15 March 2012
EMA/282360/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II assessment report

KOGENATE Bayer, Helixate NexGen

Procedure No. EMEA/H/C/000275/WS/0193

EMEA/H/C/000276/WS/0193

Worksharing applicant (WSA): Bayer Pharma AG

Note

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

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1. Background information on the procedure

1.1. Requested Type II variations

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bayer Pharma AG submitted to the European Medicines Agency on 8 September 2011 an application for a variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal products:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
KOGENATE Bayer, EMEA/H/C/000275/WS/0193	octocog alfa	See Annex A
Helixate NexGen, EMEA/H/C/000276/WS/0193	octocog alfa	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed to update section 4.1 with the new indication for the treatment of hemophilia A patients with inhibitors by immune tolerance induction.

Appointed Rapporteur for the WS procedure: Jan Mueller-Berghaus

1.2. Steps taken for the assessment

Submission date:	8 September 2011
Start of procedure:	18 September 2011
Rapporteur's assessment report circulated on:	08 December 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	15 December 2011
MAH's responses submitted to the CHMP on:	10 January 2012
Rapporteur's assessment report on the MAH's responses circulated on:	16 February 2012
CHMP opinion:	15 March 2012

2. Scientific discussion

2.1. Introduction

KOGENATE Bayer/Kogenate FS and Helixate NexGen/Helixate FS products consist of a recombinant human factor VIII (FVIII, INN: octocog alfa), which is derived from a cloned human FVIII gene

transfected into baby hamster kidney (BHK) cells. The product is formulated with sucrose as a stabilizer.

Marketing authorization of KOGENATE / Kogenate FS in the EU was first granted in August 2000. Bayer Healthcare is the license holder for rFVIII distributed by CSL Behring under the main brand Helixate, which is identical with KOGENATE / Kogenate FS.

The currently approved therapeutic indications in EU for Kogenate/Helixate are:

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

Bleeding episodes in patients with FVIII inhibitors is currently managed at the discretion of the treating physician. In most cases, the treatment depends on one hand on the in vitro potency of the inhibitors, which is reported as the number of Bethesda units (BU) per millilitre of plasma and on another side on the titer of inhibitors (high titer [peak titer >5 BU) or low titer [peak titer ≤5 BU)]. High-responding inhibitors have been shown to elicit a quick, strong immune response while low-responding inhibitors produced a slower, weaker response[1] . If the inhibitor titer is low, administration of additional FVIII doses may neutralize the inhibitor and allow continued clinically effective therapy. If the inhibitor titer is high, use of bypassing agents, such as activated prothrombin complex concentrate (APCC) or recombinant activated factor VII (rFVIIa) should be considered[2] .

The current Type II variation proposes to extend the indication for Kogenate/Helixate to the treatment of hemophilia A patients with inhibitors by Immune Tolerance induction (ITI).

Information on paediatric requirements

The application did not fall within the scope of Article 8 of the paediatric regulation.

2.2. Non clinical aspects

The applicant did not submit non-clinical study reports in support of the proposed indication of ITI.

2.3. Clinical Pharmacology aspects

The applicant did not submit pharmacokinetic or pharmacodynamic study reports to support the proposed indication of ITI.

2.4. Clinical Efficacy aspect

To support the new indication "ITI" the MAH presented data from:

- the INFACT study (global non-interventional retrospective study, KG0801,13011)
- the International ITI study (investigator-sponsored open, prospective, randomized study, 13862): 116 children (<8 yrs) with hemophilia A with inhibitors against FVIII for <24 months and a historical peak inhibitor titer between 5 and 200 BU; 39 patients received Kogenate/Helixate
- comprehensive Literature Review of Immune Tolerance Induction in Patients with Hemophilia A

[1] DiMichele DM et al., Haemophilia 2004:10 Suppl 4;140-145.
[2] Berrettini M et al., Haematologica 2001:86;640-645.

- post-marketing case collection survey of treatment of hemophilia A patients with inhibitors, data from 13 patients who had been administered Kogenate or Kogenate Bayer (KG0302)

Table 1 Clinical Studies included in the Clinical Summary for ITI application

Study name (Study number)	Study design	No. and description of patients	FVIII product type and dose
IN FACT (13011)	observational, retrospective, phase IV	**32** children (<8 years) with severe hemophilia A with inhibitors against FVIII (i.e. meeting original protocol-specified inclusion/exclusion criteria) and **8** children and adult patients in France meeting broader inclusion/inclusion criteria (i.e. ≥8 years, 2 patients with moderate hemophilia A)	Kogenate Bayer varying doses (starting dose per exposure day ranged from 50 to 364 IU/kg)
International ITI Study (13862)	investigator-sponsored, open, prospective, randomized	116 children (<8 years) with hemophilia A with inhibitors against FVIII for <24 months and a historical peak inhibitor titer between 5 and 200 BU **39**[a] patients received Kogenate Bayer	various types and brands of factor VIII (low-dose: 50 IU/kg BW 3 x/week) (high-dose: 200 IU/kg BW/day) 39 patients received treatment with Kogenate Bayer

[a] a subset of the total study population selected based on treatment with Kogenate Bayer; total number of randomized patients is 116

BU=Bethesda unit; BW=body weight; FVIII=factor VIII; IU=International unit; kg=kilogram

2.4.1. Main studies

IN FACT (KG0801): Immune Tolerance **IN**duction in hemophilia A patients with inhibitors by high-dose treatment with recombinant **FACT**or VIII - a retrospective non-interventional study.

Methods

Between May 2009 and May 2010 patient data were collected from 27 centers in Canada, France, Greece, Italy, and Spain. The observational period comprised the time from November 2001 to November 2009 (first start of ITI – last end of ITI).

Study Participants

Criteria for inclusion:

- Patients with severe hemophilia A (FVIII:C <1%) with a peak inhibitor titer > 5 Bethesda Units (BU) who received ITI treatment with KOGENATE Bayer/FS or Helixate NexGen at any dose.

- Children of age <8 years at start of ITI.

- Patients with a minimum duration of ITI treatment of 9 months or until success (which could have been earlier than 9 months).

- Written informed consent available.

Criteria for exclusion:

- Patients who underwent unsuccessful ITIs in the past with other products than KOGENATE Bayer/FS or Helixate NexGen, independent of the type of therapy (incl. immune suppressive therapy).

- Patients who switched to other FVIII products during ITI treatment before a treatment duration of 9 months or before success.

