European Medicines Agency

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ASSESSMENT REPORT
FOR
REFACTO AF

International Nonproprietary Name:
moroctocog alfa

Procedure No. EMEA/H/C/II/59-68

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

II. STEPS TAKEN FOR THE ASSESSMENT

Submission date:	16 May 2007
Start of procedure:	22 July 2007
Rapporteur's preliminary assessment report circulated on:	26 July 2007
BWP discussion:	12 September 2007
BPWP Discussion	September 2007
1st CHMP Request for supplementary information and extension of timetable adopted by the CHMP on :	20 September 2007
MAH's responses submitted to the CHMP on :	21 January 2008
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	29 February 2008, updated 13 March 2008
BPWP Report	February 2008
BWP Report :	12 March 2008
2nd CHMP Request for supplementary information and extension of timetable adopted by the CHMP on :	19 March 2008
MAH's responses submitted to the CHMP on :	28 April 2008
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	2 June 2008
BWP Report:	18 June 2008
BPWP Report	June 2008
3rd CHMP Request for supplementary information and extension of timetable adopted by the CHMP on :	26 June 2008
MAH's responses submitted to the CHMP on :	27 August 2008
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	8 October 2008
BPWP Report	October 2008
PhVig Discussion	October 2008
4th CHMP Request for supplementary information and extension of timetable adopted by the CHMP on :	23 October 2008
MAH's responses submitted to the CHMP on :	17 November 2008
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	1 December 2008
BPWP Report	27-28 November 2008
CHMP Opinion	18 December 2008

III. SCIENTIFIC DISCUSSION

3.1. Introduction

A comprehensive set of variations have, in parallel, been submitted for ReFacto, concerning various changes throughout the manufacturing process of drug substance and drug product.

The variations submitted are the following:
EMEA/H/C/232/II/59 Use of peptide resin instead of MAb resin
EMEA/H/C/232/II/60 Introduction of virus retaining filter
EMEA/H/C/232/II/61 Increase in batch size for 2000IU strength
EMEA/H/C/232/II/62 Qualification of second lyophilizer
EMEA/H/C/232/II/63 Drug product specification changes
EMEA/H/C/232/II/64 Head space change (nitrogen overlay)
EMEA/H/C/232/II/65 Drug substance and drug product assay changes
EMEA/H/C/232/II/66 Potency standard calibration change
EMEA/H/C/232/II/67 Change in drug product container closure system
EMEA/H/C/232/II/68 Albumin free cell culture process and consequential changes in the substance manufacturing process

About the product
ReFacto is a B-domain deleted recombinant FVIII (BDDrFVIII) product that was granted a marketing authorisation by the European Commission on 13 April 1999 for the treatment and prophylaxis of bleeding in patients with haemophilia A. Haemophilia A is an X-linked recessive bleeding disorder caused by a partial or total deficiency of functionally active coagulation factor VIII (FVIII). ReFacto is a purified protein produced by recombinant DNA technology. ReFacto, as per the initial authorisation, is a monoclonal antibody purified, solvent-detergent treated, and albumin-free formulated BDDrFVIII.

Clinical development programme
The clinical development programme to support the approval of moroctocog alfa (AF-CC) for use in patients with hemophilia A was initiated in 2002 and included 2 pivotal studies conducted with moroctocog alfa (AF-CC) drug substance produced at the commercial site (Biovitrum, Sweden) but lyophilized at a non-commercial site (Andover, US) and 3 supportive studies conducted with a moroctocog alfa (AF-CC) supplied by a pilot plant. These studies were intended to establish the bioequivalence of moroctocog alfa (AF-CC) and ReFacto, the bioequivalence of moroctocog alfa (AF-CC) and a currently marketed full-length Factor VIII product, Advate, and also to establish the initial efficacy and safety profile of moroctocog alfa (AF-CC) when used for prophylaxis, on demand treatment, and surgical treatment.

The assessment of the clinical documentation did not raise concerns about compliance with GMP or GCP. Based on the assessment no inspections were regarded as necessary.

Licensing status in other countries
The labelled potency of ReFacto AF is based on the European Pharmacopoeial chromogenic substrate assay, in which the manufacturing potency standard has been calibrated to the WHO International Standard using the chromogenic substrate assay. Another moroctocog alfa product approved for use outside Europe has a different potency assigned using a manufacturing potency standard that has been calibrated to the WHO International Standard using a one-stage clotting assay; this product is identified by the tradename XYNTHA. Due to the difference in methods used to assign product potency of XYNTHA and ReFacto AF, 1 IU of the XYNTHA product (one-stage assay calibrated) is approximately equivalent to 1.38 IU of the ReFacto AF product (chromogenic assay calibrated).

The ReFacto AF product, with calibration of the working potency standard by the chromogenic substrate assay, is intended for the EU market and for regions in close geographic proximity, such as Switzerland and Russia. In addition, the Australian Therapeutic Goods Administration has requested the chromogenically aligned product, ReFacto AF. The MAH will amend the approved application for

the Xyntha product in New Zealand as appropriate to substitute the chromogenically aligned product for continuity of product supply of ReFacto AF in this region. The Xyntha product, with calibration of the working potency standard by the one-stage assay versus the WHO 7th IS, is approved and will be marketed in the US and Canada.

3.2. Chemical, pharmaceutical and biological,

Background and rationale for the variations

The MAH, in May 2007 applied for several changes to the manufacturing process of ReFacto, including active substance (moroctocog alfa) manufactured using an albumin-free cell culture process (moroctocog alfa [AFCC]). Several other modifications of the manufacturing process covering almost the entire drug substance and drug product processes were applied for to improve robustness and productivity.

The ReFacto AF-CC modified manufacturing process used the original cell line for manufacture of ReFacto to generate a new master cell bank and removed the use of human serum albumin (HSA) from the cell culture process. To minimize potential product impact, the same production cell line that had been used for the original ReFacto cell banks was adapted to grow in HSA-free medium and laid down in new cell banks, thus eliminating the bovine proteins present in the current cell banks (fetal bovine serum in the master cell bank (MCB) and working cell bank (WCB). Thus, the new master cell bank was not derived from a new transfection.

For the drug substance purification process the monoclonal antibody capture step has been replaced with a capture step with a chemically synthesised peptide affinity ligand, replacing the murine monoclonal antibody sepharose resin. This eliminates a potential risk of viral contamination associated with the murine monoclonal antibody and its manufacture.

In addition to the removal of HSA from the cell banks and fermentation process a virus retaining filter has been introduced in the purification process in order to further improve the overall viral safety of the product.

Finally a potency standard calibration change has been proposed. It is proposed that the drug substance and drug product potency is assigned with a reference material calibrated against the current 7th International WHO Standard for FVIII products. The assay for the calibration remains the Ph. Eur chromogenic substrate assay, in line with the assay for potency assignment of the drug substance and drug product potency and in accordance with Ph. Eur.

A programme was designed to assess the structural and functional comparability of moroctocog alfa drug substance made from the current process and the AF-CC moroctocog alfa drug substance made from albumin-free cell culture process.

There are no changes to the drug product formulation. Drug product manufactured using the drug substance from the moroctocog alfa AF-CC process has been qualified in a second, functionally identical lyophilizer, will use tubing vials (versus the current molded vials) with a compatible stopper, and will incorporate a nitrogen overlay instead of a vacuum. Comparability of drug product made at the clinical (Wyeth, Andover fill and finish facility) and commercial (Wyeth Farma) drug product fill sites has been established through process comparison, lyophilized powder characterization, structural and biophysical characterization of the active ingredient, stability studies and results of routine release assays, which include biochemical analyses.

In view of the major changes applied to the manufacturing of ReFacto, the MAH submitted a fully revised module 3, covering the drug substance and drug product manufacturing process.

<u>Overall discussion:</u>

During the assessment of the submitted variations (EMEA/H/C/232/II/59-68), three main areas were identified as major concerns for which additional data were requested from the MAH.

These areas related to:

- The use of non-commercial site for manufacture of non-clinical and clinical supply,
- Change in N-linked oligosaccharide profile of AF-CC moroctocog alfa compared to current moroctocog alfa and
- The proposed potency calibration.

With the responses to the CHMP Requests for Supplementary Information (RSI), the Applicant provided an extensive amount of information and data, together with a fully updated Module 3 addressing satisfactorily all remaining issues and earlier major objections.

1) **Non-commercial sites**
All AF-CC moroctocog alfa materials used in the non-clinical- and main part of the supportive clinical studies (305, 306 and 307), were manufactured at sites different from the commercial AF-CC drug substance manufacturing site (Biovitrum, Stockholm) and AF-CC drug product site (Wyeth Farma, Madrid). Further information and data were requested on these non-commercial sites to conclude whether AF-CC material is representative for the commercial AF-CC material.
All data provided to address this request, support that AF-CC drug substance and drug product manufactured at the different non-commercial sites are comparable to each other and with the drug substance manufactured at the commercial site and current ReFacto, apart from the N-linked oligosaccharide differences described below. The non-commercial site issue is resolved.

It was noted that potency is one highly important parameter in the comparability exercise. However, potency data are not easily compared as they have been generated by use of reference standards available at time of manufacture (6^{th} or 7^{th} IS) together with different calibration approaches (further discussed below). However, for the purpose of demonstrating comparability of AF-CC sites and material to the current ReFacto, the potency results and subsequent specific activity values for representative ReFacto lots were revised/recalculated to reflect the proposed commercial AF-CC CS-calibrated potency standard to the 7^{th} IS. These data show comparable results among sites also with regard to potency/specific activity.

Viral safety
One other Major objection was raised based on the non-commercial site issue, which were related to the viral safety evaluation. The viral safety evaluation of the AF-CC drug substance process clearly demonstrated acceptable viral safety of the process but as it was conducted with material from the non-commercial Andover Pilot Plant, no final conclusion on the validity could be drawn. Based on the above conclusion on the various sites, the virus validation is concluded to be acceptable and the issue resolved.

2) N-linked oligosaccharide profile
The observed overall sialylation state of AF-CC moroctocog alfa compared to current moroctocog alfa needed initially to be further confirmed and addressed. The requested data for AF-CC drug substance further supported the observed shift in glycosylation profile. AF-CC material has a slightly lower amount of non- and mono-sialylation and a slightly higher amount of di- and trisialylation compared to current material.

It should be noted that the "AF-CC sialylation phenotype" is intrinsic to the AF-CC process and has been consistent throughout the AF-CC development.

The higher level of sialylation implied by the N-linked oligosaccharide profile of moroctocog alfa AF-CC could theoretically result in a slight increase in recovery or elongation of half-life. Non-clinical-, clinical- and PK data has confirmed, that this is not the case.
This issue is therefore considered resolved.

3) Potency calibration
The current ReFacto potency reference standard is chromogenic substrate assay calibrated, against the 6^{th} IS, and drug substance and drug product is potency released by chromogenic substrate assay.

Originally, the intention of the Applicant was to determine the AF-CC drug substance and drug product potency by use of a 7^{th} International Standard (IS) FVIII:C Concentrate (99/678) calibrated potency reference. This approach was acceptable, as the 6^{th} IS has been replaced with the 7^{th} IS. However, the Applicant further intended to use the one-stage assay for the calibration. This approach was chosen by the Applicant, because the use of one-stage assay is more in line with clinical

measurements of the ReFacto activity using a one-stage assay. Release of AF-CC drug substance and drug product would be conducted by chromogenic assay in compliance with the European Pharmacopoeia. The use of one-stage assay for calibration of the potency standard against the 7th IS is not in compliance with the European Pharmacopoeia. Calibration of a reference standard should be conducted with the same assay as the release assay.

The Applicant proposed to re-calibrate the AF-CC potency reference material against the 7th International Standard (IS), by use of chromogenic substrate assay. The potency measure of AF-CC is therefore done in the same way as for current ReFacto, with the exception that the 6th IS is replaced by 7th IS.

The 6th IS was a full-length recombinant preparation whereas the 7th IS is a high-purity plasma-derived FVIII standard, and the two International Standards thereby different in nature. It is well known that potency measures of different FVIII products can give rise to discrepancy in results, depending on which International Standard is used for the measurement (5th, 6th or 7th IS). Further, it is also known that the potency measure of FVIII products may be dependent on the assay used. For ReFacto there is a discrepancy between the results obtained for moroctocog alfa in the CS assay and the OS assay of around 40%, with the OS assay measuring the lowest potency. As a consequence of the originally proposed change from CS to OS calibration of the AF-CC reference material, together with a change from 6th to 7th IS, which further adds to the discrepancy in results, the Applicant considered that around 50-65% more protein should be added to the drug product vials to comply with the labelled potency.

With the new proposal to use chromogenic substrate assay for calibration of the potency standard, the only factor giving rise to discrepancy in potency results is the change from 6th to 7th IS. For moroctocog alfa the different nature of 6th and 7th IS leads to a 14% difference in potency measure. As a consequence addition of around 14% more protein in the AF-CC drug product vials, compared to the current ReFacto vials, is expected. Addition of extra protein, as a consequence of a change in International Standard is acceptable and in line with previous experiences with ReFacto and other FVIII products. Several investigations and measurements of current moroctocog alfa and AF-CC moroctocog alfa against the re-calibrated CS potency reference, support that the necessary change in protein content is due to the replacement of the 6th IS with the 7th IS and is not caused by the shift from the current manufacturing process to the AF-CC process.

Potency and specific activity release specifications for AF-CC drug substance and drug product have been re-calculated to comply with the CS-calibration approach.

Based on discussion at the March Biologics Working Party (BWP) meeting, the CHMP concluded that in view of the experience of variability in Factor VIII potency measurements and the specific history of recalibration of ReFacto reference standard, further involvement of OMCL laboratories for the calibration of the AF-CC reference standard was considered necessary. It was recommended by the CHMP that this potency confirmation of the AF-CC potency standard took place within the Sampling and Testing Programmeme 2008 for ReFacto with RIVM (NL) and MPA (SE) as OMCLs appointed by EDQM.

The appointed OMCLs labs by EDQM were RIVM (NL) and MPA (SE). Testing was carried out in April, within the, already scheduled, Sampling and Testing Programmeme 2008 for ReFacto. The reporting of results was submitted to the EMEA at the end of May 2008 and satisfactory conclusion was reached by the CHMP in their June 2008 meeting after adoption of the BWP favourable recommendations.

The OMCL report concluded that:

"Potency obtained by testing OMCLs for batches of finished products tested are coherent with potency values claimed by the MAH when using batch TS20040265 as reference standard and the method registered in the MAH marketing authorisation file.

Based on the results reported by the two testing OMCLs there is currently no indication showing that the potency value claimed by the MAH for new internal standard batch TS20040265 is incorrect when using the method registered in the MAH marketing authorisation file.

In addition to the EDQM request for testing, when the RIVM-BMT (NL) compared Coamatic (routine method at RIVM) potency results with Coatest (method used by the MAH) results, RIVM reported different results. Such discrepancy was not found by the MPA Swedish colleagues in their laboratory. The discrepant results (Coamatic vs. Coatest) is not included in the OMCL report. It was noted that the RIVM routine method is not validated for use with ReFacto. This finding will be further investigated as a follow-up measure: The MAH committed to solve the issues with ReFacto potency testing and work together with the Rapporteur (DK) and interested OMCLs.

Reference material

On request more information was provided on the AF-CC reference standard used over the time of development of the AF-CC process. The information includes site of production and all available data on release testing as well as additional characterisation studies.

Based on the conclusion reached on the non-commercial site issue (see above), that the site of production is without effect on the quality of the AF-CC material produced, together with the updated data package provided on the various AF-CC reference standards, it can be concluded that the reference standards used for the manufacture of clinical material are representative for commercial material. The issue is considered solved.

Overall conclusion:

Based on the review of the data on quality, the variation applications EMEA/H/C/23/II/59-68, for ReFacto (moroctocog alfa), in the treatment of haemophilia A, were approved.

3.3 Toxico-pharmacological aspects

The non-clinical programme for ReFacto AF includes a pharmacology study conducted in haemophilia A dogs comparing the pharmacodynamic effects of ReFacto AF and ReFacto. Moreover, a GLP-compliant 4-week toxicity study has been conducted in monkeys. In addition, a study was conducted in rats to evaluate the acute toxicity of the novel TN8.2 affinity ligand used in the moroctocog alfa process. Considering that the pharmacologic, pharmacokinetic and safety profile of ReFacto was characterised in the original application (EMEA/H/C/232), the extent of the non-clinical programme for ReFacto AF is considered adequate.

Overall, the pharmacodynamic effects of ReFacto and ReFacto AF were comparable in Haemophilia A dogs. A 29/30-day I.V. repeat-dose toxicity study was conducted in Cynomolgus monkeys daily administered ReFacto AF. For comparison, the report from a study with a similar design included in the original ReFacto marketing authorisation application has been submitted. A reduction of around 10% in red blood cell count accompanied by a 50% increase in reticulocytes was observed in females administered 50 I.U./kg ReFacto AF. Moreover, atrial oedema and uterus haemorrhage was detected in 2/3 and 1/3 females, respectively. No reduction in Factor VIII activity was observed at this dose level. The no-observed-adverse-effect level (NOAEL) for ReFacto, however, was established at 50 I.U./kg. Adjusting for the new method for establishment of potency that was initially proposed (one-stage assay), 50 I.U/kg corresponds to the average clinical dose administered (29 I.U./kg). The adverse effects observed at higher dose levels can all be ascribed to the generation of anti-ReFacto/ReFacto AF antibodies and Factor VIII inhibitors, which reduces Factor VIII activity and thereby interferes with the coagulation pathway. Sampling for neutralising antibodies was not performed on identical days for ReFacto AF and ReFacto thus it is difficult to assess whether the development of immunogenicity was comparable. Still, no major differences in immunogenic potential were observed.

The differences in the NOAELs determined in the moroctocog alfa (AF-CC) and ReFacto studies in monkeys can be attributed to slight differences in the onset and consequences of immune responses to the endogenous FVIII in the 2 studies. In clinical studies with moroctocog alfa (AF-CC), the incidence of immune responses has been similar to that of ReFacto.

The synthesized peptide ligand used in the ReFacto AF purification process, may potentially leach from the chromatographic resin into the product stream. Therefore, the possible effects of the peptide ligand on the clotting activity of rat plasma, human plasma, and factor VIII deficient human plasma containing ReFacto AF were evaluated *in vitro*. The results indicate that it is unlikely that the peptide ligand would interfere with normal clotting in a physiologic setting. The single dose toxicity of 0.6 mg/kg the peptide ligand I.V. was evaluated in female Sprague-Dawley rats. Potentially treatment-related effects consisted of decreases (10%) in red blood cells counts, haematocrit and haemoglobin 2 and 15 days following the administration of a single dose of the peptide ligand to rats. Moreover, a decrease in white blood cell counts (around 30%) was observed in the peptide ligand treated animals relative to the control group.

However, it is unlikely that patients treated with moroctocog alfa (AF-CC) purified using the peptide ligand have any risk of haemolytic effect due to the slight decreases in haematological parameters observed in the acute toxicity study using a large exaggerated dose (>12 million times the clinical dose based on body mass). Changes are probably incidental due to inter-animal variability.

The 4-week toxicity study in monkeys was GLP compliant whereas the acute toxicity assessment of the novel affinity ligand was performed as a non-GLP study. The latter is considered acceptable by the CHMP since it may be viewed as a follow-up study.

3.4 CLINICAL ASPECTS

3.4.1 Comparability of ReFacto and ReFacto AF

The objective of the process modifications to the moroctocog alfa drug substance manufacturing process was to adopt the minimal set of changes that eliminated all animal- and human-derived proteins, while maintaining product quality and purity. Additional changes were made to optimize product expression, yield, and purity. The moroctocog alfa (AF-CC) albumin-free process was developed subject to the constraint that there would be no significant changes in moroctocog alfa product characteristics, thus maintaining comparability of moroctocog alfa (AF-CC) to moroctocog alfa produced by the current registered process.

The changes in manufacturing process for moroctocog alfa (AF-CC) drug substance were implemented prior to study 3082B1-305-GL (study 305) and are fully reflected in pharmacokinetic (PK) study 305 and in safety and efficacy study 3082B1-306-GL (study 306). Study 305, using drug substance and drug product manufactured at the MAH United States (US) manufacturing facilities, demonstrated bioequivalence of moroctocog alfa (AF-CC) and ReFacto, the currently licensed product. Manufacturing sites for moroctocog alfa (AF-CC) drug substance were subsequently transferred from the US to Stockholm, Sweden, after studies 305 and 306; however, the process design and scale of manufacturing were not changed during this transfer.
Furthermore, comprehensive comparability studies performed on moroctocog alfa (AF-CC) drug substance and drug product demonstrated that all sources of moroctocog alfa (AF-CC) drug substance and drug product were functionally and biochemically equivalent.

The approach for assigning the potency of moroctocog alfa (AF-CC) has been revised during the development of ReFacto AF. Studies 305, 306 and 307 used the same approach as for the current ReFacto (i.e. the chromogenic substrate (CS) assay was used to calibrate the moroctocog alfa (AF-CC) potency standard relative to the WHO 6th International Standard (WHO 6th IS). For studies 310 and 311, the one stage clotting (OS) assay was used to calibrate the moroctocog alfa (AF-CC) potency standard relative to the WHO 7th International Standard (WHO 7th IS). Subsequently, the chromogenic substrate (CS) assay relative to the WHO 7th IS was established as the method for calibrating moroctocog alfa (AF-CC) potency standards intended for use in commercial manufacturing operations for Europe.

In some regions of the world, another moroctocog alfa product identified by the tradename XYNTHA is marketed. This uses the one stage clotting (OS) assay to calibrate the moroctocog alfa (AF-CC) potency standard relative to the WHO 7th International Standard (WHO 7th IS). Due to the difference in methods used to assign product potency, 1 IU of the XYNTHA product is approximately equivalent to 1.38 IU of the ReFacto AF product.

The table in section 3.4.2.2 provides an overview of the clinical studies and includes information on the sites of active substance manufacture and the potency calibration used.

The evaluation of moroctocog alfa (AF-CC) in study 310, using the drug product with highest protein content per IU provided robust clinical assurance that moroctocog alfa (AF-CC) is a safe treatment option for hemophilia A. The data from study 310 demonstrate that at the relatively higher protein per IU exposures over time, there was no evidence for new safety concerns relative to currently licensed ReFacto, including inhibitor development or thrombogenicity. ReFacto (AF-CC) manufactured using the OS calibrated potency standard was evaluated in clinical study 3082B2-310-WW (study 310).
Following the incorporation of the CS assay for use in potency standard calibration, moroctocog alfa (AF-CC) to be used in the European Union (EU) has approximately 27% less protein content per IU relative to the OS aligned moroctocog alfa (AF-CC) drug product used in study 310. However, commercial moroctocog alfa (AF-CC) will still have approximately 14% more protein content per IU relative to the currently licensed ReFacto product. This is a consequence of the alignment of moroctocog alfa (AF-CC) potency with the WHO 7th IS compared to ReFacto, which has potency aligned relative to the WHO 6th IS (see Table 45-1 below).

Thus, moroctocog alfa (AF-CC), now known as ReFacto AF and approved for use in the EU has a protein content per IU that is intermediate between the currently licensed original ReFacto and the material used in study 310. It is noteworthy that the original ReFacto clinical trial data were generated with ReFacto drug product prior to a recalibration of potency in 2003. Those original pivotal data were generated with original ReFacto that had even less (approximately 12% less) protein per IU than currentlythe marketed ReFacto.

Table 45-1: Estimated Protein Content for ReFacto and Moroctocog alfa (AF-CC)

Potency Standard Calibration	**WHO 6th IS CS calibrated standard**	**Revised WHO 6th IS CS calibrated standard**	**WHO 7th IS CS calibrated standard**	**WHO 7th IS OS calibrated standard**
Material	Original ReFacto[a] and Moroctocog alfa (AF-CC) Study 306 Material[b]	Current ReFacto and Moroctocog alfa (AF-CC) Study 306 Material	Moroctocog alfa (AF-CC) Commercial Material	Moroctocog alfa (AF-CC) Study 310, 311 Material
Protein Content per 1000 IU (ug)	73	83	95	131

The consistency of the clinical efficacy outcomes over time is anticipated based on the wide range of individualized dosing used in the various treatment settings in the clinic, as demonstrated in study 310 (efficacy dosing data: median dose = 30.2 IU/kg, range = 6.4 IU/kg to 76.9 IU/kg), which is significantly larger than the changes to vial protein content over time, from original ReFacto to the moroctocog alfa (AF-CC) as used in study 310 (protein content per 1000 IU: 73 to 131 µg). Thus, the comparable efficacy outcomes of moroctocog alfa (AF-CC) in study 310 and the original pivotal ReFacto studies bracket moroctocog alfa (AF-CC) intended for the EU in terms of protein per IU for the products tested and, as such, provide evidence for clinical efficacy of the drug product over a wide range of protein per IU concentrations, included that of moroctocog alfa (AF-CC) intended for the EU.

