17 January 2013
EMA/37098/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BeneFIX

International non-proprietary name: NONACOG ALFA

Procedure No EMEA/H/C/000139/II/0108

Note

Variation 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. Type II variation

Pursuant to Article 16 for single variation of Commission Regulation (EC) No 1234/2008, Wyeth Europa Ltd. submitted to the European Medicines Agency on 8 March 2012 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
BeneFIX	nonacog alfa	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

The MAH applied for an extension of the indication for the treatment and prophylaxis of bleeding in patients with haemophilia B in children less than 6 years of age. The MAH proposed the update of sections 4.2 and 5.1 of the SmPC to include information supporting the use of BeneFIX in children less than 6 years of age from Study 3090A1-301-WW and delete the statement that there are insufficient data to support the use of BeneFIX in this patient population. Section 5.2 of the SmPC was also revised to include additional pharmacokinetics parameters in children coming from a pop PK model.

The Package Leaflet was proposed to be updated in accordance.

Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template version 8.2.

The variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Information on paediatric requirements

Not applicable

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Müller-Berghaus Co-Rapporteur: Pierre Demolis

Submission date:	8 March 2012
Start of procedure:	25 March 2012
Rapporteur's preliminary assessment report circulated on:	1 June 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 June 2012
MAH's responses submitted to the CHMP on:	16 August 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	2 October 2012

Rapporteur's final assessment report on the MAH's responses circulated on:	11 October 2012
2nd request for supplementary information and extension of timetable adopted by the CHMP on:	18 October 2012
MAH's responses submitted to the CHMP on:	13 December 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	18 December 2012
CHMP opinion:	17 January 2013

2. Scientific discussion

2.1. Introduction

Haemophilia B is an X-linked disorder caused by spontaneous or inherited mutations in the FIX gene, and it primarily affects males, with a worldwide incidence estimated at approximately 1 per 30,000 live male births. The severity of the disease is dependent on the extent and nature of the gene mutation. Haemophilia B is a genetic disorder resulting in decreased blood clotting ability.

The primary treatment for persons with haemophilia B has been FIX replacement therapy. BeneFIX is a purified factor IX protein formulated as a sterile, non-pyrogenic, lyophilized powder preparation. It is produced by recombinant DNA technology with structural and functional characteristics comparable to endogenous blood coagulation factor IX. The administration of BeneFIX increases plasma levels of factor IX and can temporarily correct the coagulation defect in haemophilia B patients. As with all factor IX products, the dosage and duration of treatment depends on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition, age and recovery of factor IX.

Paediatric clinical investigation was already subject to discussion within the authorisation procedure in 1997 when BeneFIX was approved under exceptional circumstances. As BeneFIX was the only recombinant factor IX product on the European Market, the need for conclusive data in paediatric patients was overt. In the frame of specific obligation S02 079.6 the MAH agreed on a paediatric study in 25 children <6 years. However, study 3090A1 301 WW was submitted in 2008, more than 10 years post-approval, following former scientific standards. Overall, CHMP concluded that the study has followed the respective Scientific Advice (EMEA/CPMP/3192/01). However, key clinical questions have not been subject to clinical investigation and could not be updated, retrospectively.

2.2. Clinical aspects

2.2.1. Introduction

A phase 3, open-label, nonrandomized, multicenter study of at least 20 patients under 6 years of age has been completed (Study 3090A1 301 WW (hereafter referred to as study 301)). To further support the findings of study 301, the MAH has compiled additional data from non-interventional trials (several of which are completed post-approval commitments) and other sources:

- Data from a population pharmacokinetic analysis. The analysis was based on observations from 7 studies (6 conducted with Original BeneFIX and 1 conducted with BeneFIX reformulated), and included 232 patients.

- Study 3090A-101039, a Prospective Registry of European Patients Receiving BeneFIX for Usual Use, was performed to evaluate the safety of BeneFIX in the usual care setting and enrolled 33 patients <6 years of age.

- A global retrospective study (protocol 3090A-101657) which contains data from 86 patients <6 years of age including 61 patients <2 years of age.

- A confirmatory global retrospective study (protocol 3090A-100938), which contains data from 65 patients <6 years of age including 5 patients <2 years of age. This study compared the frequency of class II and III allergic reactions and FIX inhibitor development in patients taking plasma-derived FIX products with that of patients taking BeneFIX.