In contrast to the other countries participating in the IN FACT study, centers in France also included patients with moderate hemophilia A, patients 8 years and older, and patients who had undergone ITI therapy with other products unsuccessfully in the past.

Treatments

Test product, dose and mode of administration
KOGENATE Bayer/FS or Helixate NexGen: INN: octocog alfa (recombinant FVIII formulated with sucrose, rFVIII-FS), commercially available product was used to treat patients.

Treatment dose and regimen was to be decided by the treating physician. In accordance with the consensus recommendation[3] high doses were defined as ≥ 100 IU/kg per exposure day. However, since doses were reported in full vials (e.g. 2000 IU) in this study and the body weight was not followed closely, the calculation of IU/kg body weight resulted in inaccuracies in the assignment to high and low-dose treatment groups. Therefore doses of ≥ 85 IU/kg per exposure day (means also deviations up to -15% from 100 IU/kg body weight) were already considered as high-dose treatment independent of the frequency. Dosages at start of ITI treatment were used to assign patients either to the high-dose or low-dose treatment group.

Intravenous administration by bolus injections.

The decision on the duration of the ITI treatment was solely at the discretion of the attending physician and therefore, the treatment duration differed from patient to patient.

Objectives

Study objectives
Primary: To collect clinical data on immune tolerance induction (ITI) treatment with Kogenate/Helixate in order to demonstrate the feasibility of Kogenate/Helixate for ITI treatment in hemophilia A patients with inhibitors to factor VIII.

Secondary (if data are adequate): To analyze influencing factors for success as well as time to success. To collect safety data regarding the administration of Kogenate/Helixate by checking for adverse events.

Outcomes/endpoints

The patient charts were reviewed and data on the following variables were collected in Case Report Forms:

Demography, medical history, concomitant diseases:

Demographic data, anamnesis of hemophilia, pre-treatment and concomitant diseases.

[3] Astermark J et al., Haemophilia 2006:12; 363-71.

Safety parameters:

Safety analysis comprised analysis of adverse events during ITI treatment.

Efficacy parameters:

Efficacy analysis comprised duration and dosing schedule of ITI, assessment of success by physician, inhibitor measurements during ITI, recovery data during ITI, continuation of therapy after ITI as well as reasons for discontinuation of therapy after ITI.

Sample size

Due to the extremely rare nature of the disease condition it was planned to enroll approximately 20 to 30 patients.

Randomisation

This was an observational, noninterventional retrospective study. Patients had been randomized to high or low doses of octocog alfa.

Blinding (masking)

This was an open label study.

Statistical methods

The study population was a cohort sample of hemophilia A patients who had developed inhibitors against Factor VIII and who were treated with KOGENATE Bayer/FS or Helixate NexGen for immune tolerance induction. All patients who did not violate the in-/exclusion criteria were valid for the analysis of efficacy and safety. The screening population and reason for exclusion were described.

Descriptive analyses of the data were performed using summary statistics for categorical and quantitative data. Continuous data were described by mean, standard deviation (SD), minimum, 25% and 75% quartiles, median, maximum, number of non-missing values. In addition, continuous data were categorized in clinically meaningful way. Categorical data including categories of continuous data were presented in frequency tables.

Number of patients with missing data was presented as a separate category. Percentages were calculated as a proportion of each category including the category missing values. In some subgroup analyses percentages were calculated based on non-missing values (adjusted frequencies).

Safety analysis included tabulation of type (using Medical Dictionary for Regulatory Activities (MedDRA) coding) and frequency of all drug-related and not drug-related adverse events.

The seriousness, action taken, and outcome of events were described.

All adverse events (AE) reported were categorized as treatment emergent signs and symptoms (TESS) or non-TESS. The following approach was used for the definition of TESS: If an AE occurred within the time interval from start of ITI until end of ITI it was classified as TESS, otherwise it was classified as non-TESS.

Incidence rates for specific events were calculated as the number of specific events reported divided by the number of patients at risk, where the number of specific events was defined as the number of patients reporting the specific event and the number at risk was defined as all patients with

consumption of KOGENATE Bayer/FS or Helixate NexGen during the ITI treatment. For multiple occurrences of a specific event within one patient, the event was counted only once.

Results

Recruitment

The study was conducted at 27 hemophilia treatment centers in 5 countries (Canada, France, Greece, Italy, Spain).

Conduct of the study

Nineteen patients, mainly in France, were excluded from the analysis of the overall KG0801 study due to deviations from the inclusion criteria:

Table 2 Patients excluded from analysis (n=19) (KG0801)

Pat. No.	Country	Reason
101	France	FVIII activity ≥ 1%, age of patient ≥ 8 years at start of ITI
107	France	Age of patient ≥ 8 years at start of ITI
110	France	Participation in clinical study (International ITI study)
119	France	Peak inhibitor before ITI ≤ 5 BU
135	France	Age of patient ≥ 8 years at start of ITI
136	France	Age of patient ≥ 8 years at start of ITI, ITI ongoing
140	France	Age of patient ≥ 8 years at start of ITI
141	France	ITI ongoing
143	France	Participation in clinical study (International ITI study)
145	France	FVIII activity ≥ 1%
146	France	Peak inhibitor before ITI ≤ 5 BU
150	France	Age of patient ≥ 8 years at start of ITI
153	France	Age of patient ≥ 8 years at start of ITI
167	France	Age of patient ≥ 8 years at start of ITI
201	Italy	Peak inhibitor before ITI ≤ 5 BU
501	Canada	ITI ongoing
513	Canada	Participation in clinical study (International ITI study)
514	Canada	Peak inhibitor before ITI ≤ 5 BU, duration of ITI treatment ≤ 9 months and no success, unsuccessful ITIs in the past with other products
515	Canada	Participation in clinical study (International ITI study)

In the 17 haemophilia centers in France participating in the IN FACT study (IN FACT France (KG0801FR)), 28 patients were enrolled, of which 22 were included in the analysis. Out of 22 patients included in this country specific analysis, 14 patients were also included in the international analysis, 8 patients were exclusively included in this analysis (pat nos. 101, 107, 135, 140, 145, 150, 153, and 167).

Amendment 1, dated 04 DEC 2008, was locally valid only for centers located in France. Reason for amending the protocol was the local requirement in France to document patients based on in-/ exclusion criteria differing from the in-/ exclusion criteria used in the other countries. The amendment was implemented before any patient was enrolled by the affected centers; it specified the following

modifications:

- change of in-/ exclusion criteria:

Criteria for inclusion into the study:

- Patients with severe (FVIII:C <1%) or moderate haemophilia A (1% < FVIII:C < 5%) with a peak inhibitor titer > 5 BU who received ITI treatment with KOGENATE® Bayer/FS or Helixate NexGen at any dose.

