Part 2 (74 spontaneous bleeding episodes (27%) in 38 subjects, 126 trauma-related bleeding episodes (46%) in 48 subjects, and 74 episodes of unknown origin (27%) in 35 subjects). The majority of the new bleeding sites were joints.

The rate of new bleeding episodes per subject per month (of study observation), according to subject age group and adherence to the prophylactic regimen for the 274 bleeding episodes, that occurred during the initial 75 exposure days in Part 2, is shown in Table 13.

**Table 13: Rate of new bleeding episodes by age and prescribed dosing for rAHF-PFM pilot**

| Aetiology | Age | Dose per- or greater than protocol regimen* | | | | Dose below protocol regimen# | | | | All | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Min | Max | N | Mean | Min | Max | N | Mean | Min | Max |
| All | > 18 | 39 | 0.28 | 0.00 | 1.88 | 16 | 0.83 | 0.15 | 2.94 | 55 | 0.44 | 0.00 | 2.94 |
| | 10-18 | 31 | 0.46 | 0.14 | 2.28 | 21 | 0.81 | 0.00 | 3.88 | 52 | 0.60 | 0.00 | 3.88 |
| | All | 70 | 0.36 | 0.00 | 2.28 | 37 | 0.82 | 0.00 | 3.88 | 107 | 0.52 | 0.00 | 3.88 |

*Good compliance: ≥ 25-40 IU/kg per infusion for at least 80% of infusions and ≥ 3-4 infusions per week for at least 80% of the weeks on study in study Part 2.
#Less compliance: < 25 IU/kg per infusion for more than 20% of infusions or < 3 infusions per week for more than 20% of the weeks on study in study Part 2.

The overall rate of new bleeding episodes was 0.52 episodes/subject/month (range 0 - 3.88). The mean rate of all new bleeding episodes was higher (0.60) for the subjects aged between 10 and 18 years old than for subjects older than 18 years old (0.44) (Table 13). For trauma-related bleeding episodes, the mean rate was also higher for the subjects aged between 10 and 18 years old (0.53, range 0.13 - 2.11) than for subjects older than 18 years of age (0.34, range 0.13 - 1.10). In contrast, for spontaneous bleeding episodes the mean rate was higher for subjects > 18 years of age (0.48, range 0.09 - 1.96) than for subjects 10 to 18 years of age (0.36, range 0.13 - 2.17).

The mean rate of all new bleeding episodes was more than two-fold higher for the 37 subjects who were less compliant to the prophylactic regimen (0.82) than for the 70 subjects who were treated at doses and frequencies at or above those specified in the protocol (0.36) (Table 13). The effect of adherence to the prophylactic regimen appeared to be generally consistent across age groups and all bleeding aetiologies but was most prominent in the subset of bleeding episodes secondary to trauma (a bleeding rate of 0.32, range 0.13 - 2.11, in subjects with good compliance versus a rate of 0.67, range 0.13 - 1.94 in subjects with less compliance).

Of the 274 bleeding episodes that occurred during the initial 75 exposure days in Part 2, 172 (63%) occurred within 48 hours of a prophylactic dose (72 bleeding episodes within 24 hours and 100 bleeding episodes between 24 and 48 hours). Trauma-related bleeding episodes were more likely to occur 24 to 48 hours (44%) than 0 to 24 hours (28%) after a prophylactic dose. Spontaneous bleeding episodes were equally likely to occur 0 to 24 hours (20%) and 24 to 48 hours after a prophylactic dose (24%). Thus the majority of spontaneous bleeding episodes (56%) occurred more than 48 hours after the administration of the study drug.

Sixteen bleeding episodes in the pivotal study were treated with Recombinate (one spontaneous, 10 trauma-related and 5 of unknown aetiology). Fourteen of the 16 bleeding episodes had an efficacy rating of excellent/good, one of fair, and in one episode the rating was unknown. Fourteen of the episodes required treatment with one infusion, one required two infusions, and one required 3 infusions. The mean ± SD total weight-adjusted dose of Recombinate for all bleeding episodes was 32.15 ± 10.98 IU/kg (range 14.69 to 51.5).

- Interim results of the continuation study 060102

A total of 33 subjects were analysed in this interim report of study 060102 (Part 1 and 2). They all received at least one dose of study drug (any study part) and had a follow-up assessment of safety.

Of the 33 subjects 19 (58%) were 10 to 18 years of age and 14 (42%) were > 18 years of age. The mean ± SD weight was 66.9 ± 15.2 kg (range 40.8 to 105.0 kg) and the mean ± SD height 169.3 ± 10.1 cm (range 150.0 to 185.0 cm). Thirty-two subjects were Caucasian.

In Part 2 data were available for 27 subjects. Twenty-three (85.2%) of these patients were treated with a continuation of the standard prophylactic regimen used in the pivotal study and 4 (14.8%) were treated with an investigator-modified prophylactic regimen. None of the patients were treated with an

on-demand regimen. The median number of exposure days for these 27 subjects was 55 days (range 50 to 66 days) and the median total time on study was 124 days (range 111 to 140 days).

Fourteen out of 27 subjects did not report any bleeding episode during this interim period. Thirteen out of these 27 patients received at least one dose of study product for the treatment of a new bleeding episode and were included in the analysis for haemostatic efficacy for the treatment of new bleeding episodes.