- Study 3090A1-4406, is an ongoing Pharmacovigilance Evaluation being conducted in Germany and Austria. Currently, 9 patients <6 years of age have been enrolled.

- In the UK, the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) National Haemophilia Database currently contains more than 50 patients <6 years of age.

2.2.2. Clinical Pharmacology

PK data of study 301 are presented. This study was performed to characterise safety and efficacy of BeneFIX in children less than 6 years of age with severe haemophilia B in the setting of acute bleeding episodes, prophylaxis, and/or surgery. One of the secondary objectives of the study was measurement of the incremental recovery after a 75 IU/kg dose.

Additionally, a population pharmacokinetics (PK) analysis (RPT-74196), which included data from Study 301 as well as observations from 6 other studies (6 conducted with BeneFIX classic [including Study 301] and one study [Study 304] conducted with BeneFIX classic and BeneFIX reformulated) is presented.

2.2.2.1. Analysis of data submitted

In **study 301** blood samples were taken to measure FIX concentrations in plasma on Day 1, Month 1, Month 3, and every 3 months thereafter and at the final study visit. Samples were collected before the infusion, 15 to 30 minutes after the infusion and then 4 hours and 24 hours after the infusion on Day 1, Month 6, and the final study visit. For infants less than 6 months of age, blood samples were collected only before and after the infusion. PK and/or recovery were assessed in 25 children on Day 1 and fewer on subsequent evaluations.

All data from this study were included into a **population PK approach** and none of the samples were excluded; however, no samples were collected more than 24 hours after infusion of a dose. The resulting model was used to estimate individual predictions for area under the concentration time curve (AUC), clearance (CL) and elimination half-life (t½).

Population PK modeling of Factor IX (FIX) activity after BeneFIX administration in children and adult patients with haemophilia B was conducted based on pooled data from 7 BeneFIX trials (Table 1) in which PK data were collected. The objectives of the analysis were to characterize population PK of BeneFIX, including estimation of typical PK parameters and inter-individual and residual variability, and to estimate the effects of individual-specific covariate factors (body weight, race and age) on the PK in the pooled population that included children and adults.

The population PK model was built on the data of 4 post-authorization studies (labeled 'evaluation' in Table 1) and re-run on the whole data set including 3 pre-authorization studies (labeled 'reference'):

Table 1. Listing of Clinical Studies used in RPT-74196 Population Pharmacokinetic modeling of BeneFIX in children and adult patients with haemophilia

Protocol Number	Study Description	Number Enrolled	BeneFIX Dose for PK[a]	Data
C9623-21	A phase 1/2 study of BeneFIX in previously treated Japanese patients with haemophilia B	3	50 IU/kg	Evaluation
3090A1-301	A global phase 3 study of BeneFIX in children under 6 years of age with haemophilia B	25	75 IU/kg	Evaluation
3090A1-302	A global phase 3 study of BeneFIX in previously treated patients (PTPs) with haemophilia B	23	75 IU/kg	Evaluation
3091A1-304	A global phase 3 study of BeneFIX in PTPs designed to support the marketing approval of reformulated BeneFIX for haemophilia B treatment	34	75 IU/kg	Evaluation
C9407-21 /C9408-21	Segment 1: Crossover pharmacokinetic comparison of BeneFIX versus plasma-derived coagulation factor IX	56	50 IU/kg	Reference
	Segment 2: A 24-month open-label treatment period to assess the efficacy and safety of BeneFIX		50 IU/kg	Reference
	Segment 3: An assessment of efficacy and safety of BeneFIX for surgical prophylaxis		50 IU/kg	Reference
C9417-21	A phase 2/3 study in PTPs designed to support the original marketing approval for BeneFIX for haemophilia B treatment	28	50 IU/kg	Reference
C9418-21	A global phase 2/3 study in previously untreated patients (PUPs) designed to support the original marketing approval for BeneFIX for haemophilia B treatment	63	50 IU/kg	Reference

a. In the post-licensure studies, 301, 302, 304, a dose of 75 IU/kg was used for PK evaluation based on the recommendations by the Committee for Human Medicinal Products (CHMP). Source: RPT-74196, Table 3-1.

Formulation (classic BeneFIX vs reformulated BeneFIX) was not tested as a covariate because the change in formulation was in the diluents, not in the active ingredient itself. Instead of sterile water for injection, the reformulated BeneFIX had 0.234% sodium chloride for injection as the diluent. Because BeneFIX is infused by the intravenous route, the presence of a small amount of sodium chloride would not be expected to change the absorption of the administered FIX. As the results of Study 304 showed bioequivalence of classic and reformulated BeneFIX in adults; the results in children would not be expected to show a difference.