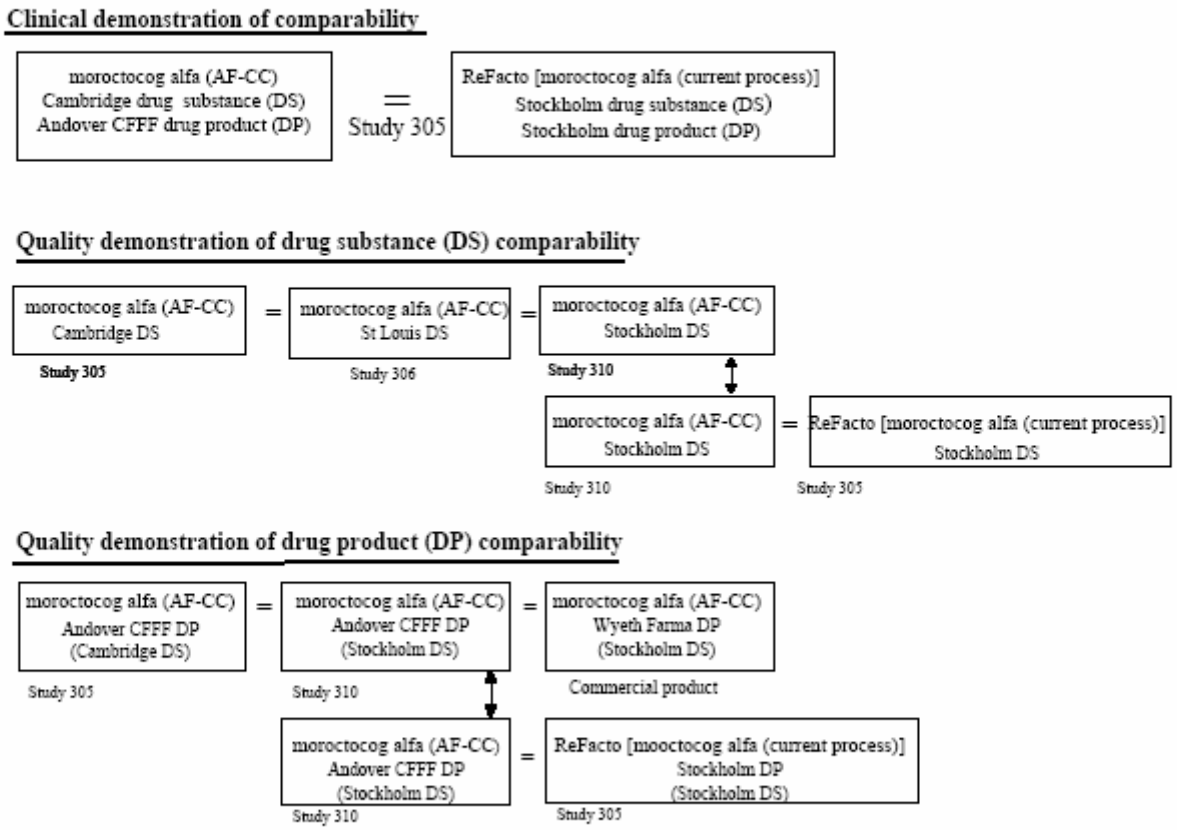
The results of study 305, as summarized below, demonstrated that the manufacturing process changes implemented for moroctocog alfa (AF-CC) have not affected the PK properties of ReFacto and support the variation of the license. Additional clinical information regarding the safety and efficacy of moroctocog alfa (AF-CC) representing material from the commercial site of moroctocog alfa (AF-CC) drug substance manufacturing, Biovitrum (Stockholm, Sweden), using the OS calibrated potency standard was obtained from clinical study 310 and is presented below, and also supports the safety of efficacy of moroctocog alfa (AF-CC) for the EU. Taken together, the demonstration of bioequivalence of moroctocog alfa (AF-CC) with ReFacto in study 305 and the evaluation of safety and efficacy of moroctocog (AF-CC) in studies 306 and 310 provided significant and sufficient clinical evidence that the changes in the manufacturing process for moroctocog alfa (AF-CC) have not affected the well-characterized clinical behaviour of moroctocog alfa.

Drug Substance

The comparability of moroctocog alfa (AF-CC) drug substance used to prepare moroctocog alfa (AF-CC) drug product in study 305 (manufactured at the Wyeth Cambridge facility, US), moroctocog alfa (AF-CC) drug substance used to prepare moroctocog alfa (AF-CC) drug product in study 306 (manufactured at the Wyeth St. Louis facility, US) and moroctocog alfa (AF-CC) drug substance used to prepare moroctocog alfa (AF-CC) drug product in study 310 (manufactured at the proposed commercial manufacturing site of moroctocog alfa (AF-CC), Biovitrum in Stockholm, Sweden) was demonstrated using a comprehensive comparability programme. The key components evaluated to assess comparability were selected based on an extensive history of manufacture of moroctocog alfa drug substance. The comparability plan was based on the knowledge of the manufacturing process and the critical factors that have the potential to impact the biochemical and functional characteristics of moroctocog alfa. The components evaluated include operational process parameters (both fermentation and purification), biochemical characterization using release assays, structural and functional characterization using non-routine methods, assessment of purity, and stability studies. The analytical methods and assessment criteria used are stringent and discriminating enough to ensure that

moroctocog alfa (AF-CC) drug substance manufactured at Cambridge US, St. Louis US, and Stockholm has comparable identity, purity, potency, and quality to each other.

The evaluations support the comparability of moroctocog alfa (AF-CC) drug substance manufactured at Cambridge US, St. Louis US, and Stockholm to each other and to moroctocog alfa (current process) drug substance from Stockholm, supporting the clinical relevance of data from study 305 linking current ReFacto to moroctocog alfa (AF-CC), and study 306 and study 310 to support the use of moroctocog alfa (AF-CC) based on drug substance from Stockholm.



Drug Product

Similar to the comparability plan used for assessing moroctocog alfa (AF-CC) drug substance, the key components evaluated for moroctocog alfa (AF-CC) drug product were selected based on the history of manufacture of ReFacto. The comparability plan was based on the knowledge of the manufacturing process and the critical factors that have the potential to impact the biochemical and functional characteristics of ReFacto. The components evaluated include operational process parameters, lyophilized product characterization, biochemical and functional characterization using release assays, structural and biophysical characterization of the active ingredient, and stability studies. The analytical methods and assessment criteria used are stringent and discriminating enough to ensure that moroctocog alfa (AF-CC) drug product manufactured at the Wyeth Andover US Clinical Fill Finish Facility (MHRA inspected) and at Wyeth Farma have comparable identity, purity, potency, and quality to each other and ReFacto manufactured at Wyeth Farma, supporting the clinical relevance of data from study 305 linking current ReFacto to moroctocog alfa (AF-CC), and study 310 to support the use of moroctocog alfa (AF-CC) drug product released from Wyeth Farma, Madrid.

Clinical Equivalence

The clinical bioequivalence of ReFacto and moroctocog alfa (AF-CC) (drug substance manufactured at Cambridge US) was demonstrated in study 305. For the study 305 PK assessments, patients were to be administered 50 IU/kg of ReFacto and moroctocog alfa (AF-CC), based upon the manufacturer's labeled potency. In calculating PK parameters for the respective drug products, actual doses administered were calculated using the product of [the actual potency assigned by the manufacturer (for the given lot number) using the CS assay, divided by a dilution factor of 4] and the volume administered. Patient plasma samples were obtained at the specified time points prior to and following the respective infusions in compliance with the CHMP Note for Guidance (NfG) and International Society of Thrombosis and Hemostasis (ISTH) recommendations. All determinations of FVIII activity in plasma (FVIII:C) in patient plasma were performed using the CS assay and measurements of FVIII:C in plasma were adjusted for baseline and normalized to a dose of 50 IU/kg. Thus, the dose of each study drug administered and FVIII:C in plasma from the patients were determined by the CS assay, thereby assuring that FVIII administered to the patients and FVIII:C in plasma from the patients were measured in identical units

A comparison of values for the key PK parameters (AUC_T, AUC_∞, and K-value) for ReFacto and moroctocog alfa (AF-CC) evaluated in study 305 is presented in Table 45-2. These data support the demonstration of comparability of moroctocog alfa (AF-CC) to ReFacto, as bioequivalence was demonstrated. AUC of FVIII from zero to the time of the last measurable concentration (AUC_T) and infinity (AUC_∞) were 14.5 ± 5.2 and 15.4 ± 6.0 IU•h/mL, respectively, for moroctocog alfa (AF-CC) and 14.5 ± 4.6 and 15.6 ± 5.6 IU•h/mL, respectively, for ReFacto. The 90% confidence intervals about the ratios of moroctocog alfa (AF-CC) to ReFacto means of AUC_T and AUC_∞ were 93.8% to 105.6 % and 92.2% to 104.3%, respectively, both of which were well within the bioequivalence window of 80% to 125%. Similarly, the K-values were 2.32 ± 0.35 IU/dL per IU/kg and 2.30 ± 0.32 IU/dL per IU/kg for moroctocog alfa (AF-CC) and ReFacto respectively. The 90% confidence interval about the ratio of the moroctocog alfa (AF-CC) to ReFacto means of K-value (97.6% to 103.6%) was well within the bioequivalence window of 80% to 125%. Thus study 305 demonstrates that the manufacturing changes associated with moroctocog alfa (AF-CC) do not alter the well-described PK of ReFacto.

Table 45-2: Key Factor VIII Pharmacokinetic Parameters for ReFacto and Moroctocog alfa (AF-CC) in Study 305

Treatment	AUC_T (h•IU/mL)	AUC_∞ (h•IU/mL)	K-value (IU/dL per IU/kg)
Moroctocog alfa (AF-CC)			
Mean ± SD	14.5 ± 5.2	15.4 ± 6.0	2.32 ± 0.35
(Min, Max)	(6.5, 24.0)	(6.7, 29.3)	(1.64, 2.91)
ReFacto			
Mean ± SD	14.5 ± 4.6	15.6 ± 5.6	2.30 ± 0.32
(Min, Max)	(6.8, 23.0)	(7.0, 28.5)	(1.72, 2.89)
	Ratio of LS means and 90% CI		
Ratio of LS means	99.5%	98.1%	100.6%

90% CI	93.8 - 105.6%	92.2 - 104.3%	97.6 - 103.6%

Abbreviations: AUC_{∞} = area under the plasma concentration-time curve from zero to infinity; AUC_T = area under the plasma concentration-time curve from zero to the last measurable concentration; CI = confidence interval; K = incremental recovery; LS = least squares; SD = standard deviation

The PK portion of study 310 demonstrated the clinical bioequivalence of moroctocog alfa (AF-CC) (drug substance manufactured at Stockholm) to a full-length recombinant FVIII product (Advate). For the study 310 PK assessments, patients were to be administered 50 IU/kg of moroctocog alfa (AF-CC) or Advate based upon the manufacturer's labeled potency. (As explained previously, in study 310, the one stage clotting (OS) assay was used to calibrate the moroctocog alfa (AF-CC) potency standard relative to the WHO 7th IS). To accommodate potential differences in methods of potency determination by the manufacturers of the 2 respective study drugs, the actual potencies of each lot of drug used in the study were determined head-to-head in the same OS clotting assay (versus a plasma standard) by the central laboratory. For calculation of PK parameters to support the primary bioequivalence analysis, the actual dose (IU) of the respective drug administered during each PK assessment was determined using the product of [the above potency (IU) as determined by the central laboratory (for a given lot number) divided by dilution factor (total diluent volume used to reconstitute each vial of the respective PK drug)] and the volume (mL) administered. Patient plasma samples were obtained at the specified time points prior to and following the respective infusions in compliance with the NfG and ISTH recommendations. All determinations of FVIII:C in patient plasma were performed using the same OS assay at the central laboratory.

For the calculation of PK parameters, measurements of FVIII:C in plasma were adjusted for baseline and normalized to a dose of 50 IU/kg based upon the central laboratory potency assessment. Thus, the dose of each study drug administered was aligned to each other, and to the FVIII:C measurements in patient plasma as determined from the patients by the same OS assay, thereby assuring that FVIII administered to the patients and FVIII:C in plasma from the patients were measured in identical units.

This study design assured that the demonstration of bioequivalence was independent of method of manufacturer's potency assignment. As such, this primary efficacy outcome of study 310 is not impacted by revision of the potency calibration procedure for the manufacturing working standard, to include the use of the CS assay, rather than the OS assay. Based on the central laboratory potency assessment, the mean FVIII:C-versus-time profiles of moroctocog alfa (AF-CC) and Advate were comparable. The 90% CIs about the ratios of moroctocog alfa (AF-CC) to Advate geometric means of AUCt, AUC∞, and K-value were within the bioequivalence window of 80% to 125%, indicating the bioequivalence of moroctocog alfa (AF-CC) and Advate when the same one stage potency assay was used to measure product potency and plasma levels.

In addition to these PK observations, the safety and efficacy data obtained for moroctocog alfa (AF-CC) manufactured at Stockholm and used in study 310 were consistent with the safety and efficacy data obtained for moroctocog alfa (AF-CC) in study 306 and for ReFacto in the original pivotal study 3082A-300-WW (study 300) in previously treated patients (PTPs), demonstrating that moroctocog alfa (AF-CC), across a range of protein content per IU that includes that of the moroctocog alfa (AF-CC) drug product intended for the EU (see Table 45-1), is a safe and efficacious treatment option for the management of hemophilia A.

The inhibitor safety profile of moroctocog alfa (AF-CC) is consistent between studies 306 and 310. The data demonstrate an absence of neoantigenicity, and are consistent with the experience observed for ReFacto. The spectrum of treatment-emergent adverse events and treatment-emergent hemophilia events observed in study 310 reflects the known complications of hemophilia A and is consistent with those previously observed in study 306. The findings demonstrate that the revision in method of potency assignment has not impacted on the safety profile of moroctocog alfa (AF-CC). Furthermore, the aggregate experience in studies 306 and 310 demonstrates that the manufacturing process changes for moroctocog alfa (AF-CC) have not adversely impacted the well-characterized safety profile of ReFacto.

Evidence for comparable clinical efficacy of ReFacto, moroctocog alfa (AF-CC) used in study 306, and moroctocog alfa (AF-CC) used in study 310 is provided by a comparison of on-demand treatment

results (Table 45-3) and prophylaxis results for the respective drug products. In pivotal study 300 that assessed ReFacto in previously treated patients, ReFacto was administered at a mean dose of 30.79 (SD 10.03) IU/kg for on-demand treatment of bleeding episodes; 88% of bleeding episodes resolved with 1 or 2 infusions. In study 306 moroctocog alfa (AF-CC) was administered on demand at a mean dose of 39.5 IU/kg (SD 16.3) IU/kg; 87% of bleeding episodes resolved with 1 or 2 infusions.
Drug product used in studies 300 and 306 had a protein content per IU less than that of moroctocog alfa (AF-CC) intended for the EU, as noted in the Table 45-1. In study 310, moroctocog alfa (AF-CC) was administered on demand at a mean dose of 33.7 IU/Kg (SD 11.6); 92.5 % of bleeding episodes resolved with 1 or 2 infusions). Drug product used in study 310 had a protein content per IU greater than that of moroctocog alfa (AF-CC) intended for the EU. Although not compared directly in the same study, these results show that a comparable spectrum of dosing for ReFacto and moroctocog alfa (AF-CC), regardless of manufacturing location or method for potency assignment, produced comparable treatment results in the on-demand setting in similar patient populations.

Table 45-3: Number (%) of Bleeding Episodes Resolved With One or Two Infusions in ReFacto Study 300 and Moroctocog alfa (AF-CC) Studies 306 and 310

	--------ReFacto--------	Moroctocog alfa (AF-CC)	Moroctocog alfa (AF-CC)
	Study 300	Study 306	Study 310
Mean dose (IU/kg) for on demand treatment (SD)	30.79 (10.03)	39.5 (16.3)	33.7 (11.6)
Median dose (IU/kg) for on demand treatment	29.94	37.6	30.6
Percentage of bleeds resolving with 1 or 2 infusions	88%	87%	92.5%

Efficacy of prophylaxis treatment with moroctocog alfa (AF-CC), relative to the on-demand experience with ReFacto, has been demonstrated in studies 306 and 310. In study 306 a mean overall annual bleeding rate (ABR) of 7.7 episodes per year was observed in patients during prophylaxis treatment. In study 310 a mean overall ABR of 3.9 episodes per year was observed in patients during prophylaxis treatment. These results are consistent with the ABR of 10 episodes per year observed in ReFacto study 300 during periods of prophylaxis and compare favorably with the overall ABR of 25 episodes observed in ReFacto study 300 during periods when prophylaxis treatment was not administered. Differences in ABRs between ReFacto study 300 and moroctocog alfa (AF-CC) studies 306 and 310 may be entirely explained by differences in the prophylaxis regimens used in these respective studies. These data demonstrate that the changes in manufacturing process, across a range of protein content per IU which brackets that of moroctocog alfa (AF-CC) intended for market, has not compromised the prophylactic efficacy of moroctocog alfa (AF-CC).

The MAH considered that based on the above described information, comprehensive comparability studies performed on moroctocog alfa (AF-CC) drug substance and drug product demonstrate that all sources of moroctocog alfa (AF-CC) drug substance and drug product are equivalent.
Clinical information and data obtained for moroctocog alfa (AF-CC) drug substance from Cambridge and from St Louis are viewed as representative of moroctocog alfa (AF-CC) drug substance from Stockholm. These data provide supportive evidence that conclusions regarding the clinical bioequivalence of moroctocog alfa (AF-CC) drug substance manufactured at Cambridge to ReFacto (from study 305) may be extrapolated to moroctocog alfa (AF-CC) drug substance from Stockholm.

Potency assignment of Moroctocog alfa (AF-CC) and impact on protein content
In accordance with the recommendations from CHMP, the potency of commercial moroctocog alfa (AF-CC) drug substance and drug product will be assigned using the CS assay relative to a potency standard calibrated against the WHO 7th IS by the CS assay.

A consequence of this approach, due to the transition from the WHO 6th International Standard to the WHO 7th International Standard, is that there will be an increase in the protein content for moroctocog alfa (AF-CC) when compared to ReFacto of approximately 14%.

The MAH is of the opinion that the analysis and the understanding of the typical dosing practices used in the management of hemophilia it can be concluded that there is no safety risk to the patient with the

administration of moroctocog alfa (AF-CC) containing an increase in protein content compared with moroctocog alfa (current process). Most importantly, the results of clinical study 310, using a drug product with a protein content per IU greater than that of moroctocog alfa (AF-CC) intended for the EU market, coupled with historical data for original ReFacto that had protein content per IU that is less than that of moroctocog alfa (AF-CC) intended for the EU demonstrate that there is no impact to safety and efficacy with the use of moroctocog alfa (AF-CC) for the management of hemophilia.

Active Ingredient Concentration in Reconstituted Solution

Due to a change in the International Standard used for calibration of the moroctocog alfa (AF-CC) manufacturing standard, reconstituted moroctocog alfa (AF-CC) solutions will contain approximately 14% higher active ingredient concentrations than in moroctocog alfa (current process) (see Table 45-4). The nominal dosage strengths will remain unchanged; thus, there will be approximately 14% more moroctocog alfa (AF-CC) protein per IU in a given dose.

Table 45-4: Protein Concentration of ReFacto and Moroctocog alfa (AF-CC) After Reconstitution With Normal Saline Diluent

Dosage Strength	ReFacto[a] estimated concentration (mg/mL)	Moroctocog alfa (AF-CC)[b] Representing material evaluated in studies 310 and 311 estimated concentration (mg/mL)	Moroctocog alfa (AF-CC)[c] Representing proposed commercial material estimated concentration (mg/mL)
250	0.005	0.008	0.006
500	0.011	0.016	0.012
1000	0.021	0.033	0.024
2000	0.042	0.066	0.048

a. Potency of material determined using CS assay and a CS calibrated standard relative to the WHO 6th IS.
b. Potency of material determined using CS assay and a OS calibrated standard relative to the WHO 7th IS.
c. Potency of material determined using CS assay and a CS calibrated standard relative to the WHO 7th IS.

For the 250, 500, and 1000 IU dosage strengths, the concentration of moroctocog alfa protein in the moroctocog alfa (AF-CC) intended for the EU will be well below the active ingredient concentration in the ReFacto 2000 IU dosage strength. The 2000 IU dosage form of ReFacto was approved in 2003 and currently represents a significant portion of ReFacto commercial supplies. Therefore, the 14% increase in moroctocog alfa (AF-CC) protein per IU concentration in the 250, 500, and 1000 IU/vial dosage strengths is not anticipated to result in any new safety issues.

Thus, for the 2000 IU dosage strength, the protein concentration of moroctocog alfa (AF-CC) will be about 14% above the current value for ReFacto but less (approximately 27% less) than the 2000 IU dosage strength tested in ongoing study 311. The use of this dosage form with the proposed increase in protein is also supported by experience in non-clinical studies filed as part of the Original ReFacto Marketing Application, as summarized briefly here.

A number of non-clinical studies in both rats and cynomolgus monkeys were performed at concentrations greater than the moroctocog alfa protein concentration in moroctocog alfa (AF-CC) reconstituted 2000 IU. In these studies, no systemic or local toxic effects due to the concentration of active ingredient were seen. (In some of the monkey studies, administration of moroctocog alfa protein induced antibodies that recognized the endogenous monkey FVIII.)
The exposure of test animals to these high concentrations of moroctocog alfa, without any systemic or local toxic effects due to the concentration of moroctocog alfa protein, supports the safety of the increase in moroctocog alfa protein final concentration in moroctocog alfa (AF-CC) due to the transition of manufacturing standard calibration from the WHO 6th International Standard to the WHO 7th International Standard.

Total Moroctocog Alfa (AF-CC) Dose

Current moroctocog alfa clinical experience was reflected in study 310; the median dose administered per infusion was 30.2 IU/kg with a range of 6.4 to 76.9 IU/kg. Infusions of moroctocog alfa (AF-CC) over this dosing range were well tolerated with no instance of moroctocog alfa (AF-CC)-related infusion reactions. These data support the conclusions that the increase in moroctocog alfa (AF-CC)

protein content resulting from the transition of manufacturing standard calibration from the WHO 6th International Standard to the WHO 7th International Standard is well within the wide dosing range utilized in study 310 and that the increased protein concentration resulting from the revised method for potency assignment is safe and well tolerated.

In general, the data support the conclusion that the increase in moroctocog alfa protein content per vial for moroctocog alfa (AF-CC) is well within the normal dosing regime for the management of hemophilia A, and it is also well below the doses administered to test animals in non-clinical studies with moroctocog alfa.

The MAH has provided information during the assessment of the scientific data by the CHMP to support that study 305 provided evidence for bioequivalence between currently marketed ReFacto and ReFacto AF moroctocog alfa (AF-CC) intended for market in EU. Furthermore, the MAH has reviewed the possible clinical impact of the differences in protein content resulting from the changes in potency assignment incurred by the changes from the 6th to 7th WHO international standard. These requirements results in an increased protein content per IU as compared to the currently marketed ReFacto, but a lower content per IU compared to the version of moroctocog alfa (AF-CC) used in some of the clinical trials in support of the variation. It is important to stress that these changes in protein content is not a result of the manufacturing changes, but solely a result of the change in international standard; a change that would have happened sooner or later for ReFacto despite this variation. The clinical trials provided in support of the variation – using moroctocog alfa (AF-CC) with a higher protein content than that intended for the EU market – have provided convincing evidence for comparable efficacy and safety of moroctocog alfa (AF-CC) and both original and current marketed ReFacto.

Overall the MAH provided good evidence that moroctocog alfa (AF-CC) is bioequivalent with the current version of ReFacto, and also with another marketed F-VIII product, Advate (when both products are assayed with the same one-stage potency assay), and that ReFacto AF (moroctocog alfa (AF-CC) intended for the EU marked will have a comparable efficacy and safety as the current ReFacto

3.4.2Clinical data

An overview of the clinical data presented throughout the entire assessment periods of this application is given below.

3.4.2.1 Pharmacokinetic data

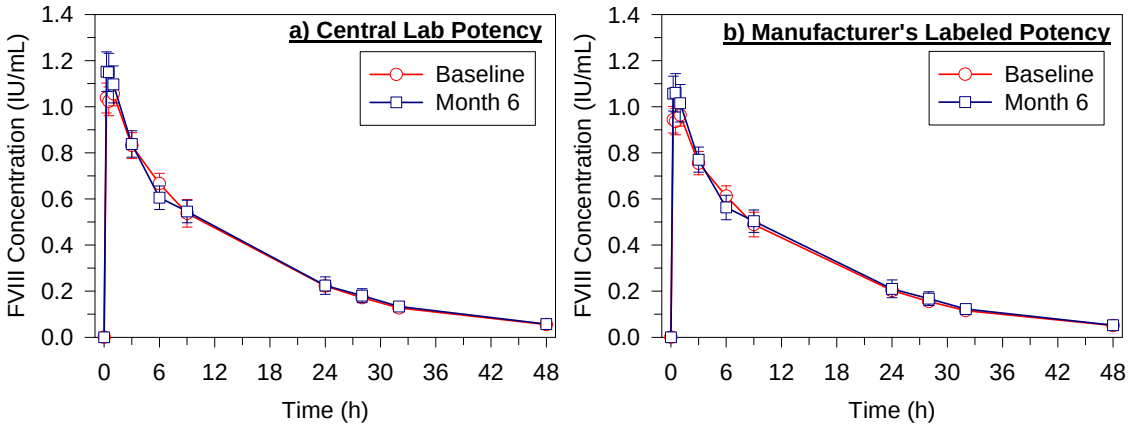
Single- and repeat-dose pharmacokinetic (PK) data for moroctocog alfa (AF-CC) are primarily derived from the PK assessments conducted in pivotal study 310 at a single dose of 50 IU/kg. This study assessed the bioequivalence of moroctocog alfa (AF-CC) and a full-length recombinant factor VIII product (FLrFVIII, Advate). Moreover, PK data for moroctocog alfa (AF-CC) after 6 months treatment were compared to baseline. Available recovery data from the ongoing pivotal study of moroctocog alfa (AF-CC) for surgical prophylaxis (study 311) are also presented. Bioequivalence between the current marketed ReFacto and moroctocog alfa AF-CC was studied in Study 305. PK data were also collected in studies 306 and 307.

- ***Bioavailability***

Moroctocog alfa (AF-CC) is administered IV; thus, by definition the bioavailability is 100%.

In study 310 analysis of moroctocog alfa (AF-CC) PK over time (at baseline and month 6) was also performed with reference to the central laboratory potency assessment and the manufacturer's labeled potency, as described below. The central laboratory potency assessment was measured in units versus a plasma standard by a one-stage assay. The manufacturer's labeled potency was based on calibration using a 7th IS, one stage-calibrated, AF-CC potency standard. Plasma levels were measured by a one stage assay. The plots of plasma FVIII:C-versus-time (mean ± standard error) for moroctocog alfa

(AF-CC) at baseline and month 6 for the 25 evaluable patients based on both the central laboratory and manufacturer's labeled potency assessments are presented in the figure below.



The plasma FVIII:C-versus-time profiles for moroctocog alfa (AF-CC) at baseline and month 6 PK visits are comparable based on central laboratory potency assessment. Comparable plasma FVIII:C-versus-time profiles were also observed at the baseline and month 6 PK visits based on manufacturer's labeled potency. The key PK parameters, K-value, AUC_t, and AUC_∞, were approximately 9% lower when based on the manufacturer's labeled potency compared with the central laboratory potency. These values are consistent with the lower potencies (approximately 93% of labeled potency) observed for the various batches of moroctocog alfa (AF-CC) based on the central laboratory potency assessment.

The key PK parameters, K-value, AUC_t and AUC_∞ were unchanged at the month 6 visit compared to those at the baseline visit based on either manufacturer's labeled potency or central laboratory potency assessment.