A total of 51 new bleeding episodes were reported for these 13 subjects. Forty-nine bleeding episodes occurred in 12 subjects while on standard treatment (12 (24%) spontaneous, 27 (55%) trauma-related, and 10 (20%) of unknown origin). Two spontaneous bleeding episodes occurred in one subject while on the investigator-modified prophylactic regimen.

The overall haemostatic efficacy for rAHF-PFM commercial and the overall number of infusions required for the treatment of new bleeding episodes are shown in the Tables 14 and 15, respectively.

**Table 14: Overall haemostatic efficacy for rAHF-PFM commercial in the treatment of new bleeding episodes (study 060102)**

| | **N (%)** |
|---|---|
| Excellent/good | 32 (63) |
| Fair | 17 (33) |
| None | 1 (2) |
| Unknown | 1 (2) |
| Total | 51 (100) |

The new bleeding episode that was rated by the patient as having no response, occurred in the right elbow. The patient infused himself with one dose of study drug for the treatment of this new bleeding episode. He used no other factor VIII replacement products but did use naproxen for three days. No factor VIII inhibitors were detected at two subsequent visits one and 4 months later.

**Table 15: Overall number of infusions of rAHF-PFM commercial required for treatment of new bleeding episodes (study 060102)**

| **Number of infusions** | **N (%)** |
|---|---|
| 1 | 44 (86) |
| 2 | 3 (6) |
| 3 | 1 (2) |
| ≥ 4 | 3 (6) |
| Total | 51 (100) |

*Clinical studies in special populations*
At the time of this submission no data on haemostatic efficacy in children under the age of 6 years are available.

*Supportive study(ies)*
*Study 069902* is described in the pharmacokinetic part of this document.
Results from ten patients, enrolled at five sites between February 2001 and September 2001, are presented in an interim analysis. One subject was withdrawn from the study but was included in the analysis of efficacy and safety.

All patients were treated with rAHF-PFM pilot (5 lots in total). Administration of rAHF-PFM was at the discretion of the investigator. All patients received a pre-operative loading dose sufficient to

increase the patients' factor VIII level between 60 and 100% (for dental procedures) or between 80 and 120% (for the other procedures). In the intra-operative and post-operative period patients were treated with bolus or continuous infusion regimens or both. Finally, home replacement therapy was prescribed by the investigator for up to 6 weeks from the surgery date for major orthopaedic procedures and up to 2 weeks from the surgery date for all other procedures. The total period of study participation per subject varied from 2 days to 6 weeks, depending on the type of surgical procedure.

Six patients underwent a major surgical procedure. Five of the six had orthopaedic surgery (total hip replacement, knee joint replacement, knee arthrodesis, left elbow synovectomy, and right knee arthroscopy plus chondroplasty plus synovectomy) and the sixth patient underwent a transposition of the left ulnar nerve. Four patients underwent a minor surgical procedure (dental extraction, wisdom teeth extraction, multiple teeth extraction and insertion of a Mediport).

The mean ± SD age of the 10 patients was 31.2 years ± 17.7 (range 14 to 64). The mean ± SD weight was 65.1 kg ± 12.6 (range 42.5 to 87) and the mean ± SD height 169.5 ± 6.1 cm (range 160 to 177). Nine out of ten patients were Caucasian.

For all 10 subjects, intra- and post-operative assessments were reported as excellent/good by the surgeon and the investigator, respectively. One patient had a post-operative drain. Control of bleeding from this drain was assessed as excellent/good. None of the subjects developed a post-operative haematoma. Only one subject, who underwent a left elbow synovectomy, experienced a new bleeding in this elbow on post-operative day 28. This bleeding episode was treated with 3 daily infusions, the haemostatic efficacy of which was rated as excellent.

Actual blood loss was within the predicted average and maximal range of blood loss in 9 out of 10 patients. For the remaining patient, who underwent a total hip joint replacement, actual blood loss (2900 ml) was greater than the predicted average (1000 ml) and maximal blood loss (2000 ml). Although the intra-operative efficacy should have been rated as fair, according to the Sponsor's criteria, the surgeon rated the haemostatic outcome as good.

Seven patients received concomitant treatment with antifibrinolytics. One subject used Immunate AHF two days prior to surgery. Two subjects received blood or related products (one patients received 550 ml of fresh frozen plasma, 1045 ml of Sagman (solution which consists of saline, adenine, glucose and mannitol (SAGMAN) which is added to the red blood cells) and a blood transfusion, the other patient received 500 ml of albumin).

*Discussion on clinical efficacy*

In detail, data on the haemostatic efficacy of rAHF-PFM pilot are mainly derived from Part 2 of the pivotal study. The results from this study give reassurance of the efficacy of rAHF-PFM pilot, as the haemostatic efficacy was rated 'excellent/good' in 86% of the 510 new bleeding episodes. Moreover, 81% of these bleeding episodes required only a single infusion of rAHF-PFM pilot. The effects of age and adherence to the prophylactic regimen on the rate of bleeding episodes per subject per month show no unexpected results.