Data were analysed using nonlinear mixed-effects modelling with the NONMEM software system. Age, weight, and race were examined as covariates for the ability to explain inter-individual variability in FIX PK. A two-compartment model with first-order elimination and a zero-order input was chosen as the structural model. Allometric models were used to incorporate known physiological relationships into the covariate-parameter models. The adequacy of the final model was to be assessed via a predictive check method and nonparametric bootstrap procedures.

2.2.2.2. Results

Key PK parameters in study 301 are summarised in Table 2:

Table 2. Summary (Mean ± SD) of coagulation factor IX pharmacokinetic parameters in paediatric patients with severe haemophilia B receiving 75 IU/kg BeneFIX

Parameter	Visit 2 (n=23)	Visit 3 (n=21)	Visit 4 (n=20)	Visit 5 (n=6)	Visit 6 (n=1)	Visit 999 (n=20)
Age (years)[a]	2.0	2.0	2.0	2.0	2.0	2.0
Weight (kg)	14.9 ± 3.8	15.0 ± 3.6	15.8 ± 3.3	15.3 ± 2.9	13.7	16.7 ± 3.6
C_{max} (IU/dL)	43.0 ± 6.9[b]	41.3 ± 7.9	43.2 ± 5.6[d]	43.2 ± 13.8	56.4	45.9 ± 7.1[d]
K-value (IU/dL per IU/kg)	0.57 ± 0.09[b]	0.55 ± 0.11	0.58 ± 0.07[d]	0.58 ± 0.18	0.75	0.61 ± 0.10[d]
In vivo Recovery (%)	31.5 ± 5.4[b]	30.3 ± 5.9	31.2 ± 4.1[d]	31.1 ± 9.8	37.8	33.0 ± 5.2[d]
$t_{1/2}$ (h)	11.0 ± 2.2[c]	ND	ND	13.4 ± 3.1	ND	11.4 ± 1.7[e]
AUC_{∞} (IU·h/dL)[f]	566 ± 102	ND	ND	625 ± 46	ND	615 ± 122
CL (mL/h/kg)[f]	13.8 ± 3.2	ND	ND	12.1 ± 0.9	ND	12.6 ± 2.0

a. Data shown are median.
b. n=22
c. n=21
d. n=19
e. n=17
f. Based on a 2-compartment model (NONMEM).

Note: Visit 2 is Day 1; Visit 3 is Month 1; Visit 4 is Month 3; Visit 5 is Month 6; Visit 6 is Month 9; and Visit 999 is the last patient visit (could be Month 6, 9, or 12 unless withdrawn early).

Abbreviations: AUC_{∞}=area under the curve from time zero to infinity; CL=clearance; C_{max}=peak plasma FIX activity; FIX=factor IX; K-value=incremental recovery; ND=not determined because of limited number of protocol-specified sampling time; $t_{1/2}$=terminal-phase elimination half-life.

Source: Wyeth Clinical Pharmacology.

The PK parameters appeared to be stable over time in the children studied on more than one occasion.

According to the population PK analysis of the full dataset age and race had no discernible effects on FIX PK in the population studied. The inter-individual variability in CL, central volume of distribution (V1), peripheral volume of distribution (V2) was moderate, with coefficients of variation (CV) of 30%, 46% and 48% respectively. However, the inter-individual variability of inter-compartmental clearance (Q) was quite high with a %CV of 104%. The inter-occasion variability was low for both CL and V1, with %CV of < 12%. The residual errors for the 2 different populations were also moderate with 54% for paediatrics (≤ 15 years) and 40% for adult (> 15 years) patients. The developed model adequately describes both sparse and rich data with no apparent bias to one another. In adults, model-predicted PK parameters were comparable to the values from non-compartmental analysis. Therefore, the model may be used to estimate PK parameters in other age groups.