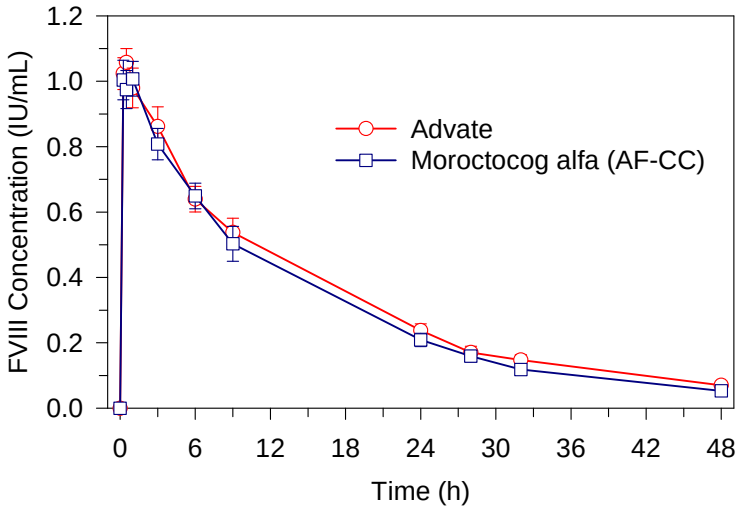
Only limited PK data are available from study 311. At the data cutoff date for the application (10 Jan 2007), 7 patients had completed surgery, and all were prescribed bolus injection replacement therapy in a peri-operative setting. Preliminary recovery data are available for 6 of the 7 patients. The 6 patients included in the PK analysis were white males ranging in age from 18 to 40 years. The mean (±SD) C_{max}, K-value, and in vivo recovery value were 1.113 (±0.26) IU/mL, 2.23 (±0.52) IU/dL per IU/kg, and 105% (± 25%), respectively.

- ***Bioequivalence***

Study 310 investigated the bioequivalence of Moroctocog Alfa (AF-CC) and Advate based on Central Laboratory Potency Assessment.

The plots of plasma FVIII:C-versus-time (mean ± standard error) for moroctocog alfa (AF-CC) and Advate for the 30 patients evaluable for bioequivalence testing based on the central laboratory potency assessment are presented in the figure below. A summary of FVIII:C PK parameters and the results from the statistical analysis of these data are presented in the following table.

Mean (±Standard Error) Plasma Factor VIII:C-Versus-Time Profiles for Moroctocog Alfa (AF-CC) and Advate in Previously Treated Patients With Hemophilia A in Study 3082B2-310-WW (Based on Central Laboratory Potency Assessment)



Pharmacokinetic Parameter Estimates for Moroctocog Alfa (AF-CC) and Advate in Previously Treated Patients With Hemophilia A in Study 3082B2-310-WW (Based on Central Laboratory Potency Assessment)

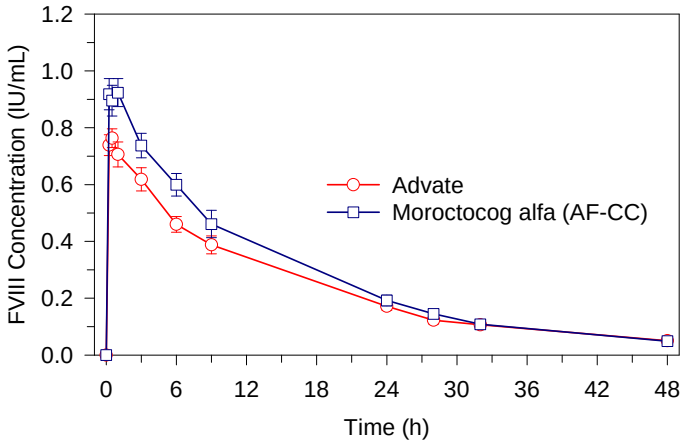
Treatment	C_{max} (IU/mL)	AUC_t (IU·hr/mL)	AUC_∞ (IU·hr/mL)	$t_{1/2}$ (hr)	K-value (IU/dL per IU/kg)	In vivo Recovery (%)
Advate						
Mean ± SD	1.19 ± 0.32	15.0 ± 5.4	16.5 ± 6.3	13.3 ± 5.8	2.39 ± 0.65	114 ± 30
(Min, Max)	(0.64, 2.06)	(6.5, 24.2)	(7.5, 26.7)	(5.9, 31.2)	(1.28, 4.13)	(59.7, 200)
N	30	30	30	30	30	30
Moroctocog alfa (AF-CC)						
Mean ± SD	1.17 ± 0.23	13.8 ± 5.7	14.7 ± 6.1	11.2 ± 5.0	2.35 ± 0.47	112 ± 22
(Min, Max)	(0.66, 1.62)	(4.8, 27.1)	(5.4, 28.7)	(3.5, 33.9)	(1.32, 3.25)	(60.7, 152)
N	30	30	30	30	30	30
Ratios of geometric LS means and 90% confidence intervals[a]						
Ratio of geometric LS means	---	89.8%	88.0%	---	100%	---
90% Log-transformed CI	---	83.3%-96.9%	81.6%-94.8%	---	92.5%-108%	---

a. The 90% confidence intervals (CI) about the ratio of the moroctocog alfa (AF-CC)-to-Advate means were obtained using the average bioequivalence procedure for a 2×2 crossover design provided in WinNonlin Professional version 4.1. Abbreviations: AF-CC=albumin-free cell culture; AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_T = area under the plasma concentration-time curve from zero to the last measurable concentration; CI=confidence interval; C_{max} = peak concentration; K = incremental recovery; LS = least squares; Max=Maximum; Min=Minimum; SD=standard deviation; $t_{1/2}$ = terminal-phase elimination half-life.

As can be seen from the figure above, mean plasma FVIII:C-versus-time profiles for moroctocog alfa (AF-CC) and Advate are comparable.

A supplemental analysis of bioequivalence of moroctocog alfa (AF-CC) and Advate based on manufacturer's labeled potency was also performed and the mean (± standard error) FVIII:C-versus-time data for the 30 patients who were eligible for bioequivalence testing are shown in the figure below. A summary of FVIII:C PK parameters and the results from the statistical analysis are found in the following table.

Mean (±Standard Error) Plasma Factor VIII:C Versus Time Profiles for Moroctocog Alfa (AF-CC) and Advate in Previously Treated Patients With Hemophilia A in Study 3082B2-310-WW (Based on Manufacturer's Labeled Potency)



Pharmacokinetic Parameter Estimates for Moroctocog Alfa (AF-CC) and Advate in Previously Treated Patients With Hemophilia A in Study 3082B2-310-WW (Based on Manufacturer's Labeled Potency)

Treatment	C_{max} (IU/mL)	AUC_t (IU·hr/mL)	AUC_∞ (IU·hr/mL)	$t_{1/2}$ (hr)	K-value (IU/dL per IU/kg)	In vivo Recovery (%)
Advate						
Mean ± SD	0.86 ± 0.24	10.8 ± 3.8	11.9 ± 4.5	13.3 ± 5.8	1.72 ± 0.47	82.2 ± 21.5
(Min, Max)	(0.52, 1.42)	(4.5, 17.3)	(5.2, 19.0)	(5.9, 31.2)	(1.04, 2.84)	(49.2, 137)
n	30	30	30	30	30	30
Moroctocog alfa (AF-CC)						
Mean ± SD	1.08 ± 0.22	12.7 ± 5.2	13.5 ± 5.6	11.2 ± 5.0	2.15 ± 0.44	103 ± 21
(Min, Max)	(0.58, 1.41)	(4.1, 23.6)	(4.7, 25.0)	(3.5, 33.9)	(1.15, 2.83)	(52.8, 132)
n	30	30	30	30	30	30
Ratios of geometric LS means and 90% confidence intervals[a]						
Ratio of geometric LS means	---	114%	112%	---	127%	---
90% Log-transformed CI	---	105% - 124%	103% - 122%	---	117% - 138%	---

a. The 90% confidence intervals (CI) about the ratio of the moroctocog alfa (AF-CC)-to-Advate means were obtained using the average bioequivalence procedure for a 2×2 crossover design provided in WinNonlin Professional version 4.1.
Abbreviations: AUC∞ = area under the plasma concentration-time curve from time zero to infinity; AUCt = area under the plasma concentration-time curve from zero to the last measurable concentration; CI=confidence interval; Cmax = peak concentration; K = incremental recovery; LS = least squares; Max=maximum; Min=minimum; SD=standard deviation; t1/2 = terminal-phase elimination half-life

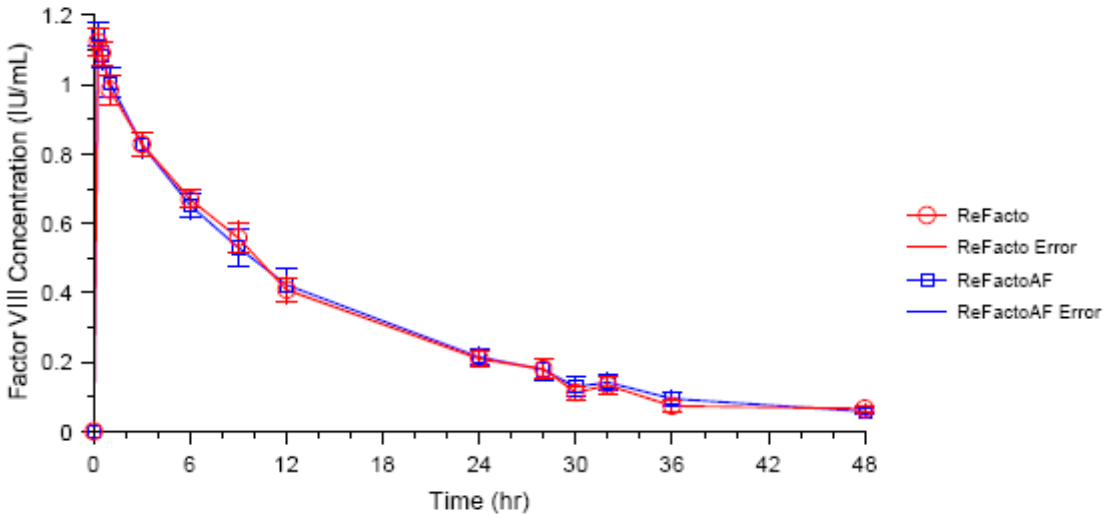
Based on the manufacturer's labeled potency, the plasma peak FVIII:C values were approximately 27% higher (based on the ratio of geometric means) for moroctocog alfa (AF-CC) compared to Advate; the mean (±SD) C_{max} values were 1.08 (±0.22) and 0.86 (±0.24) IU/mL for moroctocog alfa (AF-CC) and Advate, respectively. These concentrations are consistent with the lower central laboratory potency assignment observed with Advate lots (74% of labeled potency) compared to moroctocog alfa (AF-CC) lots (93% of labeled potency). Two of the 3 key PK parameters, AUC_t and AUC_∞, met the bioequivalence criteria (90% CIs within the window of 80% to 125%). The upper bound of the 90% CI for K-value exceeded 125% (the 90% CI was 117% to 138%), indicating the K-value did not meet bioequivalence criteria. The clinical consequences of this is considered limited by the CHMP.

Overall, study 310 has demonstrated bioequivalence between moroctocog alfa (AF-CC) produced at the commercial site and lyophilized and filled at a non-commercial site and the full-length F-VIII

product Advate when central laboratory potency assessment was measured in units versus a plasma standard by a one-stage assay and plasma levels were measured by a one stage assay. These results do however not provide any evidence that the moroctocog alfa (AF-CC) commercial product is clinically comparable to currently marketed ReFacto.

In supportive study 305 the plasma concentration-time profile of factor VIII after the 2-minute IV infusion of moroctocog alfa (AF-CC) preparation was found to be essentially identical to that seen with ReFacto (see figure below). Plasma concentrations of factor VIII increased sharply in response to the 2-minute IV infusion of either the moroctocog alfa (AF-CC) or ReFacto preparation, with a Cmax of 1.16 ± 0.17 IU/mL for moroctocog alfa (AF-CC) and 1.15 ± 0.16 IU/mL for ReFacto, observed mostly within the first half-hour. After the end of the infusion, the decline of the plasma concentration of factor VIII exhibited multiphasic disposition characteristics. In the initial phase, plasma concentrations dropped at a rate consistent with relatively rapid but limited distribution into an extra vascular space. The Vss was 49.9 mL/kg for moroctocog alfa (AF-CC) and 51.1 mL/kg for ReFacto. During the terminal phase, the rate of decline in plasma concentrations was slower with a $t_{½}$ of approximately 9.9 ± 3.2 hours for moroctocog alfa (AF-CC) and 10.9 ± 4.5 hours for ReFacto. The AUCs of factor VIII from zero to the time of the last measurable concentration (AUC_T) and infinity (AUC_∞) were 14.5 ± 5.2 and 15.4 ± 6.0 IU·h/mL, respectively, for moroctocog alfa (AF-CC) and 14.5 ± 4.6 and 15.6 ± 5.6 IU·h/mL, respectively, for ReFacto. The 90% confidence intervals about the ratios of moroctocog alfa (AF-CC) to ReFacto means of AUC_T and AUC_∞ were 93.8% to 105.6 % and 92.2% to 104.3%, respectively, both of which were well within the bioequivalence window of 80% to 125%.

SF 8-1: Mean (±SE) Plasma Factor VIII Concentration Versus Time Profiles of ReFacto AF and ReFacto in 25 Patients With Hemophilia A



In calculating PK parameters for the respective drug products in Study 305, actual doses administered were calculated using the product of [the actual potency assigned by the manufacturer (for the given lot number) using the CS assay, divided by a dilution factor of 4] and the volume administered. Patient plasma samples were obtained at the specified time points prior to and following the respective infusions in compliance with the NfG and International Society of Thrombosis and Haemostasis (ISTH) recommendations. All determinations of FVIII activity in plasma (FVIII:C) in patient plasma were performed using the CS assay and measurements of FVIII:C in plasma were adjusted for baseline and normalized to a dose of 50 IU/kg. Thus, the dose of each study drug administered and FVIII:C in plasma from the patients were determined by the CS assay, thereby assuring that FVIII administered to the patients and FVIII:C in plasma from the patients were measured in identical units

Both the review of the quality data as well as the MAH responses to various CHMP requests for supplementary information has clearly demonstrated that the moroctocog alfa AF-CC drug product used in study 305 is fully comparable to the drug product intended for market. Study 305 can therefore

be regarded as sufficient for demonstration for bioequivalence between the current marketedReFacto and the future moroctocog alfa AF-CC intended for market.

3.4.2.2 Clinical efficacy

The application consisted of 2 pivotal studies and 3 supportive studies conducted with moroctocog alfa (AF-CC) as shown in the table below:

ReFacto AF-CC clinical development programme				
Study No.	**Study Design**	**Patient Population**	**No. Enrolled Patients**	**Study Status**
Pivotal studies				
3082B2-310-WW Drug substance manufacturing site: Sweden Potency: one stage	Double-blind, randomized crossover PK period to assess BE of ReFacto AF-CC and Advate , followed by open-label period to evaluate efficacy and safety of ReFacto AF-CC for use in prophylaxis and on-demand treatment of bleeding. ReFacto AF-CC PK at 6 months also evaluated for patients who completed PK period.	Male PTPs ≥12 years of age with moderately severe or severe hemophilia A (FVIII:C ≤1% in PK period; FVIII:C ≤2% in SE period) and ≥150 EDs to any FVIII product	94	Completed
3082B2-311-WW Drug substance manufacturing site: Sweden Potency: one stage	Open-label efficacy and safety study of ReFacto AF-CC for use in surgical prophylaxis when administered by bolus or continuous infusion	Male PTPs ≥12 years of age with moderately severe or severe hemophilia A (FVIII:C ≤2%) and ≥150 EDs to any FVIII product undergoing elective major surgery	22 (25 planned)	Ongoing
Supportive studies				
3082B1-305-GL Drug substance manufacturing site: US Potency: chromogenic substrate	Double-blind, randomized, crossover study of BE of ReFacto AF-CC and ReFacto and PK of ReFacto AF-CC	Male PTPs ≥12 years of age with severe hemophilia A (FVIII:C ≤1%) and ≥250 EDs to any FVIII product	30	Completed
3082B1-306-GL Drug substance manufacturing site: US Potency: chromogenic substrate	Open-label efficacy and safety study of ReFacto AF-CC for use in routine prophylaxis, on-demand treatment of bleeding, and surgical prophylaxis. PK at 3 months also evaluated for patients who completed study 3082B1-305-GL.	Male PTPs ≥12 years of age[b] with moderately severe or severe hemophilia A (FVIII:C ≤2%) and ≥250 EDs to any FVIII product	110	Completed
3082B1-307-GL Supportive study Drug substance manufacturing site: US Potency: chromogenic substrate	Open-label, long-term efficacy and safety study of ReFacto AF-CC for use in prophylaxis, on-demand treatment of bleeding, and surgical prophylaxis. Recovery over time also evaluated.	Patients who completed study 3082B1-306-GL	98	Terminated[c]

Abbreviations: AF-CC = albumin-free cell culture; BE = bioequivalence; ED = exposure day; FVIII = factor VIII; FVIII:C = factor VIII activity in plasma; GL = global; PK = pharmacokinetics; PTPs = previously treated patients; SE = safety and efficacy; WW = worldwide. b: The lower age limit was decreased from 12 to 6 years when 10 patients accrued 50 EDs. c: Study 3082B1-307-GL was terminated early by the applicant after the drug substance manufacturing site was changed from the US to Sweden and the procedures to assign product potency were revised.

The pivotal studies were:

1. Study 3082B2-**310**-WW, a double-blind, randomized crossover PK period to assess BE of moroctocog alfa (AF-CC) and Advate, followed by open-label period to evaluate efficacy and safety of moroctocog alfa (AF-CC) for use in prophylaxis and on-demand treatment of bleeding.
2. Study 3082B2-**311**-WW an open-label efficacy and safety study of moroctocog alfa (AF-CC) for use in surgical prophylaxis when administered by bolus or continuous infusion.

The supportive studies were:

1. Study 3082B1-**305**-GL, Double-blind, randomized, crossover study of BE of moroctocog alfa (AF-CC) and ReFacto and PK of moroctocog alfa (AF-CC).
2. Study 3082B1-**306**-GL, an open-label efficacy and safety study of moroctocog alfa (AF-CC) for use in routine prophylaxis, on-demand treatment of bleeding, and surgical prophylaxis. PK at 3 months also evaluated for patients who completed study 3082B1-305-GL.
3. Study 3082B1-**307**-GL, an open-label, long-term efficacy and safety study of moroctocog alfa (AF-CC) for use in prophylaxis, on-demand treatment of bleeding, and surgical prophylaxis. Recovery over time also evaluated. During the conduct of study 3082B1-307-GL the manufacturing process was changed, including a change in the drug substance manufacturing site from the US to Sweden, and a revision to the potency assignment method for the manufacturing standard. Therefore, the applicant decided to terminate study 3082B1-307-GL early and initiate clinical trials with ReFacto AF manufactured at the new site with the new potency assignment.

3.4.2.2.1 Study 3082B2-310-WW

Study 310 included 94 previously treated patients treated with at least one dose of moroctocog alfa for routine prophylaxis and treatment of bleeding episodes. 94 patients in study **3082B2-310-WW** received moroctocog alfa (AF-CC) for routine prophylaxis and, in some cases, for intermittent prophylaxis (n=17) supplementing routine prophylaxis. A total of 6406 infusions of moroctocog alfa (AF-CC) with a median dose per infusion of 30.2 IU/kg (range, 6.8 to 76.9 IU/kg) were administered for prophylaxis. Only 7 dose escalations were prescribed for 6 patients during the course of the study.

All 94 patients were followed-up for 19.757 person days. This study included only male patients and 3.803 person days involved patients between 12-16 years of age. One patient was from Asian origin, 89 patients were white and 4 patients were classified as other.

In study 310 patients were monitored in a manner consistent with the CHMP "Note for Guidance on the Investigation of Recombinant Factor VIII and IX Products," dated October 2000. Initial PK assessments were performed on 31 patients and 27 patients underwent repeat PK assessments following 6 months of treatment with moroctocog alfa (AF-CC). In the safety and efficacy portion of study 310, 94 previously treated patients with FVIII activity in plasma (FVIII:C) ≤2% (including the above PK patients) received moroctocog alfa (AF-CC) study drug for 6 months (or 50 exposure days [EDs]) for routine prophylaxis supplemented with on-demand treatment as necessary. PK results for moroctocog alfa (AF-CC) were stable over time, which is consistent with original pivotal data for ReFacto, and only 2 transient inhibitors were observed—both at a single point in time with subsequent negative inhibitor assay results—indicating the absence of any new inhibitor safety signals, relative to the original ReFacto.

The MAH proposed that their understanding is that for modified products the NfG does not require that patients receive treatment with the previous product prior to entry into the clinical trial. Therefore, study 310 did not require prior treatment with ReFacto as an inclusion criterion, and during the 30 days prior to study entry, patients participating in study 310 received treatment with a variety of FVIII-containing products. For 12 of these patients, use of ReFacto was reported during the 30-day interval preceding entry into study 310. None of these 12 patients developed an inhibitor. Additional data for moroctocog alfa (AF-CC) treatment in patients who have received prior treatment with ReFacto are provided in the context of supporting study 306; pre-study use of ReFacto was reported

for 13 patients. None of these 13 patients developed a confirmed inhibitor. (Note that 1 patient [363-562] had a local laboratory BIA value of 0.9 BU that was clinically silent and was considered a false positive; samples taken the same day and analyzed at the central laboratory were negative and all succeeding values at the local laboratory were negative

Prophylaxis treatment and number of bleeding episodes

Most patients (57 of 94; 60.6%) in study 3082B2-310-WW reported no spontaneous bleeding episodes while on routine prophylaxis, and 45.7% (43 of 94) of patients had no bleeding episodes of any type (spontaneous or injury related) while on routine prophylaxis during the course of their study participation. The median annualized bleed rate (ABR) was 1.9 (mean 3.9, range 0 to 42.1). The median ABR for spontaneous and traumatic bleeding episodes individually was 0 for both types of bleeding, with a mean ABR of 1.9 and 2.0 for spontaneous and traumatic bleeding episodes, respectively. Most bleeding episodes (110 of 180; 61.1%) during routine prophylaxis occurred ≤48 hours after the last dose of moroctocog alfa (AF-CC). However, the majority of bleeding episodes reported to occur ≤48 hours after the last routine prophylaxis dose were traumatic (64 of 110; 58.2%). In contrast, a relatively greater proportion of bleeding episodes that occurred >48 hours after the last routine prophylaxis dose were spontaneous (42 of 70; 60.0%).

In study 310, 51 of 94 enrolled patients had 180 bleeding episodes while receiving moroctocog alfa (AF-CC) for routine prophylaxis. There were 206 separate locations of bleeding associated with the 180 bleeding episodes reported during routine prophylaxis. The locations of bleeding consisted of 131 instances of bleeding in joints, 61 instances of bleeding in soft tissue, and 14 instances of bleeding in other locations.

The incidence rate of LETE in study 3082B2-310-WW during prophylaxis was low (0.4%; 25 episodes per 6347 prophylactic infusions). 53 patients in study 3082B2-310-WW received moroctocog alfa (AF-CC) for on-demand treatment during the study (including patients who reported on-demand use before beginning their routine prophylaxis). A total of 282 on-demand infusions of moroctocog alfa (AF-CC) were administered with a median dose per infusion of 30.6 IU/kg (range, 6.4 to 74.4 IU/kg). The median number of infusions per patient was 3 (range, 1 to 26 infusions). Regardless of location, 92.5% (173 of 187) of all bleeds resolved with 1 or 2 infusions of moroctocog alfa (AF-CC). Of the 187 initial infusions to treat a bleeding episode, the response to 132 (70.6%) infusions was rated either “excellent” or “good,” including 44 (23.5%) infusions rated “excellent” and 88 (47.1%) infusions rated “good”.

Cases of inhibitors observed in study 310

Two instances of low-titre transient inhibitors were observed in study 310 (patients 4114 and 4404). Each instance was associated with detection of an inhibitor at a single point in time with negative follow-up Nijmegen inhibitor assays. Each patient had previously been treated with plasma-derived FVIII concentrates, and neither had received prior treatment with ReFacto. The MAH has previously obtained extended follow-up data for each of these patients after their completion of study participation. These data were included in the respective subject narratives provided in the application.

Patient 4114:
Subsequent to final study contact, 2 communications were provided regarding clinical inhibitor status of this patient. In the first communication received 5 months subsequent to the final study contact, the study site communicated that during the interval subsequent to study participation, patient 4114 had 10 clinical contacts with the study site. Over this interval the patient received prophylaxis (approximately 15-20 IU/kg administered 2-3 times per week) and experienced 2 bleeding episodes, both responsive to treatment with commercial FVIII concentrate. In the second communication received approximately 12 months after completion of study participation, the study site communicated that the patient had no symptoms of inhibitor since he concluded his participation in study 310. The standard of care at this respective study site is to perform inhibitor titres only when clinically indicated. Since there have been no perceived treatment failures and since the prior inhibitor finding was transient, no follow-up inhibitor assays have been performed

Patient 4404:
In the 5 months subsequent to the final study contact (per communication from study site), patient 004404 had 2 clinic visits and several telephone contacts with the study site. Over this interval the patient was treated on demand. He averaged about 2 bleeding episodes per month and received 1000 IU of FVIII concentrate (approximately 15 IU/Kg) following every bleed with good clinical results. Standard of care at the study site is to perform inhibitor titres only when clinically indicated. Since there have been no perceived treatment failures and since the prior inhibitor finding was transient, no follow-up inhibitor assays have been performed. An inquiry has been made to the study site for further follow-up regarding the clinical inhibitor status of patient 4404, response to this inquiry is pending.

In study 310, adverse events considered by the investigator to be related to moroctocog alfa (AF-CC) (both treatment-emergent adverse events and treatment-emergent hemophilia events) included the above instances of inhibitor to FVIII (2 patients) and asthenia, hemorrhage, and arthralgia (1 patient each); these latter events are not unexpected in this study population. Of the 3 severe treatment-emergent adverse events and 3 severe treatment-emergent hemophilia events reported in study 310, none were considered related to moroctocog alfa (AF-CC).