- Patients with a minimum duration of ITI treatment of 9 months or until success (which could be earlier than 9 months).

- Written informed consent (in the required format).

Criteria for exclusion from the study:

- Patients who switched from KOGENATE Bayer/FS or Helixate NexGen to other Factor VIII products during ITI treatment before a treatment duration of 9 months or before success.

- change of patient validity criteria

Amendment 2, dated 07 OCT 2009: only administrative changes.

Baseline data

A total of 32 male patients with severe hemophilia A (FVIII:C <1%) were included in the analysis. Twenty-five patients were Caucasian (78.1%). Two patients were black and two patients were of Asian descent. The ethnicity of 3 patients was specified as "other". The median age at which the inhibitor was first detected was 1.0 years (mean 1.2 ± 1.0 years), median age at start of ITI treatment was 2.0 years (mean 2.2 ± 1.4 years).

Table 3: Age at diagnosis, start of hemophilia, first inhibitor detection and start of ITI

	Non-Missing	Median	Mean ± SD	Range
Age at diagnosis (years)	27	0.0	0.3 ± 0.7	0 – 3
Age at start of hemophilia A treatment (years)	26	0.0	0.5 ± 0.8	0 – 3
Age at first inhibitor detection (years)	30	1.0	1.2 ± 1.0	0 – 4
Age at start of ITI treatment (years)	32	2.0	2.2 ± 1.4	0 – 5

Table 4: History of FVIII inhibitor before the start of ITI

	Non-Missing	Median	Mean ± SD	Range
Days between first positive inhibitor test and start of ITI	30	260	298 ± 280	6 – 1166
Days between peak titer and start of ITI	31	96	201 ± 260	0 – 1131
Days between last positive inhibitor test and start of ITI	32	11	37 ± 75	0 324
Titer at first positive inhibitor test [BU]	32	7	24 ± 40	1 – 199
Peak titer before ITI [BU]	32	19	64 ± 118	5 – 520
Titer at last positive inhibitor test [BU]	32	6	24 ± 91	<1 520

Numbers analysed

70 patients were screened, 51 patients were enrolled, of which 32 were included in the analysis.

Outcomes and estimation

A total of 32 male subjects suffering from severe hemophilia A were included in the analysis. Median age at which the inhibitor was first detected was 1.0 years (mean 1.2 ± 1.0 years), median age at start of ITI treatment was 2.0 years (mean 2.2 ± 1.4 years). About two thirds of the patients (n=21, 65.6%) received a high-dose therapy (≥85 IU/kg per exposure day), 11 patients (34.4%) received a low-dose therapy. The starting dosage per exposure day ranged from 38 to 250 IU/kg. The initial frequency of recombinant FVIII formulated with sucrose (rFVIII-FS) infusions was 3 times per week in 53.1% of patients and daily in 34.4%. Three patients (9.4%) received rFVIII-FS every other day and one patient 3 times per day (3.1%) in the first three days. For the individual patients widely disparate dosing regimens were used.
The patients completed ITI after a median duration of 1.8 years (mean 1.8 ± 1.1 years, range 39 days to 4.5 years) receiving a median of 1,021,000 IU rFVIII (mean 1,236,880 ± 1,072,031 IU, range 46,500 to 4,012,000 IU). The median consumption of rFVIII-FS in the subgroup of patients on high-dose therapy was 1,068,000 IU compared to 443,000 IU for patients on low-dose therapy. The maximum treatment dose per exposure day ranged from 50 to 364 IU/kg for all patients.

ITI was successful in 22 patients (68.8%) and failed in 10 patients (31.3%), while the criteria used to define 'success" differed (Table 5). In 5 patients the criteria for success were a negative inhibitor assay, a normal recovery (≥66% of expected) and a normal FVIII halflife (≥6 h). In 9 patients a negative inhibitor assay and normal FVIII recovery were used to define success. In 8 patients a negative inhibitor assay was the only documented criterion.

Evaluation of success rates by subgroups of patients showed differences with regard to peak titers before start of ITI, titers at start of ITI and time between inhibitor detection and start of ITI: The success rate increased to 79.0% for patients who started ITI within less than one year after inhibitor detection and to 93.3% for patients with an inhibitor titer > 5 and < 10 BU at the time of start of ITI.

All 32 patients completing ITI successfully continued KOGENATE Bayer/FS or Helixate NexGen therapy as prophylactic treatment. In none of these patients a recurrence of inhibitor after end of ITI until enrollment was observed.

Table 5: ITI outcome success by defined subgroups of patients

	No. of patients*	Success rate (%)
Total	32	68.8
Type of therapy		
- High-dose therapy	21	66.7
- low-dose therapy	11	72.7
Interruptions of ITI (> 2 days)		
- No	28	67.9
- Yes	4	75.0
Events of MedDRA SOC Infections and infestations		
- No	14	71.4
- Yes	18	66.7
Peak titer before start of ITI		
- > 5 and < 10 BU	6	83.3
- 10 – 50 BU	18	72.2
- 51 – 100 BU	4	75.0
- > 100 BU	4	25.0
Titer at start of ITI		
- ≥ 10 BU	17	47.1
- > 5 and < 10 BU	15	93.3
Time between inhibitor detection and start of ITI		
- - ≥ 1 year	11	45.5
- < 1 year	19	79.0
Intravenous catheter during ITI		
- No	7	71.4
- Yes	25	68.0
Catheter site / Device related infection during ITI		
- No infection	19	73.7
- Infection	6	50.0
- No catheter	7	71.4

*categories with missing values are not presented

Ancillary analyses

IN FACT France (KG0301FR)

A total of 22 male subjects suffering from severe or moderate hemophilia A were included in the analysis. Median age at which the inhibitor was first detected was 1.5 years (mean 7.0 ± 11.8 years), median age at start of ITI treatment was 3.0 years (mean 10.6 ± 15.2 years).

About two thirds of the patients (n=15, 68.2%) received a high-dose therapy (≥85 IU/kg per exposure day), 7 patients (31.8%) received a low-dose therapy.

The patients completed ITI after a median duration of 1.4 years (mean 1.6 ± 1.0 years, range 108 days to 3.6 years) receiving a median of 1,489,750 IU rFVIII-FS (mean 2,007,707 ± 1,692,490 IU, range 162,000 to 6,114,000 IU).