Estimated results of the full dataset are shown in Table 3. Children appear to have higher CL, larger volume of distribution (Vss), shorter t1/2, and lower recovery than adults:

Table 3. Mean (±SD) PK Parameters in Infants, Children and Adults Based on Individual Bayes Estimates From NONMEM's Post Hoc Step

Parameter	Infants (<2 years)	Children (2 to 12 years)	Adults (>12 years)
Number of patients	53	39	99
CL (mL/hr/kg)	13.1 ± 2.1	13.2 ± 2.8	8.5 ± 2.2
V_{SS} (mL/kg)	252 ± 35	260 ± 26	229 ± 55
$t_{1/2}$ (hr)	15.6 ± 1.2	16.7 ± 1.8	22.9 ± 4.8
Incremental recovery (IU/dL per IU/kg)	0.61 ± 0.10	0.59 ± 0.08	0.72 ± 0.18

Source: RPT-74196, Table 4-7. CL is clearance; Vss is steady-state volume of distribution, t½ is half life of elimination.

The Evaluation Data set used in the population PK analysis included 73 subjects, of whom 67 had severe haemophilia (FIX activity <1 %) and the remaining 6 subjects had baseline FIX activity of 2% (n=5; aged 16, 17, 19, 21, and 56 years) and 3% (n=1, aged 16 years).

The concentration-time profiles observed in the 6 individuals are consistent with those of the other subjects, and well predicted by the model. Removing them would be unlikely to change the results of neither the final population PK model, nor the resulting predicted parameters for the children who are the focus of this supplement.

In response to the proposal that PK data be collected in subjects with severe haemophilia, there are little data to support a concern that including subjects with moderate and moderately severe haemophilia would make the PK parameter estimates invalid. Ewenstein et al[1] measured recovery in 14 individuals with FIX activity below 1%, 21 individuals with FIX activity between 1% and 5%, and 3 others with FIX activity above 5%. The differences observed did not reach statistical significance and may simply reflect intersubject differences. No other reports appear to have been published.

The only subjects in the analysis who did not have severe haemophilia were adolescents and adults (>12 years of age). Table 4 presents the PK results for all 49 adolescents and adults in the Evaluation Data set and for only those 43 adolescents and adults with severe haemophilia.

[1] Ewenstein BM, Joist JH, Shapiro AD, et al. Pharmacokinetic analysis of plasma-derived and recombinant FIX concentrates in previously treated patients with moderate or severe hemophilia B. Transfusion 2002;42(2):190-7.

Table 4. Mean ± SD PK Parameters in Adolescents and Adults (>12 Years of Age) Based on Individual Bayes Estimates from Population PK Analysis

	All Subjects	Subjects With Severe Haemophilia
Number of subjects	49	43
Clearance (mL/h/kg)	8.5 ± 2.2	8.4 ± 2.4
Vss (mL/kg)	229 ± 55	229 ± 57
Elimination half-life (h)	22.9 ± 4.8	23.1 ± 4.4
FIX increase (IU/dL per IU/kg)	0.72 ± 0.18	0.72 ± 0.19

As the removal of the 6 adolescent and adult subjects with moderate and moderately severe haemophilia makes little difference to the results, the Marketing Authorisation Holder (MAH) proposed to revise Table 2 of the section 5.2 Pharmacokinetic properties of the SmPC to include data from all 49 adolescent and adult subjects (see table below).

Table 5. Mean ± SD PK Parameters Based on Individual Bayes Estimates from Population PK Analysis

Age Group (years)	Infants <2	Children 2 to < 6	Children 6 to < 12	Adolescents 12 to < 18	Adults 18 to 60
Number of subjects	7	16	1	19	30
Clearance (mL/h/kg)	13.1 ± 2.1	13.1 ± 2.9	15.5	9.2 ± 2.3	8.0 ± 0.6
Vss (mL/kg)	252 ± 35	257 ± 25	303	234 ± 49	225 ± 59
Elimination half-life (h)	15.6 ± 1.2	16.7 ± 1.9	16.3	21.5 ± 5.0	23.9 ± 4.5
FIX increase (IU/dL per IU/kg)	0.61 ± 0.10	0.60 ± 0.08	0.47	0.69 ± 0.16	0.74 ± 0.20

Impact of lower exposure in children vs adults

Predicted FIX activity (FIX:C) was simulated using the post hoc PK parameters from the Evaluation Data assuming doses of 50 IU/kg administered to a 20-kg child (1000 IU) and a 70-kg adult (3500 IU). As may be seen in Figure 1, the child would be predicted to have lower FIX:C than the adult because of the large increase in weight-adjusted clearance (13.2 mL/h/kg in children and 8.5 mL/h/kg in adults) and modest increase in weight-adjusted volume of distribution (260 mL/kg in children and 229 mL/kg adults). As may be noted, with the same dose and frequency, the predicted time post dose that FIX:C would drop below 1 IU/dL would be 60 hours for children and 90 hours for adults. The clinical impact of this difference has not been evaluated, although it is recommended in the Summary of Product Characteristics (SmPC) that in younger patients, shorter dosage intervals may be necessary.