3.4.2.2.1 Study 3082B2-311-WW

Study 311 included 22 patients who received moroctocog alfa for surgical prophylaxis. All 22 patients were followed up for 1.327 person days. This study only included white male patients between the ages of 16-65 years. Study 311 was designed in accordance with the CHMP "Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX Products," dated October 2000.
For new products, the NfG specifies provision of physician-reported information pertaining to efficacy of hemostasis, loss of blood, and requirement for transfusion for a minimum of 5 patients undergoing at least 10 surgical procedures. For modified products, the NfG specifies provision of available surgical data with no requirement for a minimum number of patients. In addition, to establish the efficacy and safety of continuous infusion therapy, the NfG specifies that the study be carried out in at least 12 severe hemophilia A (FVIII<1%) patients undergoing elective major surgical procedures. The MAH had provided all available surgical efficacy and safety data from study 311 pertaining to the use of moroctocog alfa (AF-CC), a modified recombinant FVIII product, for surgical prophylaxis in the variations.

The original progress report for study 311 described 8 patients enrolled into the study as of the data cut off date (10 Jan 2007). Of these 8 enrolled patients, 7 were assigned to receive moroctocog alfa (AF-CC) by bolus injection (BI) and underwent elective major surgery, and 3 patients completed the study. Safety results for all 8 enrolled patients and efficacy results pertaining to investigator's assessment of hemostatic efficacy, blood loss, and transfusion requirements for all 7 patients who underwent elective major surgery were described in the original progress report. As well, data on 6 additional patients who underwent and completed major surgery (using criteria of study 311) in the context of supporting study 3082B1-306-GL (study 306) have been provided. Surgical operative efficacy of moroctocog alfa (AF-CC) for these 6 patients was rated as "very useful" for 5 procedures and "useful" for 1 procedure. Data regarding preoperative and perioperative dosing, operative efficacy assessments, transfusion requirements (if any), blood loss in surgery, and blood loss following surgery for these 6 patients is provided in table 1

Table 1
Characteristics of Major Surgeries Performed and Use of Moroctocog alfa (AF-CC) in Study 306

Investigator/ Patient No.	Surgical Procedure [a]	Preoperative Dose (IU/kg)	Total Perioperative Dose (IU/kg) [b]	Operative Efficacy Assessment	Require Transfusion?	Blood Loss In Surgery (mL)	Blood Loss After Surgery (mL)
247/461	Open Reduction with Internal Fixation of Left Ulna and Radius	52.7	2823.0	Useful	No	0	0

552/701	Arthroscopy	59.7	3820.0	Very Useful	No	0	0
552/703	Arthroscopy	68.2	4775.0	Very Useful	No	0	0
562/727	Right Ankle Arthrodesis	(Not Recorded)	0	Very Useful	No	0	0
1254/181	Resect Right Radial Head	28.4	2130.0	Very Useful	No	5	0
1312/951	Right Ankle Fusion	51.3	3748.0	Very Useful	No	<50	0

a. Considered major surgery according to the study 3082B2-311-WW protocol.
b. Total perioperative dose is the sum of all doses administered during the pre-operative and intra-operative periods.
Sources: SX_001a – 04 Oct 05, and GLB_001a2 - 04 Oct 05

The MAH upon request from the CHMP provided updated surgical data with a cut off date of 01 Jun 2007. The updated progress report describes 22 patients enrolled into the study as of the data cutoff date, including the 8 patients described in the original progress report. Of the 22 enrolled patients, 14 were assigned to receive moroctocog alfa (AF-CC) by bolus injection (BI) and 8 patients by continuous infusion (CI). Twenty-one (21) patients underwent elective major surgery, including 14 BI patients and 7 CI patients. The remaining patient assigned to receive CI had received moroctocog alfa (AF-CC) for pharmacokinetic assessment but had not undergone surgery.) Eleven (11) patients had completed the study as of the data cutoff date, including 10 BI patients and 1 CI patient. Safety results for all 22 enrolled patients and efficacy results for all 21 patients who underwent elective major surgery are described in the updated progress report and are also provided in the table below:

Listing of Surgical and Postsurgical Efficacy Outcomes in Study 311

			Hemostatic Efficacy		Transfusion(Yes/No)			Blood Loss (mL)				
Subject	Description of Surgical Procedure	BI or CI	Visit 3	Visit 5	Predicted	Actual Intraop	Actual Postop	Predicted	Actual Intraop	Normal Abnormal Intraop[a]	Actual Postop	Normal Abnormal Postop[a]
000101	Laparoscopic ventral incisional hernia repairs and scar revisions	CI	Excellent	Excellent	No	No	Yes	30	60	N	2400	AB
000601	Total right knee arthroplasty	BI	Good	Excellent	Yes	No	No	600	400	N	0	
001301	Left ulnar nerve transposition release	BI	Excellent	Excellent	No	No	No	None	0		0	
001801	Right elbow synovectomy	BI	Good	Excellent	No	No	No	60	200	N	0	
002101	Right knee synovectomy	BI	Excellent	Excellent	No	No	No	100	100	N	50	N
002102	Left knee synovectomy	BI	Excellent	Excellent	No	No	No	100	50	N	0	
002301	Total left knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	1050	N
002302	Total right knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	1260	N
002303	Total right knee replacement	BI	Excellent	Excellent	No	No	No	1500	100	N	1170	N
002304	Total left knee replacement, followed by revision and debridement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	450	N
002305	Total left knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	1200	N
002306	Total right knee replacement	BI	Excellent	Excellent	Yes	No	Yes	1500	200	N	1350	N
002307	Total left knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	1230	N
002308	Total left knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	980	N
002702	Total right knee replacement	BI	NESE	NESE	Yes	Yes	No	1500	1700	N	0	
002703	Right hip replacement	CI	NESE	NESE	Yes	Yes	No	1200	950	N	500	N
002704	Total left knee replacement	CI	NESE	NESE	Yes	Yes	No	1500	1300	N	0	
002705	Total right knee replacement	CI	Good	Good	Yes	Yes	No	1500	1050	N	0	
002706	Right knee arthroscopy	CI	Excellent	Excellent	No	No	No	200	0		0	
002707	Total right knee replacement	CI	Good		Yes	Yes		1500	1350	N		

002709	Total right knee replacement	CI	Good		Yes	No	1500	500	N	
002710		CI			No		1500			

a. Abbreviations: Intraop = intraoperative period; Postop = postoperative period; CI= continuous infusion; N = Normal; AB = Abnormal; BI = bolus injection; NESE = Not evaluable for surgical efficacy.

Only a limited number of patients in Study 311 have been treated with continuous infusion (CI), but the CHMP considered it important to stress that neither current marketed ReFacto nor moroctocog alfa (AF-CC) will have a posology supporting continuous infusion (CI), given the limited clinical data..

Cases of inhibitors in study 311

One instance of a low-titre inhibitor has been reported in study 311.

Subject 2102: This was an instance of a clinically-silent low-titre inhibitor that was initially detected by the central laboratory only during routine protocol-specified surveillance prior to surgery. The local laboratory was negative at the time. The low-titre inhibitor (0.8857 BU/mL) occurred after several injections of plasma-derived FVIII concentrate that were preceded by only a single does of moroctocog alfa (AF-CC) for a PK assessment. The clinical course of the patient is described in the subject narrative in the updated progress report for study 311. The patient proceeded with surgery and had an excellent hemostatic response to moroctocog alfa (AF-CC) and no bleeding complications. The patient was clinically asymptomatic throughout the study. Repeat inhibitor testing at the time of his final visit showed a persistent positive result from both the central and local laboratory of 1.5108 BU/mL and 1.4 BU/mL, respectively. This patient had received treatment with plasma-derived FVIII prior to study and did not have a history of treatment with ReFacto. One communication received 9 months following completion of study participation, has been provided by the study site regarding clinical inhibitor status of this patient. The patient has been treated on demand since study completion. He was retested at the local laboratory for FVIII inhibitors on 2 occasions, on 17 May 2007 (result 1.6 BU) and 11 Jul 2007 (results 0.8 BU). During this interval he experienced 6 bleeding episodes, 3 have been treated with recombinant factor VIIa, and 3 have been treated with plasma derived FVIII concentrates. No information is available regarding treatment results.

As described in the updated progress report for study 311, the above event of a low-titre inhibitor was the only adverse event (both treatment-emergent adverse events and treatment-emergent hemophilia events) considered by the investigator to be related to moroctocog alfa (AF-CC).

The current updated results from study 311 contains efficacy and safety data from 21 patients undergoing elective major surgery giving good evidence in support of a preserved and comparable efficacy and safety as current ReFacto.
The study is still ongoing and the MAH committed to provide the final results upon completion of the study.

3.4.2.2.3 Studies 3082B1-306-WW and 3082B1-30-7WW

Study 307 was a continuation study for patients who completed study 306.

Ninety-eight patients from study 306 were enrolled in the extension study 307. Study 307 was initiated to provide data related to extended use of moroctocog alfa (AF-CC), and patient exposure to moroctocog alfa (AF-CC) in study 307 was significantly longer in duration than in study 306 (median exposure days, 169).

In the study 3082B1-306-GL (study 306), 110 patients had a median exposure of 58 exposure days (range 5-140).

In conclusion, the efficacy results supports the findings in the pivotal studies. There are minor differences that can be explained by the difference between US and EU in treatment regimes, e.g. the use of prophylactic treatment and on-demand treatment.

3.4.2.3 Discussion on efficacy data

3.4.2.3.1 Assessment of on–demand treatment using the 4-point response scale

During the assessment, the MAH was asked to clarify the assessment of on demand treatment using 4-point response scales in studies 306 and 310. The 4-point response scale used in study 306 is different from the one used in pivotal studies and the results are therefore not comparable. In study 306 the "best responses seen with other FVIII products with similar bleeds or procedures" is assessed. It is very unlikely that patient/guardian have the qualification necessary to make this judgement because the experience with other product may have been short, a long time ago or only have been treated with one product.

The MAH agreed that the 4-point clinical response scale in supportive study 306 differs from the 4-point response scale for on-demand treatment used in studies 310 and 311. Despite the differences in the rating scales, The MAH submits that rating results from the clinical response scale in study 306 remain supportive of the results observed in study 310. The clinical response scales in studies 306 and 310 are presented below in Table 54-1.

Table 54-1: Clinical Response Scales in Studies 306 and 310

Rating	Study 306	Study 310
Excellent:	A satisfactory response—as much and as rapid improvement as the best responses seen with other FVIII products with similar bleeds or procedures	Abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single infusion
Good:	A satisfactory response—as much and as rapid improvement as most responses seen with other factor VIII products with similar bleeds or procedures	Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an infusion, but possibly requiring more than one infusion for complete resolution
Moderate:	A less than satisfactory response—not as good as most responses seen with other factor VIII products with similar bleeds or procedures	Probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requires more than one infusion
No Response:	No improvement at all	No improvement at all, or condition worsens.

In general these discriminators permit an excellent response to be distinguished from a good response. An excellent response is characterized by a more rapid onset and a more complete clinical response relative to a good response (Excellent = abrupt pain relief and/or improvement in signs of bleeding as opposed to Good = definite pain relief and/or improvement in signs of bleeding). In addition a requirement for more than 1 infusion to effect bleed resolution precludes assignment of an excellent rating. While there is the potential for some nominal overlap between excellent and good ratings, this overlap is small in magnitude and is entirely mitigated by the fact that excellent and good results are pooled in the presentation of rating efficacy data.

The use of 4-point subjective response scales to assess efficacy of on-demand treatment has been a feature of nearly all studies evaluating efficacy of recombinant FVIII products; furthermore, pooling of excellent and good rating results has been a common feature across studies in discussing efficacy results. The pooled descriptions for excellent and good responses in study 310 capture all infusions for which a substantial/satisfactory clinical response has been observed. While not identical in text, the pooled descriptions for excellent and good responses in supportive study 306 also capture all infusions for which a substantial/satisfactory clinical response has been observed.

Inclusion criteria for study 306, across all protocol versions, included requirements of ≥250 prior EDs, severe hemophilia (FVIII:C ≤2%), and age ≥6 years. The MAH proposed that these criteria ensured that each participating patient (or his caregiver) had sufficient past experience with responses to FVIII replacement therapy using other product(s) to assess moroctocog alfa (AF-CC) treatment responses relative to other FVIII treatment product(s). Protocol design for study 306 specified that upon

achieving 50 EDs to moroctocog alfa (AF-CC), patients were to exit the study with the option of continuing moroctocog alfa (AF-CC) treatment on extension study 3082B1-307-GL (study 307). Of the 110 patients enrolled in study 306, 104 received prophylactic therapy, 18% on a >3 dose per week regimen, 66% on a 3 dose per week regimen, and 16% on a 2 dose per week regimen. In the context of these dosing schedules, completion of the protocol specified 50 EDs would be anticipated within a 6-month period, an interval sufficiently short to ensure that patients (or their providers) could reflect upon prior experience with FVIII replacement therapy as they assessed moroctocog alfa (AF-CC) on-demand treatment results.

Based upon comparability of pooled excellent/good assessments for studies 310 and 306, the extensive FVIII product treatment experience patients in study 306 had prior to study entry, and the limited duration of study 306, The MAH proposed that rating scale results from study 306 are indeed supportive of the results observed in pivotal study 310.

The MAH recognizes the limitations and differences of The The use of the 4-point rating scale used in study 306 and 310 respectively, but has provided arguments in favour of its use as supportive information. This was accepted by CHMP.

3.4.2.3.2 Efficacy and safety in major surgery

The efficacy and safety endpoints used to characterize the use of ReFacto AF-CC in patients undergoing major surgery are relevant except for "A comparison of the predicted and actual estimated blood loss and transfusion requirements." With many different centres recruiting patients the numbers of surgeons is going to be large leading to subjective evaluation of bleeding that can hardly be used to predict bleeding from centre to centre. It can only predict bleeding from surgeon to surgeon but this is not relevant for this study.

The MAH agreed with the above CHMP comments that, given the number of centres recruiting patients and given the large number of surgeons, the subjective evaluation of bleeding by surgeons can hardly be used to predict bleeding from centre to centre. However, that prediction of bleeding from centre to centre, or from surgeon to surgeon, is not the intent of this secondary objective. The intent of this secondary objective is a within-patient comparison of predicted and actual blood loss and a within-patient comparison of predicted and actual transfusion requirements.

The protocol for study 311 specifies that "the investigator must prospectively predict the estimated blood loss and transfusion needs of the patient, for both bolus injection (BI) and continuous infusion (CI) patients." The protocol further specifies that "in their estimate, the investigators should assume the surgery will be completed without major complications and may use their standard transfusion guidelines, if available. This estimate will be compared to the actual recorded blood loss during surgery and any transfusions occurring in surgery." These specifications are made at the study site level by the investigator, based upon typical experience at that study site for a given surgical procedure. Although clinical practices, operating room techniques, and supportive care guidelines may vary across treatment centres, these practices are generally uniform within a given treatment centre. Furthermore, at hemophilia treatment centres, clinical practice is to have all surgical procedures of a given type performed by a given surgeon. Thus, the protocol-specified within-patient comparison of projected and actual blood loss and transfusion requirements eliminates the variables of multiple surgeons and differing treatment practices across study sites from the comparison of predicted and actual blood loss and transfusion requirements. The only variables remaining are the use of moroctocog alfa (AF-CC) FVIII replacement therapy and the patient. Therefore, as designed in the protocol, the comparison of predicted and actual blood loss and transfusion requirements on a within-patient basis is an appropriate secondary objective as hemostatic efficacy is assessed in the surgical setting. Consistent with this investigational design, results pertaining to transfusion requirements and blood loss are discussed as a summary of the respective within-patient experiences, referencing departures from predicted rather than absolute measures for bleeding or transfusion requirements.

The CHMP considered the MAH clarifications on the purpose of the endpoint and its limitations acceptable.

3.4.2.3.3 Data on induction of immune tolerance

Clinical information regarding use of moroctocog alfa (AF-CC) in immune tolerance is very limited. In studies 306 and 307, patients who had an inhibitor could continue treatment with the same or a higher dose of moroctocog alfa (AF-CC) at the discretion of the investigator. In these studies, an immune tolerance regimen could be considered, if appropriate. During study 306, 2 recurrent and 1 *de novo* FVIII inhibitor were detected for 3 patients. One of these patients was withdrawn from the study and 2 patients underwent immune tolerance therapy (ITT) with moroctocog alfa (AF-CC). The latter 2 patients subsequently enrolled in long-term extension study 307 and continued their ITT with moroctocog alfa (AF-CC). Each patient had experienced clinical resolution of his inhibitor.

During the clinical study of ReFacto in PUPs, 32 cases of inhibitor development were reported. Sixteen patients developed high-responder inhibitors (>5 BU) and 16 patients developed low-responder inhibitors. Of the 16 patients who developed high-responder inhibitors, 15 underwent ITT with disappearance of inhibitor in 11 of these patients, for a success rate of 73% (11/15). Of the 16 patients who developed low-responder inhibitors, 10 underwent ITT with disappearance of the inhibitor in 9 of these patients, for a success rate of 90% (9/10). Insofar as moroctocog alfa (AF-CC) is the same molecular entity as ReFacto and comparability has been established between moroctocog alfa (AF-CC) and ReFacto, the MAH maintains that comparable outcomes may be anticipated when moroctocog alfa (AF-CC) is used in the off-label setting, for the induction of immune tolerance.

The International Study of Immune Tolerance Therapy is an independent, ongoing study that is assessing outcomes for 2 different regimens of ITT. Each patient is treated with a commercially available product of his physician's choice. Once market authorization is granted for moroctocog alfa (AF-CC), some patients enrolled in this study may be treated with moroctocog alfa (AF-CC). Results for this study are currently blinded, but information regarding outcomes is being captured on a product-by-product basis and is expected to be available at study completion. These results may serve to further inform expectations of clinical outcomes when using moroctocog alfa (AF-CC) for ITT.

3.4.2.3.4 Patient population and neoantigenicity

The MAH provided evidence on whether or not the patient population selected for study 306 did not consist of patients receiving factor VIII regularly. This may be an important difference between the pivotal and supportive studies when assessing neoantigenicity. The applicant was asked to justify the impact on the results presented.

In study 310, patients were required to receive moroctocog alfa (AF-CC) for routine prophylaxis 3 times per week over 6 months during the safety and efficacy period of the study. Of the 94 enrolled patients, 89 patients (95%) accrued at least 50 EDs to moroctocog alfa (AF-CC). The median time on study for all 94 enrolled patients was 240.5 days (range 149-301 days), or approximately 8 months. This duration includes a median time on routine prophylaxis (from day of first routine prophylactic dose to day of last study visit) of 178 days.

In comparison, patients enrolled in supportive study 306 beginning with protocol amendment 1 were required to receive moroctocog alfa (AF-CC) for routine prophylaxis at least 2 times per week (with the exception of patients continuing from study 305 who had the option to administer moroctocog alfa (AF-CC) on an on-demand basis) for a minimum of 50 EDs. No patient was enrolled under the original protocol. Based on this study design, patients who received routine prophylaxis at least 2 times per week were expected to accrue 50 EDs in 6 months or less.

One hundred ten patients were enrolled in study 306, and 104 patients received routine prophylaxis at least 2 times per week. Of the 110 enrolled patients, 98 patients (89%) had at least 50 EDs, 6 patients (5%) had between 45 and 49 EDs, and 6 patients (5%) had fewer than 45 EDs (range 5 to 39 EDs). The median time on study for all 110 patients was 157.5 days (range 29-546 days), or approximately 5 months.

Based on this comparison, the MAH proposed that the pattern of exposure to moroctocog alfa (AF-CC) was sufficiently similar between study 310 and supportive study 306 such that there was no impact on the assessment of neoantigenicity between the studies. Based on the additional information provided above, t he CHMP considered the MAH justifications acceptable.

3.4.2.3.5 Bleeding frequency

When comparing the frequencies of bleeding in study 3082B1-306-GL with study 3082B2-310-WW some differences were noticed. In study 3082B2-310-WW 60.6% had no spontaneous bleeding compared to 49% in study 306 and 45.7% had no bleeding at all compared to 24% in study 306. Furthermore, the observed ABR in this study differs from the ABR observed in the pivotal study 3082B2-310-WW

Statistics	**3082B2-310-WW Pivotal**	**3082B1-306-GL Supportive**	**3082B2-310-WW Pivotal**	**3082B1-306-GL Supportive**
	Spontaneous	Spontaneous	Total	Total
Median	0	1.3	1.9	5.2
Mean	1.9	4.2	3.9	7.7
Std Dev	4.1	6.5	6.5	8.6
Min	0	0	0	0
Max	30.1	44.7	42.1.1	44.7
95 % CI	(1.1, 2.7)		(2.6, 5.2)	

These findings could support the concern on whether the supportive studies really are supportive or studies with a different dose regime in a different study population with a study drug with different efficacy than the one commercially available. The applicant was asked during the procedure to comment on these findings and the impact on the results with two different dosing strategies (2 times a week (supportive studies) and 3 times a week (pivotal studies)).

The MAH proposed that the observed differences in prophylaxis efficacy outcomes between study 310 and supportive study 306 can be attributed to differences in protocol-specified criteria regarding the selection of dosing regimen and dose escalation during routine prophylaxis, rather than to differences in the efficacy of moroctocog alfa (AF-CC) in these studies.

In study 310, routine prophylactic dosing was initiated using the same dosing regimen at step 1 (30 ± 5 IU/kg 3 times per week) for all patients. Predefined escape criteria provided rules for dose escalation to higher intensity dosing regimens, initially to step 2 (45 ± 5 IU/kg 3 times a week), and then to more frequent or higher doses as determined by the investigator. Escape criteria for escalating to a higher step (eg, step 1 to step 2) were either (a) 2 spontaneous (atraumatic) bleeding episodes into major joints such as elbow, ankle, or knee joint(s) or other target joints over a 28-day period, or (b) 3 or more spontaneous bleeding episodes over a 28-day period. In study 310, patients received 6347 infusions of moroctocog alfa (AF-CC) for routine prophylaxis, with a median dose per infusion of 30.2 IU/kg. The incidence of dose escalation was low, with only 7 dose escalations prescribed for 6 patients.

In comparison, patients in study 306 were to receive moroctocog alfa (AF-CC) at least 2 times per week for routine prophylaxis, at a dose and schedule as determined by the investigator. There were no protocol-specified criteria for dose escalation in the study. In study 306, the majority of prophylactic infusions (66%, 3592/5483) were administered 3 times per week, followed by >3 times per week (18%, 992/5483) and 2 times per week (16%, 899/5483). (Note, that patients who were on multiple regimens are counted more than once in this distribution.) The median dose per prophylactic infusion was 31.6 IU/kg for the 2 times per week regimen, 30.1 IU/kg for the 3 times per week regimen, and 40.0 IU/kg for the >3 times per week regimen.

The median and mean ABR for spontaneous bleeds were 0.0 and 1.9 respectively in study 310 compared with 1.3 and 4.2 respectively in study 306 (Table 55-1).

Table 55-1: Annualized Spontaneous Bleeding Rates in Studies 310 and 306

Statistic	310 Pivotal Overall	306 Supportive Overall	306 Supportive 2 times per week	306 Supportive 3 times per week	306 Supportive >3 times per week
Median	0	1.3	1.1	0	2.6
Mean	1.9	4.2	5.0	4.2	6.1
SD	4.1	6.5	8.7	6.9	9.3
Min	0	0	0	0	0
Max	30.1	44.7	31.2	44.7	33.1
95 % CI	(1.1, 2.7)	ND	ND	ND	ND

Abbreviations: CI = confidence interval; ND = not determined; SD = standard deviation

Several elements of the design of study 306 contribute to these observations.

- A subset of prophylaxis treatment in study 306 was delivered at a low frequency (2 infusions per week) relative to that specified in study 310 (3 infusions per week). The subset of patients treated at this frequency, in its entirety, would have received more intensive routine prophylaxis treatment *a priori* in the context of the protocol for study 310, most likely resulting in a lower ABR.
- The protocol for study 306 did not have pre-specified criteria for prophylaxis dose/frequency escalation; dose/frequency escalation was instead at the investigator's discretion. Therefore patients experiencing spontaneous breakthrough bleeding episodes could undergo dose escalation on a delayed basis or not at all, in either instance contributing to an increased ABR across prophylaxis regimens.

As well, results of prophylaxis treatment in study 306 are consistent with investigator bias in assigning treatment regimens. There was very modest variation in the ABR for spontaneous bleeds across treatment regimens suggesting that intensity of treatment regimens was titrated based upon observed or historic susceptibility to bleeding episodes. Patients displaying more susceptibility to bleeding were most likely assigned to more intensive regimens. The design of prophylaxis in study 310 did not allow for such bias in assignment of prophylaxis treatment regimens

The median and mean ABR for all bleeds was 1.9 and 3.9, respectively, in study 310 compared with 5.2 and 7.7, respectively, in study 306 (Table 55-2). As is the case for the observed spontaneous ABR, differences in protocol design can account for the increased ABR for all bleeding episodes that was observed in study 306. These differences include the lower intensity of prophylaxis that was permitted in study 306 and the absence of prespecified dose-escalation criteria. As was the case for with spontaneous bleed results, results for all bleeds in study 306 are also consistent with an investigator bias in assigning treatment regimens. Mean ABR is comparable for all bleeds across treatment regimens, suggesting that investigators in study 306 prescribed the dose and/or frequency of moroctocog alfa (AF-CC) according to the severity of patients' clinical presentation. Such dosage adjustments were based on the investigator's clinical judgment and may not have achieved the degree of hemostasis in all patients that a standard prophylactic regimen would have. Increases in bleeding rates due to variations in dose and/or frequency have been reported for other FVIII products, whether due to variable compliance of the patient population or differences in practices with regard to intensity of prophylaxis treatment.

Table 55-2: Annualized Overall Bleeding Rates in Studies 310 and 306

Statistic	310 Pivotal Overall	306 Supportive Overall	306 Supportive 2 times per week	306 Supportive 3 times per week	306 Supportive >3 times per week
Median	1.9	5.2	2.9	5.7	5.1
Mean	3.9	7.7	8.1	8.0	8.2
Std Dev	6.5	8.6	11.6	9.0	9.3
Min	0	0	0	0	0
Max	42.1.1	44.7	41.6	44.7	33.1
95 % CI	(2.6, 5.2)	ND	ND	ND	ND

Abbreviations: CI = confidence interval; ND = not determined; SD = standard deviation

Thus, the observed differences in bleeding rates between pivotal study 310 and supportive study 306 are accounted for by differences in study design. Efficacy of prophylaxis treatment with moroctocog alfa (AF-CC) in both studies is demonstrated when compared to the ABR of 23 bleed rates observed for patients during on-demand treatment in the pivotal study of ReFacto in previously treated patients (3082A1-300-GL). Therefore, the MAH maintains that efficacy results from study 306 corroborate those from study 310, and that moroctocog alfa (AF-CC) was efficacious in the control and prevention of bleeding in both studies.