As assessed by the attending physician, ITI was successful in 13 patients (59.1%), partially successful in 3 patients (13.6%) and failed in 6 patients (27.3%). In 2 patients the criteria for 'success' were a negative inhibitor assay, a normal recovery and a normal FVIII half-life. In 8 patients a negative

inhibitor assay and normal FVIII recovery were used to define 'success'. In 3 patients a negative inhibitor assay was the only documented criterion.

Evaluation of success rates by subgroups of patients showed differences with regard to peak titers before start of ITI and titers at start of ITI: The success rate increased to 83.3% for a subgroup of 6 patients with a peak inhibitor titer > 5 and < 10 BU before start of ITI.

All 16 patients completing ITI successfully or partially successfully continued KOGENATE Bayer/FS or Helixate NexGen therapy as prophylactic treatment. In three patients with outcome partial success a recurrence of inhibitor after end of ITI until enrollment was observed.

International ITI Study (13862): Prospective, randomized, unblinded, international trial comparing two FVIII dosing regimens for ITI: low-dose (50 IU/kg three times weekly) versus high-dose (200 IU/kg daily).

Methods

An investigator-initiated, open, prospective study, conducted between July 2003 and November 2009 at 90 centers in 17 American, European, and Asian countries.

Study Participants

Criteria for inclusion

- Severe hemophilia A (FVIIIC <0.01 IU/ml)
- Patients ≤ 7 years of age at start of ITI
- Maximum historical inhibitor of between 5 BU and 200 BU
- Inhibitor titer was to be <10 BU at the start of ITI
- Inhibitor had to be present for ≤ 24 months

Criteria for exclusion

- Previous attempt of ITI

Treatments

Test drugs investigated in this multicenter international study included recombinant and plasma derived Factor VIII products from numerous manufacturers; however, for the purposes of this report, only the data from those patients who received Kogenate/Helixate are included in the analyses of efficacy and safety.

Dose
Low dose: 50 IU/kg rFVIII 3 times weekly OR High dose: 200 IU/kg rFVIII daily IV.

Duration of treatment
Minimum 9 months and maximum 33 months of ITI therapy, plus 12 months of prophylactic treatment.

ITI treatment was to continue without any change in product-type until the inhibitor had disappeared and the patient met the criteria for either successful or partial tolerization or until the patient had fulfilled the criteria for treatment failure. The maximum specified duration of ITI treatment was 33

months. If ITI was successful, the dose of FVIII was reduced to a regular prophylactic dose-level. Prophylaxis was continued for 12 months following the completion of ITI and patients were monitored for signs of relapse.

Objectives

- To compare the efficacy, response time, morbidity and economics of a high-dose and a low-dose immune-tolerance protocol
- To identify predictors of successful ITI

Outcomes/endpoints

Study data to be collected included demographic information; details of FVIII administered for ITI; treatment for intercurrent bleeding; and inhibitor titers, FVIII recovery, and FVIII half-life determinations. Data reflecting concomitant therapy capable of affecting the immune system, intravenous catheter insertions, and infections and non-catheter related infections was also collected. The number of hospital in-patient days during the study and serious adverse events (SAEs) were recorded as well.

For the purposes of this report, only data collected for those patients who received treatment with Kogenate/Helixate is presented.

Criteria for evaluation efficacy / clinical pharmacology

Extensive efficacy analyses were planned for the main study protocol; however, only limited data were available for the patients who received treatment with Kogenate/Helixate.
Treatment outcome was measured by the following criteria:

- **Success** was defined as the abolition of the inhibitor (<0.6 BU using the Bethesda Assay or <0.3 BU using the Nijmegen modification) within 33 months of ITI as defined by a FVIII recovery ≥66% of expected and half-life ≥ 6h, and measured after a 72-hour treatment-free washout period.
- **Treatment failure** was defined as the failure to fulfill the criteria for full or partial success within 33 months. **OR** Following the first 3 months of treatment and prior to completing 33 months of ITI, failure to achieve an ongoing ≥20% reduction in inhibitor titer, during each interim non-overlapping, 6-month period of ITI in the absence of documented infection. This implies that 9 months was the minimum treatment period and 33 months the maximum possible duration of unsuccessful ITI. **OR** Withdrawal from the study for any other reason**.**

A post-hoc analysis of efficacy was also performed for those patients who received sufficient ITI (defined as at least 9 months of ITI therapy, without the requirement for 12-month prophylaxis).

The post-hoc analysis of success used the following criteria:

- **Most stringent:** Sustained negative inhibitor AND recovery ≥66% AND half-life ≥ 6h (including patients who did not have a complete subsequent 12 month prophylactic phase)
- **Moderately stringent:** Sustained negative inhibitor AND recovery ≥66% (including patients who did not have a complete subsequent 12 month prophylactic phase)
- **Least stringent:** Sustained negative inhibitor (including patients who did not have a complete subsequent 12 month prophylactic phase)

Safety was assessed based upon the nature and frequency of serious adverse events (SAEs), coded using the MedDRA 14.0 dictionary. Non-serious adverse events were not recorded.

Sample size

Power calculations were performed using the software package nQuery Advisor using assumptions based on the published literature. The time required to achieve tolerance was the main outcome measure examined. If the sample size in each group was approximately 75, a 0.05 significance level two-sided log rank test for equality of survival curves would have a theoretical 80% power to detect a difference between the 2 treatment arms if 80% of the high-dose group and 50% of the low-dose group achieved tolerance after 9 months ITI (a constant hazard ratio of about 3.00). This calculation assumes no dropouts before 9 months.

The estimate of sample size allowed for the small loss of statistical power incurred by 2 planned interim analyses.

For the purposes of this report, only those patients who received treatment with Kogenate FS/KOGENATE Bayer or Helixate FS/Helixate NexGen (n=39) were to be assessed for efficacy and safety parameters. All presentations of data for this subset of patients were to be descriptive in nature. No power calculations were performed. 75 patients per treatment group were planned for the full study.

Randomisation

Patients were randomized to either the low-dose arm or the high-dose ITI treatment.

Blinding (masking)

This was an open label trial.

Statistical methods

For the main study analysis, response times were to be analysed using Cox proportional hazard models, with allowance made for center effects (clustering). Alternatively, "success" (a binary outcome assessed at the end of the study period) was to be analysed using multiple logistic regression (again allowing for clustering of data). Two interim analyses were planned.

