SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Kogenate Bayer. This scientific discussion has been updated until 1 January 2003. For information on changes after this date please refer to module 8B.

1. Introduction

KOGENATE Bayer is a recombinant human antihaemophilic factor VIII (INN: octocog alfa), which is derived from a cloned human factor VIII gene transfected into baby hamster kidney (BHK) cells. The approved therapeutic indications are as follows:
Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). This preparation does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease.

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

KOGENATE Bayer is a modification of the already licensed product KOGENATE. Both are produced by the same genetically engineered BHK cell line. The fermentation process is the same as for KOGENATE. In contrast to the parent product, KOGENATE Bayer is purified and formulated without the addition of human albumin as stabiliser. This was accomplished by the development of a new purification process, including a solvent/detergent treatment viral inactivation step, and a new formulation with sucrose.

The product is formulated with sucrose, glycine, histidine, calcium chloride and sodium chloride and is isotonic for intravenous injection. The protein to excipient ratio has been altered to produce three different fill sizes of equal volume after reconstitution.

The applicant submitted applications for KOGENATE Bayer and Helixate NexGen which are identical products.

Abbreviations used in this report

aPTT	Activated partial thromboplastin time
BHK	Baby hamster kidney
HBNLO	Highly branched N-linked oligosaccharides
MTP	Minimally treated patient
rFVIII	KOGENATE (parent product)
rFVIII-SF	KOGENATE Bayer (modified product); SF stands for sucrose formulated.
PTP	Previously treated patient
PUP	Previously untreated patient
vWF	von Willebrand Factor

2. Chemical, pharmaceutical and biological aspects

RFVIII-SF is a sterile, lyophilised powder for injection presented in glass vials with rubber stoppers. It is marketed in three dosage forms (250 IU, 500 IU, 1000 IU). The powder is reconstituted with 2.5 ml water for injections Ph. Eur. The powder and solvent vials are supplied in the final package.

Active Substance:	Octocog alfa			
Nominal Potency:	IU/vial			**Specification**
	250	500	1000	
Excipients:	mg/vial			
Sucrose	28	28	28	Ph.Eur.
Histidine	8.0	8.0	8.0	Ph.Eur.
Glycine	58	58	58	Ph.Eur.
Sodium Chloride	4.4	4.4	4.4	Ph.Eur.
Calcium Chloride	0.7	0.7	0.7	Ph.Eur.

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

For each dosage form, 2.5 ml solvent per vial is required for reconstitution. To ensure an extractable volume of 2.5 ml, an overfill of 0.6 ml is used to compensate for losses in transfer.

The lyophilised powder for injection is presented in 10 ml, Type I glass (Ph.Eur.) vials with grey bromobutyl rubber (Ph.Eur.) stoppers. The solvent is presented in 10 ml, Type II glass vials (Ph.Eur.) with grey chlorobutyl rubber (USP) stoppers.

Active substance

Structure

Octocog alfa is a glycoprotein. The full length protein consists of 2332 amino acids with a molecular weight of approx. 265 kD before, and more than 300 kD after glycosylation. The single chain protein is rapidly processed in cell culture resulting in a heterodimer with an 80 kD light chain deriving from the C-terminus, and a family of heavy chains with molecular weights between 90 and 210 kD, including the 90 kD N-terminal sequence and varying amounts of the B-domain. In the B-domain, which is not required for the co-factor activity of FVIII, most of the potential N-linked glycosylation sites are located. The protein also contains 10-12 O-linked glycans. Evidence suggests that all or most of the O-linked glycans reside in the B-domain.

Gene construction, producer strain, cell banks

The production cell line is the same as that used for the parent product KOGENATE.

A master cell bank (MCB) and a working cell bank (WCB) of the production cell line (31A3BS-R3) were established. Factor VIII mRNA was isolated from MCB and post-production cells and completely sequenced. No point mutations or deletions were detected, indicating that FVIII is accurately transcribed and stable. It could be demonstrated that no detectable rearrangements occurred during fermentation.

Fermentation and purification

The process steps of fermentation and harvesting are identical to those for the parent product KOGENATE. Harvest is continuously collected from production scale fermenters. A plasma master file for the documentation of the human plasma protein used as starting material for the production of the human plasma-derived component of the fermentation media has been submitted. The manufacturing steps of fermentation and harvesting are monitored by adequate in-process controls.

The purification process to remove host cell impurities and process-related impurities consists of chromatographic steps, a virus inactivation step and an ultrafiltration/diafiltration step. The clearance capacity of the purification process for fermentation and purification related impurities was analysed. The process is monitored by adequate in-process controls. Reproducibility of the commercial scale purification process with regard to operational parameters is sufficiently shown. The product received at the end of purification is considered as the active substance.

Active substance characterisation

The active substance has been extensively characterised using state of the art techniques. The presence of functional sites consistent with plasma-derived FVIII was verified. Von Willebrand Factor is the carrier protein of FVIII in plasma. The binding of activated FVIII to phospholipids is a prerequisite for the physiologic function of FVIII as cofactor of activated factor IX. Binding of rFVIII-SF to vWF and phospholipids was tested and verified *in vitro* by ELISA-techniques.