The reported haemostatic efficacy of rAHF-PFM pilot/commercial in the surgical study 069902 also indicate that rAHF-PFM is effective. Taking into account that the comparability of rAHF-PFM pilot and rAHF-PFM commercial was established on a quality viewpoint and considering the results of the bioequivalence study, that demonstrated the bioequivalence of rAHF-PFM pilot and rAHF-PFM commercial, it was expected that the haemostatic efficacy of rAHF-PFM commercial would be comparable to the efficacy of rAHF-PFM pilot.

A sufficient number of patients within the continuation study could be evaluated regarding efficacy with good/excellent results and evidence for clinical efficacy was shown.

However, the outcome of efficacy during the main and supportive studies was based on an insufficient number of clinical endpoints (which have been partly implemented to the studies by protocol

amendments). As far as EC requirements are concerned the subjective evaluation of the response to treatment i.e. number, site, type of bleeding episodes are not the only parameters required to assess haemostatic efficacy. This efficacy should be assessed as well by calculating the CONSUMPTION of factor VIII, expressed as number of infusions and IU/Kg per month and per year, as well as IU/Kg per event (prophylaxis, on-demand and surgery).

Meanwhile these data were obtained with the pilot product but not yet for the commercial product and should be also presented.

**Clinical safety**

The safety of rAHF-PFM was addressed in all 4 submitted clinical studies (Table 1) [1].

The risk of the development of factor VIII inhibitors was assessed in the pivotal study, study 060102 and study 069902. Immunogenicity data were not included in the interim report of the paediatric study.

The risk of antibody development to heterologous proteins (CHO protein, murine IgG, human recombinant VWF) was only assessed in the pivotal study.

*Patient exposure*
A summary of study drug exposure data for rAHF-PFM pilot in the pivotal study and rAHF-PFM commercial in the continuation study is presented in Table 16.

The safety population in study 069901 consisted of 108 patients. Baseline characteristics of these patients are summarised in the Tables 8 and 9 of this report. The median number of exposure days to rAHF-PFM pilot in study 069901 was 117 (range 17 to 200) (Table 16). Additionally, 51 patients received one dose rAHF-PFM commercial in Part 3 of study 069901. The median dose of r AHF-PFM commercial was 50 IU/kg (range 47 to 55). The safety population in the interim analysis of study 060102 consisted of 33 patients. The safety population of study 069902 consisted of 10 patients. Finally, all 14 patients in Part 1 of study 060101 were exposed to one dose of rAHF-PFM commercial.

[1] In this report, the terms adverse drug reactions and adverse events are used according to the current EU legislation. An adverse drug reaction is defined by a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. A reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected. An adverse event does not necessarily have a causal relationship with the treatment. Finally, the term "severe" is not synonymous with serious. Severe is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe).

A definition of the terms used to express the result of the causality assessment (certain, probable/likely, possible, unlikely, conditional/unclassified, unassessible/unclassifiable) may be found on the WHO collaborating centre (http://www.who-umc.org/).

Frequencies are expressed according to the EU guideline on summary of product characteristics (Report from CIOMS Working Group III, Geneva 1995 terminology) Very common (>1/10) Common (>1/100, <1/10) Uncommon (>1/1,000, <1/100) Rare (>1/10,000, <1/1,000) Very rare (<1/10,000), including isolated reports.

**Table 16: Summary of study drug exposure in the pivotal and the continuation study**

| Parameter | rAHF-PFM pilot pivotal study | rAHF-PFM commercial continuation study |
|---|---|---|
| Exposure days: median (range) | 117 (17 - 200) | 55 (50 - 66)* |
| Total number of infusions | | |
| Pharmacokinetics# | 172 | 14 |
| New bleeding episodes | 727 | 72 |
| Prophylaxis | 11647 | 1442 |
| Total number of patients infused | | |
| Pharmacokinetics# | 107 | 14 |
| New bleeds | 83 | 13 |
| Prophylaxis | 107 | 27 |
| Number of infusions per patient | | |
| Median (range) | 118 (18 - 200) | 55 (50 - 71)* |
| Dose per infusion (IU/kg) | | |
| Prophylaxis: median (range) | 30.7 (9.4 - 110.7) | 30.7 (17.2 - 53.9) |
| Treatment new bleed: median (range) | 32.9 (8.7 - 225.8) | 34.5 (20.3 - 72.7) |
| Dose administered per month (IU/kg/mth) | 384.8 (157.9 - 20051.4) | 406.9 (262.1 - 532.7) |
| Prophylaxis: median (range) | 19.5 (0.9 - 3439.2) | 31.1 (7.65 - 225.6) |
| Treatment new bleed: median (range) | | |
| Dose administered per year (IU/kg/year) | | |
| Prophylaxis: median (range) | 4620 (1896.4 - 240748.4) | 4885 (3147 - 6395) |
| Treatment new bleed: median (range) | 233.8 (10.4 - 41292.7) | 372.8 (91.9 - 2709) |
| Cumulative dose (IU/kg): median (range) | 3,735.6 (771.0 - 9194.9) | 1678 (49 - 2833) |
| Number of lots (total) | 8 | 5 |

* The data in the summary statistics are calculated only for the 27 patients who participated in Part 2 of the continuation study. Six patients only participated in Part 1; their data are not included.
#Pharmacokinetics in the pivotal study includes the Part 2 recovery studies.