The MAH provided good evidence in support of the view that the observed differences in prophylaxis efficacy outcomes between study 310 and supportive study 306 can be attributed to differences in protocol-specified criteria regarding the selection of dosing regimen and dose escalation during routine prophylaxis, rather than to differences in the efficacy of moroctocog alfa (AF-CC) in these studies.

3.4.2.3.6 Consumption calculation for bleeding episodes

The Note for Guidance suggests consumption calculations for bleeding episodes (on-demand-regimen) and (major) surgery: Clinical efficacy should be assessed by calculating the consumption of FVIII, expressed as IU/kg per event (prophylaxis, on-demand, and surgery). In the light of inconsistencies and individual deviations concerning the 4-point response scales this information could be useful. The MAH was asked to calculate the dose (IU) per kg per bleeding episode, and the dose (IU) per kg per surgical procedure.These numbers are easily comparable and might be more meaningful than an individual response scale.

In study 310, 51 of 94 enrolled patients had 180 bleeding episodes while receiving moroctocog alfa (AF-CC) for routine prophylaxis. All values expressed in IU/kg were provided including the total dose of all infusions, the dose of the first infusion, and the mean dose per infusion administered per bleeding episode.

In study 311, 22 enrolled patients were assigned to receive moroctocog alfa (AF-CC) by BI (n=14) and or CI (n=8) as of 01 Jun 2007. Twenty-one patients, including 14 BI and 7 CI patients, each underwent 1 surgical procedure. (One patient was assigned to receive CI had received moroctocog alfa (AF-CC) for pharmacokinetic assessment but had not undergone surgery.) All values expressed in IU/kg were provided including the dose administered during the preoperative, operative, and postoperative periods as well as the total dose administered across all these periods by Bolus infusion per patient (or surgical procedure) and by Continuous Infusion per surgical procedure.

The CHMP concluded that there is no cause for concern with regard to the efficacy of moroctocog alfa (AF-CC).

3.4.2.3.7 Overview of patient population

Of the 116 patients enrolled in the pivotal studies at the time of filing, 18 paediatric patients (aged 12 to 16 years) had been exposed to moroctocog alfa (AF-CC) (Tables below).

Table 0-1: Clinical Trial Exposure by Age Group and Gender (Study 310)

	Persons		Person days	
Age Group at First Study Entry	M	F	M	F
12-16 years	18	0	3803	0
17-65 years	76	0	15954	0

Abbreviations: F=female; M=male. DEMO4_RISK - 19MAR08 10:10

Table 0-2: Clinical Trial Exposure by Age Group and Gender (Study 311)

	Persons		Person days	
Age Group at First Study Entry	M	F	M	F
17-65 years	22	0	1327	0

Abbreviations: F=female; M=male. DEMO4_RISK - 19MAR08 10:06

Clinical trial exposure information for studies 3082B1-305-GL (305), 306, and 307 is shown in Tables below. A total of 51 paediatric patients (aged 6 to 16 years) were exposed to moroctocog alfa (AF-CC) in these studies: 49 patients from study 306 (including 46 patients who later participated in study 307) and 2 patients who participated in study 305 but did not participate in studies 306 and 307.
Of the 30 patients enrolled in study 305, 30 received a single dose of moroctocog alfa (AF-CC) (50 IU/kg) and 29 received a single dose of ReFacto (50 IU/kg).

Table 0-3: Clinical Trial Exposure by Duration (Study 305)

Duration of Exposure	Persons	Person days
Cumulative up to 1 month	30	349
Cumulative up to 3 months	30	362

Total person time in the study : 362 days. DEMO4_RISK_CT_305 - 19MAR08 10:16

Table 0-4: Clinical Trial Exposure by Dose (Study 305)

Total Exposure in IU	Persons	Person days by Quartiles
0 - 3330	8	90
3331 – 3562	7	92
3563 – 3835	8	75
> 3835	7	105

DEMO4_RISK_CT_305 - 19MAR08 10:16

Table 0-5: Clinical Trial Exposure by Age Group and Gender (Study 305)

	Persons		Person days	
Age Group at First Study Entry	M	F	M	F
12 years - 16 years	6	0	84	0
17 years - 65 years	23	0	270	0
> 65 years	1	0	8	0

Abbreviations: F=female; M=male. Minimum age is 12 years, maximum age is 70 years.
DEMO4_RISK_CT_305 - 19MAR08 10:16

Table 0-6: Clinical Trial Exposure by Ethnic Origin (Study 305)

Race	Persons	Person days
Black	2	15
Caucasian	25	329
Hispanic	3	18

DEMO4_RISK_CT_305 - 19MAR08 10:16

In study 306, 110 patients received more than 16 million IU given over 7035 infusions over 6860 exposure days. The median dose per infusion was 32.2 IU/kg (range, 10.2 to 127 IU/kg), and the median number of infusions per patient was 59.5 (range, 5 to 156).

Table 0-7: Clinical Trial Exposure by Duration (Study 306)

Duration of Exposure	Persons	Person days
Cumulative up to 1 month	110	3299
Cumulative up to 3 months	110	9718

Table 0-7: Clinical Trial Exposure by Duration (Study 306)

Duration of Exposure	Persons	Person days
Cumulative up to 6 months	110	16620
Cumulative up to 12 months	110	18377
Cumulative up to 18 months	110	18701

Total person time in the study : 18701 days. DEMO4_RISK_CT_306 - 19MAR08 10:16

Table 0-8: Clinical Trial Exposure by Dose (Study 306)

Total Exposure in IU	Persons	Person days by Quartiles
0 - 108278	27	4193
108279 - 135629	28	4836
135630 - 169876	27	4270
> 169876	28	5402

DEMO4_RISK_CT_306 - 19MAR08 10:16

Table 0-9: Clinical Trial Exposure by Age Group and Gender (Study 306)

	Persons		Person days	
Age Group at First Study Entry	M	F	M	F
6 years - 11 years	14	0	1972	0
12 years - 16 years	35	0	5517	0
17 years - 65 years	59	0	10924	0
> 65 years	2	0	288	0

Abbreviations: F=female; M=male. Minimum age is 7 years, maximum age is 70 years.
DEMO4_RISK_CT_306 - 19MAR08 10:16

Table 0-10: Clinical Trial Exposure by Ethnic Origin (Study 306)

Race	Persons	Person days
Asian	1	128
Black	5	1169
Caucasian	95	16204
Hispanic	6	755
Other	3	445

DEMO4_RISK_CT_306 - 19MAR08 10:16

In study 307, 96 patients received in excess of 41.7 million IU of moroctocog alfa (AF-CC) administered over a minimum of 17,169 infusions over at least 16,948 exposure days (median, 169 exposure days per patient).

Table 0-11: Clinical Trial Exposure by Duration (Study 307)

Duration of Exposure	Persons	Person days
Cumulative up to 1 month	97	2910
Cumulative up to 3 month	97	8686
Cumulative up to 6 month	97	17414
Cumulative up to 12 months	97	32330
Cumulative up to 18 months	97	43457
Cumulative up to 2 years	97	48846
Cumulative up to 3 years	97	49127

Total person time in the study : 49127 days.DEMO4_RISK_CT_307 - 19MAR08 10:16

Table 0-12: Clinical Trial Exposure by Dose (Study 307)

Total Exposure in IU	Persons	Person days by Quartiles
0 - 210756	25	7597
210757 - 362772	24	10552
362773 - 584595	24	14572
> 584595	24	16406

DEMO4_RISK_CT_307 - 19MAR08 10:16

Table 0-13: Clinical Trial Exposure by Age Group and Gender (Study 307)

	Persons		Person days	
Age Group at First Study Entry	M	F	M	F

Table 0-13: Clinical Trial Exposure by Age Group and Gender (Study 307)

	Persons		Person days	
Age Group at First Study Entry	M	F	M	F
6 years - 11 years	13	0	5708	0
12 years - 16 years	33	0	19763	0
17 years - 65 years	50	0	23056	0
> 65 years	1	0	600	0

Abbreviations: F=female; M=male. Minimum age is 7 years, maximum age is 70 years.
DEMO4_RISK_CT_307 - 19MAR08 10:16

Table 0-14: Clinical Trial Exposure by Ethnic Origin (Study 307)

Race	Persons	Person days
Asian	1	349
Black	4	1472
Caucasian	83	42320
Hispanic	6	2879
Other	3	2107

DEMO4_RISK_CT_307 - 19MAR08 10:16

3.4.2.4 Discusion on safety data

3.4.2.4.1 Safety profile in the paediatric population

Data pertaining to test article exposure and safety (treatment-emergent adverse events and hemophilia events) from study 306 have been analyzed for the following age groups: all ages (n=110), 6 to 11 years (n=14), 12 to 16 years (n=35), 17 to 65 years (n=59), and older than 65 years (n=2). Comparisons are made between either paediatric age group (6 to 11 years, 12 to 16 years) versus adult patients aged 17 to 65 years.
For patients aged 6 to 11 years, the median dose per infusion was 45.2 IU/kg (range, 22.6 to 127.0 IU/kg), and the median number of exposure days was 56 (range, 51 to 88). For patients aged 12 to 16 years, the median dose per infusion was 37.8 IU/kg (range, 12.3 to 106.5 IU/kg), and the median number of exposure days was 60 (range, 48 to 114). In comparison, the median dose per infusion was 29.1 IU/kg (range, 10.2 to 126.9 IU/kg) and the median number of exposure days was 59 (range, 5 to 140) for adult patients.
The higher doses administered to paediatric patients may reflect the common practice to use full vials of moroctocog alfa (AF-CC), without discarding any drug, as well as the relatively lower weight of these patients compared with adult patients.

Comparison of events across age groups revealed few differences in the safety profile of moroctocog alfa (AF-CC) in paediatric patients compared with the overall study population. Events reported with an incidence ≥10% and at least 2 times higher in patients aged 6 to 11 years than in adult patients were fever (29% vs 3%, respectively), vomiting (29% vs 3%), nausea (21% vs 2%), cough increased (21% vs 10%), rhinitis (21% vs 8%), abdominal pain (14% vs 2%), and pharyngitis (14% vs 3%). Events reported with an incidence ≥10% and at least 2 times higher in patients aged 12 to 16 years than in adult patients were infection (34% vs 17%, respectively), pharyngitis (29% vs 3%), back pain (14% vs 7%), and diarrhea (14% vs 2%). These events largely reflect the spectrum of illnesses commonly seen in paediatric and adolescent patients and are observed in these populations at a higher frequency than in adults. None of these differences were deemed clinically important. These safety results are similar to those obtained for paediatric patients (12 to 16 years) in study 310 according to the MAH.

In addition to the above data, the CHMP requested the MAH to commit to provide the final study report of study 3082B2-313WW ongoing in the paediatric population and perform additional studies in children (see RMP/Post marketing studies).

Information on frequencies of adverse events in paediatric population compared to adults

The applicant states that some reported adverse events occurred at a higher frequency in the age groups 6 to 11 and 12 to 16 years compared to adults. However, the majority of these reported events also included events that were considered to be unrelated by the investigator. Therefore, the applicant further analyzed these data taking into account the causality to assess if there was evidence for an age-related difference in the incidence of related adverse events or hemophilia events.

The applicant has performed an age-stratified analysis of treatment emergent adverse events and hemophilia events that were judged by the investigator to be at least possibly related to moroctocog alfa. This analysis showed a similar frequency of moroctocog alfa related events on a per-patient basis across age groups, the frequency of moroctocog alfa-related events on a per-infusion basis may also be expected to be similar if study drug exposure was comparable across age groups since examination of dose administration information from studies 306 and 310 indicates that the median number of infusions was similar between age groups.

With regard to frequencies of AEs in children, the CHMP interpretation of the data provided does not fully concur with that of the applicant.
The applicant states that, that there is a higher frequency of reported AEs in children compared to adults. However according to the applicant further to an age-stratified analysis, there is a higher frequency reported AEs in children compared to adults. However, according to the applicant this seems not to be found anymore.
There is still a higher frequency rate observed in children although the number of patients in the children groups is limited. In study 310, the supportive tables seem to confirm the higher frequency rate of AE in children (5.6 versus 2.6). Again, this higher frequency is observed even though limited data are provided in children compared to adults.

Although data in children are limited, there seems to be a slightly higher frequency of AEs in the younger age-groups. The CHMP recommended that the SPC included a statement along the following lines: *"Although a limited number of children have been studied, there is a tendency for higher frequencies of AEs in children aged 7-16 as compared to adults. A clinical trial evaluating use of moroctocog alfa (AF-CC) in children less than 6 years is on going.*

3.4.2.4.2 Incidence of inhibitors

Incidence of inhibitors in studies 305, 306 and 307

Since there might have been a signal from these studies of increased immunogenicity due to manufacturing change, the company was requested to provide more detailed information on incidence of inhibitors in studies 305, 306 and 307. The following information was provided.

Moroctocog alfa (AF-CC) manufactured using a chromogenic substrate (CS) calibrated working potency standard was evaluated in studies 3082B1-306-GL (306) and 3082B1-307-GL (307). The dosing used in these studies is therefore similar to that of currently licensed ReFacto.

De novo inhibitors in previously treated patients (PTPs) are most important for identification of a signal of increased immunogenicity following a manufacturing change. To distinguish the signal of inhibitor occurrence in a study secondary to product-related immunogenicity (a *de novo* inhibitor) from the low but persistent background rate of inhibitor development in PTPs, clinical trials in PTPs seek to exclude patients with past history of inhibitor. Thus any inhibitor development during the study should correspond to *de novo* inhibitors and therefore may be attributed to the study product with greater confidence. In study 306, 3 of 110 patients developed inhibitor to factor VIII (FVIII); all 3 patients also developed anti-moroctocog alfa (AF-CC) antibodies as detected by enzyme-linked immunosorbent assay (ELISA). However, only one of the patients had a *de novo* inhibitor. The remaining 2 patients had a recurrent inhibitor and were considered to be at higher risk of inhibitor development. Of these 2 patients, the first had a history of low-titre inhibitor and was admitted into the study in violation of study entry criteria, and the second had a history of low-level Bethesda inhibitor assay (BIA) results (<0.6 BU) that did not meet the study exclusion criteria (≥0.6 BU). Thus, the incidence of de novo inhibitors observed in study 306 was 1 of 110 patients and is comparable with

that reported for study 3082B2-310-WW (310) and also to that reported in the literature for other recombinant FVIII products during registration clinical trials that were similar in general design.

One patient in study 307 developed a *de novo*, low-titre inhibitor to FVIII, without developing anti-moroctocog antibodies by ELISA. Two patients who had inhibitor detected in study 306 continued into study 307. Both these patients began on immune tolerance induction therapy during study 306 and tested negative for inhibitor while participating in study 307.

Comparison of Study 3082B1-306-GL and 3082B1-307-GL Results to the Literature

The risk of inhibitor development is an important safety concern associated with the use of FVIII products. Though many studies of inhibitor development have been performed, a single estimate of incidence is not available. Meta analysis of these studies has not been feasible because of variability in study designs, patient populations, and treatment modalities as well as insufficient information relating to data collection techniques. Inhibitor development rates in previously treated patients (PTPs) are not well defined in the literature; however, in a surveillance programme described in the literature, incidence rates between 1.9% and 3.0% were reported.

The incidence of *de novo* inhibitors was 0.9% (1/110 patients) in study 306 and 1.0% (1/98 patients) in the continuation study 307; these rates are consistent with those reported in the literature. In comparison, the incidence of inhibitors in the pivotal phase 3 PTP study of ReFacto, which is also manufactured by using the CS calibrated working potency standard, was 0.9% (1/113 patients) According to the MAH, these results are consistent with the absence of any signal of increased immunogenicity following the introduction of the manufacturing changes associated with production of moroctocog alfa (AF-CC).

An analysis of the incidence rate of inhibitors by intent-to-treat (ITT), including both de novo inhibitors and recurrent inhibitors in study 306 (2.7%; 3 in 110 patients) and the continuation study 307 (1%; 1 in 98 patients), revealed rates that are also consistent with the published literature describing recombinant factor VIII products. The data for each rFVIII product is summarized below:

- Kogenate (Bayer): full-length recombinant FVIII (FLrFVIII). High-titre inhibitors developed in 2.3% or 2 of 86 PTPs. In one of these inhibitor patients, Western blot analysis of baseline samples detected antibody to FVIII.
- Recombinate (Baxter): FLrFVIII. Inhibitors developed in 2.9% or 2 of 69 PTPs. One patient had a history of a previous low-titre inhibitor, and 1 patient had a low-titre inhibitor at baseline that became a high-titre inhibitor.
- Kogenate Bayer (Bayer): FLrFVIII. Inhibitors developed in 1.4% or 1 of 71 PTPs. This patient had a low-titre inhibitor (0.39 BU) prior to study entry and was considered to have developed a recurrent inhibitor based on this prior history.
- Advate (Baxter): FLrFVIII. Inhibitors developed in 0.93% or 1 of 108 PTPs.

Thus, it may be concluded that the incidence of inhibitors in study 306 and in study 307 is consistent with the previously described experience with ReFacto as noted above, and also with the reported experience for other licensed recombinant factor VIII products. The MAH concluded that study 306 and study 307 provide no signal of increased immunogenicity following the manufacturing changes associated with production of moroctocog alfa (AF-CC). These data are also consistent with the outcomes of study 3082B2-310-WW, which tested this product using a protein content per vial that is even higher than currently intended for EU commercialization.

The CHMP concluded that these results do not give any signs of increased occurrence of inhibitors with moroctocog alfa AF-CC as compared to currently marketed ReFacto or any other recombinant FVIII products. Further data on incidence of inhibitors will be obtained from post-authorisation studies.

3.4.2.4.3 Comparative safety analysis of products with different potencies but same IU/kg dosing practice in case of inadvertent substitution of products with different potencies

Review of data from studies 310 and 306 permits a comparison of the safety of moroctocog alfa (AF-CC) with different potencies and administered by the same dosing practice. Moroctocog alfa (AF-CC) manufactured using the OS calibrated working potency standard was evaluated in study 310, while moroctocog alfa (AF-CC) manufactured using the CS calibrated working potency standard was evaluated in study 306. In both studies, moroctocog alfa (AF-CC) was administered on an IU/kg basis. The median dose per infusion was 30.2 IU/kg (range, 6.4 to 76.9 IU/kg) in study 310 compared with 32.2 IU/kg (range, 10.2 to 127.0 IU/kg) in study 306.

Comparison of safety data (treatment-emergent adverse event and hemophilia events) from studies 310 and 306 reveals similar safety profiles. In study 310, the most common events (incidence ≥10%) affected the body as a whole (headache, infection, pain, and accidental injury), respiratory system (pharyngitis), and musculoskeletal system (arthralgia). In study 306, the most common events (incidence ≥10%) affected the body as a whole (headache, infection, accidental injury, pain, and back pain), respiratory system (cough increased, pharyngitis, and rhinitis), and musculoskeletal system (arthralgia). The incidences of these events in both studies are summarized in table below.

Table 1-15: Number (%) of Patients With Treatment-Emergent Adverse Events and Hemophilia Events With Incidence ≥10% in Study 310 or 306

Event	Study 310 (n=94)	Study 306 (n=110)
Any event	62 (66)	98 (89)
Body as a whole		
Accidental injury	10 (11)	48 (44)
Back pain	6 (6)	11 (10)
Headache	23 (25)	26 (24)
Infection	17 (18)	26 (24)
Pain	12 (13)	18 (16)
Musculoskeletal system		
Arthralgia	18 (19)	26 (24)
Respiratory system		
Cough increased	3 (3)	15 (14)
Pharyngitis	13 (14)	15 (14)
Rhinitis	6 (6)	11 (10)

In both studies, the majority of events were rated mild or moderate in severity and few severe or life-threatening events were reported. In study 310, 5 patients had one or more severe events consisting of accidental injury (2 patients), arthralgia (2 patients), pharyngitis (1 patient), and pain (1 patient). None was judged as related to study drug. There were no life-threatening events. In study 306, 14 patients had 1 or more severe events consisting of FVIII inhibitor and arthralgia (3 patients each); infection and accidental injury (2 patients each); and cyst, flu syndrome, hematoma, mouth pain, vomiting, ecchymosis, arthritis, joint disorder, myalgia, insomnia, asthma, pneumonia, respiratory disorder, and urinary tract infection(1 patient each). One patient had 2 life-threatening events of retroperitoneal hemorrhage and healing abnormality. Of the above events, the cases of FVIII inhibitor in 3 patients (1 de novo, 1 recurrent, and 1 false positive), and arthralgia and cyst in 1 patient were judged as related to study drug.
The comparable outcomes in studies 310 and 306 provide evidence for similar clinical safety of moroctocog alfa (AF-CC) over a wide range of protein per IU concentrations that bracket that of moroctocog alfa (AF-CC) intended for the European Union (EU).

3.4.2.4.4 Population studied/ not studied with refactoAF

The MAH during the procedure was requested by the CHMP to provide detailed information on the population not studied with Refacto manufactured with the new process and was asked to specifically describe this in the relevant RMP section including the section dealing with important missing information.

Table 2 compares the population of hemophilia A patients treated with ReFacto for which clinical knowledge is available and the population of hemophilia A patients treated with moroctocog alfa (AF-CC) for which clinical knowledge is available.
Populations for which clinical knowledge regarding treatment with moroctocog alfa (AF-CC) is not available are paediatric patients under the age of 6 with hemophilia A, previously untreated patients (PUPs) with hemophilia A and hemophilia A patients with inhibitors receiving treatment with FVIII (Table 2).

Table 2: Populations Studied in Clinical Trials of ReFacto and Moroctocog alfa (AF-CC)

ReFacto	Moroctocog alfa (AF-CC)
Adult PTPs with severe or moderately severe hemophilia A (FVII:C <2%)	Adult PTPs with severe or moderately severe hemophilia A (FVIII:C ≤2%)
Patients with severe or moderately hemophilia A (FVIII:C≤5%) undergoing surgery	PTPs with severe or moderately severe hemophilia A (FVIII:C ≤2%) undergoing surgery
Paediatric patients with severe or moderately severe hemophilia A (FVIII:C <2%) ages 0-16	Paediatric patients with severe or moderately severe hemophilia A (FVII:C ≤2%) Age 12-16 years studied in study 310 Age 6-16 years studied in study 306 **Children under age 6 have not been studied**
PUPs with severe or moderately severe hemophilia (FVIII:C <2%)	Not studied
Hemophilia A patients with inhibitors receiving treatment with ReFacto	Not studied

Abbreviations: FVIII:C = factor VIII activity in plasma; PTPs = previously treated patients; PUPs = previously untreated patients

With regards to the population not previously studied; ongoing study 3082B2-313-WW (study 313) is evaluating prophylaxis treatment, efficacy, safety, and PK of moroctocog alfa (AF-CC) in children under the age of 6 with hemophilia A (FVIII:C<2%).

To further assess populations not previously studied, the MAH proposed to conduct separate postmarketing safety and efficacy study of moroctocog alfa (AF-CC) in previously treated (greater than 50 EDs) children under 6 years of age and to include patients at high risk for inhibitors (those with less than 50 EDs to FVIII products). (see later in the report)

3.4.3 Summary on clinical studies data

In summary, data from studies 305, 306, and 310 (and 311) support the demonstration of comparable clinical efficacy for ReFacto and moroctocog alfa (AF-CC).
The efficacy result supports the findings in the pivotal studies. There are minor differences that can be explained by the difference between US and EU in treatment regimes, e.g. the use of prophylactic treatment and on-demand treatment.

Efficacy and safety in subpopulations
The experience with moroctocog alfa (AF-CC) in paediatric patients is limited. Moroctocog alfa (AF-CC) was studied in PTP children and adolescents (n=18 patients aged 12-16 years in pivotal study 3082B2-310-WW; n=49 patients aged 7-16 years in supportive study 3082B1-306-GL). In study 3082B2-310-WW, there were no apparent differences in the severity or incidence of treatment-emergent adverse events between patients ≤16 years of age (n=18) and patients >16 years of age (n=76).
The applicant intends to initiate a phase 4 study to evaluate moroctocog alfa (AF-CC) in PTPs less than 6 years of age with severe to moderately severe haemophilia A.

Conclusion on efficacy
The efficacy results presented in the pivotal and supportive studies are within what is acceptable as per guideline. However, the CHMP guideline on clinical investigation of recombinant FVIII and IX products (CPMP/BPWG/1561/99) is currently under revision. The overall risk benefit has therefore been viewed in the light of the proposed updated guideline.

Study 310 provided evidence for comparable pharmacokinetics between moroctocog alfa (AF-CC) intended for market and Advate (when the manufacturer's labeled potency for moroctocog alfa (AF-CC) was based on calibration using a 7th IS, one stage-calibrated, AF-CC potency standard and plasma levels were measured by a one stage assay). Study 310 also provided evidence of clinical efficacy and further support for preserved efficacy comes from the supportive
Study 305 clearly demonstrating bioequivalence between current marketed ReFacto and moroctocog alfa AF-CC intended for market.
The current updated results from study 311 contains efficacy and safety data from 21 patients undergoing elective major surgery giving good evidence in support of a preserved and comparable efficacy and safety as current ReFacto. The study is still ongoing and the MAH has committed to provide the final results upon completion of the study. Only a limited number of patients in Study 311 have been treated with continuous infusion (CI), but it is important to stress that neither current marketed ReFacto nor moroctocog alfa (AF-CC) will have a posology supporting continuous infusion (CI).

- *Patient exposure*

Pivotal studies

Ninety-four patients were enrolled in study 3082B2-310-WW and were treated with at least 1 dose of moroctocog alfa (AF-CC). Of these 94 patients, 31 were enrolled in the PK period of the study as well as the SE period of the study, and 27 of these patients also completed the final PK assessment after the SE period of the study (i.e., the 6-month follow-up assessment for moroctocog alfa [AF-CC] PK parameters).

The cumulative number of EDs for all 94 patients was 6741. The median number of EDs per patient was 76 (range 1 to 92 days). A total of 6775 infusions of moroctocog alfa (AF-CC) were administered with a median dose per infusion of 30.2 IU/kg (range 6.4 to 76.9 IU/kg). The median number of infusions per patient was 76 (range 1 to 93).