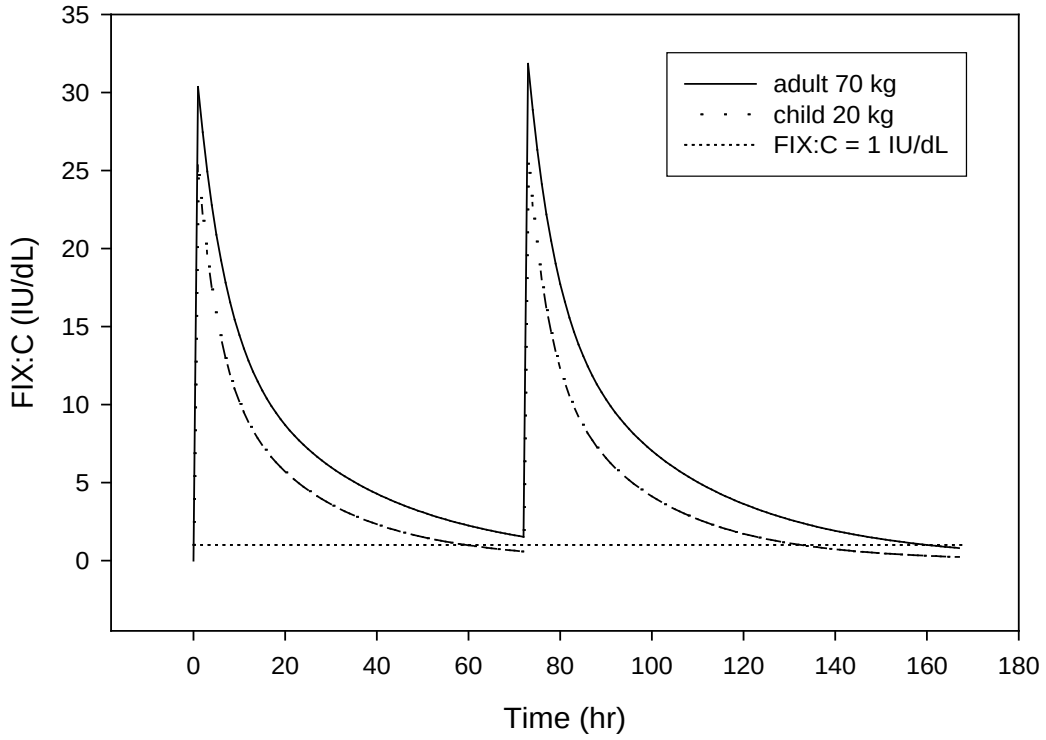

Figure 1. Simulated FIX Activity After 50 IU/kg Doses

2.2.2.3. Discussion and conclusion on clinical pharmacology

The MAH's approach of analysing paediatric data and correlating the results with data derived from adult subjects is noted.

Population PK modelling was done in order to assess the influence of age, race and weight on the PK of BeneFIX. Weight was identified as the only covariate having an impact on key PK parameter. A possible age effect could not be found. The MAH argued that a) different models might lead to (slightly) different conclusions, b) the age effect found in one of the analysis models is quite modest.

The MAH's conclusion that dosing based on age and weight might not be justified is considered plausible in the light of the correlation between age and weight and the only modest age effect found in one of these models.

Therefore, from a PK perspective, because weight was the only covariate that appeared to influence PK parameters, weight-based dosing is justified in children <6 years of age as it is in older children and adults. Children have higher CL and shorter t1/2 than adults. It would be reasonable to use more frequent dosing than in adults during prophylactic treatment. Children have lower recovery than adults; therefore, it would also be reasonable to use higher doses to achieve the desired factor IX increase than in adults. Dosing based on race does not appear to be supported by available PK data.

During the assessment of this variation, the MAH was requested to discuss the reliability of the analyses with regard to age due to lack of data in the 7 to 12 age group.