*Adverse drug reactions/adverse events*

Pivotal study 069901

Of the 108 patients who received at least one study drug infusion in the pivotal study, 101 patients reported a total of 877 adverse events, 867 of which were non-serious and 10 were serious.

Among the 867 non-serious events, 506 (58%) occurring in 88 patients were rated mild, 326 (38%) occurring in 67 patients were rated moderate, 22 (3%) occurring in 13 patients were rated severe, and 13 (2%) occurring in 2 subjects were not rated with respect to severity by the subject or investigator. The most common non-serious observed adverse events were injuries (n=252), nervous system disorders (n=141), musculoskeletal and connective tissue disorders (n=109), infections and infestations (n=86), and general disorders and administration site conditions (n=69).

A summary of all adverse experiences according to their serious/non-serious classification, severity and causal relationship with the administration of the investigational medicinal product is provided in Table 17.

**Table 17: Table detailing the adverse drug reactions/events observed in study 069901**

| Adverse reactions/events | Number of reports | Number of subjects (%)* |
|---|---|---|
| **Serious** | **10** | **6 (6)** |
| Unrelated | 10 | 6 (6) |
| Possibly related | 0 | 0 (0) |
| Probably related | 0 | 0 (0) |
| **Non-serious** | **867** | **101 (94)** |
| **Mild** | **506** | **88 (81)** |
| Unrelated | 500 | 88 (81) |
| Possibly related | 6 | 4 (0) |
| Probably related | 0 | 0 (0) |
| **Moderate** | **326** | **67 (62)** |
| Unrelated | 314 | 66 (61) |
| Possibly related | 5 | 3 (3) |
| Probably related | 7 | 2 (2) |
| **Severe** | **22** | **13 (12)** |
| Unrelated | 20 | 12 (11) |
| Possibly related | 2 | 1 (1) |
| Probably related | 0 | 0 (0) |
| **Unknown** | **13** | **2 (2)** |
| Unrelated | 13 | 2 (2) |
| Possibly related | 0 | 0 (0) |
| Probably related | 0 | 0 (0) |

*Number of subjects in subgroup do not total to 101 since a subject could have more than one AE.
Percent relative to 108. Percentages are not additive since an individual subject could have AEs in more than one category.

The adverse reactions/events that occurred in at least 5% of study subjects are summarised in Table 18. The vast majority of these events appear to be related to trauma, inter-current mild respiratory disease, or well-described complications of haemophilia. Of the 119 headaches, 49 occurred on the same day as an infusion of rAHF-PFM pilot: 17 occurred after an infusion, 7 occurred before an infusion, and 25 had unknown onset times. Five of the 17 headaches that occurred after an infusion, were associated with other signs and symptoms suggestive of an infectious aetiology. Only 2 episodes of headache in 2 subjects were considered by the investigator to be related to the administration of the product.

**Table 18: Summary of adverse reactions that occurred in ≥ 5% of the patients (study 069901)**

| System organ class | Preferred term | Nr. of reports | Nr of subjects (%) |
|---|---|---|---|
| Injury, poisoning and procedural complications | Limb injury NOS | 136 | 42 (39) |
| Nervous system disorders | Headache NOS | 119 | 40 (37) |
| Musculoskeletal and connective tissue disorders | Arthralgia | 50 | 22 (20) |
| Injury, poisoning and procedural complications | Accident NOS | 41 | 20 (19) |
| Respiratory, thoracic and mediastinal disorders | Cough | 26 | 16 (15) |
| Infections and infestations | Nasopharyngitis | 23 | 16 (15) |
| General disorders and administration site conditions | Fall | 21 | 16 (15) |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | Pyrexia | 21 | 15 (14) |
| Gastrointestinal disorders | Pharyngolaryngeal pain | 14 | 12 (11) |
| Infections and infestations | Upper respiratory tract infection NOS | 15 | 12 (11) |
| Respiratory, thoracic and mediastinal disorders | Nasal congestion | 13 | 10 (9) |
| Musculoskeletal and connective tissue disorders | Pain in limb | 15 | 9 (8) |
| Gastrointestinal disorders | Vomiting NOS | 6 | 6 (6) |
| Infections and infestations | Sinusitis NOS | 10 | 7 (6) |
| Gastrointestinal disorders | Nausea | 8 | 7 (6) |
| Injury, poisoning and procedural complications | Joint sprain | 6 | 6 (6) |
| Injury, poisoning and procedural complications | Sports injury | 23 | 6 (6) |
| Musculoskeletal and connective tissue disorders | Back pain | 7 | 6 (6) |
| Musculoskeletal and connective tissue disorders | Joint swelling | 9 | 7 (6) |
| Nervous system disorder | Dizziness (excl vertigo) | 7 | 7 (6) |
| Skin and subcutaneous tissue disorder | Contusion | 8 | 6 (6) |

nos: not otherwise specified

Twenty of the 867 non-serious reactions were considered to be related to the administration of the product: 19 (12 possibly related and 7 probably related) of the 20 non-serious reactions occurred in 7 patients who were treated with rAHF-PFM pilot and one possibly related reaction occurred in a patient receiving Recombinate. These 19 related reactions included taste perversion (n=3), headaches (n=2), fever (n=1), diarrhoea (n=1), dizziness (n=3), hot flashes (n=2), pain in upper abdomen (n=1), pain in lower chest (n=1), shortness of breath (n=1), sweating (n=1), nausea (n=1), rigors (n=1), and pruritus (n=1).