The oligosaccharide structure of glycoproteins for human therapeutic use can affect the pharmacokinetic profile, immunogenicity, specific activity, and physico-chemical characteristics.

Both KOGENATE and KOGENATE Bayer products continue to be manufactured by the identical fermentation process conditions and facilities. Investigations to date indicate that improved growth conditions during the cell scale up have resulted in a change of oligosaccharide pattern with an increase of highly branched N-linked oligosaccharides (HBNLO).

In the development of rFVIII, the oligosaccharide structures were reported to be qualitatively equivalent to plasma derived FVIII (pd FVIII). In both rFVIII and pd FVIII, highly branched N-linked oligosaccharides were observed as well as other structures representing the normal mammalian repertoire. In literature similar results were reported for porcine FVIII and another licensed recombinant FVIII product. From these data it was concluded that the presence of HBNLO in rFVIII and rFVIII-SF is consistent with the natural presentation of the molecule and not a unique feature of these preparations.

Specification of the active substance

Every batch released has to meet the documented specifications established. The control methods used to routinely analyse the active ingredient have been described in detail, including standards, controls and test validity criteria. The validation of the methods has been carried out sufficiently. An oligosaccharide-mapping test has been implemented. A release specification for alpha-galactose will be implemented.

Batch to batch consistency

Satisfactory batch analysis data are provided.

The main objective was the comparison of pilot scale and commercial scale batches. The results demonstrated comparability of the batches purified by the pilot scale and the commercial scale processes. Both production scales were also compared in a pharmacokinetic study (see Part IV).

Stability of active ingredient

The stability of the active ingredient is being investigated in an ongoing study. The submitted results of two research scale and two pilot scale purification batches are provided. The results predict a 24 month storage period at an intended temperature of –30°C or colder. Three commercial scale batches will be placed into the long-term stability program.

Other ingredients

Excipients are of Ph.Eur. Quality.

Product development and finished product

Product development

The main objective was to develop a stable, pharmaceutically acceptable formulation without the addition of human albumin as stabiliser. The selection of the formulation is comprehensively discussed. The choice of excipients has been evaluated and justified.

The fill size and injection volume was minimised to 2.5 ml for all dosage forms (250, 500, 1000 IU/vial). Based on the physico-chemical characterisation of the formulation, the conditions for a new lyophilisation cycle were developed. The choice of the conditions have been sufficiently evaluated and justified.

Clinical trial formula

The same batch formula has been used for production of pilot and commercial scale batches used in clinical trials.

Manufacturing process

The manufacturing process is typical for a protein parenteral product. Briefly, one or more purification batches containing the active ingredient, diluted with formulation buffer to target potency and sterile filtered, undergo aseptic filling and freeze-drying.

Appropriate in-process controls including processing times and prefiltration bioburden are performed.

Finished product specification

The manufacturer has set appropriate release criteria for the finished product. Control tests are adequately described. The potency is determined by one-stage assay, which is also used for potency determinations of the already licensed product KOGENATE/Helixate. The US standard Mega-1, an intermediate purity concentrate, is used, which was calibrated against the 3rd WHO-Standard. Discrepancies in potency determinations of recombinant FVIII concentrates depending on the method and the standard used have been observed for all presently available recombinant FVIII products. The Company will undertake a study with the objectives to establish a recombinant FVIII standard calibrated against the 6th International Standard.

Batch analyses

The release specifications were validated with batch analysis data from five qualification batches.

Finished product stability

The proposed shelf life is 23 months, including 21 months storage at 2°C to 8°C and two months at temperatures not more than 25°C. The product should be used immediately after reconstitution.

The applicant is carrying out an extensive, ongoing stability study over 24 months covering all dosage forms. Regarding the time points for analysis of the test parameters, the study is following the ICH Guideline on Stability Testing of Biologicals/Biotechnologicals. Stability is monitored by a variety of methods. Results support the proposed shelf life.

Immunoaffinity matrix

The immunoaffinity matrix used for the purification of rFVIII-SF is identical to the one employed for purification of the parent product.

Sufficient data were provided about the process validation and for consistency of the murine antibody and immunomatrix production. The analytical validation of the methods used is sufficient. The stability of the MAb and the immunomatrix has been demonstrated in sufficient detail.

Viral safety

Cell line development and fermentation require several additives of biological origin. The Company appropriately discussed the virus safety of these components. Materials of bovine origin used during cell bank development, fermentation and purification were sourced from countries that have no reported cases of BSE. A human plasma-derived product is used for fermentation. As the source material for this product was tested according to the requirements for plasma derived products and the manufacturing process contains, besides other steps, pasteurisation for virus inactivation, there is in principle no virus safety concerns with the use of this material.

Cell line testing was performed according to the current guidelines by *in vitro* and *in vivo* assays.

Routine testing for adventitious viruses is performed.

The effectiveness of the S/D step for the inactivation of enveloped viruses has been demonstrated. The immunoaffinity chromatography contributes to virus safety but its effectiveness is strongly virus specific.