A separate statistical analysis plan was prepared for the subset of the main data presented in this report. For the n=39 patients who received treatment with Kogenate/Helixate the primary analysis of efficacy (treatment outcome) was based upon the valid per protocol patient population (n=13; protocol driven-analysis). An additional analysis of outcome was also performed for the full subset (n=39). Further, a post-hoc analysis of treatment outcome was performed for the n=35 patients who received sufficient ITI.

Results

Participant flow

A summary of patient disposition is shown in Table 6.

Table 6: Summary of patient disposition

Reason for discontinuation (N[%])	Low (N = 20)	High (N = 19)	Total (N =39)
Deviation from protocol not otherwise specified	1 (5.0)	5 (26.3)	6 (15.4)
Withdrawal of informed consent	1 (5.0)	1 (5.3)	2 (5.1)
Incompliance	3 (15.0)	1 (5.3)	4 (10.3)
Study closure	5 (25.0)	6 (31.6)	11 (28.2)
Treatment failure	**4 (20.0)**	**3 (15.8)**	**7 (17.9)**
Treatment success	**4 (20.0)**	**2 (10.5)**	**6 (15.4)**
Physician decision	2 (10.0)	1 (5.3)	3 (7.7)

Recruitment

The study centers that provided treatment to the subset of patients whose data was analyzed for this report comprised a subset of centers from a multicenter international study (International ITI Study).

Conduct of the study

An interim analysis of the data collected in the International ITI study was performed in 2008. The International ITI Study was terminated early due to significantly higher rates of bleeding with low-dose versus high-dose ITI both early and late in the course of treatment.

Following enrollment, patients were treated using bypass therapy on demand, until their inhibitor titer fell below 10 BU/ml. The inhibitor titer was monitored monthly during this period.

Baseline data

A summary of demographic and baseline characteristics is shown in Table 7. All 39 patients were male. The median age of patients was 22.0 months (range 10-59 months). Inhibitor titers at the time of study entry ranged from 1.0 to 69.0 BU (mean 6.9 BU [SD=10.5 BU]).

Table 7: Summary of demographic and baseline characteristics (by treatment group)

	Low (N = 20)	High (N = 19)	Total (N = 39)
Sex (N[%])			
Male	20 (100)	19 (100)	39 (100)
Female	0	0	0
Ethnicity (N[%])			
White	14 (70.0)	14 (73.7)	28 (71.8)
Black	1 (5.0)	1 (5.3)	2 (5.1)
Asian	2 (10.0)	3 (15.8)	5 (12.8)
Other	3 (15.0)	1 (5.3)	4 (10.3)
Weight [kg]			
N with data	20	19	39
Mean	13.36	13.29	13.33
SD	2.75	2.90	2.78
Min	9	9	9
Median	13.00	12.70	13.00
Max	18	18	18
Age at randomization [month]			
N with data	20	19	39
Mean	25.25	26.68	25.95
SD	10.62	12.01	11.19
Min	10	13	10
Median	23.00	21.00	22.00
Max	59	49	59
Age at first diagnosis [month]			
N with data	20	19	39
Mean	19.55	21.26	20.38
SD	10.66	10.25	10.36
Min	6	6	6
Median	16.00	18.00	17.00
Max	54	38	54
Time between first diagnosis and start of ITI [month]			
N with data	20	19	39
Mean	5.15	4.89	5.03
SD	2.39	3.75	3.09
Min	0	0	0
Median	4.50	4.00	4.00
Max	10	13	13
Familiy history (N[%])			
Yes	3 (15.0)	5 (26.3)	8 (20.5)
No	17 (85.0)	14 (73.7)	31 (79.5)

	Low (N = 20)	High (N = 19)	Total (N = 39)
Inhibitor at diagnosis [BU]			
N with data	20	19	39
Mean	20.77	20.74	20.75
SD	28.08	38.40	33.06
Min	1	1	1
Median	9.90	9.20	9.80
Max	100	175	175
Maximum historic inhibitor [BU]			
N with data	20	19	39
Mean	37.07	41.86	39.41
SD	38.44	44.73	41.14
Min	5	7	5
Median	19.75	25.00	22.40
Max	160	175	175
Inhibitor at study entry [BU]			
N with data	20	19	39
Mean	5.48	8.31	6.86
SD	2.48	14.86	10.47
Min	1	1	1
Median	5.80	5.70	5.70
Max	9	69	69

Numbers analysed

A total of 116 children were enrolled in the overall study; a total of 39 patients received treatment with Kogenate/Helixate and were analyzed (n= 20 in the low-dose group and n=19 in the high-dose group).

Outcomes and estimation

The mean duration of treatment was 15.6 months (range 3 to 36 months).

A summary of the treatment failure and treatment success of ITI in patients treated with octocog alfa is shown in Table 8.

Table 8: Summary of Patient Disposition (Patients treated with Kogenate/Helixate in International ITI Study)

Reason for discontinuation (N[%])	Low (N = 20)	High (N = 19)	Total (N =39)
Deviation from protocol not otherwise specified	1 (5.0)	5 (26.3)	6 (15.4)
Withdrawal of informed consent	1 (5.0)	1 (5.3)	2 (5.1)
Incompliance	3 (15.0)	1 (5.3)	4 (10.3)
Study closure	5 (25.0)	6 (31.6)	11 (28.2)
Treatment failure	**4 (20.0)**	**3 (15.8)**	**7 (17.9)**
Treatment success	**4 (20.0)**	**2 (10.5)**	**6 (15.4)**
Physician decision	2 (10.0)	1 (5.3)	3 (7.7)

For the 21 patients who achieved a negative titer during ITI therapy, the time to negative titer ranged from 2.4 to 33.6 months (median = 6.3 months).

The results of the 13 patients who completed the study according to the protocol are presented in Table 9.

Table 9: Summary of ITI outcomes by ITI success criteria (per protocol population)

	Low (n = 8)	High (n=5)	Total (n=13)
Success	4 (50.0)	2 (40.0)	6 (46.2)
Failure	4 (50.0)	3 (60.0)	7 (53.8)

A total of 14 patients continued to receive therapy with Kogenate FS/KOGENATE Bayer or Helixate FS/Helixate NexGen following the completion of ITI therapy with these agents. The patients who most commonly chose to continue treatment were those (6/39; 15.4%) for whom ITI treatment was deemed successful.