The MAH argued that inclusion of data spanning the range of interest was indeed important for the reliability of a pharmacokinetic analysis testing for the importance of a continuous covariant. However, if there was a remarkable interval within this range with no or only very limited data, interpolations

have to be made (at least implicitly) that might impact the reliability of the model, especially in case of relatively small datasets. The CHMP considered acceptable the MAH's response.

The inter-individual variability in CL, central volume of distribution (V1), peripheral volume of distribution (V2) was moderate, with coefficients of variation (CV) of 30%, 46% and 48% respectively. However, the inter-individual variability of inter-compartmental clearance (Q) was quite high with a %CV of 104%. The inter-occasion variability was low for both CL and V1, with %CV of < 12%. The residual errors for the 2 different populations were also moderate with 54% for paediatrics (≤ 15 years) and 40% for adult (> 15 years) patients. The developed model adequately describes both sparse and rich data with no apparent bias to one another. In adults, model-predicted PK parameters were comparable to the values from non-compartmental analysis. Therefore, the model may be used to estimate PK parameters in other age groups as reflected in section 5.2 Pharmacokinetic properties of the SmPC.

In relation to the CHMP concerns regarding the potential impact of the difference between classic and reformulated BeneFIX formulation, the MAH provided an acceptable justification.

2.2.3. Clinical efficacy

Study 301 (3090A1-301-WW) and an ongoing pharmacovigilance evaluation (**3090A1-4406**) have been presented to support clinical efficacy in paediatric subjects < 6 years of age.

2.2.3.1. Main study

Study 301 was a Phase 3, open-label, non-randomised, multicentre study designed to have at least 20 patients with severe haemophilia B who would complete the study before the age of 6 years both previously treated patients (PTPs) and previously untreated patients (PUPs) were eligible.

Methods

Study participants

Study 301 enrolled 25 children below the age of 6 years. The efficacy evaluable population consisted of PTPs with at least 30 EDs to rFIX over a 6- to 12-month period and PUPs and minimally treated patients (MTPs) with at least 10 EDs to rFIX and 12 months on study. Of the 25 patients in this study, 22 were evaluable for efficacy.

Of the 22 evaluable children in the efficacy population (25 patients), 10 acquired >50 EDs, 5 acquired 40-50 EDs, and 7 acquired 30-40 EDs. Of the 25 patients enrolled, 24 patients received study treatment for ≥6 months; 1 enrolled patient was subsequently found to be ineligible for enrollment.

Treatments

Patients were treated with rFIX on demand for acute bleeding episodes and/or on a prophylaxis regimen, and as needed for surgery. Treatment was administered at home, at the investigative site, and/or in a hospital setting depending on the patient's circumstances.

Patients were to return to the investigative site after 1 month of treatment for safety and FIX recovery assessments, again after 3 months of treatment, and every 3 months thereafter until the patient concluded the study. During these interim visits, the following assessments were made: vital sign measurements, weight and height, FIX inhibitor and anti-FIX antibody status, FIX recovery (with a washout period of at least 4 days), selected chemistry and haematology (at Month 6), thrombogenicity, observation for red blood cell (RBC) agglutination, and other adverse events (AEs). A

1-time blood sample was obtained for FIX genotyping analysis. At the final study visit, as part of a limited pharmacokinetic (PK) assessment, additional blood samples were collected at 4 and 24 hours after the time of the infusion.

Objectives

The primary objective of this study was to characterize the safety and efficacy of rFIX in children less than 6 years of age with severe hemophilia B in the setting of acute bleeding episodes, prophylaxis, and/or surgery.

The secondary objectives of the study were to:

- Measure the incremental recovery of rFIX in children after a 75-IU/kg bolus infusion.
- Describe the immunogenicity/neoantigenicity of rFIX in patients regardless of previous FIX treatment by monitoring for inhibitor development (BIA) during the trial.
- Perform surveillance for other EOIs: thrombogenicity, hemorrhage/lack of effect, allergic-type manifestations, and RBC agglutination.

Outcomes/endpoints

Efficacy measurements were made based on the patient/caregiver or investigator's assessment of response to on-demand treatment of bleeding episodes according to a 4-point rating scale (*Excellent*, *Good*, *Moderate*, and *No Response*) as well as rFIX use (mean dose [IU/kg] and number of infusions per bleeding episode). For prophylaxis, the number of infusions, dose per infusion, number of bleeding episodes (spontaneous and traumatic), and time between last infusion to start of new bleeding episode were assessed. For surgery, information on haemostasis, estimated blood loss, amount of transfusions, mean dose (IU/kg), and occurrence of thromboembolic episode was also collected and evaluated, if applicable. The investigators used a 5-point Global Assessment of Efficacy scale (*Very Useful*, *Useful*, *Slightly Useful*, *Useless*, or *Unfavourable*) for assessing efficacy at clinical visits and during surgical treatments.