The effectiveness of sanitisation of columns was investigated.

Immunoaffinity matrix

For fermentation of the MAb, two human plasma-derived additives were used. The production of both additives includes a pasteurisation step for viral inactivation. The purification procedure of the MAb includes steps, which contribute to the virus safety. In addition, the coupling process has a high effectiveness for viral inactivation. Therefore, there is no viral safety concern arising from the use of the immunoaffinity column.

Discussion on chemical, pharmaceutical and biological aspects

The newly developed purification process is described and appropriately monitored by in-process parameters. Validation data revealed the robustness of the purification process concerning the removal of impurities. The active substance has been extensively characterised using state of the art techniques. The presence of functional sites consistent with plasma-derived FVIII was verified and glycosylation extensively studied. Virus safety with regard to enveloped viruses was demonstrated. On the basis of the data provided and the agreed follow-up measures, the quality of the product is satisfactory for the grant of a Marketing Authorisation.

3. Toxico-pharmacological aspects

Introduction

The development of rFVIII-SF included the production of a pilot scale for clinical studies supply, followed by an approximate 3-fold increase in the purification scale for commercial lot production. Evaluation of rFVIII-SF derived from the full-scale process was also performed to assess potential alterations.

Pharmacodynamics

Activity of the compound was demonstrated *in vitro* in both clotting and FXa assays and the molecule was demonstrated to bind von Willebrand Factor (vWF). rFVIII-SF was found to be similar to the parent compound rFVIII (KOGENATE) in its ability to induce coagulation in FVIII deficient animals.

Safety pharmacology investigated the cardiovascular and respiratory systems since assessment of other organ systems was not considered necessary based on the mechanism of action and the fact that the parent product (rFVIII) was not found to affect other organ systems. In studies performed with rFVIII-SF in rats and rabbits no relevant safety issues were detected.

Pharmacokinetics

Nine pharmacokinetic studies were performed. Parameters assessed included area under the curve (AUC), maximum plasma concentration (C_{max}), terminal half-life ($t_{½}$), plasma clearance (CL) and volume of distribution at steady state (Vss). There were no significant differences between rFVIII-SF and the parent compound, rFVIII, or between the different scale and fill size products.

Changes in oligosaccharide pattern induced slight but not significant changes in pharmacokinetic parameters, with a tendency towards increased bioavailability.

Toxicology

Acute toxicity

Single infusion toxicity was studied in mice, rats and rabbits with rFVIII-SF from different scales or an excipient control. Even doses several fold higher than the recommended clinical dose (related to body weight) failed to demonstrate any acute toxic effects for rFVIII-SF.

Subacute toxicity

Male and female rabbits and dogs received injections of rFVIII-SF or an equal amount of excipient control for five consecutive days. One group of animals was sacrificed one day after, the second group 28 days after the last infusion. All animals tolerated the infusions. There were no unusual necropsy

observations found. There were no adverse effects except the development of antibodies to the rFVIII-SF protein (four of six rabbits, three of four dogs).

Mutagenic potential

Mutagenicity studies were not performed with rFVIII-SF. rFVIII-SF utilizes the same cell bank and fermentation starting materials used in rFVIII. Prior tests of the parent molecule, rFVIII, included reverse mutation assays, a chromosome aberration test and a male dominant lethal test, all of which were negative.

Oncogenic/carcinogenic potential

Oncogenic potential of rFVIII had been evaluated by an *in vitro* transformation assay and tumorigenicity of the cell line and BHK DNA in nude athymic mice. In those studies, no transforming activity was observed. No carcinogenicity study was performed in view of the nature of the product and its proposed indication.

Reproductive toxicology

Reproductive toxicology studies were not performed as FVIII deficiencies primarily occur in male patients.

Neoantigenicity

In order to determine if the new process for purification induces physical or conformational changes that produce new epitopes on the rFVIII model, several neoantigenicity studies were performed. In different studies, different pilot and full scale lots as well as different fill sizes were tested. No evidence for the existence of new epitopes on the rFVIII-SF molecule was seen in any of the tests.

It has to be recognised that these types of experiments do not provide reliable information about neoantigenicity in man.

Toxicity of excipients

Excipients are sucrose, histidine, sodium chloride, calcium chloride and glycine. Data were provided on the lowest published toxic dose for each component and toxicities associated with multiple dose administration. From the data provided, no risk to patients would be expected from the excipients used.

Discussion on non-clinical aspects

The pharmacodynamic studies presented show that FVIII-SF is able to affect bleeding time and aPTT as parameters of bleeding disorder. The acute and subacute toxicological investigations provide no evidence that rFVIII-SF has a different toxicological risk than the parent compound rFVIII. The results of the non-clinical investigations show that rFVIII-SF is a product with acceptable preclinical pharmacological and toxicological properties. Concerning neoantigenicity, only clinical data can provide valid information.

4. Clinical aspects

The approved therapeutic indications are as follows:

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). This preparation does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease.