Five of these reactions (pain in upper abdomen, pain in lower chest, shortness of breath, sweating and nausea) all occurred on the same day, at the same time and in the same subject.

Twelve of the 19 reactions were moderate in severity, 5 were mild and two were severe. The two severe reactions (headache and fever) occurred in one subject. The patient was treated with 1500 mg of acetaminophen and the symptoms resolved in 2 days.

Vital signs were examined in Part 1 and Part 3, before infusion of the study drug, immediately post-infusion and 30 minutes post- infusion. The mean percent change from pre-infusion values to either the immediately or 30 minutes post-infusion time point was minimal for all the parameters evaluated following the single infusions of the two investigational medicinal products.

Continuation study 060102

Of the 33 patients who received at least one study drug infusion in the continuation study, 25 patients reported a total of 89 adverse drug reactions/adverse events, none of which were serious. Thirteen out of 89 reactions/events began during the pivotal study prior to enrolment in the continuation study.

Among the 89 non-serious adverse drug reactions/events, 64 (72%) occurring in 19 patients were rated mild, 23 (26%) occurring in 14 patients were rated moderate, and 2 (2%) occurring in one patient were severe. None of the events were judged by the investigator to be related to the infusion of rAHF-PFM commercial.

**Table 19: Summary of adverse reactions/events occurring in at least 5% of study subjects (study 060102)**

| System organ class | Preferred term | Nr. of reports | Nr of subjects (%) |
|---|---|---|---|
| Gastrointestinal disorders | Pharyngolaryngeal pain | 5 | 5 (15) |
| General disorders and administration site conditions | Pyrexia | 4 | 3 (9) |
| Infections and infestations | Lower respiratory tract infection NOS | 2 | 2 (6) |
| | Upper respiratory tract infection NOS | 3 | 3 (9) |
| Injury, poisoning and procedural complications | Limb injury NOS | 23 | 8 (24) |
| | Mouth injury | 2 | 2 (6) |
| | Sports injury | 5 | 4 (12) |
| Musculoskeletal and connective tissue disorders | Arthralgia | 3 | 2 (6) |
| Nervous system disorders | Headache NOS | 4 | 4 (12) |
| Psychiatric disorders | Depression NOS | 2 | 2 (6) |
| | Insomnia | 2 | 2 (6) |
| Respiratory, thoracic and mediastinal disorders | Cough | 4 | 3 (9) |

nos: not otherwise specified

Surgery study 069902

In study 069902, a total of 4 adverse events were reported in 3 of the 10 patients included in the interim report. All 4 adverse events (post-operative anaemia, hypoproteinemia, oral pain after dental extraction and arthralgia) were mild and assessed as unrelated to infusion of rAHF-PFM.

*Serious adverse events and deaths*
No patients died during any of the clinical studies.

Serious reactions/events were only reported in study 069901. All ten serious cases occurred during Part 2 of the study and were classified as serious since the patients were hospitalised.

Four out of 10 serious events occurred in the same subject in association with a single hospitalisation. These four events can be considered as components of a single adverse experience, leading to a total of 7 serious adverse events in 6 patients: atrial fibrillation; injuries to left elbow and abdomen resulting from a bicycle accident and blood in the urine resulting from the same bicycle accident; right upper extremity haemorrhage resulting from an assault; port-a-cath infection; elective urethral dilatation to correct an urethral stricture; head trauma resulting from a fall.

None of the serious events was considered to be possibly or probably related to the infusion of the investigational medicinal product.

*Laboratory findings*
During all parts of study 069901 changes in haematological and clinical chemistry parameters were evaluated to determine the toxicity of the investigational products rAHF-PFM pilot and rAHF-PFM commercial. The results from the analysis of these parameters did not reveal evidence of any toxicity for any of the product. The investigator judged most abnormal laboratory values to be related to the patient's underlying disease or pre-existing medical conditions.

For study 069902 haematological and clinical chemistry parameters were assessed at screening and at study termination. None of the patients had clinically significant abnormal haematological parameters at these time-points. Abnormalities in clinical chemistry parameters were considered to be related to the patient's underlying medical condition. Transiently elevated D-dimer levels were observed in 3 patients, who underwent major orthopaedic surgery. In all 3 subjects the prothrombin time remained within the normal range and the fibrinogen concentration was either normal or elevated, suggesting that disseminated intravascular coagulation was not present.

*Immunological events*

In the pivotal study blood samples for factor VIII inhibitor testing were to be drawn at screening, prior to the pharmacokinetic infusions (Parts 1 and 3), at interval study visits (every 15 ± 2 exposure days), and at study termination. According to the study procedure, every effort was made to draw blood for the factor VIII inhibitor determination at least 48 hours after the subject's last infusion. Forty-one patients (38%) had blood draws within 48 hours of a prophylactic dose.