In study 3082B2-311-WW, 8 patients have been enrolled and 3 patients have concluded the study as of 10 Jan 2007. Of the 8 patients, 7 patients have had elective major surgery, including 3 patients who had a synovectomy, 3 patients who had a knee replacement, and 1 patient who had a nerve transposition; the remaining 1 patient has completed the second visit for pre-surgical baseline PK assessment. Updated results from study 311 contains efficacy and safety data from 21 patients undergoing elective major surgery giving good evidence in support of a preserved and comparable efficacy and safety as current ReFacto.

Supportive studies

In study 3082B1-305-GL, of the 30 patients enrolled, 29 patients received a single dose of ReFacto and 30 received moroctocog alfa (AF-CC).In the study 3082B1-306-GL, total exposure was 110 patients and in study 3082B1-307-GL, exposure data were available for 97 patients, for details please refer to the clinical assessment.

- *Adverse events*

Factor VIII inhibitors / LETE

Pivotal study

In study 3082B2-310-WW transient, clinically silent, low-titre FVIII inhibitors were detected in only 2 of 94 patients (2.1% of the study population). Neither patient had clinical findings suggestive of an inhibitor; there were no spontaneous bleeding episodes while on routine prophylaxis, no bleeding within 72 hours of a prophylactic dose, no on-demand treatment failures, and no instances of LETE. In both cases the inhibitors were low titre, absent on repeat testing, and were associated with negative ELISA assays for anti-moroctocog alfa (AF-CC) antibody.

Supportive studies

No patient in study 3082B1-305-GL developed FVIII inhibitor. As no assessment of clinical efficacy took place in this study no cases of LETE were detected.
In study 3082B1-306-GL, 3 patients had detectable FVIII inhibitors. One (1) of these patients had de novo inhibitor development. The development of inhibitors in the other 2 patients was considered to

reflect recurrent inhibitors. The 3 patients with detectable inhibitor levels also had positive ELISA results for anti-moroctocog alfa (AF-CC) antibody. 5 cases of LETE were reported in this study.

In study 3082B1-307-GL, 1 patient developed a low-titre FVIII inhibitor; this patient did not have a positive moroctocog alfa (AF-CC) antibody titre by ELISA. As this study was terminated prematurely no efficacy assessment took place.

- *Serious adverse events and deaths*

In study 3082B2-310-WW, 2 SAEs (accidental injury and cellulitis) were reported in a total of 2 patients (1 event in each patient). These were not related to the study drug.

No patients died during pivotal studies 3082B2-310-WW and 3082B2-311-WW, nor were there any deaths in the supportive studies.

- *Laboratory findings*

There were no post-baseline changes of clinical importance in other clinical laboratory evaluations in studies 3082B2-310-WW and 3082B2-311-WW. Similarly, there were no clinically important post-baseline changes in studies 3082B1-305-GL, 3082B1-306-GL, and 3082B1-307-GL.

- *Safety related to drug-drug interactions and other interactions*

No formal analyses of potential drug interactions were performed.

- *Discontinuation due to AES*

In study 3082B2-310-WW, only 1 patient discontinued treatment for safety-related reasons per protocol; the patient was withdrawn after detection of a transient, clinically silent inhibitor. The patient had had 38 exposure days before inhibitor detection, followed by an additional 28 exposure days before being withdrawn from the study. One other patient in the study also developed a transient, clinically silent inhibitor but was not withdrawn from the study because inhibitor was detected at his final study visit. There were no withdrawals due to AEs in study 3082B2-311-WW.

- ***PSUR cycle***

The MAH proposed that adverse event reports for ReFacto and moroctocog alfa AF-CC will be presented separately within the PSUR and, to the extent that this information is available, will be analyzed for adverse event trends individually.

The company should ensure that PSURs reports will include sufficient information regarding switch to Refacto AF such as :

- inform/document on cases of inhibitor, LETE on ReFacto AF,
- updated information on how many patients have switched to ReFacto AF
- information regarding issues with laboratory measurement
- information regarding stock status of Refacto according to initial Company plan for switching

Regarding routine pharmacovigilance, appropriate questionnaires for hypersensitivity and LETE effect should be proposed by the company. Of note, the allergic reactions occurred at a frequency of 2% which is not rare as stated by the company.

The MAH commits to undertake an FUM to include the reporting of patient/ site, inhibitor development and LETE in the 6 month PSURs.

The applicant agrees to cease all distribution of Refacto in the EU after the commercialization/ rapid transition of moroctocog alfa and to provide details in the 6 month PSURs that Refacto stock has been depleted in the EU distribution centres. The applicant agreed to undertake a FUM providing status of inventory for the first year of launch of moroctocog alfa (AF-CC) in the 6 month. PSUR cycle

The CHMP considered that the PSUR cycle The CHMP suggested that the PSUR cycle should be shifted to a 6-monthly frequency at the time of introduction of moroctocog alfa AF-CC into the EU market.

In conclusion, the MAH is required to submit PSURs at 6-monthly intervals for the first two years. Then PSURs should be submited once a year for the following 3 years.

3.5 RISK MANAGEMENT PLAN AND POST AUTHORISATION SAFETY STUDIES

The MAH provided a In various CHMP Requests for Supplementary Information, major objections and other concerns were raised in relation to the initially proposed Risk Management Plan (RMP) during the review. Following the assessment the applicant was asked to submit a revised RMP in compliance with the conclusions of the review of FVIII products undertaken by the Pharmacovigilance Working Party and it was agreed that the RMP should cover both ReFacto and ReFacto AF.
In the RMP presented further details have been provided in relation to the various post authorization studies either ongoing or to be conducted.

3.5.1 Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

3.5.2 Risk Management plan

The MAA submitted a risk management plan which included risk minimisation activities.

With regards to the RMP discussion, this report does refer to selected key issues discussed extensively during the procedure. In addition, The summary of the agreed RMP is provided later on in this report.

3.5.2.1 Identified risks

- Inhibitor development

The development of inhibitors is an event of special interest. Within study 310, two clinically silent, low-titre, transient inhibitors were observed in 94 patients with a median exposure of 76 exposure days (ED, range 1-92), corresponding to 2.2% of the 89 patients with at least 50 ED. In a supporting study of ReFacto AF (study 306), 1 *de novo* and 2 recurrent inhibitors (all low-titre, central laboratory determination) were observed in 110 patients; median exposure of 58 ED (range 5-140) and 98 patients had at least 50 ED to ReFacto AF. Ninety-eight (98) of the original 110 patients continued treatment in a second supportive study (study 307) and had subsequent extended exposure to ReFacto AF with a median of 169 additional ED (range 9-425). One additional low titre *de novo* inhibitor was observed. The frequency of inhibitors observed in these studies is within the expected range.

As with all coagulation Factor VIII products, patients should be monitored for the development of inhibitors that should be titrated in Bethesda Units (BU) using appropriate biological testing. The risk of developing inhibitors is correlated to the exposure to anti-hemophilic Factor VIII, this risk being highest within the first 20 exposure days. Inhibitors are common in previously untreated patients and have been observed in previously treated patients on Factor VIII products.

- Less than expected therapeutic effect (LETE)

The incidence rate of LETE during prophylaxis in study 310 was 0.4% (25 episodes/6347 routine prophylactic infusions). There were 13 (out of 94) patients who were considered to have 25 episodes of LETE for prophylaxis. The events resolved, were not serious and not fatal. The incidence of LETE

in the on-demand setting was 0.5% (1 event of LETE/187 bleeding episodes treated with on-demand infusions across patients). The event resolved, was not serious and not fatal. The incidence rate of LETE for the on demand indication was 1.86 incident cases per 100 patient years and for the prophylaxis indication this was 26.15 incident cases per 100 patient years (95% CI: 13.92-44.71).

For study 310, the potency of the investigational product was assigned on the basis of a reference standard calibrated against the 7th IS by a one-stage assay. One IU of this investigational product is approximately equivalent to 1.38 IU of the ReFacto AF product (chromogenic assay calibrated). Since this difference in expression of potency could have affected the observed incidence of LETE, CHMP requested that the SmPC retains the qualitative wording on LETE from the authorised ReFacto SmPC until it has further data from post-authorisation studies with ReFacto itself.

- Allergic type hypersensitivity reactions

Two local reactions were reported (injection site inflammation and injection site reaction). Both were considered not serious, not fatal and not related to moroctocog alfa (AF-CC), by the investigator. Upon review by the MAH, both were classified as adverse reactions to moroctocog alfa (AF-CC). One resolved without treatment. The other persisted with no treatment. The incidence proportion 2.13%. Patients with past hypersensitivity to the active substance or any of the excipients or patients with known allergic reactions to hamster proteins are at increased risk for allergic type hypersensitivity reactions.
Hypersensitivity or allergic reactions are included in section 4.8 and a statement is included in section 4.4 of the SPC on how to handle in case hypersensitivity reactions occur. Moroctocog alfa is contra-indicated in patients with known hypersensitivity to the active substance or to any of the excipients.

3.5.2.2 Potential risks

- **Potential for Medication Error/Product Confusion between ReFacto and ReFacto AF-CC**

The MAH was requested to modify its initial proposal to keep the tradename ReFacto, in order to obtain reliable pharmacovigilance data. Furthermore, the CHMP considered it misleading to healthcare professionals and patients to keep the same name with such major changes to the manufacturing process and strongly recommended differentiation by name. Consequently, the MAH renamed the product ReFacto AF at the same time as the product manufactured by the revised process is introduced. The MAH was requested to adequately address how Refacto and ReFacto AF will be differentiated on the market.

Moroctocog alfa (AF-CC) is intended to replace ReFacto in all global markets. The MAH recognizes that one of the inherent challenges that exists when introducing an updated version of a currently marketed product is the potential for product confusion during the period of time when both products are circulating for use. The drug administration kit and the dosage formula will not vary from ReFacto, and as such, the MAH does not anticipate any increase in medication or dosage errors with the introduction of moroctocog alfa (AF-CC). Moroctocog alfa (AF-CC) intended for the EU will be clearly differentiated from ReFacto by the use of a modified trade name for moroctocog alfa (AF-CC). As well, vial dimensions for moroctocog alfa (AF-CC) will differ from those of current ReFacto, and the MAH logo is intended for the seal of moroctocog alfa (AF-CC). These features will further differentiate the appearance of moroctocog alfa (AF-CC) from current ReFacto.

The packaging for ReFacto AF has been differentiated from that of ReFacto in the following ways (see Table 14-1 below).

Table 14-1: Differentiation Between Packaging for ReFacto and ReFacto AF

	ReFacto AF (moroctocog alfa AF-CC)	ReFacto
1.Logo and Design	Blue coloured arch on top of Invented Name (ReFacto AF), which is in black. Blue arch also cuts into the colour banding on the top left hand side of the carton.	No blue arch on carton packaging. Invented name appears in black.
2.Strength color and banding	Strength is same color as color band on the carton eg, 250 IU is in yellow. Color band for 250 IU on the top of the carton is also yellow.	Strength is in black integrated into the color band at the top of the carton, eg, 250 IU is in black color on a yellow band on the top of the carton.
3.Strength colors	Will be maintained as per ReFacto: yellow for 250 IU, blue for 500 IU, green for 1000 IU, and red for 2000 IU.	No change in strength colors: Yellow for 250 IU, blue for 500 IU, green for 1000IU, and red for 2000 IU.
4.Background color	Carton has a subtle background on which black text will be superimposed. Background color to match strength, eg, 250 IU will have subtle yellow background.	Carton has a dark background on which black text is superimposed.
Anti-Counterfeit Measures	Printed packaging components will contain both covert and overt security features that are not visible on the PDF files supplied for submission. These measures are applied during the production stages	No anti-counterfeit measures are printed on the current packaging

The MAH was requested to modify its inital proposal in order to obtain reliable pharmacovigilance data and adequately address how Refacto and ReFacto AF-CC will be differentiated on the market. Furthermore, the CHMP considered misleading to health care professionals and patients to keep the same name with such major changes to the manufacturing process and strongly recommended differentiation by name.
In summary, the Company proposes to distinguish moroctocog alfa (AF-CC) from current ReFacto in several ways. These are described below.

- By name: Moroctocog alfa (AF-CC) intended for the EU market, which will utilize a potency standard that has been calibrated against the WHO 7th IS using the CS assay, will be differentiated from current ReFacto by trade name and will be called ReFacto AF.
- By vial: The vials that will be used with moroctocog alfa(AF-CC) will be significantly smaller and lighter than current ReFacto vials.
- By vial label: the new vial labels will also be different. While both old and new labels contain two peel-off labels, the current label is a single layer around the vial, whereas the new label will be a leaflet label. The new leaflet label will require patients to unfold the leaflet in order to access the peel-off portion.
- By pack: it is proposed to alter the physical appearance of the carton to reflect a new color scheme and logo. Further information will be shared with the regulators when plans are further defined
- By product security features: The incorporation of anti-counterfeiting measures and tamper-evident seals will enhance product security as well as provide additional methods of differentiation. The carton dust flaps will have "The MAH" embossed on them and the outer cartons will have a tamper evident seal that will need to be broken by the patients in order to access the kit. These features are not included in the current ReFacto kit.

The MAH will routinely solicit the lot numbers of product used in association with any immunogenicity event. This together with the change in invented name will permit the MAH to allocate any reports of immunogenicity to the correct product. An event-specific questionnaire is sent

with the follow-up requests for all spontaneous medically confirmed reports of events of special interest (inhibitor development and less than expected therapeutic effect). Lot number as well as vial strength information is requested.

A specific questionnaire will also be developed for the follow up of all hypersensitivity reactions to FVIII.

The MAH has revised the follow-up questionnaires for both inhibitors and less than expected therapeutic effect to capture the respective product trade name and to include a prominent space for affixing peel-off labels from the product pack that include the batch number. Furthermore, the product labeling (including both the Summary of Product Characteristics and the Patient Information Leaflet) will highlight the availability and potential use of these peel-off labels, as will educational materials provided to both patients and prescribers.

As regards the actual information to go into the peel-off label (product name, nominal dosage strength, lot number and expiry date) these were all acceptable to the CHMP.

- **Potential risks resulting from missing information**

Risk Induced by the Use of Different Assays for Patient Monitoring

When monitoring patients' factor VIII activity levels during treatment with ReFacto AF, use of the European Pharmacopoeial chromogenic substrate assay is strongly recommended. Nevertheless, the monitoring of Factor VIII activity (FVIII:C) in patients using FVIII replacement therapy is often performed using an OS clotting assay referenced to a plasma standard in the clinical laboratory.

The potency of ReFacto is assigned relative to the World Health Organization 6th International Standard for Blood Coagulation Factor VIII:C Concentrate (WHO 6th IS) using a chromogenic substrate (CS) assay. The FVIII:C values associated with ReFacto are typically lower as determined using the OS assay compared to values determined using the CS assay. As an aid to clinical laboratories using the OS assay to measure FVIII:C in plasma samples containing ReFacto, The MAH has made available a product specific laboratory standard, the ReFacto Laboratory Standard (RLS).

For moroctocog alfa (AF-CC) intended for the EU, the potency is assigned using a working potency standard calibrated against the WHO 7th IS using the CS assay. The MAH intends to make available a moroctocog alfa (AF-CC) product specific standard for use in clinical laboratories that utilize the OS clotting assay to monitor FVIII:C levels of patients treated with moroctocog alfa (AF-CC) intended for the EU. The use of this moroctocog alfa (AF-CC) specific standard, when performing clinical monitoring by the OS clotting assay, will provide a means of aligning one-stage clinical laboratory FVIII activity assays with the product label. The RLS currently available for ReFacto is not intended for use with moroctocog alfa (AF-CC).

A consequence of the change to the WHO 7th IS for assignment of product potency for moroctocog alfa (AF-CC) is that FVIII:C values for samples containing moroctocog alfa (AF-CC) obtained relative to the RLS will typically be greater than that expected based on the product label. Should the FVIII:C value for a moroctocog alfa (AF-CC)-containing sample be obtained versus the RLS and used to adjust patient dosing, the potential for administering a lower dose of moroctocog alfa (AF-CC) exists.

CHMP questioned the practicality of using two laboratory standards during the transition period from ReFacto to ReFacto AF. The MAH agreed with the CHMP that supporting two standards is not practical. The MAH does not plan to maintain 2 laboratory standards during the transition period from ReFacto to moroctocog alfa (AF-CC).

An updated ReFacto AF (moroctocog alfa [AF-CC] intended for the EU) laboratory standard will be made available at commercialization of ReFacto AF. The MAH will stop supplying the current

ReFacto Laboratory Standard at the time that ReFacto AF becomes commercially available. Upon receipt of the new laboratory standard for moroctocog alfa (AF-CC) intended for the EU, clinical laboratories will be instructed, via letters specifically aimed at laboratory scientists, to discard any remaining quantities of the ReFacto Laboratory Standard in order to assure that the ReFacto laboratory standard is not erroneously used during clinical monitoring of ReFacto AF treatment. This plan for introduction of the ReFacto AF laboratory standard is aligned with the plan that was used for the successful introduction of a new ReFacto laboratory standard at the time that the potency of ReFacto was recalibrated in 2003. Educational materials addressing introduction of the new laboratory standard for ReFacto AF (moroctocog alfa [AF-CC] intended for the EU) are to be provided.

The applicant have provided reassurance that only one laboratory standard will be available at any time. Moreover, as described in the applicant's proposal for updated RMP an Educational Programme will provide laboratories with appropriate information in relation to introduction of ReFacto AF and the need for a new laboratory standard.

When a clinician wants to precisely tailor a FVIII:C level, the laboratory details regarding the determination of FVIII:C levels should be considered. Although a laboratory standard will be available to clinical laboratories, the available clinical data and practical experiences with ReFacto suggest that either assay (OS and CS) may be used to monitor patient therapy. The use of a product-specific laboratory standard for moroctocog alfa (AF-CC) is not implied as a requirement for the administration or evaluation of moroctocog alfa (AF-CC).

Launch of ReFacto AF in EU Member States

The MAH remains fully committed to achieving a transition phase that is as short as possible. The MAH plans to make moroctocog alfa (AF-CC) commercially available simultaneously across all markets in the EU, where possible. However, due to pricing and reimbursement negotiations that may need to occur in some EU Member States, it may not be feasible to launch simultaneously in every EU Member State. In order to update the CHMP on the progress of the commercialization of ReFacto AF throughout the EU, the MAH commits to undertake a follow-up measure (FUM) that will update the CHMP on the commercialization status of ReFacto AF and the inventory status of ReFacto to demonstrate that inventory of ReFacto is being depleted through their distribution centres. The MAH believes this will demonstrate its efforts to ensure that ReFacto AF is introduced as quickly as possible throughout the EU *Risk Induced by the Existence of Product of Different Potencies Across Regions*

For moroctocog alfa (AF-CC) intended for other global markets, the potency is assigned using a working standard calibrated against the WHO 7th IS using the OS assay. This results in different protein per IU content for the respective moroctocog alfa (AF-CC) products (greater protein content per IU in moroctocog alfa [AF-CC] intended for other global markets). Global differentiation of moroctocog alfa (AF-CC) by region-specific potency from ReFacto will occur with the use of a new/modified trade name (from ReFacto to ReFacto AF in the EU from ReFacto to Xyntha in the US and Canada) unique to the respective assigned potency of the product. Patient and clinician educational efforts will clearly communicate the differences in product potencies, the respective trade names, and the respective considerations for routine measurement of FVIII:C levels in the clinical laboratory.

The ReFacto AF product, with calibration of the working potency standard by the chromogenic substrate assay, is intended for the EU market and for regions in close geographic proximity. The Xyntha product, with calibration of the working potency standard by the one-stage assay versus the WHO 7th IS, is approved and will be marketed in the US and Canada.

Due to the difference in methods used to assign product potency of XYNTHA and ReFacto AF, 1 IU of the XYNTHA product (one-stage assay calibrated) is approximately equivalent to 1.38 IU of the ReFacto AF product (chromogenic assay calibrated).

The potential risk is for patients coming from the US using local supply in Europe, because the vials labeled with the same IU will contain less Factor VIII activity, and patients could potentially be underdosed. The CHMP strongly highlighted that the main point for the EU and non-EU products, is not only to have both products clearly differentiable in appearance but that their difference in potency is made clear to the prescriber and the patient (educational programme & product information, SPC/PL).

Patients should be encouraged by their health care providers to appropriately plan for product use when traveling between regions where products with differing potencies may exist. The communication of this message to health care providers and patients will be facilitated by the addition of text in the product information regarding planning for product supply prior to travel. The product information also indicates what the difference is between regions and gives practical information on what to do if patients need to use moroctocog AF-CC in different regions.

3.5.2.3 Evaluation of the need for risk minimisation measures

3.5.2.3.1 Switch and transition period

The current database only includes 25 patients who have switched from ReFacto to ReFacto AF and, therefore, the MAH has commited to undertake a post-authorisation study to investigate this aspect further.

The MAH is proposing a modified transition plan aimed at reducing the period of time where both ReFacto and moroctocog alfa (AF-CC) will be available within the EU at the same time. As the MAH's primary concern is to maintain continuity of supply to all of their patients, the MAH will convert drug substance manufacturing operations from ReFacto to moroctocog alfa (AF-CC) after EC decision. This will ensure that all patients continue to have sufficient supply of ReFacto throughout the transition of manufacturing and distribution to moroctocog alfa (AF-CC).

The MAH proposes to make the product commercially available simultaneously across all EU markets at a point in time where adequate supplies of moroctocog alfa (AF-CC) have been produced to support an EU launch and when the MAH can assure that the existing inventory of ReFacto that will need to be returned from the market can be minimized. The MAH commits to undertake a launch of ReFacto AF in all EU/EEA countries where ReFacto is currently marketed by end June 2009 where possible whilst also in compliance with national requirements for Pricing and Reimbursement.

Once the product is commercially available, the MAH intends to execute an immediate transition from ReFacto to moroctocog alfa (AF-CC) across the EU. That is, once the MAH begins distribution of moroctocog alfa (AF-CC), the MAH will cease to distribute all dosage strengths of ReFacto and only distribute moroctocog alfa (AF-CC).

As there is comparability of moroctocog alfa (AF-CC) to ReFacto, the company recommends that patients may exhaust their inventory of ReFacto before converting to moroctocog alfa (AF-CC). If any existing ReFacto inventory remains in the market on 31 Dec 2009, the MAH proposes to institute an exchange programme. While the MAH would not expect much, if any, ReFacto to remain in the market by this time, the MAH will request patients, hospitals, and distributors to exchange any remaining ReFacto packs for moroctocog alfa (AF-CC) packs as of 01 Jan 2010. Finally, in an effort to minimize the in-market transition from ReFacto to moroctocog alfa (AF-CC), as well as to minimize any existing ReFacto inventory remaining in the market on 31 Dec 2009, the MAH will direct targeted education and communication at all appropriate stakeholders prior to the product being commercially available as follows:

<u>Distributors</u>
Three months prior to moroctocog alfa (AF-CC) introduction, communications will be delivered to distributors to encourage them to reduce their inventory levels of current ReFacto in order to plan for the launch of moroctocog alfa (AF-CC).

Physicians
Three months prior to the introduction in the EU, physicians in each market will receive communications informing them of the upcoming moroctocog alfa (AF-CC) launch. At that time, physicians will be encouraged to transition current patients over to moroctocog alfa (AF-CC) as quickly as possible.

Patient Advocacy Groups
Three months prior to the introduction in the EU, patient advocacy groups in each market will receive communications informing them of the upcoming moroctocog alfa (AF-CC) launch. They will be encouraged to communicate the following information to patients:

- ReFacto will no longer continue to be commercially available to patients once moroctocog alfa (AF-CC) has been launched.
- Patients should use up all packs of original ReFacto before starting to use moroctocog alfa (AF-CC) and not switch back to ReFacto.

Other
The MAH will provide an updated version of the moroctocog alfa (AF-CC) laboratory standard, free of charge to clinical laboratories using the current RLS, approximately 1 month prior to the release of the new moroctocog alfa (AF-CC) batches. Clinical laboratories will be instructed to discard the RLS in order to assure that it is not erroneously used during clinical monitoring of moroctocog alfa (AF-CC) treatment.

For moroctocog alfa (AF-CC) intended for other global markets, the potency is assigned using a working standard calibrated against the WHO 7th IS using the OS assay This results in different protein per IU content for the respective moroctocog alfa (AF-CC) products (greater protein content per IU in moroctocog alfa [AF-CC] intended for other global markets). Global differentiation of moroctocog alfa (AF-CC) intended for the EU, moroctocog alfa (AF-CC) intended for other global markets and ReFacto will occur by use of new/modified trade names unique to the assigned potency of the respective moroctocog alfa (AF-CC) product. Patient and clinician educational efforts will clearly communicate the differences in product potencies, the respective trade names, and the appropriate laboratory standard for routine measurement of FVIII:C levels in the clinical laboratory.

Patients should be encouraged by their health care providers to appropriately plan for product use when travelling between regions where products with differing potencies may exist. The communication of this message to health care providers and patients will be facilitated by the addition of text in the product information regarding planning for product supply prior to travel. The product information also indicates what the difference is between regions and gives practical information on what to do if patients need to use moroctocog AF-CC in different regions.

3.5.2.3.2 Educational materials

The educational material was discussed during the procedure with the MAH. The CHMP reminded the MAH that the aim of the information should be at reducing the risk. As a result, the agreed educational material is presented in Section IV.1 of this report.

3.5.3 Summary of the Risk management plan

The table below describes the agreed RMP with the MAH during the procedure.