The company submitted documentation on the following studies:

1.) Two pivotal studies (Study BAY 14-2222/0102 in North America [NA] and Study BAY 14-2222/0101 in Europe [EU]) in previously treated patients (PTP) with severe haemophilia A (FVIII<2%), divided into:

Stage I: pharmacokinetic trial, cross-over with rFVIII, n= 35 patients (20 in NA and 15 in EU)

Stage II/III: repeat pharmacokinetic trial at week 24, n=24 patients (19 in NA and 5 in EU)

Stage II/III: clinical efficacy and safety over 6 months, n= 71 patients (38 in NA and 33 in EU)

Stage IIIS: surgical procedures, n=15 (3 in NA and 12 in EU)

Stage IIIE: clinical efficacy and safety over 18 (NA) and 24 (EU) months, n= 65 patients (35 in NA and 30 in EU).

2.) Study BAY 14-2222/100124, pharmacokinetic bioequivalence study (n=20 patients) comparing the rFVIII-SF from pilot scale production used in the above mentioned trials with products from the commercial-scale production.

3.) Study BAY 14-2222/0104 (EU) and Bay 14-2222/0105 (NA): two open trials of efficacy and safety in paediatric patients (previously untreated or minimally treated, PUP, MTP), started in October 1997, intended to enrol a total of 60 patients with a minimum of 18 PUPs each in US and Europe. Final study analysis is scheduled for when all patients have completed 2 years on study, or 20 exposure days, whichever comes later.

Pharmacodynamics

Pharmacological and toxicological studies, detailed in Part III of the dossier, showed the biological activities and safety pharmacology of rFVIII and rFVIII-SF to be comparable. Therefore, human pharmacodynamic studies were not considered necessary. Pharmacodynamic parameters were studied in the pharmacokinetic studies performed in patients.

Pharmacokinetics

Study BAY 2222/0102 (NA) and 2222/0101(EU)

Both studies were of open label, randomised, cross-over design comparing administration of 50 IU/kg of either rFVIII or rFVIII-SF given intravenously over 10 minutes. Administration of either product was on two different days separated by a washout period of at least 5 days in the NA study and 4 days in the EU study. As primary pharmacokinetic (PK) parameters, the area under the curve (AUC) and the maximum concentrations C_{max} were calculated. Further, the terminal half-life ($t_{½}$) and the incremental FVIII recovery (%·kg/IU) were determined. Blood was sampled pre-infusion and within 10 minutes of the end of the infusion, then at 30 min, 1, 3, 6, 9, 12, 24, 30 (EU) or 36 (NA) and 48 hours. For determination of FVIII the one-stage assay was used. The estimated potency per vial was used for the labelling of batches and for the calculation of PK parameters.

Stage I

20 [NA] and 15 [EU] male patients with severe hemophilia A (<2%) were recruited. In both, the NA and the EU study, the pharmacokinetic parameters determined were comparable, but there was a tendency for higher FVIII levels after rFVIII infusions than after rFVIII-SF (see table 1). In the NA study, bioequivalence of rFVIII and rFVIII-SF for the calculated PK parameters AUC, C_{max}, $t_{½}$ could be demonstrated. In the EU study, statistical analysis failed to show equivalence between rFVIII and rFVIII-SF for the parameters AUC and C_{max}, whereas $t_{½}$, mean residence time (MRT) and recovery values were equivalent. The Company presented a reasonable explanation. In both studies, aPTT values showed similar degrees of shortening appropriate to the level of FVIII following infusion of both rFVIII and rFVIII-SF. The aPTT values are comparable with those obtained after infusion of plasma-derived FVIII.

Table 1: Pharmacokinetic parameters from Stage I – comparison of rFVIII-SF vs. rFVIII

	RFVIII-SF		**RFVIII**	
	NA (n=20)	**EU (n=15)**	**NA (n=20)**	**EU (n=15)**
(0-48 h)				
AUC (%·h·kg/IU)	27.3 ± 6	31.6 ± 11.7	31.6 ± 6.1	41.9 ± 15.6
C_{max} (%·kg/IU)	2.2 ± 0.4	2.1 ± 0.6	2.4 ± 0.6	2.9 ± 0.7
$t_{½}$ (h)	13.25 ± 1.56	17.2 ± 4.3	13.93 ± 2.45	16.8 ± 4.7
MRT		22.5 ± 5.0		21.9 ± 4.9
Recovery	2.2	2.0 ± 0.5	2.4	2.7 ± 0.7

Stage II/III – Repeat pharmacokinetic investigation at week 24

Following administration of rFVIII-SF over 24 weeks, a 48-hour repeat pharmacokinetic profile was obtained. All 19 of the NA Stage I patients who continued into Stage II/III participated in the week 24 pharmacokinetic study. Five patients participated in the repeat kinetic part of the EU study. For the NA study, equivalence was demonstrated for AUC, C_{max} and $t_{½}$ (see table 2). Concerning the EU study, data obtained at week 24 appeared comparable although the small number of patients precluded formal statistical conclusions.