All factor VIII inhibitor tests were performed using the Bethesda method both at the local haemostasis laboratory of the investigative site and in the study's central laboratory. If a factor VIII inhibitor (≤ 1 Bethesda Units or BU) was detected during the course of the study, the presence of an inhibitor was to be confirmed by performance of the Nijmegen modification of the Bethesda assay in the central laboratory. If a factor VIII inhibitor (Bethesda titre >1 BU and <5 BU or >5 BU) was detected during the course of the study, the presence of an inhibitor was to be confirmed in the central laboratory with a new blood sample obtained at least 48 hours after the last dose of rAHF-PFM.

No subject developed a high titre inhibitor in study 069901. One patient developed a low titre inhibitor to factor VIII during the study. The 95% confidence interval for the risk of developing a high titre inhibitor to rAHF-PFM pilot was 0 to 2.78% ('rule of three'). The 95% confidence interval for the risk of developing a low titre inhibitor was [0.02, 5.19].

The patient who developed a low titre inhibitor was a 55 year-old male with severe haemophilia A who was randomised to Part 2 and Part 3 of the study. During the 6 months prior to study enrolment the patient had been treated exclusively on-demand (15 infusions for new bleeding episodes). At the time of enrolment his baseline factor VIII inhibitor assay results were negative both in the local and in the central laboratory. Results from the recovery study at the beginning of Part 2 (June 11, 2001) showed that factor VIII levels were 122%, 114%, and 100% of normal at the 30-minute, 1-hour, and 3-hour time points, respectively, after infusion of 51.6 IU/kg of rAHF-PFM pilot. At the interval study visit for 15 exposure days (July 25, 2001) the factor VIII inhibitor test result was negative in the central laboratory (not tested in the local laboratory). The patient was subsequently withdrawn from the study. At that time he had completed 26 exposure days, including one for the treatment of a spontaneous bleeding episode. There was no clinical evidence of inhibitor development as assessed from the interval history taken from the patient. The inhibitor assay result from the 30 day exposure visit was negative in the local laboratory, but showed titres of 2 BU by the Bethesda assay and 2.4 BU by the Nijmegen assay, both performed at the central laboratory.

After termination from the study the patient returned to the study site November 13, 2001 for further evaluation. He reported to have had a severe ankle bleeding since his visit in September that was successfully treated with 2 infusions of Recombinate. A new sample was sent to both the local and the central laboratory for inhibitor testing and both results were negative. In vivo recoveries of factor VIII at 1 and 3 hours after infusion of 50 IU/kg Recombinate were 140% and 120%, respectively. A full evaluation for the presence of a circulating anti-coagulant antibody was inconclusive.

In study 060102 blood samples for factor VIII inhibitor testing are to be drawn at screening, at interval study visits during Part 2 (first visit after 15 ± 2 exposure days, subsequent visit three months later), and at study termination. All factor VIII inhibitor tests are to be performed using the Bethesda method both at the local haemostasis laboratory and in the study's central laboratory. If a factor VIII inhibitor is detected during the course of the study, the presence of the inhibitor is to be confirmed by performance of the Nijmegen assay in the central laboratory. If the Nijmegen assay detects an

inhibitor, the assay will be confirmed in the central laboratory with a new blood sample obtained at least 48 hours after the last dose of rAHF-PFM.

None of the 27 evaluable patients had developed a detectable inhibitor of any kind at the time of the interim analysis.

In study 069902, factor VIII inhibitor testing is to be performed at screening and at study termination. At any time during the study, inhibitor testing should be performed if a patient does not respond to rAHF-PFM therapy or has excessive unexplained bleeding episodes.

None of the subjects had any factor VIII inhibitors at study screening and at study termination.

ELISA for detection of antibodies to CHO protein, murine IgG and recombinant human VWF were to be performed at screening and at each interval study visit in Part 2 of study 069901. The ELISA tests utilised for measurement of antibodies to CHO and murine IgG were modified from those utilised in the clinical development plan for Recombinate. The applicant modified the assays to allow for actual titration of antibody in test samples. Results from these assays showed that all patients had detectable anti-CHO and anti-murine IgG in all serum samples tested, including baseline samples. This precluded the use of the originally planned classification scheme ('no antibody response, pre-existing antibody response, new onset or anamnestic antibody response'), which was also utilised to stratify patients in the Recombinate trials.

As an alternate approach the results of the assays were examined for a trend over time using a linear regression. The regression model of antibody level on time-on-study was estimated for each subject and a hypothesis of zero slope tested using a t-statistic. Additionally, graphs of antibody levels with nominal exposure days were generated for all subjects having more than one data point. For patients with evidence of an upward trend in heterologous anti-CHO or anti-murine antibody levels, the serologic findings were interpreted in relationship to the occurrence and type of adverse reactions/events reported.

A total of 108 patients had serum samples tested for anti-CHO protein. For two out of 108 patients only baseline samples were submitted. Therefore results from one or more treatment samples are available for 106 patients who were followed on study over a period of 17 to 200 rAHF-PFM pilot exposure days.