Table 0-15: Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Identified Risks		

Table 0-15: Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Identified Risks		
Inhibitor Formation	Routine Pharmacovigilance including specific analysis in PSUR Event with Special Circumstances (Inhibitor Development) Questionnaire Study 3082B2-4432 (Switch Study) – A Postauthorization Safety Surveillance Study of Patients Switching to ReFacto AF from ReFacto or other factor VIII Products in Usual Care Settings Study 3082B2-4433 (Study of ReFacto AF PK plus S & E<12 years of age) – A Non-Randomized, Open Label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics (PK) of ReFacto AF in Previously Treated Children Less than 12 Twelve Years of Age with Severe Hemophilia A (FVIII:C<1%). Study 3082B2-4434 (ReFacto AF) – A Postauthorization Study of the Safety and Efficacy of ReFacto AF in Previously Untreated Patients in Usual Care Settings. Study number to be assigned (ReFacto AF PUP registry) - A Postauthorization Safety Surveillance Registry of ReFacto AF in Previously Untreated Patients (PUPs) in Usual Care Settings Study 3082B2-4420, Pharmacovigilance evaluation of ReFacto AF in Germany and Austria, which will specifically evaluate patients who switch from ReFacto to ReFacto AF, will follow all switches during the transition period.	Routine Activity: SPC Section 4.2 Posology and Administration: Patients using factor VIII replacement therapy are to be monitored for the development of factor VIII inhibitors. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if factor VIII inhibitors are present. SPC Section 4.4 Special Warnings and Precautions: The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the Nijmegen modification of the Bethesda assay.. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days. Inhibitors have been observed in previously treated patients receiving factor VIII products, including ReFacto AF. Cases of recurrence of inhibitors (low titre) have been observed after switching from one recombinant factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development. Patients treated with recombinant coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

Table 6-1: Summary of the Risk Management Plan (Cont'd)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Inhibitor Formation (Cont'd)	Study 3315 (Pediatric Study, Xyntha, US/Canada) – An Open-Label Study to Evaluate the Efficacy and Safety of Xyntha in Children <6 Years of Age in Usual Care Settings. (Proposed study to enroll minimally treated children or PUPs who have less than 50 EDs to FVIII products). All subjects will receive treatment with Xyntha formulation of moroctocog alfa [AF-CC]).	SPC Section 4.8 Undesirable Effects: The occurrence of neutralising antibodies (inhibitors) to factor VIII is well known in the treatment of patients with haemophilia A. If such inhibitors occur, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.
	Study 313 (Pediatric Study, Xyntha) – An Open-Label Study to Evaluate Prophylaxis Treatment, and to Characterize the Efficacy, Safety, and Pharmacokinetics of Xyntha in Children With Haemophilia A (ongoing study enrolling previously treated patients less than 6 years of age, as they convert to Xyntha from ReFacto or as they convert to Xyntha from other products.) Study 3082B2-4418 (Xyntha only, US/Canada) - Post-authorization safety surveillance study of moroctocog alfa (AF-CC) in usual care settings.	In a clinical study with ReFacto AF in previously treated patients, the incidence of factor VIII inhibitors was the primary safety endpoint. Two clinically silent, low-titre, transient inhibitors were observed in 94 patients with a median exposure of 76 exposure days (ED, range 1-92), corresponding to 2.2% of the 89 patients with at least 50 ED. In a supporting study of ReFacto AF, 1 de novo and 2 recurrent inhibitors (all low-titre, central laboratory determination) were observed in 110 patients; median exposure of 58 ED (range 5-140) and 98 patients had at least 50 ED to ReFacto AF. Ninety eight (98) of the original 110 patients continued treatment in a second supportive study and had subsequent extended exposure to ReFacto AF with a median of 169 additional ED (range 9-425). One (1) additional low titre*de novo* inhibitor was observed. The frequency of inhibitors observed in these studies is within the expected range.
Inhibitor Formation (Cont'd)		In a clinical study with ReFacto in PTPs, 1 inhibitor was observed in 113 patients. Also, there have been spontaneous post-marketing reports of high-titre inhibitors involving previously treated patients. There are no clinical data on previously untreated patients (PUPs) with ReFacto AF. In a clinical trial, 32 out of 101 (32%) PUPs treated with ReFacto developed inhibitors: 16 out of 101 (16%) with a titre >5 BU and 16 out of 101 (16%) with a titre ≤5 BU. The median number of exposure days up to inhibitor development in these patients was 12 (range 3-49). Of the 16 patients with high titres, 15 received immune tolerance (IT) treatment. Of the 16 patients with low titres, IT treatment was started in 10. IT had an efficacy of 73% for patients with high titres and 90% for those with low titres. For all 101 treated PUPs, regardless of inhibitor development, the median number of exposure days is 197 (range 1-1299).
Less Than	Routine Pharmacovigilance	SPC Section 4.4 Special Warning and

Table 6-1: Summary of the Risk Management Plan (Cont'd)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Expected Therapeutic Effect (LETE)	Event with Special Circumstances (LETE) Questionnaire Study 3082B2-4432 (ReFacto AF switch study) Study 3082B2-4433 (Study of ReFacto AF PK plus S & E <12 years of Age) Study 3082B2-4434 (ReFacto AF PUP study)	Precautions for Use: Reports of lack of effect, mainly in prophylaxis patients, have been received in the clinical trials and in the post-marketing setting for ReFacto. The reported lack of effect with ReFacto has been described as bleeding into target joints, bleeding into new joints or a subjective feeling by the patient of new onset bleeding. When prescribing ReFacto AF it is important to individually titrate and monitor each patient's factor level in order to ensure an adequate therapeutic response.
Allergic Type Hypersensitivity Reactions	Routine Pharmacovigilance Event with Special Circumstances (hypersensitivity reactions) Questionnaire Study 3082B2-4432 (ReFacto AF switch study) Study 3082B2-4433 (Study of ReFacto AF PK plus S & E <12 years of Age) Study 3082B2-4434 (ReFacto AF PUP Study) Study 3315 (Pediatric Study-US) Study 313 Study 3082B2-4418	SPC Section 4.3 Contraindications: Hypersensitivity to the active substance or to any of the excipients. Known allergic reaction to hamster proteins. SPC Section 4.4 Special Warnings and Special Precautions for Use: As with any intravenous protein product, allergic type hypersensitivity reactions are possible. The product contains traces of hamster proteins. Patients should be informed of the early signs of hypersensitivity reactions (including hives, generalised urticaria, tightness of the chest, wheezing, hypotension) and anaphylaxis. If allergic or anaphylactic reactions occur, administration of ReFacto AF is to be discontinued immediately, and an appropriate treatment must be initiated. In case of shock, the current medical standards for treatment of shock are to be observed. Patients are to be advised to discontinue use of the product and contact their physician or seek immediate emergency care, depending on the type and severity of the reaction, if any of these symptoms occur. SPC Section 4.8 Undesirable Effects: Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headaches, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently ReFacto, and may in some cases progress to severe anaphylaxis (including shock). If any reaction takes place that is thought to be related to the administration of ReFacto AF the rate of infusion is to be decreased or the infusion stopped, as dictated by the response of the patient.

Table 6-1: Summary of the Risk Management Plan (Cont'd)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Potential Risks		
Potential for Medication Error/Product Confusion		
Risk of confusing ReFacto with moroctocog alfa AF-CC	Routine Pharmacovigilance including specific analysis in PSUR Follow-up questionnaires to include space for affixing 2 peel off labels that will contain batch/lot number information.	SPC Section 2 Qualitative and Quantitative Composition: The invented name has been changed to ReFacto AF. SPC Section 4.4 Special Warnings and Precautions for Use: In the interest of patient safety, it is recommended that every time ReFacto AF is administered, the name on the carton and batch number of the product are recorded. Patients can affix one of the peel-off labels found on the vial to document the batch number in their diary or for reporting any side effects. Instructions on record keeping are included in the Patient Information Leaflet. A second peel-off label is provided to help facilitate this process. Differentiation in packaging for moroctocog alfa (AF-CC) versus ReFacto. Educational Programme regarding the transition plan of ReFacto to moroctocog alfa (AF-CC).
Potential Risks (Cont'd)		
Risk induced by the use of different assays for pt. monitoring	Routine Pharmacovigilance including specific analysis of ADRs related to the use of different assays in PSUR	Routine Activity: SPC Section 4.2 Posology: Informs that the chromogenic assay yields results which are higher than those observed with use of the one-stage clotting assay. Typically, one-stage clotting assay results are 20-50% lower than the chromogenic substrate assay results. The ReFacto AF laboratory standard can be used to correct for this discrepancy.

Table 6-1: Summary of the Risk Management Plan (Cont'd)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
		Educational Programme: Prior to the launch of moroctocog alfa (AFCC), Wyeth will provide a new lab standard for moroctocog alfa (AF-CC) and will provide specific information on the differences in the ReFacto Laboratory Standard (RLS) and the moroctocog alfa (Af-CC) laboratory standard and instructions for using the appropriate standard with the appropriate assay. Wyeth will stop supplying the current RLS at the time moroctocog alfa (AF-CC) becomes commercially available. Upon receipt of the new laboratory standard for moroctocog alfa (AF-CC), clinical laboratories will be instructed to discard any remaining quantities of the ReFacto laboratory standard to assure that the ReFacto laboratory standard is not erroneously used during clinical monitoring of moroctocog alfa (AF-CC) treatment. Wyeth will have an exchange policy if at the end of the transition period from ReFacto to moroctocog alfa (AF-CC) intended for the EU/EEA (31 December 2009) there is ReFacto product to be returned.

Table 6-1: Summary of the Risk Management Plan (Cont'd)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Potential Risks (Cont'd)		
Risk induced by the existence of product of different potencies across regions	Routine Pharmacovigilance including specific analysis in PSUR	SPC Section 2. Qualitative and Quantitative Composition: Describes how the potency is determined. SPC Section 4.2 Posology and Method of Administration: The labelled potency of ReFacto AF is based on the European Pharmacopoeial chromogenic substrate assay, in which the manufacturing potency standard has been calibrated to the WHO International Standard using the chromogenic substrate assay. Another moroctocog alfa (AF-CC) product approved for use outside Europe has a different potency assigned using a manufacturing potency standard that has been calibrated to the WHO International Standard using a one-stage clotting assay; this product is identified by the tradename XYNTHA. Due to the difference in methods used to assign product potency of XYNTHA and ReFacto AF, 1 IU of the XYNTHA product (one stage assay calibrated) is approximately equivalent to 1.38 IU of the ReFacto AF product (chromogenic assay calibrated). If a patient normally treated with XYNTHA is prescribed ReFacto AF, the treating physician may consider adjustment of dosing recommendations based on factor VIII recovery values. Based on their current regimen, individuals with hemophilia A should be advised to bring an adequate supply of factor VIII product for anticipated treatment when traveling. Patients should be advised to consult with their healthcare provider prior to travel. Patient Information Leaflet: Consult with your healthcare provider before you travel. You should bring enough of your factor VIII product for anticipated treatment when traveling. Educational programmeme

Table 6-1: Summary of the Risk Management Plan (Cont'd)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Missing Information		
Pediatric Patients (including children under 6 years of age)	Routine Pharmacovigilance including specific analysis in PSUR Study 3082B2-4433 (Study of ReFacto AF PK plus S & E <12 years of Age) Study 3082B2-4434 (ReFacto AF PUP Study) Study number to be assigned (ReFacto AF PUP registry) Study 3315 (Pediatric Study-US) Study 313	None, (the SPC reflects the experience previously acquired with ReFacto)
Use in Patients Switching from ReFacto to ReFacto AF	Study 3082B2-4432 Study 3082B2-4433 Study 3082B2-4420	-
Use in Previously Untreated Patients (PUPs)	Study 3082B2-4434 Study number to be assigned (ReFacto AF PUP registry) Study 3315 (Pediatric Study)	SPC Section 4.8 Undesirable Effects There are no clinical data on previously untreated patients (PUPs) with ReFacto AF.) However, clinical trials are planned in previously untreated patients (PUPs) with ReFacto AF
Important Missing Information (Cont'd)		
Use in Patients with History of Inhibitors	Routine Pharmacovigilance including specific analysis in PSUR Event with Special Circumstances (Inhibitor Development) Questionnaire	SPC Section 4.4 Special Warnings and Precautions: Cases of recurrence of inhibitors (low titre) have been observed after switching from one recombinant factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development. Patients treated with recombinant coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests

Table 6-1: Summary of the Risk Management Plan (Cont'd)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Use in patients receiving anti-fibrinolytic agents, medications known to influence platelet function (i.e. aspirin or certain NSAIDs) and concomitant therapy with immunosuppressive drugs	Routine Pharmacovigilance including specific analysis in PSUR	-
Important Missing Information (Cont'd)		
Patients with organ system impairment	Routine Pharmacovigilance including specific analysis in PSUR	SPC Section 4.2 Posology and Method of Administration informs that dose adjustment for renal and hepatic impaired patients has not been studied.
Lactating and pregnant women	Routine Pharmacovigilance including specific analysis in PSUR	SPC Section 4.6 Pregnancy and lactation; warns that animal reproductive studies have not been performed on factor VIII
Patients with genetic polymorphisms	Routine Pharmacovigilance including specific analysis in PSUR	-

3.6 Post authorisation safety studies

A summary of studies expected to be ongoing or planned for initiation subsequent to approval of moroctocog alfa (AF-CC) is provided in Table below.

Table 9-1:

Study Identification		Study Description	Features	Number of Patients
PROPOSED POST-AUTHORISATION SURVEILLANCE STUDIES DEVELOPED TO MEET CHMP REQUIREMENTS				
PTP Investigations Using ReFacto AF				
Switch Study 4432 (New Study)	Meets CHMP requirement for safety surveillance and switch studies as specified in Comments 1 and 2 of the 4th RSI.	A Post-authorization Safety Surveillance Study of Patients Switching to ReFacto AF from ReFacto or other Factor VIII Products in Usual Care Settings	➢ PTPs, ≥ 12 years of age, >150 ED, FVIII:C <1% ➢ Duration: 100 ED ➢ Baseline Recovery with Prior FVIII Product before ReFacto AF use begins ➢ Mandatory Inhibitor assays included at 1 ED, 10-15 ED, and ED 50, Segment 1 ➢ Mandatory Inhibitor assays every 6 months until 100 ED during Segment 2 ➢ Incremental Recovery tests with Inhibitor Testing	300 PTPs ➢ 150 switching from ReFacto ➢ 150 switching from other FVIII products
Pediatric Investigations using ReFacto AF				
Children's Study 4433 (New Study)	Meets CHMP requirement for pediatric studies (S&E in PTPs <6 yrs regardless of prior exposure, and PK/dosing in 6 to <12 yrs) as specified in Comments 4 and 5 of the 4th RSI.	A Non-randomized, Open-Label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics (PK) of ReFacto AF in Previously Treated Children Less Than Twelve Years of Age with Severe Hemophilia A (FVIII:C <1%) in the Usual Care Settings	➢ PTP Children, <12 years, FVIII:C <1% o 6-12 years of age, >150 ED ▪ Full PK on ED 1 o <6 years of age, at least 1 prior ED ▪ FVIII recovery on ED 1 ➢ Duration: 100 ED or 2 years provided at least 50 ED achieved (patients with <50 ED at 2 years continue at 6 months intervals to 50 ED) ➢ Inhibitor assays included at baseline on 1 ED, 10-15 ED and 50 ED are mandatory ➢ Inhibitor assays every 6 months after 50 ED are mandatory ➢ Factor consumption and clinical efficacy including LETE monitored closely	50 PTP Children: ➢ At least 20 efficacy evaluable age 6-12 >150 ED ➢ At least 20 efficacy evaluable <6yrs MTPs/PTPs ≥1 ED (rolling enrollment to accommodate for MTPS who develop inhibitors)
PUP Study 4434 (New Study)	Meets CHMP requirements for a PUP study as specified in Comment 3 of the 4th RSI	A Post-authorization Study of the Safety and Efficacy of ReFacto AF in Previously Untreated Patients in the Usual Care Settings	➢ PUP, FVIII:C <1% ➢ Duration: 100 ED or 2 years provided at least 50 ED achieved (patients with <50 ED at 2 years continue at 6 month intervals to 50 ED) ➢ Inhibitor assays included at 1 ED, 10-15 and 50 ED are mandatory, ➢ Inhibitor assays every 6 months after 50 ED are mandatory ➢ Factor consumption and clinical efficacy, LETE monitored closely	50 PUPs
PUP Registry Number *Unassigned* (Registry)	Meets CHMP requirement for a PUP Registry to supplement data collection in PUPs Comment 3 of the 4th RSI	A Post-authorization Safety Surveillance Registry of ReFacto AF in Previously Untreated Patients (PUPs) in Usual Care Settings	➢ PUP, FVIII:C <1% ➢ Duration: 5 years ➢ Inhibitor, assays recommended at Day 0 (1 ED), 10-15 ED, 50 ED and every 6 months after 50 ED ➢ Dosing, Factor consumption, LETE	Unlimited numbers of PUPs, with at least 50 PUPs projected

Table 9-2:

Study Identification	Study Description	Features	Number of Patients
OTHER STUDIES WITH MOROCTOCOG ALFA (AF-CC)			
PTP Non-Interventional Study Using ReFacto AF			
4420 (Austria/Germany only)	➢ Pharmacovigilance evaluation of ReFacto AF in Germany and Austria	➢ All exposure histories, all ages, all severities ➢ Duration: at least 36 months, with potential for extension ➢ Inhibitor testing to include baseline, 10-15 and 50 ED – clear recommendation, but not mandatory due to non-interventional study design	180 ➢ 140 ReFacto Patients ➢ 40 Non-ReFacto Patients
PTP Study Using Xyntha (US Study)			
4418 Xyntha only (US/Canada)	A Post-authorization Safety Surveillance Study of Moroctocog Alfa (AF-CC) in Usual Care Settings	➢ PTPs, ≥ 12 yearsof age, ≥150 ED, all severities (majority expected FVIII:C <1%) ➢ Duration: 100 ED or 2 years ➢ Inhibitor assays included at baseline and every 6 months	50 Xyntha patients
3315 Xyntha only (US/Canada)	Post-Marketing Open-Label Study to Evaluate the Efficacy and Safety of Xyntha in Children <6 Years of Age in Usual Care Settings.	➢ MTP-PUP, age <6 years, <50 ED, FVIII ≤ 2% ➢ Safety and efficacy ➢ Duration: 100 ED or 2 years ➢ Inhibitor assays included at baseline and every 6 months	At least 20
313 (US/Canada/EU/LA)	Open-Label Study to Evaluate Prophylaxis & Characterize the Efficacy, Safety and PK of Xyntha in PTP (≥50 ED) Children (under age 6)	➢ PTP, age <6 years, ≥50 ED, FVIII:C ≤2% ➢ Duration: Treatment for 2 years ➢ Inhibitors testing at baseline, 1 month, 3 months and then every 3 months – mandatory	72

- **Study 3082B2-4432 "A Post-authorisation Safety Surveillance Study of Patients Switching to ReFacto AF from ReFacto or other Factor VIII Products in Usual Care Settings"**

The MAH has developed a protocol, 3082B2-4432 (Study 4432) entitled "A Post-authorisation Safety Surveillance Study of Patients Switching to ReFacto AF from ReFacto or other Factor VIII Products in Usual Care Settings", to be conducted in Europe, exclusively with ReFacto AF (potency assignment aligned to the chromogenic substrate (CS) assay). This study reflects the incorporation of enhanced objectives relative to those of Study 4418 in consideration of CHMP requests to evaluate both ReFacto and non-ReFacto patients who switch to ReFacto AF with mandatory inhibitor testing over an extended observation period.

The original postmarketing study, Study 4418, will proceed in the US and Canada, exclusively using Xyntha as planned.

Key protocol design features that have been incorporated into Study 4432 to meet the CHMP requests and concerns raised include the following:

This study will include a primary cohort of at least 150 patients switching from ReFacto to ReFacto AF. In addition, a second cohort of 150 patients switching to ReFacto AF from products other than ReFacto will be enrolled. All 300 patients will be followed with mandatory inhibitor and recovery tests, at pre-defined visits, over at least 100 EDs. Data related to the occurrence of LETE will be obtained for patients in each cohort. The primary cohort of study 4432 (patients switching from ReFacto to ReFacto AF) replaces study 4420 for the objective of evaluation of efficacy and safety (including inhibitor development, recurrence of inhibitors and LETE) in patients switching from ReFacto to ReFacto AF.

At study entry, all patients will be PTPs (> 150 EDs), all with severe haemophilia A (<1%), and all at least 12 years of age. All patients will be included in the study prior to starting ReFacto AF, and patients in either cohort will have an initial baseline recovery test with their prior Factor VIII replacement therapy and will then be followed with mandatory inhibitor surveillance testing and recovery assessments, as noted above, through at least 100 EDs. For all subjects, the interval between the protocol mandated inhibitor assessment at screening and initial exposure to ReFacto AF will be no greater than 21 days. As well, for each subject, a baseline inhibitor assessment will be obtained immediately prior to administration of the initial ReFacto AF dose. Thus documentation of subject inhibitor status at the time of initial ReFacto AF exposure will be assured.

During the first segment of the study, inhibitor testing will occur at ED 1, ED 10-15 and ED 50. During the second segment of the study, inhibitor testing will occur every 6 months until at least 100 ED is reached. For those subjects who have infrequent use of ReFacto AF, 6 month interval assessments may actually precede ED 10-15 or ED 50. These patients may also continue on the study longer than 2 years to achieve the requisite 100 ED mandatory inhibitor surveillance testing. Central laboratory inhibitor testing will be performed using the Nijmegen modification of the Bethesda assay, and Factor VIII activity in plasma to assess recoveries at baseline and over time will be performed with a validated CS assay in the central laboratory. Details of the study may be found in the full protocol in the Risk Management Plan.

Based on the expectation that the transition time from ReFacto to ReFacto AF will be relatively brief due to the depletion of ReFacto drug product from the EU market, the protocol design must be operationally feasible to facilitate rapid patient recruitment of reasonable numbers of patients. The design of Study 4432 has chosen to target a balanced enrollment number of ReFacto patients and non-ReFacto patients into each of two cohorts to allow for analysis of data from within the same study in aggregate and by cohort subset. It is believed that accrual of 150 ReFacto patients from across many regions in the EU prior to their first dose of ReFacto AF would be at the limit of what is operationally feasible in the short timeframe required. This is based on recent MAH market survey data that indicates ReFacto market share in Europe is only approximately 15% of patients with the very rare condition of haemophilia A. Thus, The MAH is able to commit to this number of patients for assessment of ReFacto to ReFacto AF switching in the context of an interventional study with mandatory inhibitor testing throughout the extended proposed study treatment period through 100 EDs.

Study population

To provide for balanced enrollment of patient numbers in the two cohorts a total of 300 patients is targeted for study enrollment. The MAH believes the design of a study with balanced enrollment of 150 patients in each of two cohorts (ReFacto and non-ReFacto prior use) is robust and justified. This study design is also consistent with the number of patients reported in a Belgian series by Peerlinck et al, [Factor VIII inhibitors in previously treated haemophilia A patients with a double virus-inactivated plasma derived factor VIII concentrate. Thromb. Haemost. 1997; 77 (1) 80-6], which described the identification of an inhibitor safety signal in Belgium when 8 of 140 multi-transfused patients with severe hemophilia A developed inhibitors.

The Belgian experience clearly describes the temporal relationship of inhibitor development with respect to exposure days following use of the new Factor VIII product, all affected patients developed inhibitors shortly after changing their treatment (exposure day ranging from ED9 to ED 45) indicating that mandatory testing in Study 4432 through 100 EDs is robust and should be sufficient to detect any clinically important inhibitor development following introduction of ReFacto AF into the EU marketplace.

With regard to the age of patients eligible for enrollment into Study 4432 (PTPs with > 150ED, age at least 12 years), the MAH considered the opportunity to include PTP children as young as age 6. Recent MAH market survey data indicate that ReFacto market share is only approximately 15% in Europe, furthermore fewer than 15% of these EU ReFacto patients are children age 6-12 years. Thus, at best, a very small number of patients could be expected to enroll in Study 4432, should the age limit be lowered to age 6. Furthermore, the MAH believes that the most critical study outcome parameter for Study 4432 is inhibitor development. In this regard, subjects are all required to be PTPs with >

150 EDs at study entry. Since prior exposure (> 150 ED) rather than age is believed to be the most relevant eligibility parameter for inhibitor risk assessment, the MAH believes it is most appropriate to collect inhibitor development data from subjects age 12 or greater, provided the requisite prior exposure of > 150 EDs is provided. Furthermore, the inclusion of PTP (> 150 ED) children aged 6-12 in a study focused on the important safety outcome of inhibitors will likely result in delays to expedited review and approval by the various Competent Authorities and ethics committees. Since delays to study activation would adversely affect ongoing efforts to expedite the study initiation in advance of ReFacto AF market introduction, and may significantly risk meeting the objective to capture sufficient numbers of patients prior to initiating ReFacto AF treatment, the MAH will restrict enrollment into Study 4432 to subjects who are at least 12 years of age.

Additional studies in children using ReFacto AF, to further analyze safety, and efficacy, LETE, and including the potential for dosing adjustments in relation to PK data will be undertaken in children age 6-12, as well as in younger children (age < 6) and PUPs (including neonates).

The FVIII:C analyses in Study 4432 will use a single central laboratory, the same laboratory supporting other MAH hemophilia studies, including Study 4418. The protocol for Study 4432 will clearly indicate that factor VIII activity assessments for the recovery tests will be performed in a central laboratory and the provision of instructions and supplies for collection of patient plasma for central laboratory testing will be included. The central laboratory will use the chromogenic (CS) factor VIII activity assay to analyze Factor VIII activity in plasma from patients using ReFacto AF in Study 4432. In addition, the Nijmegen modified Bethesda assay will be used to detect factor VIII inhibitors in patient plasma. The separation of Study 4432 laboratory analyses from those of Study 4418, which evaluates Xyntha using the one-stage (OS) factor VIII activity assay, provides additional reassurance that operational errors will not occur in the central laboratory. This will be reinforced with trainings and laboratory reference manuals.

Timing for study initiation

The MAH will assure that Study 4432 is initiated at sites throughout the EU at or in advance of ReFacto AF market introduction. This will assure the opportunity to capture baseline data on all enrolled patients prior to their first ReFacto AF dose.
Based on current timeline projections, The MAH anticipates site initiations followed by consenting initial patients for study participation in May, 2009. This will assure the opportunity to capture baseline data on all enrolled patients prior to their first ReFacto AF dose. While completion of enrollment into the ReFacto cohort is anticipated over 6-12 months following study initiation, it is anticipated that the majority of enrollment of the ReFacto cohort will be achieved during the first 3 to 4 months following initiation of the study, coincident with the time required for replacement of ReFacto with ReFacto AF throughout most of the EU marketplace. The enrollment of patients using products other than ReFacto will likely require up to 2 years based on the expectation that these patients will be more difficult to identify. The majority of all enrolled patients are expected to achieve the requisite 100 EDs in 2 years, such that the study should be completed in a 4 year period of time, inclusive of the 2 year enrollment period.