Table 2: Pharmacokinetic parameters from Stage II/III – comparison of rFVIII-SF data from stage I vs. data obtained after 24 week treatment

	NA (N=19)		EU (N=5)	
	Stage I	**Week 24**	**Stage I**	**Week 24**
(0-48h)				
AUC (%·h·kg/IU)	27.7 ± 5.8	25.5 ± 6.0	38.8 ± 15.8	39.6 ± 10.5
C_{max} (%·kg/IU)	2.20 ± 0.4	2.1 ± 0.4	2.4 ± 0.5	2.2 ± 0.3
$t_{½}$ (h)	13.4 ± 1.5	14.4 ± 4.1	17.0 ± 5.0	25.8 ± 5.5

The values obtained from the EU study, especially the repeat PK study, are higher than from the NA study. In contrast to the NA-study, in the EU-studies most of the patients did have residual (i.e. prior to the infusion) FVIII levels >1 (up to 4) IU/dl. These high residual values influence the concentration-time-curve. Thus, it was concluded that the PK data obtained in the NA study were more reliable.

It can be concluded from the data provided that the pharmacokinetic profile of rFVIII-SF is consistent with the profile for the parent product rFVIII and other FVIII products. The data from the repeat pharmacokinetic study in NA demonstrate that rFVIII-SF can maintain a consistent pharmacokinetic profile over a 24-week period of treatment.

Study BAY 2222/100124

Pilot vs. Commercial-scale product bioequivalence study

This was a single centre, randomised, crossover bioequivalence study conducted in 22 PTPs with severe haemophilia A. Two lots of pilot-scale material and one lot of commercial-scale material were used. Twenty patients received two single infusions of rFVIII-SF including one infusion of the pilot-scale and one infusion of the commercial-scale product. These were administered in a cross-over fashion with a minimum of 5 days washout between treatments. The patients received approximately 50 IU/kg of the study drug during both infusions. Comparison of the pharmacokinetic parameters for the pilot-scale and the commercial-scale products yielded comparable results, documenting bioequivalence in terms of AUC and C_{max} (table 3).

Table 3: Pharmacokinetic parameters in pilot vs. commercial-scale products

(0-48 h)	**Pilot-scale (n=20)**	**Commercial scale (n=20)**
AUC (%·h·kg/IU)	32.26 ± 6.16	30.21 ± 6.4
C_{max} (%·kg/IU)	2.11 ± 0.31	2.01 ± 0.26
$t_{½}$ (h)	16.01 ± 3.19	17.11 ± 4.79

The PK parameter values tend to be higher than in the PK studies of stage I (at least compared to the NA data). This is partly related to the relatively high residual FVIII levels in 3 of the patients in this study. Furthermore, the use of a less concentrated solution (100 IU/ml compared with 200 IU/ml in the stage I trial) may have resulted in less dosing losses during the administration of the product.

This study demonstrated bioequivalence between pilot and commercial scale products.

The Company will perform a pharmacokinetic study to further investigate the influence of changes in oligosaccharide pattern on pharmacokinetic parameters in man.

Clinical trials

The Company presented studies meeting the requirements of the available CPMP Note for Guidance CPMP/198/95 final. In order to evaluate the efficacy and safety of rFVIII-SF, two open labelled multicenter studies were performed, study BAY 14-2222/0102 in NA and study BAY 14-2222/0101 in EU. Both studies were designed to include efficacy and safety investigation following administration for a six-month period (Stage II/III) as well as administration to patients undergoing surgery (stage IIIS). Those patients who participated in the stage I and II/III pharmacokinetic trial were included in these studies. One patient in the EU participated in stage IIIS only. Sixty-five patients completed an extended 24 (EU, n=30) and 18 (NA, n=35) month follow-up (stage IIIE). During the first 2 (EU) and 4 (NA) weeks of home treatment, patients were to be given prophylactic infusions three times weekly with a dose of 20 IU/kg intravenously. After this period patients returned to their pre-study regimen, either continuous prophylaxis or on-demand treatment for bleeding episodes. Dosage was according to patient needs. FVIII recovery was measured on samples taken at pre- and 10 minutes post-infusion at weeks 4, 12 and 24. FVIII concentrations were measured using a one-stage method.

Clinical efficacy

Efficacy in PTPs

The primary clinical efficacy variable was the number of treatments required per bleed during stage II/III/IIIE. A secondary variable was the subjective patient assessment (no response, moderate, good, excellent). In the NA study (n=35), during the 18-month observation period, a total of 1710 bleeding episodes were reported which were treated with a mean dosage of 27.5 ± 8.1 IU/kg. Of these 1710 bleeding episodes 13.8% were severe bleedings. Overall, 95% of bleeds responded to 1 or 2 infusions. Patients rated their overall responses as excellent (23.9%), good (59.1%), moderate (15.8%) or no response (0.8%). In the EU study (n=29), during the 24-month observation period, a total of 875 bleeding episodes were reported, of which 15% were severe bleedings. Overall, 91% of bleeds responded to treatment with one or 2 infusions. Patients rated their overall response as excellent (17.4%), good (58.4%), moderate (16.6%), or no response (0.9%). In both studies, FVIII recovery levels remained consistent from baseline across stage II/III (24-week period) with no loss of activity.