Table 10: Continuation of therapy after ITI and reasons for termination of study

Continuation of therapy	Reason for study termination	Low (n=20)	High (n=19)	Total (n=39)
Yes	Total	8 (40.0)	6 (31.6)	14 (35.9)
	Deviation from protocol not otherwise specified	1 (5.0)	2 (10.5)	3 (7.7)
	Withdrawal of consent	0	1 (5.3)	1 (2.6)
	Incompliance	2 (10.0)	0	2 (5.1)
	Study closure	0	0	0
	Treatment failure	1 (5.0)	1 (5.3)	2 (5.1)
	Treatment success	4 (20.0)	2 (10.5)	6 (15.4)
	Physician decision	0	0	0
No	Total	12 (60.0)	13 (68.4)	25 (64.1)
	Deviation from protocol not otherwise specified	0	3 (15.8)	3 (7.7)
	Withdrawal of consent	1 (5.0)	0	1 (2.6)
	Incompliance	1 (5.0)	1 (5.3)	2 (5.1)
	Study closure	5 (25.0)	6 (31.6)	11 (28.2)
	Study failure	3 (15.0)	2 (10.5)	5 (12.8)
	Study completed successful	0	0	0
	Physician decision	2 (10.0)	1 (5.3)	3 (7.7)

Ancillary analyses

Of the 35 patients who had a sufficient duration of ITI therapy (9-33 months) to assess failure irrespective of completion of the prophylaxis period, 24 (69%) had a successful response as determined by a sustained negative inhibitor test. Eighteen (51%) of patients achieved a successful response based upon a sustained negative inhibitor test plus normalized FVII recovery. Eleven (31%) of patients met all 3 success criteria.

Table 11: Summary of ITI outcomes by post-hoc success criteria (patients with sufficient duration of ITI)

Regimen	Low n (%) n=18	High n (%) n=17	Total n (%) n=35
Success in 3 of 3 Criteria	7 (38.9)	4 (23.5)	11 (31.4)
Success in 2 of 3 Criteria	11 (61.1)	7 (41.2)	18 (51.4)
Success in 1 of 3 Criteria	13 (72.2)	11 (64.7)	24 (68.6)

Note: Success in 3 of 3 criteria = negative inhibitor assay, recovery ≥66%, and half-life ≥6 h. Success in 2 of 3 criteria = negative inhibitor assay, recovery ≥66%. Success in 1 of 3 criteria = sustained negative inhibitor assay.

No important differences were observed in the rate of SAEs by treatment group. Hemorrhage (5 patients; 12.8%), device-related infections (5 patients; 12.8%), and central venous catheterizations (5 patients; 12.8%) were the most commonly reported SAEs.

The following table summarises the number of patients that successfully completed ITI treatment from the main studies supporting the present application.

Table 12: Summary of patients who completed ITI treatment

Study cohort	Number (%) of patients successfully completing ITI
IN FACT International cohort	22/32 (68.8%)[a]
IN FACT French cohort with modified inclusion/exclusion criteria	2/8 (25.0%)[a]
International ITI study	24/35 (68.6%)[b]

[a]According to the assessment of the physician

[b]Based on successful response by means of a sustained negative inhibitor test only for patients considered to have received sufficient duration of therapy (i.e. 9 months)

2.4.2. Discussion of efficacy

The IN FACT study is a retrospective collection of data from an observation period November 2001 to November 2009. The participating haemophilia centers in 5 countries documented all haemophilia A patients who had developed inhibitors against Factor VIII and who were treated with Kogenate/Helixate for immune tolerance induction. Dose and frequency of FVIII administration were at the discretion of the attending physician. The data presented in Table 5, the success rate of ITI treatment with octocog alfa was 93.3% when the inhibitor titer was between 5 and 10 BU at the start of ITI compared to 47.1 % when inhibitor titer was ≥10 BU at start of ITI. This data support the current wording in the SmPC in section 4.2 "……*If the inhibitor is present at levels less than 10 Bethesda Units (BU) per ml, administration of additional recombinant coagulation factor VIII may neutralise the inhibitor and permit continued clinically effective therapy with KOGENATE Bayer. However, in the presence of an inhibitor the doses required are variable and must be adjusted according to clinical response and monitoring of plasma factor VIII activity. In patients with inhibitor titres above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa) preparations has to be considered…..".*

The International ITI study was a prospective, randomised study two dose regimens for the treatment of ITI. The study was terminated prematurely due to a higher number of bleeding events in the low-dose group compared to the high-dose group. The data presented in Table 9 showed that the success

rates for the 13 (33.3%) patients who completed the study according to the protocol were 50% (4/8 patients) for patients in the low-dose group and 40% (2/5 patients) for patients in the high-dose group. The overall success rate was 46.2%.

Due to the small number of patients in both studies and the kind of study design, the data was not considered reliable to evaluate the factors influencing ITI success. Moreover, the doses of octocog alfa administered in the individual studies ranged widely and thus no conclusions can be drawn regarding an optimized treatment regimen for ITI. A literature review reported inconclusive data with regard to influencing factors, optimal dosing regimen and ITI treatment duration as well. Therefore, treatment decisions will still be at the discretion of the treating physician, as stated in the current SmPC.

2.5. Clinical Safety aspects

The exposure of patients to Kogenate Bayer/ Helixate NexGen in the ITI studies IN FACT and International ITI study is shown in Table 13 and 14, respectively.

Table 13: Extent of exposure per patient during ITI – IN FACT study

	No. of patients	Median	Mean	±	SD	Range		
Total consumption during ITI treatment (IU/patient)	32	1,021,000	1,236,880	±	1072,031	46,500	-	4,012,000
- High-dose therapy	21	1,068,000	1,314,762	±	937,985	46,500	-	3,324,000
- Low-dose therapy	11	443,000	1,066,309	±	1,328,925	183,000	-	4,012,000
Total duration of ITI treatment in days	32	661	653	±	387	39	-	1632
- ITI outcome success	22	497	559	±	356	39	-	1317
- ITI outcome failure	10	842	859	±	388	353	-	1632

Table 14: Extent of exposure during ITI treatment (by the treatment) – International ITI study

	Low (n = 20)	High (n = 19)	Total (n = 39)
Expected number of infusions(a)			
N with data*	19	17	36
Mean	204.59	498.06	343.17
SD	111.05	287.31	257.21
Min	52	117	52
Median	169.71	379.00	264.29
Max	479	1023	1023
Duration of time in study [month]			
N with data*	19	17	36
Mean	15.26	15.88	15.56
SD	8.43	9.34	8.75
Min	4	3	3
Median	12.00	12.00	12.00
Max	36	33	36
Total dosage [1000 IU/kg] (b)			
N with data*	19	17	36
Mean	142.0876	1333.3139	704.6112
SD	96.0533	871.4036	645.9541
Min	7.23	135.31	7.23
Median	129.3420	1130.8670	302.2695
Max	356.61	3030.50	3030.50