Levels of anti-CHO protein in baseline samples (n=102) varied over a range of 21 to 417 µg/mL. A graphical analysis of longitudinal anti-CHO protein levels for each patient did not demonstrate clear evidence of an upward trend in antibody levels as a function of increasing exposure to rAHF-PFM. For 74 (70%) of the patients the level of anti-CHO protein antibody in the last serum sample was the same or lower than that observed in the baseline sample. A significant upward trend was observed in only one patient, whose anti-CHO concentration increased from 83 µg/mL at baseline to 118 µg/mL at 75 exposure days (slope:0.18; p=0.004). This patient experienced 13 adverse events, 5 of which concerned an orthopaedic problem and 6 of which were consistent with an upper respiratory infection. One event was an episode of brief itching at the site of an infusion of rAHF-PFM pilot and one was a headache lasting 4 hours following infusion with Recombinate. None of the events were consistent with an allergic or hypersensitivity response to the study medication.

A total of 108 patients had serum samples tested for anti-murine IgG. Results from one or more treatment samples are available for 106 patients who were followed on study over a period of 17 to 200 rAHF-PFM pilot exposure days.

Baseline levels of anti-murine IgG (n=102) varied from 129 to 28,444 ng/mL. No subject demonstrated clear evidence of an upward trend in antibody levels as a function of increasing exposure to rAHF-PFM.

For 76 (72%) of the patients the level of anti-murine IgG antibody in the last serum sample was the same or lower than that observed in the baseline sample. Three subjects exhibited a significant trend

towards increasing antibody levels and one patient exhibited a sharp increase in anti-murine IgG levels coincident with the 75th and 90th exposure day study visits. The latter patient did not report any adverse event during his participation in the study. None of the events experienced by the other 3 patients was consistent with an allergic or hypersensitivity response to the study agent.

Results of anti-VWF assays were available on one or more samples from 104 patients. No patient participating in study 069901 exhibited evidence of anti-VWF antibody in any serum sample tested.

Finally, the assessment of the Quality part of the Application revealed a systematic decrease in factor VIII-potency and specific activity of the rAHF-PFM lots with increasing storage time and temperature. The decrease in factor VIII potency during storage is a marked difference between rAHF-PFM and Recombinate, which might be linked to the fact that rAHF-PFM is albumin-free. The decrease in potency raises the possibility that the structural integrity of the factor VIII molecule is affected during storage resulting in the formation of degradation products which might attribute to immunogenicity. The applicant should have addressed this issue by providing immunogenicity data in patients who were treated with batches of rAHF-PFM commercial near the end of their expiry period.

The age of rAHF-PFM lots at the time of infusion was divided into six-month intervals, representing the four quartiles of the rAHF-PFM lot age (the claimed shelf-life of rAHF-PFM is two years from the date of manufacture).

In study 069901, 108 subjects received a total of 3932 infusions (29% of all infusions) of rAHF-PFMpilot with ages ranging from 13 to 18 months. In addition, 50 subjects received a total of 1496 infusions (11% of all infusions) of rAHF-PFMpilot with ages ≥ 19 months. One low titre inhibitor was observed in study 069901 after infusion of product with an age of 13 to 18 months. No inhibitors were observed after infusion of product with an age months ≥ 19 months or after infusion of study product with an age < 13 months.

The subject who developed an inhibitor received two different lots of rAHF-PFMpilot. This patient received 16 infusions of the first lot with ages ranging from 232 days (7.6 months) to 317 days (10.4 months) relative to manufacturing date.

He then received 10 infusions of a different lot with ages ranging from 517 days (17.0 months) to 554 days (18.2 months). As previously reported, this subject was withdrawn from the study by the investigator due to non-compliance with the prophylactic treatment regimen at this study visit, prior to the receipt of the inhibitor assay results for the sample obtained at that visit. After receiving a positive low responder inhibitor result for the subject, the investigator called him for a test infusion with Recombinate rAHF. The investigator reported that in-vivo recovery of factor VIII at the 1- and 3-hour post-infusion time points was within the normal range, suggesting that this subject may have developed a transient inhibitor. Although samples drawn 8 weeks after the inhibitor was first detected were negative at the central laboratory and factor VIII in-vivo recoveries were similar to or higher than those estimated at enrolment, the factor VIII inhibitor could not formally be classified as transient, because these tests occurred after the subject's withdrawal from the study (see also response to question number 18).

No inhibitor formation has been observed in studies 069902 (surgery study), 060101 (paediatric study), and 060102 (continuation study).

Overall, the vast majority of both pilot and commercial scale rAHF-PFM products used in the clinical studies were older than 7 months. No inhibitors were observed after infusion of product with an age ≥ 19 months or after infusion of study product with an age < 13 months, whereas the only inhibitor was seen in the quartile 13 to 18 months.

Nevertheless this question refers to a possibility that the integrity of the factor VIII molecule is affected during storage resulting in the formation of degradation products which may contribute to immunogenicity. No increase in immunogenicity with batches near the end of their expiry period (yet)

was observed and the applicant did not investigate a possible formation of degradation products of factor VIII.

*Discussion on clinical safety*

Meanwhile the safety profile of rAHF-PFM commercial was evaluated in 42 patients in study 060102 in the second interim report. A total of 99 AEs were reported in 27 subjects, 5 events in 3 subjects were reported as serious. None of the serious adverse events were considered to be related to the infusion of rAHF-PFM commercial. Seven out of the remaining 94 adverse drug reactions were possibly or probably related to the administration of the product.