Table 4: Overview of efficacy parameters from the PTP studies

	NA			**EU**		
	all patients *(n=35)*	prophylactic treatment *(n=9)*	on-demand treatment *(n=26)*	all patients *(n=31)*	prophylactic treatment *(n=19)*	on-demand treatment *(n=12)*
IU/kg/Exp.	28 ± 5	28 ± 5	27 ± 4	26 ± 8	23 ± 7	32 ± 6
Exp./month	7.1 ± 4	11.1 ± 2.1	5.5 ± 2.4	10 ± 7.6	13.5 ± 7.7	4.3 ± 1.3
IU/kg/proph.	23.5 ± 5	27.1 ± 6	22 ± 4	22.5 ± 12	21.4 ± 6.6	24.3 ± 17
IU/kg/bleed.ep.	41.9 ± 27	60 ± 38	35 ± 16	74 ± 89	90.3 ± 108	48 ± 33
Bleed./month	2.5 ± 1.7	0.9 ± 0.7	3.1 ± 1.6	1.2 ± 1.3	0.5 ± 0.7	2.2 ± 1.3
Bleed./year	30 ± 21	11 ± 8	37 ± 20	14 ± 15.2	6.3 ± 8.4	26.1 ± 15.8
IU/kg/year	2482 ± 1422	4019 ± 1300	1868 ± 924	2861 ± 1957	3625 ± 2142	1652 ± 580

In the NA study, 3 surgical procedures were performed in three patients In the EU study, surgical procedures were performed in 12 patients who underwent 19 surgical procedures. rFVIII-SF was administered per protocol in bolus infusions. One of the patients was given a continuous infusion in violation of the protocol. Haemostasis was rated as either good or excellent. No post-operative complications were reported. Of the total of 22 surgical procedures, 11 were minor procedures (e.g. teeth extraction). The patients with minor surgical procedures received 393 ± 192 IU/kg/surgery over 9.4 ± 5 exposure days. The patients with major surgical procedures received 1747 ± 766 IU/kg/surgery over a mean of 25.6 ± 14 exposure days. Blood transfusion was necessary during two surgical procedures.

In general, from the data provided (number of infusions, patients' response), rFVIII-SF was shown to be an effective replacement therapy for the treatment and prophylaxis of bleedings in haemophiliacs

including surgical procedures. In a few cases where patients received more than 4 follow up treatments for bleeding, the company was asked to comment and provided satisfactory explanations.

In order to fully assess the efficacy data, the number of infusions used to control bleeding episodes was correlated with the FVIII total consumption per bleeding episode and the number of bleeding episodes during the observation period. The values of mean consumption per body weight and per year and the mean number of bleedings per year (see table 4) are in accordance with values from other plasma-derived or recombinant FVIII products. The Company also provided the individual values of the FVIII consumption per bleeding episode (summarised dosages from all follow-up treatments). Individual data confirmed that the values achieved during treatment with rFVIII-SF lie within the expected range for other FVIII products.

Efficacy in PUPs and MTPs (BAY 14-2222/0104 (EU) and BAY 14-2222/0105 (NA))

In October 1997, two clinical trials were initiated in Europe and North America to study the safety and efficacy of rFVIII-SF in young children with severe haemophilia A who have been previously untreated (PUPs) or minimally treated (MTPs). The Company provided interim reports up to the end April 1999. Up to the date of this analysis, a total of 61 patients had been treated with at least one infusion, i.e. in the EU study 31 (19 PUPs and 12 MTPs) and in the NA study 30 (18 PUPs and 12 MTPs). Of these 61 patients, 53 patients are severe haemophiliacs with a residual FVIII activity <1% and 8 patients have a residual FVIII activity between 1 and 2%. Exposure data for all patients are summarised in Table 5.

Table 5: Exposure data for all patients in the PUP/MTP study up to end April 1999

Range of exposure days	1-10	11-20	21-50	51-100	>100
No. of patients	35	9	7	5	5

Approximately 90% of bleeding episodes responded to treatment with one or two infusions. The data upon consumption and frequency of bleeding is summarised in Table 6.

Table 6: Overview of the efficacy parameters from the PUP/MTP study up to end April 1999

	EU		**NA**	
	PUP (n=19)	**MTP (n=12)**	**PUP (n=18)**	**MTP (n=12)**
IU/kg/Exp.	60.5 ± 18	47.1 ± 12	58.7 ± 29	43.9 ± 12
Exp./month	3.0 ± 2.9	3.4 ± 3.3	3.1 ± 5.8	3.1 ± 4.3
IU/kg/proph.	56.8 ± 25	47.0 ± 13	49.3 ± 19	33.6 ± 5
IU/kg/bleed.ep.	101.6 ± 63	58.2 ± 22	*40.4 ± 21.1**	*40.5 ± 18**
Bleed./month	0.9 ± 0.6	1.2 ± 1.1	0.5 ±0.4	0.3 ± 0.4
IU/kg/month	174.9 ± 180	147.4 ± 121.8	135.6 ± 326	116.9 ± 160

(*data not per bleeding episode)

On the basis of the available data, rFVIII-SF does not appear to be different to other FVIII products in terms of effective treatments of PUPs and MTPs.