Results will be made available as soon as possible based on enrollment rates. However an analysis of results from this study will not be available in advance of the commercial introduction of ReFacto AF in the EU marketplace.The MAH commits to report observed inhibitors in this study in expedited fashion, as it does for inhibitors in general. Therefore occurrences of inhibitors will be shared with EMEA and all SWITCH study investigators during the study as such events occur. This will allow for expeditious communications with the agency and investigators participating in the study, and will permit the opportunity to share information with the health care community in a timely manner if it is determined that a safety signal is detected. This would be consistent with the usual manner in which the MAH interprets and processes safety information on its marketed products. As well, the provision of quarterly line listing reports which include inhibitor cases, every 6 month PSUR updates, and clinical trial safety update reports will provide a vehicle to report interim observations from this study on an ongoing basis.

The MAH has committed to provide a full calculation for justification of the sample size for this study, and if necessary amend the protocol. In addition, calculations of the inhibitor rates as currently known, for all studies should be provided.

In addition, the company was asked to introduce into the protocol interim analysis at appropriate time points, which will be done in accordance with CHMP request.

The CHMP agreed that the revised MAH proposal meets the requirements previously addressed to the MAH during the procedure including for example, mandatory inhibitor monitoring at baseline and at pre-defined following visits, appropriate number of patients, duration of follow up for 100 ED.

German Pharmacovigilance Study (Study 4420)

The MAH proposal to assess the patient switch from ReFacto to ReFacto AF originally relied significantly on the German Pharmacovigilance study (Study 4420) which is a non-interventional study. Study 4420 projected that approximately 180 patients would be enrolled, including 140 patients who previously used ReFacto.The study provided for inhibitor testing at the investigator's discretion based on the non-interventional study design. While it is anticipated that approximately 50% of enrolled patients would submit to inhibitor testing without a mandate, the MAH accepts the EMEA position which seeks assurance that such tests are obtained via mandatory testing. However, since this study is non-interventional in design, it is not possible to amend Study 4420 as requested by the CHMP to mandate inhibitor laboratory testing at the required collection times during the surveillance period. The MAH will, however, modify the protocol for study 4420 to "strongly encourage" inhibitor surveillance testing and will provide a final protocol to CHMP by the end of December 2008. Study 4420, however, will not be relied upon as the main ReFacto AF post-marketing study to assess ReFacto to ReFacto AF switching in light of the newly proposed study (Study 4432) described previously.
Since the MAH introduced the new study 4432, meeting the CHMP requirements, this is considered acceptable by the CHMP.

With regard to the comment on the feasibility of German Pharmacovigilance Study 4420, the duration of Study 4420 will be extended beyond 36 months if necessary to complete enrollment. Enrollment of the planned 180 patients in Study 4420 is considered feasible if this protocol is offered as a non-interventional study. In Germany and Austria, preliminary feasibility assessments indicated that there are approximately 140 ReFacto treated patients already identified as potential candidates for transition to ReFacto AF who may be interested in participating in the non-interventional study. Early enrollment of these patients into study 4420 may be anticipated as ReFacto AF replaces ReFacto in the EU marketplace. The remaining 40 additional patients are largely expected to transition from other Factor VIII products. In the context of an interventional trial with mandatory inhibitor testing, feasibility assessment indicated significantly fewer patients (20-30%) would be willing to participate. This would result in less data generated for analysis. Thus, Study 4420 will proceed as a non-interventional regional study, and Study 4432 will capture the requisite number of ReFacto AF switching patients as a multinational trial offered throughout the EU.

The MAH agrees to amend the protocol for Study 4420 as requested to indicate that inhibitor testing at baseline and at follow-up visits is strongly encouraged, and should be obtained and recorded as part of routine surveillance for inhibitors. The reference to testing being conducted at the discretion of the physician will be deleted from the protocol. The MAH explained that as Study 4420 is a non-interventional study designed in accordance with PASS recommendations, it is not considered appropriate to mandate inhibitor testing. However, the MAH believes that these new recommendations for inhibitor testing at baseline and follow-up visits will provide increased data for a robust analysis and will support the data collected in Study 4432. The amended protocol for Study 4420 is provided in the RMP.

CHMP noted that study 4420 will not be relied upon as the main ReFacto AF post-marketing study to assess ReFacto to ReFacto AF switching. As another switching study is proposed (Study 4432,

described above) and is considered adequate, CHMP considered that the proposed protocol for study 4420 was acceptable.

Previously Untreated Patients study

- *Study 4434*

The MAH proposes, upon request by the CHMP during the procedure, to conduct a post authorization study of moroctocog alfa (AF-CC) intended for the EU (ReFacto AF) in previously untreated patients (PUPs). Results from this study will supplement clinical data for other patient populations that was included in the dossier for the modified product, moroctocog alfa (AF-CC), and will augment other proposed post authorization studies to meet requirements for a revised RMP in compliance with the review of FVIII products undertaken by the Pharmacovigilance Working Party, and requests from the CHMP for additional data. As well, the MAH will also initiate a European registry of PUPs treated with ReFacto AF to supplement data collected in the newly proposed PUP study.

The newly proposed study (Study 3082B2-4434, Study 4434) of PUPs (0 prior ED to FVIII products) will enroll at least 50 subjects with severe haemophilia A (<1% FVIII activity) regardless of age, including neonates. Subjects will be monitored for safety and efficacy. All adverse events will be recorded safety monitoring will include monitoring by inhibitor assays using the Nijmegen modification of the Bethesda assay. All subjects will have mandatory inhibitor and recovery samples drawn at regular intervals including ED 1, 10-15, and 50. Subjects will be followed at 6 month intervals for 100 ED or 2 years whichever comes first. All subjects will be followed for at least 50 ED. Inhibitor assays and FVIII activity levels using the CS assay will be accomplished in a single central laboratory. Subjects will have factor consumption and efficacy documented by infusion logs, bleeding record, and infusion response rating scales. This study (Study 4434) will be the sole interventional study enrolling ReFacto AF treated PUPs.

PUP study data to be collected

Data to be collected will include information on patient demographics (age, ethnicity), medical history (general health status, infections, surgery), hemophilia history (age at first FVIII exposure, treatment regimens, reasons for treatment, dosage and exposures, FVIII mutation in patients developing inhibitors) and family hemophilia history (including inhibitors, concomitant treatments including vaccinations). Safety observations will capture the frequency of adverse events including clinically significant inhibitors. Clinically significant inhibitors have been defined in the study synopsis per recommendations from the EMEA Report of Expert Meeting on Factor VIII Products and Inhibitor Development (2007). All patients will have mandatory inhibitor and recovery samples drawn at regular intervals including ED 1, 10-15, and 50. Subjects will be followed for 100 ED or 2 years whichever comes first. All subjects will be followed for at least 50 ED. FVIII:C activity will be measured for all subjects, using the CS assay at a central laboratory. Efficacy outcomes will be assessed by ReFacto AF exposure, dose and consumption as well as by outcomes of bleeding episodes including type, location and severity of episode and response of bleeding episodes to the initial ReFacto AF infusion. Frequency of LETE will be reported.

Study Sample size

CHMP raised the issue that a study of 50 patients would not be sufficient to provide scientifically robust conclusions on the inhibitor incidence of ReFacto AF in PUPs because of the multiple non-product related risk factors that contribute to inhibitor risk in PUPs. The MAH acknowledged that multiple risk factors may contribute to inhibitor risk in PUPs, however it believes it is beyond the capacity of a single sponsor evaluating a single product to characterize the epidemiological impact of these various parameters on inhibitor development. As well, recruitment feasibility must be factored into the study design to assure the operational feasibility of the proposed study. PUPs are generally of a very young age, and include newborns, and comprise a small proportion of hemophilia A patients. In the United States Uniform Data Collection (UDC) Study sponsored by the centres for Disease Control, only 3% of hemophilia A patients are under age 2 years; thus, only half that amount, 1-2%, of hemophilia A patients are born each year. With only 1-2% of this population available on an annual basis as PUPs, it is apparent that, very few PUPs would be available, on an annual basis to enroll in a

new study of ReFacto AF. This is consistent with reported enrollment progress on Baxter's Advate PUP study which has taken 5.5 years to complete enrollment with 50 PUPs. Since most PUPs now begin treatment with the Advate, identification of PUPs for enrollment in a ReFacto AF PUP study will be particularly challenging, especially since recent MAH market survey data indicates ReFacto market share is only approximately 15% in Europe. Therefore the enrollment projections for 50 PUPs into a new study of ReFacto AF reflect this reality according to the MAH. The CHMP considered the justification provided as valid but reinforced the need to gather data in PUPs in the shortest possible timeframe and to gather more extensive data by other approaches.

Study timing

The MAH has provided a synopsis for PUP Study 4434 in the RMP. The MAH will provide a full protocol to the CHMP by end of March 2009 as agreed during the procedure. The MAH projects study enrollment initiating by September 2009. Given the low frequency of hemophilia A PUPs, it is anticipated that an extended time interval of up to 5 years will be required to complete enrollment of this study. Initiation of this study will not be dependent on additional data from PTP studies in patients age 12 or older. Based on the expected 2 year duration of study participation, the MAH anticipates completion of the study in approximately 7 years following initiation.

PUP registry

To augment data regarding use of ReFacto AF in PUPs with severe hemophilia A, The MAH also proposes to initiate a registry of PUPs with hemophilia A treated with ReFacto AF. This registry will be reflected in a study (number to be designated) that is non randomized, prospective and is conducted in major hemophilia treatment centres in Europe and other regions of the world where ReFacto AF is commercially available. The registry will capture safety and epidemiologic observations based on EMEA guidance for evaluating recombinant FVIII replacement product safety, including: patient demographics, medical history, treatment history, disease severity, FVIII genotype (if available), and family hemophilia and inhibitor history. The registry will be open to enrollment of all PUPs treated with ReFacto AF at a dose and frequency prescribed by the treating physician. Infusion days, infusion reason, and treatment regimen will be ascertained using an infusion logbook. The registry is intended to enroll patients over a five year period and will capture observations on each patient for 5 years. Thus, this registry will take approximately 10 years to complete following initiation.

The MAH plans to prioritize enrollment into PUP Study 4434 over the PUP Registry. To avoid competing with Study 4434 for PUP enrollment, the MAH anticipates opening the registry to enrollment as the first PUPs in Study 4434 complete 50 ED and approach completion of study participation (eg 100 ED or 2 years). As such, this approach will permit enrollment of patients directly into the registry and will also allow for patients in PUP Study 4434 to enroll in the Registry, providing for extended follow-up of these patients as well. Based upon the annual enrollment assumptions, the MAH anticipates that an additional 50 unique PUPs may be available to join the registry over its anticipated 5 year enrollment period. Since there is no pre-specified limit on registry enrollment, the potential does exist for greater than 50 PUPs to enroll in the registry. Based on the assumption that most PUPs participating in study 4434 will roll over into the registry, long term data in PUPs may be available on at least 100 patients.

Treatment results from any PUPs who might be enrolled in the US Xyntha paediatric study 3082B2-3315-WW may also provide supplementary data that contributes to the understanding of ReFacto AF safety and efficacy in PUPs, since that study also evaluates moroctocog alfa (AF-CC), albeit with a different final potency assignment.

The MAH has taken on board the request from the CHMP during the procedure to consider gathering further data on treatement of PUPs from a registry. A synopsis is provided for the proposed registry in the RMP and the MAH commits to provide a full protocol for the registry by end of March 2009.

Studies in PTPs less than 6 years

- *Paediatric study 313*

Paediatric study 3082B2-313-WW (study 313) is assessing prophylactic effectiveness, safety, efficacy and pharmacokinetics of Xyntha in children under age 6. The study is being conducted in the United States, New Zealand, South America, Mexico and in the EU. As patients have already enrolled, the study will need to continue without modification in order to support an ongoing US FDA regulatory commitment for Xyntha. The MAH confirms that paediatric study 313 utilizes only the Xyntha drug product and does not utilize moroctocog alfa (AF-CC) intended for the EU (ReFacto AF).

- *Study 4433*

A new Paediatric PTP Study (study 3082B2-4433, study 4433) using ReFacto AF is proposed by the MAH which will enroll subjects less than 12 years of age with severe hemophilia (FVIII<1%) treated with ReFacto AF and will include 2 cohorts of patients.

The first cohort will study children under age 6 with prior exposure of at least 1 ED [MTPs (minimally treated patients) or true PTPs] to FVIII containing products (at least 20 efficacy evaluable patients). Data accrued from this first cohort of study 4433 is aligned with the new product requirements in the draft NfG governing conduct of a paediatric study in 20 children under the age of 6 years, regardless of prior treatment, in order to assess PK, safety and efficacy.

The second cohort in study 4433 will study children ages 6 to <12 years with >150 ED to FVIII containing products (N=25, to assure evaluable PK data on at least 20).

Subject participation in this study will conclude after 100 EDs or 2 years, whichever occurs first. However patients not achieving 50 ED by 2 years will continue study participation to 50 ED.

Study 4433: Cohort 1 Study Assessments in Children < 6 years of age

PK assessments

Subjects in the cohort of children < 6 years of age (cohort 1) will undergo an initial incremental recovery study following a single dose of ReFacto AF (50 IU/kg). Blood will be sampled for FVIII activity pre-dose and at 30 minutes (± 5 minutes) after the ReFacto AF infusion. FVIII:C in plasma will be measured by chromogenic substrate assay performed in a central laboratory. Results from this recovery study will provide potency dependent PK parameters (recovery, K value) for ReFacto AF in this age group. These results will be supplemented with results for potency independent PK parameters (clearance, half life) obtained from Xyntha Paediatric Study 313 and, together, will assure that PK parameters for ReFacto AF in children under age 6 is fully characterized.

Safety observations

Safety observations in this study will capture the incidence of adverse events (by severity and by relatedness to ReFacto AF) including the incidence of clinically significant FVIII inhibitor development. Clinically significant inhibitors have been defined in the study synopsis per recommendations from the EMEA Report on Expert Meeting on Factor VIII Products and Inhibitor Development (2007). Mandatory central laboratory-based assessments for FVIII inhibitor will be conducted at the ED 1, ED 10-15, ED, 50 ED, at 6 month intervals and the Final/Early Termination visits. It is recommended that investigators will obtain serial follow-up inhibitor testing for any patient with a FVIII inhibitor result ≥0.6 BU until the result is <0.6 BU or the patient reaches the Final visit. Subjects will be followed for 100 ED or 2 years whichever comes first. All subjects will be followed for at least 50 ED.

Efficacy

For all participants, efficacy observations will include the annualized bleed rate (ABR), incidence of less than expected therapeutic effect (LETE), consumption of ReFacto AF, number of infusions given per bleeding episode, assessment of response to each bleeding episode (4-point scale of assessment). For those on preventive regimens, frequency and dose of infusions, time interval between bleed onset and prior ReFacto AF prophylaxis dose, incidence of prophylaxis regimen escalation, and compliance with assigned preventive regimen.

Sample size
Enrollment in the first cohort of paediatric study 4433 will remain open until approximately 20 efficacy evaluable patients are assured. This rolling enrollment paradigm has been adopted to account for any attrition among minimally treated patients that might be contained in this first cohort (age 0 to less than 6 years) who develop inhibitors.

Study 4433: Cohort 2 Study Assessments in Children 6 to < 12 years of age
Pharmacokinetics (PK)
Approximately 25 children ages 6 to <12 years with over 150 ED at the time of study entry will have a full PK study done at ED1 to ReFacto AF with appropriate baseline and timed FVIII assays using the CS assay at a single central laboratory. Sample collection will take place on a PK schedule modified for a paediatric age group and will include sampling times prior to and 0.5, 1, 3, 6, 9, 24, 28, 32 and 48 hours after a ReFacto AF infusion on Day 1. This will provide the requested PK data for the patient population age 6 to less than 12 years and will permit correlation of PK results with ReFacto AF consumption and efficacy results for treatment with ReFacto AF (including LETE) that are also collected during this study.

Safety
Safety observations for this cohort will include the incidence of adverse events (by severity and by relatednessto ReFacto AF) including the incidence of FVIII inhibitor development. All study subjects will have mandatory inhibitor and recovery samples drawn at ED 1, 10-15, and 50, at 6 month intervals and the Final/Termination Visit. Inhibitor assays, by the Nijmegen modification of the Bethesda assay, and FVIII activity levels using the CS assay will be accomplished in a single central laboratory. Subjects will have factor consumption and efficacy documented by infusion logs, bleeding record, and infusion response rating scales. Subjects will be followed for 100 ED or 2 years whichever comes first. All subjects will be followed for at least 50 ED.

Efficacy
For all participants, efficacy observations will include the annualized bleed rate (ABR), incidence of less than expected therapeutic effect (LETE), consumption of ReFacto AF, number of infusions given per bleeding episode, assessment of response to each bleeding episode (4-point scale of assessment). For those subjects on preventive regimens, frequency and dose of infusions, time interval between bleed onset and prior ReFacto AF preventive dose, incidence of preventive regimen escalation, and compliance with assigned preventive regimen will be collected.

Sample size
Sample size for the proposed cohort age 6 up to 12 years of age has been chosen to align with criteria in the draft NfG on the clinical investigation of a new recombinant FVIII product in 20 children and as such will be sufficient to provide the requested PK and efficacy data.

Timelines for study 4433
Study enrollment is projected to initiate as soon as possible following ReFacto AF EU market introduction, by September 2009. Based on an anticipated 1 year enrollment period and 2 year study participation period, it is expected that this study will take 3 years to complete following initiation. A synopsis for the proposed paediatric Study 4433 is provided in the Risk Management Plan. The MAH was requested to provide to the CHMP a full protocol will be provided by the end of March 2009.

3.7 Changes in the product information

A number of modifications of the SPC were discussed between the CHMP and the MAH during the assessment throughout the whole procedure. A short list of the main modifications discussed is presented below.

Revison of section 4.2 Posology and method of administration.
The MAH was requested to include a statement regarding the different potencies used in different regions of the world in the SPC and make clear that the products with different potencies used in different regions of the world can be easily distinguished.

Revision of section 4.8 Undesirable effects

- Request to indicate adverse events per patient and not per infusion.

Revision of section 5.2 pharmacokinetics

The complete PI is provided in annexes of the CHMP opinion.

IV GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

The annexes of the opinion are amended in order to take into account the educational materials agreed by the CHMP as well as the change in the PSUR cycle.

IV.1 THE CONDITIONS OR RESTRICTIONS WITH REGARD TO SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

The conditions or restrictions with regard to safe and effective use of the medicinal product are the following:

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to prescribe/use ReFacto AF, all laboratories that are expected to monitor patients receiving ReFacto AF and all EU Haemophiliac patients associations are provided with Educational packs.

The educational pack should contain the following

- Summary of Product Characteristics and Patient Information Leaflet for ReFacto AF
- The educational materials.

The educational pack for Healthcare Professionals should include multiple educational patient's materials to be provided by prescribers to patients before they receive RefactoAF.

The educational materials for Healthcare professionals, patients and haemophiliac patients associations should include the following key elements:

- The main differences between ReFacto AF and ReFacto
- Changes highlighted in the Summary of Product Characteristics and Patient Information Leaflet for ReFacto AF
- The visual points of differentiation in packaging for ReFacto AF versus ReFacto
- Specific instructions regarding the proper identification, dosing and monitoring of ReFacto AF.
- That after switching to ReFacto AF, patients should remain on ReFacto AF and not switch back to ReFacto.
- The potential risks for medication errors in using different assays or laboratory standard for patient monitoring. Information that the chromogenic substrate assay is strongly recommended to be used by laboratories when monitoring patients receiving ReFacto AF and that typically one stage clotting assay results are 20-50% lower than the chromogenic substrate assay results

- The existence of another moroctocog alfa containing product for use outside Europe with a different potency assigned using a one stage clotting essay and the need for patients to take an adequate supply of their ReFacto AF for anticipated treatment while traveling. Advice for health care professionals on possible need to adjust dosages for patients normally treated outside Europe with Xyntha.

- The importance to report suspected adverse reactions (including inhibitor occurrence) detailing the name and the batch number of the product used. The importance to report medication errors, and their causes and consequences.

- Instructions on record keeping with recommendation to record, the name and batch number of the product received, using the peel-off labels provided on the vial.

- Additional messages regarding the transition plan for replacement of ReFacto with ReFacto AF in the Member State(s)

The educational programme for laboratories should inform about the following key elements:

- The main differences between ReFacto AF and ReFacto

- Specific instructions regarding the proper monitoring of ReFacto AF.

- The potential risks for medication errors in using different assays or laboratory standard for patient monitoring

- Strong recommendation to use the chromogenic substrate assay when monitoring patients. Information that typically one stage clotting assay results are 20-50% lower than the chromogenic substrate assay results.

- The purpose of the laboratory standard. The differences in the new laboratory standard for ReFacto AF as compared to the laboratory standard for ReFacto and instructions on when to change to using the ReFacto AF laboratory standard.

- Additional messages regarding the transition plan for replacement of ReFacto with ReFacto AF in the Member State(s)

The Marketing Authorisation Holder shall agree the educational material with the national competent authorities in all the Member States prior to the launch of the product

IV.2 OTHER CONDITIONS

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 05 December 2005, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4.7 of the Risk Management Plan (RMP) and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

PSUR cycle

The MAH is required to submit PSURs at 6-monthly intervals for the first two years. Then PSURs should be submited once a year for the following 3 years.

V OVERALL CONCLUSION ON BENEFIT RISK ASSESSMENT AND RECOMMENDATION

The MAH filed a series of variations to support various manufacturing changes of ReFacto (moroctocog alfa). These changes included the use of an albumin-free cell culture process (moroctocog alfa (AF-CC)) using the original cell line for manufacture of ReFacto to generate a new albumin-free master cell bank together with removal of human serum albumin from the cell culture process. The purification process is further refined by introduction of a chemically synthesized peptide affinity ligand to replace the murine monoclonal antibody sepharose resin and addition of a virus-retaining filtration step to further enhance the viral safety profile of moroctocog alfa (AF-CC) drug product. These changes all add to the benefit of the product.

Together, these variations provided evidence that the moroctocog alfa (AF-CC) drug product is comparable to currently marketed ReFacto and therefore is therapeutically equivalent. The applicant has provided evidence that moroctocog alfa (AF-CC) is bioequivalent to the currently marketed ReFacto (study 305) as well as supportive evidence for bioequivalence to the full-length Factor VIII product Advate (Study 310) when the FVIII potencies were assigned by a central laboratory (one stage assay versus plasma standard). Evidence for clinical comparability in terms of efficacy and safety for use in prophylaxis or on-demand treatment of bleedings have additionally been provided by the open-label extension of this study (310) and the supportive study (306). A single pivotal study in surgical prophylaxis is still ongoing. Thus the current knowledge of the clinical efficacy and especially safety of moroctocog alfa AF-CC supports comparability.

The applicant has responded to a set of questions posed in relation to the proposed post-authorisation studies. The applicant has proposed a number of new studies in order to satisfy the demands for adequate safety precautions for this new albumin free formulation of Refacto.

In summary the applicant has proposed the following:
A post-authorisation “Safety Surveillance Switch Study” in PTPs (>150 ED) with FVIII <1%. This study will ensure mandatory inhibitor monitoring for at least 100 Exposure Days (EDs), and will include a central laboratory using the Nijmegen modified Bethesda Inhibitor assay. Factor VIII activity in plasma will be assayed using the Chromogenic Substrate Factor VIII activity assay. The study will assess patients who are: a) switching from ReFacto to ReFacto AF (N=150) and b) switching from Factor VIII products other than ReFacto to ReFacto AF (N=150).
A study to evaluate PUPs and also a PUP Registry
A new “Children’s Study.” This Children’s Study will assess ReFacto AF in previously treated children < 6 years of age regardless of prior exposure, and ReFacto AF including full pharmacokinetics in PTPs children (>150 ED) age 6-12, all with FVIII:C <1%.

A summary of each of the key features of the aforementioned studies are listed in Table 9-1 and *Table 9-2* included in this report. With these studies it is considered that the applicant has satisfactorily addressed the comments of the CHMP regarding post-authorization inhibitor surveillance and provision of post-authorization data in the paediatric population

The applicant had been asked to submitted a revised RMP in compliance with the review of FVIII products undertaken by the Pharmacovigilance Working Party[a] and it was agreed that the RMP should cover both the currently marketed ReFacto and ReFacto AF. Following the responses assessed above an adequate RMP are now in place for this new albumin-free version of Refacto (in the future to be called Refacto AF) including a proper transition plan and post-marketing surveillance studies.

In conclusion, the MAH has complied with all the issues and detailed questions raised by the CHMP. Of particular note is a new study (4432) to investigate the safety (and efficacy) when switching from ReFacto to ReFacto AF or switching from other r-FVIII products. This study is to be undertaken in a reasonable number of patients and is planned to start prior to the intended date on market launch of ReFacto in EU. In addition the previous 'German switch study' will continue as already planned, but with an additional effort to obtain inhibitor measurements at later time points than originally planned. In addition, two other new studies are planned – one PK study in PTP children (4433) especially to address the issue regarding potential for a different PK in the 6-12 year old patients. The other study is a study in PUPs. Furthermore, the MAH is planning to create a PUP register, which is strongly welcomed.

The CHMP, having considered the data submitted, was of the opinion that,

- Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- Additional risk minimisations activities were required (see as detailed in section IV.1 Conditions or restrictions with regard to the safe and effective use of the medicinal product).

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk benefit balance of Refacto AF in the prophylaxis and treatment of patients with haemophilia A is favourable.

V. CONCLUSION

On 18 December 2008 the CHMP considered these Type II variations to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and annex IV.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these Follow-up Measures.
An updated letter of undertaking was submitted on 15 December 2008 and agreed with the CHMP.

VII. EPAR CHANGES

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope:
EMEA/H/C/232/II/59 Use of peptide resin instead of MAb resin
EMEA/H/C/232/II/60 Introduction of virus retaining filter
EMEA/H/C/232/II/61 Increase in batch size for 2000IU strength
EMEA/H/C/232/II/62 Qualification of second lyophilizer
EMEA/H/C/232/II/63 Drug product specification changes

[a] "EMEA completes the review of recombinant factor VIII products and inhibitor development" (EMEA/310225/2007 Corr).

EMEA/H/C/232/II/64 Head space change (nitrogen overlay)
EMEA/H/C/232/II/65 Drug substance and drug product assay changes
EMEA/H/C/232/II/66 Potency standard calibration change
EMEA/H/C/232/II/67 Change in drug product container closure system
EMEA/H/C/232/II/68 Albumin free cell culture process and consequential changes in the substance manufacturing process