* Three Patients (1 from low dose group and 2 from high dose group) have no data.

a. Patients in the high dose group were expected to receive 7 infusions of 200 IU/kg per week, but they either received 7 infusions at 200 IU/kg or 14 infusions at 100 IU/kg per week (100 IU/kg twice daily). Patients in the low dose group were expected to use 3 infusions at 50 IU/kg per week. The expected number of infusions were therefore calculated as weeks in ITI x 3 for the low dose treatment group and weeks in ITI x 7 for the high dose treatment group.

b. Calculated as the sum of all FVIII dosages per patient during ITI

In the IN FACT study, treatment-emergent AEs were documented in 23 (71.9%) of the 32 patients who received Kogenate Bayer during ITI. A further 14 AEs were documented in 5 of the 8 patients in the French cohort with modified inclusion/exclusion criteria.

For the IN FACT international cohort, the most frequently reported treatment-emergent AE was device-related infection, which was reported in 6 (18.8%) patients. AEs of gastroenteritis, traumatic brain injury, and hemarthrosis were each reported in 3 patients. Several of the events that were reported in only 1 or 2 patients, such as bronchitis, ear infection, pneumonia, tonsillitis, varicella, nasopharyngitis, fall, contusion, traumatic fracture, and traumatic hemorrhage, which are either common childhood events or known events in this population.

For the IN FACT French cohort with modified inclusion/exclusion criteria, the only treatment-emergent AE reported in more than 1 patient was device-related infection, which was reported in 2/8 (25.0%) patients. No information on non-serious AEs was available for the subset of 39 Kogenate Bayer patients in the International ITI study.

Table 15: Summary of reported adverse events – IN FACT study

	Number of patients	Percentage patients	Number of events	Percentage events
Total	32	100.0	72	100.0
AE	23	71.9	72	100.0
ADR*	1	3.1	1	1.4
SAE	14	43.8	35	48.6
SADR*	0	0.0	0	0.0

*relation to KOGENTA Bayer/FS or Helixate NexGen = yes

Only one of the events (diarrhea) was assessed as drug-related. 97.2% of the AEs were recovered/resolved, for one AE each (1.4%) the outcome was assessed as recovering/resolving or unknown at the end of the observation period. For none of the patients a fatal outcome was observed. No patient had to discontinue ITI due to AEs.

Table 16: Summary of reported adverse events – IN FACT study

System Organ Class and Preferred Term	N	%
Any System Organ Class	**23**	**71.9**
Infections and infestations	**18**	**56.3**
Device related infection	6	18.8
Gastroenteritis	3	9.4
Bronchitis	2	6.3
Nasopharyngitis	2	6.3
Staphylococcal sepsis	2	6.3
Arthritis bacterial	1	3.1
Catheter site infection	1	3.1
Cellulitis	1	3.1
Ear infection	1	3.1
Escherichia sepsis	1	3.1
Klebsiella infection	1	3.1
Lobar pneumonia	1	3.1
Pharyngitis streptococcal	1	3.1
Pneumonia	1	3.1
Staphylococcal bacteriaemia	1	3.1
Tonsillitis	1	3.1
Varicella	1	3.1
Injury, poisoning and procedural complications	**7**	**21.9**
Traumatic brain injury	3	9.4
Fall	2	6.3
Post procedural hemorrhage	2	6.3
Contusion	1	3.1
Subdural hematoma	1	3.1
Traumatic fracture	1	3.1
Traumatic hemorrhage	1	3.1
General disorders and administration site conditions	**7**	**21.9**
Catheter site hematoma	2	6.3
Pyrexia	2	6.3
Catheter site hemorrhage	1	3.1
Catheter site rash	1	3.1
Mass	1	3.1
Unevaluable event	1	3.1
Gastrointestinal disorders	**6**	**18.8**
Abdominal pain	1	3.1
Constipation	1	3.1
Diarrhea	1	3.1
Intra-abdominal hematoma	1	3.1
Lip hemorrhage	1	3.1
Vomiting	1	3.1

System Organ Class and Preferred Term	n	%
Musculoskeletal and connective tissue disorders	**4**	**12.5**
Hemarthrosis	3	9.4
Arthritis	1	3.1
Eye disorders	**1**	**3.1**
Conjunctivitis	1	3.1
Investigations	**1**	**3.1**
Blood alkaline phosphatase increased	1	3.1
Skin and subcutaneous tissue disorders	**1**	**3.1**
Ingrowing nail	1	3.1
Vascular disorders	**1**	**3.1**
Hematoma	1	3.1

Serious Adverse Events

Serious adverse events were reported in both the IN FACT and International ITI studies. In the IN FACT international cohort, 35 SAEs were reported in 14/32 (43.8%) patients. The most frequently reported SAEs were device related infection in 4 (12.5%) patients, traumatic brain injury in 3 (9.4%) patients, and staphylococcal sepsis, post procedural haemorrhage, and haemarthrosis, each in 2 (6.3%) patients. The majority of SAEs were serious because of the requirement for or prolongation of hospitalization.

In the IN FACT French cohort with modified inclusion/exclusion criteria, 11 SAEs were reported in 4/8 (50.0%) patients. The only SAE reported in more than 1 patient was device related infection, in 2 (25.0%) patients. The profile of SAEs was similar to that for all AEs as the majority (11 of 14) of AEs reported were considered serious.

In the International ITI study, 44 SAEs were reported in 18 (46.2%) of the 39 Kogenate Bayer-treated patients. 23 SAEs were reported in the low-dose group and 21 SAEs were reported in the high-dose group. More than half of the SAEs were catheter-related SAEs; catheter-related SAEs were reported in 9 of the 18 patients for whom SAEs were reported.

Adverse event data from the supportive studies from the literature did not reveal any additional safety issues for the use of Kogenate Bayer for ITI.

Table 17: Summary of reported serious adverse events (by treatment group) – International ITI study

	Low (n=20)	High (n=19)	Total (n=39)
Patients with at least one SAE	9 (45.0)	9 (47.4)	18 (46.2)
Catheter-related SAE	4 (20.0)	5 (26.3)	9 (23.1)
Procedure-related SAE	1 (5.0)	2 (10.5)	3 (7.7)
Product-related SAE	0	0	0

All SAEs were considered serious due to the requirement for or prolongation of hospitalization.