Clinical safety

Safety in PTPs (studies BAY 14-2222/0102 and 0101)

From the 73 patients included in the PTP studies, 58 patients (79.5%) reported adverse events (AE) and thereof 13 (17.8%) patients reported drug-related AEs. These 13 patients reported 24 drug-related AEs of which 19 (80%) were classified as mild, 4 (16%) as moderate and 1 (4%) as severe. This severe AE, attributed as possibly drug-related, was observed in a patient who developed intermittent chest pain and palpitations. The drug-related AEs were rash/pruritus (4 patients), injection site reaction (3), chest pain/malaise (2), hypertension (1), inhibitor increase (1), unusual taste in the mouth (1), sweating (1), rhinitis (2). Further AE's classified as only remotely drug related were seborrheic dermatitis increase, diarrhoea, stinging in the face, lipothymia and hyperesthesia (arms).

No vital sign changes or laboratory abnormalities in renal, hepatic, or haematologic function were associated with infusions of rFVIII-SF. As the majority of patients had pre-existing hepatitis and/or

HIV disease, elevated transaminase values could be seen at baseline and intermittently throughout the study. However, no patient showed a persistent or progressive elevation in hepatic transaminases during treatment.

Development of FVIII inhibitors (BU>0.6) was regularly screened at baseline and after 4, 12 and 24 weeks of treatment and once or twice during Stage IIIE. In the EU study, inhibitor titre was measured using the Nijmegen-modified Bethesda assay whereas in the NA study the classical Bethesda Assay was performed. The Nijmegen modification results in fewer false positive inhibitor values. FVIII inhibitor formation was observed in one of the 71 patients in Stage II/III. This patient with a pre-existing low-titre inhibitor (0.5 BU) experienced a transient increase in inhibitor titre (up to 1.34 BU).

ELISA determinations were performed to detect antibodies to mouse (C7F7), baby hamster kidney (BHK) cells and rFVIII protein. Again these investigations were performed at baseline and after 4, 12 and 24 weeks of treatment. Two patients in the EU study showed transient positive ELISA measurements to rFVIII protein. Another patient had elevated ELISA measurements at pre-study and at nearly all other time points. However, FVIII recovery measurements were not affected in these patients.

In general, the presented data indicate that the adverse event profile for rFVIII-SF in PTPs does not differ from that of plasma-derived or other recombinant FVIII products. Concerning immunogenicity of rFVIII-SF, from 71 patients enrolled in stage II/III there are 59 patients with severe haemophilia (FVIII<1%) who had received more than 10 exposures (range 14-178) over a 6 month observation period. Taking into account the difficulties to assure reliable inhibitor measurements in some cases, so far there has been no evidence of development of *de novo* inhibitors in PTPs. There were 5 isolated cases where patients received another FVIII product during the study. Explanations were provided and in no case was insufficient efficacy with rFVIII-SF the reason for the administration of another product.

Safety in PUPs and MTPs (Study BAY 14-2222/0104 (EU) and BAY 14-2222/0105 (NA))

Of 61 patients who received at least one infusion, in 44 patients a total of 249 AEs were reported. Only 8 of these AEs were considered as possibly or probably related to the rFVIII-SF, i.e. 6 cases of inhibitor development, a forearm bleed following venipuncture and one case of constipation. In total 8 patients have developed an inhibitor (4 PUP and 4 MTP, 3 low and 5 high titre inhibitors). The inhibitors occurred after a median of 6.5 days (range: 2-16).

Given the still small number of patients who have more than 20 exposure days (17/61, approx. 30%), a final estimation of efficacy and safety in PUPs and MTPs, especially incidence of inhibitors, is not possible. The Company will provide ongoing data on a regular basis.

Based on the results for studies (Study Bay 14-2222/0104 and Study Bay 14-2222/100074) the Company (May 2002) applied to update section 4.8 (Undesirable effects) of the SPC to include the inhibitor incidence rate in PUPs (Previously Untreated Patients) in line with the core SPC for Factor VIII products. In addition, the MAH introduced a minor modification in the paragraph regarding allergic reactions to mouse/hamster proteins and added an ADR (fever), as requested by CHMP following the assessment of the 2nd and 3rd PSURs

Clinical experience with batches showing a changed glycosylation pattern

As previously described in this report, a change in glycosylation pattern (higher HBNLO levels) has been observed in final batches of rFVIII-SF and rFVIII.

Clinical experience with rFVIII-SF

In ongoing trials in PTPs and PUPs, two batches with higher HBNLO levels have been used. These batches were used in the PTP studies in 25% and 37%, respectively, of total infusions. There has been no clear trend associated with these lots in terms of number of infusions used to control bleeding. Recovery data are only available for two PUPs. No AE were reported in any trial as specifically related to these two batches. Furthermore, there was no meaningful difference in AE reporting based on exposure to these batches. No patients in PTP trials displayed a change in inhibitor status. Of the reported inhibitors in the PUP trials, all occurred prior to exposure to these batches.