The applicant also has evaluated 65 subjects in the continuation study who had at least 50 exposure days regarding immunogenicity, especially inhibitor development (major clinical objection). None of these patients developed an inhibitor.

In summary, the safety assessments demonstrated that rAHF-PFM did not reveal any unknown safety signal.

Although the results are encouraging there are no sufficient safety data on previously untreated patients (PUPs patients) younger than 6 years and administration via continuous infusion mode which led to changes in the SPC. For authorisation of these aspects more data on the intended use is needed, (see "Note For Guidance On The Clinical Investigation Of Recombinant Factor VIII and IX Products", CPMP/BPWG/1561/99).

Also it is desirable that besides the view on inhibitor development there is a further focus on the increase of antibody levels against heterologous proteins due to the recombinant origin of the product (see follow up measures).

**Overall conclusions, benefit/risk assessment and recommendation**

**Quality**

The newly developed, protein-free fermentation process and the modified purification process for ADVATE are sufficiently described and adequately monitored by in-process controls. Extensive validation of the manufacturing process for the drug substance at commercial scale demonstrated the production of drug substance of consistent and comparable quality in both designated manufacturing suites. The drug substance has been extensively characterised showing the comparability of pilot scale and commercial scale lots by using state of art techniques. Virus safety with regard to enveloped viruses was demonstrated. Compliance with the TSE guideline has widely been shown. The final drug product is formulated in a protein-free buffer containing trehalose as stabiliser and is adequately controlled using validated methods.
In summary, on the basis of the data provided and the agreed follow-up measures, the quality of the product is satisfactory.

**Preclinical pharmacology and toxicology**

The non-clinical development strategy was to demonstrate the comparability of rAHF-PFM to Recombinate rAHF. This was accomplished by comparing the physico-chemical, pharmacodynamic, pharmacokinetic and toxicological profiles of Recombinate rAHF and rAHF-PFM.

The non-clinical testing programme for ADVATE raised no safety concerns.

**Efficacy**

ADVATE is a recombinant anti haemophilic factor VIII, made by a plasma/albumin free method. The new method does not employ any human or animal-derived additives in the cell culture, purification or formulation of the final product. The only other proteins present in the final product are trace quantities of murine immunoglobulin, host cell (i.e. CHO) protein and recombinant human von

Willebrand factor. This virtually eliminates any risk of transmission of human blood-borne viruses or other adventitious agents that could, in theory, be introduced by the use of animal proteins.

In clinical studies plasma levels and pharmacokinetics of ADVATE (commercial production) were almost sufficiently investigated by the applicant. Based on reliable pharmacokinetic trials, the values of AUC0-48 (1494 IU*h/dl), Cmax (123 IU/dl) and t1/2 (11.7 h) after application of 50 IU/kg ADVATE comply with plasma-derived or other recombinant FVIII products. Further, these values document that the achieved amount of FVIII and the maintenance of plasma levels is as expected according to the posology in the SPC.

In terms of efficacy data like number of infusions needed and estimated treatment outcome, ADVATE is effective to prevent and control bleedings in previously treated patients with severe haemophilia A.

**Safety**

The incident rates for the most common adverse events in previously treated patients, i.e. dysgeusia, headache, dizziness and hot flushes, rash/pruritus, injection site reaction, chest pain, haematuria and unusual taste in the mouth, indicate that drug-related adverse events were similar in nature and number to those in clinical trials with other FVIII products. The amount of allergic reactions and inhibitor development is not unusual compared to other recombinant products. However, a more thoroughly assessment of the adverse event pattern cannot be performed until more patients have been treated with ADVATE.

Concerning previously untreated patients and children less than six years, studies are planned and commencing, and the company will submit further data on these populations.

There has been one major safety concern regarding immunogenicity due to possible differences between pilot batches and commercial scale batches, which could be sufficiently enlightened.

**Benefit/risk assessment**

In order to answer a number of unresolved issues identified during the procedure, the CPMP considered that concerning the clinical pharmacokinetics:

- The applicant committed himself to present appropriate pharmacokinetic data also for the commercial product, using a minimum of two additional rAHF-$PFM_{commercial}$ lots obtained in the post-marketing study.

In addition, on a clinical efficacy viewpoint:

- The applicant committed himself to a further differentiated evaluation of the continuous infusion mode within the surgical study.

Finally, in order to better characterise the safety profile of ADVATE:

- The applicant committed himself to a further differentiated evaluation of the continuous infusion mode within the surgical study.
- The applicant committed himself giving detailed data on any allergic/immunological event within the PSURs (focussing on PUP/PTP inhibitors and on antibodies against heterologous proteins).
- The applicant committed himself to summit reassuring data to the possibility of degradation products during storage, which may contribute to immunogenicity.

Data provided by the MAH and supplemented as requested in the List of Questions show that the risk of experiencing an (serious) adverse event can be considered small in relationship to the benefit in therapy with this newly formulated FVIII product in at least previously treated patients.

Therefore the Benefit Risk Assessment for ADVATE is considered to be positive

**Recommendation**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of ADVATE in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) was favourable and therefore recommended the granting of the marketing authorisation.