Table 18: Summary of serious adverse events (by SOC and PT) – International ITI study

System Organ Class/ Preferred Term (a)	Low (n=20)	High (n=19)	Total (n=39)
Number of patients with at least 1 SAE	9 (45.0)	9 (47.4)	18 (46.2)
Vascular disorders	5 (25.0)	4 (21.1)	9 (23.1)
Haemorrhage	2 (10.0)	3 (15.8)	5 (12.8)
Haematoma	2 (10.0)	0	2 (5.1)
Deep vein thrombosis	1 (5.0)	0	1 (2.6)
Lip haemorrhage	1 (5.0)	0	1 (2.6)
Thrombosis	0	1 (5.3)	1 (2.6)
Tongue haemorrhage	1 (5.0)	0	1 (2.6)
Infections and infestations	3 (15.0)	3 (15.8)	6 (15.4)
Device related infection	2 (10.0)	3 (15.8)	5 (12.8)
Pneumonia	2 (10.0)	0	2 (5.1)
Ear infection viral	0	1 (5.3)	1 (2.6)
Surgical and medical procedures	3 (15.0)	2 (10.5)	5 (12.8)
Central venous catheterisation	3 (15.0)	2 (10.5)	5 (12.8)
Tooth extraction	1 (5.0)	0	1 (2.6)
Injury, poisoning and procedural complications	1 (5.0)	3 (15.8)	4 (10.3)
Post procedural haemorrhage	1 (5.0)	1 (5.3)	2 (5.1)
Infusion-related reaction	0	1 (5.3)	1 (2.6)
Mouth injury	0	1 (5.3)	1 (2.6)
General disorders and administration site conditions	1 (5.0)	2 (10.5)	3 (7.7)
Medical device complication	0	2 (10.5)	2 (5.1)
Vessel puncture site haematoma	1 (5.0)	0	1 (2.6)
Investigations	1 (5.0)	1 (5.3)	2 (5.1)
Bacterial test positive	1 (5.0)	0	1 (2.6)
Blood culture positive	0	1 (5.3)	1 (2.6)
Candida test positive	1 (5.0)	0	1 (2.6)
Musculoskeletal and connective tissue disorders	1 (5.0)	0	1 (2.6)
Haemarthrosis	1 (5.0)	0	1 (2.6)

Literature review

The most common AEs observed in patients undergoing ITI are catheter related. Infections are the most frequent complications associated with the use of central venous lines in hemophilia patients. Several retrospective studies that include data from a substantial number of patients have reported approximately 0.2–0.3 infections per 1000 catheter-days (mainly Port-A-Cath). Some studies have shown a much higher frequency of infections, 1-2/1000 catheter-days[4] . As ITI typically requires daily (or 3 times weekly/every other day) infusions, the frequency of infection is higher in ITI patients compared with those who do not develop an inhibitor[5, 6, 7, 8].

[4] Ljung R, Br J Haematology:2007:138:580-586
[5] Ljung R et al.,Acta Paediatr 1992:81:918-920.
[6] Blanchette VS et al., Blood Coagulation and Fribinolysis 1996:7:S39-S44
[7] McMahon C et al., Br J Haematology 2000:110:461-468.
[8] Morado M et al., Haemophilia 2001:7:551-556.

2.5.1. Discussion on safety

There were no new drug adverse reactions found in either of the studies. Catheter-related infections, which lead to hospitalization or prolongation of an existing hospitalization, were the most commonly reported serious adverse events reported in the literature, in the IN FACT study and in the International ITI study. Catheter-related SAEs were not related to octocog alfa itself but were reported in 6/32 (18.8%) patients in the international IN FACT study, in 2/8 (25%) patients in the French cohort of IN FACT, and in 9/39 (23.1%) patients in the International ITI study in the group treated with octocog alfa. A warning statement concerning the occurrence of catheter-related complications was approved in the type II safety variation EMEA/H/C/WS00198.

2.6. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed after some minor modifications:

Section 5.1 of the SmPC:

[…]

Immune Tolerance Induction (ITI)
Data on Immune Tolerance Induction have been collected in patients with haemophilia A who had developed inhibitors to FVIII. A retrospective review has been done on 40 patients, and 39 patients were included in a prospective investigator-initiated clinical study. Data show that Helixate NexGen has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with Kogenate/Helixate NexGen again, and the patient could continue with prophylactic treatment as maintenance therapy.
[…]

Changes were also made to the PI to bring it in line with the current QRD template v8.0.

3. Overall conclusion and impact on the benefit/risk balance

The MAH has submitted two studies, one retrospective study (IN FACT) and a prospective, randomised International ITI study analysing the subset of patients that used Kogenate Bayer/Helixate NexGen. These studies reflect the current clinical use of octocog alfa but do not provide relevant new information supporting the indication on ITI. It was acknowledged that although high doses of octocog alfa have been used for more than 30 years in the treatment of haemophiliacs with inhibitors, the current approach was to treat inhibitors on an individual basis as there is no approved regimen. The international ITI study was designed to provide the efficacy data and guidance on a treatment for ITI. Unfortunately the study was terminated prematurely. Thus, CHMP noted that there was still uncertainty on certain aspects of octocog alfa administration for the ITI indication such as no established dose recommendation, choice of dose regimen depending on inhibitor titer, schedule of ITI with or without bypassing agents or immunosuppressive therapy, duration of ITI treatment, definition of success and rate of recurrence. Therefore, the CHMP was of the opinion that there were not enough robust clinical data in the studies submitted to support the indication and that the benefit-risk balance for the applied indication "Treatment of haemophilia A patients with inhibitors by Immune Tolerance Induction (ITI)" was negative. However, it was agreed that information on the major results of the studies and on ITI treatment could be included in section 5.1 of the SmPC.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of section 5.1 of the SmPC in order to add information on study results from the INFACT and the International ITI study concerning the use of octocog alfa in immune tolerance induction. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.0.

The requested worksharing procedure proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

5. 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

Update of section 5.1 of the SmPC in order to add information on study results from the INFACT and the International ITI study concerning the use of octocog alfa in immune tolerance induction. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.0.

Summary

The applicant applied for new indication for immune tolerance induction (ITI). The CHMP considered that benefit-risk was negative for the new indication. However, it was agreed to include information on the study results of the INFACT study and the International ITI study in section 5.1 of the SmPC.