Clinical experience with rFVIII

Three different treatment clinics were actively surveyed regarding their evaluation of safety and efficacy associated with a marketed rFVIII batch with higher HBNLO levels. 600 000 units of this batch were distributed in the area serviced by these three clinics. There were no adverse events reported. In an ongoing prophylactic infusion trial, 5 patients received this batch and 15 received a batch with a low level of HBNLO. No adverse events, inhibitor formation or joint bleeds were reported during the time periods that either the high level or low level batches were used for infusion therapy.

Post-marketing surveillance study

From the presented clinical experience for batches of both products with an increase in HBNLO content (rFVIII: 19 batches; rFVIII-SF: 2 batches), no apparent adverse or inferior safety or efficacy observations have been identified. Therefore, there are no concerns related to this change that would prevent the granting of a marketing authorisation. However, the Company will perform a post-marketing surveillance study with rFVIII-SF with particular focus upon any associations with HBNLO content.

Discussion on clinical aspects

On the basis of the presented studies which included overall 73 patients, KOGENATE Bayer is an effective and safe replacement therapy in PTPs. Given the small number of PUPs and MTPs who have more than 20 exposure days (17/61, approx. 30%), a final estimation of efficacy and safety (especially incidence of inhibitors) is not possible. Nevertheless, from the available data, KOGENATE Bayer does not appear to be different from other FVIII products in terms of efficacy and safety in the treatment of PUPs and MTPs. Therefore, a statement in the SPC regarding limited experience in paediatric patients is not considered necessary. The outcome of the ongoing PUP/MTP study and future studies will be reported on an ongoing basis with the periodic safety update reports.

5. Overall conclusions and benefit/risk assessment

Quality

On the basis of the submitted data and the agreed follow-up measures, the quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety and batch to batch consistency have been documented and the relevant tests will be performed according to the agreed specifications. Change in glycosylation pattern is being appropriately investigated in on-going studies. Appropriate testing has been implemented to assure batch to batch consistency with respect to glycosylation.

Non-clinical (pre-clinical) studies

The pharmacodynamic studies presented show that rFVIII-SF is able to affect bleeding time and aPTT as parameters of bleeding disorder. The acute and subacute toxicological investigations provide no evidence that rFVIII-SF has a higher or different toxicological risk than the parent compound rFVIII. In view of the pathogenesis of haemophilia A, reproductive toxicity has not been studied. It is acceptable that studies on mutagenic and carcinogenic potential have not been performed with rFVIII-SF since prior investigations did not show that the parent compound had such toxicological risks. An animal model was used to assess neoantigenicity, however only therapeutic administration to patients can provide information regarding possible neoantigenicity. In conclusion, rFVIII-SF does not show evidence of toxicological risks as far as is assessable from animal toxicological studies.

Pharmacokinetic studies in rabbits indicate that oligosaccharide pattern changes may influence pharmacokinetic parameters with a tendency to increased bioavailability.

Clinical efficacy and safety

Based on the pharmacokinetic trials the values of AUC_{0-48} (27-32 kg·h/IU), C_{max} (2.1-2.2 %·kg/IU) and $t_{½}$ (13-16 h) after application of 50 IU/kg rFVIII-SF comply with plasma-derived or other recombinant FVIII products. Further, these values demonstrate that the achieved amount of FVIII and the maintenance of plasma levels are as expected according to the posology in the SPC.

The clinical data show that rFVIII-SF is effective to prevent and to control bleedings in PTPs with severe haemophilia A. Taking into account the difficulties to assure reliable inhibitor measurements in some cases, there has been no evidence of development of *de novo* inhibitors in PTPs. The incidence rates for the most common adverse events, i.e. rash/pruritus, injection site reaction, chest pain/malaise, and unusual taste in the mouth, indicate that drug-related adverse-events were similar in nature and number to those in similar clinical trials with other FVIII products. Post-marketing data on further patients treated with rFVIII-SF will be needed in order to make a final assessment of the adverse event pattern.

Given the small number of PUPs and MTPs who have more than 20 exposure days, a final estimation of efficacy and safety (especially incidence of inhibitors) is not possible. Nevertheless, from the available data, KOGENATE Bayer does not appear to be different from other FVIII products in terms of efficacy and safety in the treatment of PUPs and MTPs. Therefore, a statement in the SPC regarding limited experience in paediatric patients is not considered necessary. The outcome of the ongoing PUP/MTP study will be reported on an ongoing basis with the periodic safety update reports.

Benefit/risk assessment

Further information on the change in glycosylation pattern was requested from the company and the issue was referred to the CPMP's Biotechnology Working Party, where the company also provided an oral clarification. On the basis of the available information from on-going studies, the introduction of testing to assure batch-to-batch consistency, and relevant follow-up measures, the quality issues were considered resolved.

The animal pharmacokinetic studies and clinical safety and efficacy data on batches with the changed glycosylation pattern, did not raise any concerns that would prevent the granting of a marketing authorisation and relevant follow-up measures will be undertaken.

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