Results

Most (89.1%) on-demand bleeding episodes were resolved with 1 or 2 infusions of BeneFIX (median dose per infusion was 63.3 IU/kg [mean: 75.9 and range: 27.5 to 187.2 IU/kg]) (Table 5). This favourable outcome was not restricted to any specific bleed location as 87.5% of joint bleeds and 88.6% of soft tissue/muscle bleeds resolved with 1 or 2 BeneFIX infusions.

Most infusions to treat a bleed were rated *Excellent* or *Good* (88.3%) by the caregiver or investigator; similarly, most first infusions to treat a bleed were rated *Excellent* or *Good* (85.9%) by the caregiver or investigator. The high ratings were consistent over the different bleed locations.

During the study, 22 children with haemophilia B (<6 years of age) were prescribed BeneFIX for prophylaxis at a schedule of 1 or 2 infusions per week. The majority of the patients (54.5%, 12 of 22 patients) followed a prophylaxis dose regimen of 2 doses of BeneFIX per week. The mean duration of routine prophylaxis treatment during the study was 28.3 weeks (median, 27.1 weeks: range 8.0 to 48.9 weeks). The median dose for prophylaxis was 57,6 IU/kg per infusion (mean: 64,6; range: 27.9-187.2) whereas the median dose for on-demand treatment was 63,3 IU/kg per infusion (mean: 75.0; range: 27.5-115.2).

Table 6. Study 301 – Summary of Coagulation Factor IX Dose Administration and Exposure Days for Evaluable Patients

	Reason for Infusions				
Variables	PK/ Recovery	On-Demand/ Follow-up Treatment	Prophylaxis[a]	Surgery related[b]	Total
Number of patients	22	16	22	2	22
Total rFIX units (IU) per patient					
N	22	16	22	2	22
Cumulative	112109.7	95940.0	825730.0	21522.0	1055301.7
Median	5375.3	3825.0	35980.0	10761.0	46918.2
Mean	5095.9	5996.3	37533.2	10761.0	47968.3
SD	1196.0	5909.1	16425.8	4976.6	14927.9
Range	2875-7164	510-24480	9180-74970	7242-14280	16015-80368
Dose (IU/kg) per infusion					
No. of infusions	95	90	803	24	1012
Median	75.2	63.3	57.6	97.1	59.2
Mean	75.8	75.0	64.6	91.7	67.2
SD	5.4	24.6	21.3	21.2	21.4
Range	49.0-84.3	27.5-115.2	27.9-187.2	59.3-130.5	27.5-187.2

Note: A patient may be given doses multiple times in 1 day for different reasons. Includes commercial BeneFIX and rFIX study drug C012421.

a. Includes 787 routine prophylaxis and 16 intermittent infusions.

b. Includes 24 bolus and 0 continuous infusions.

Abbreviations: PK = pharmacokinetic; rFIX = recombinant factor IX; SD = standard deviation.

Source Study 301 CSR.

Seventeen (17) of 22 patients (77.3%) did not experience any spontaneous bleeding episodes while receiving routine BeneFIX prophylaxis treatment. Seven (7) of these 22 patients (31.8%) had neither a spontaneous nor an injury-related bleed. Forty-four (44) bleeding episodes (44 of 64 bleeding episodes; 68.8%) were reported in 15 patients while using routine prophylaxis over a mean period of 28.3 weeks (median, 27.1 weeks; range, 8.0 to 48.9 weeks). The monthly bleeding rate was 0.303. Seven (7) of 44 bleeding episodes were spontaneous (0.048 spontaneous bleeding episodes per month) and 37 were due to injury (0.255 injury-related bleeding episodes per month). During the study, the dose of one patient (301-1190-220) receiving once-weekly prophylaxis was increased to 55 IU/kg from 42 IU/kg due to a bleeding episode and poor FIX recovery. There were no other changes in prophylaxis regimens. The majority of bleeding episodes (61.4%) occurred >48 hours after the last BeneFIX administration.

To clarify the reasons for infusions and amount received, the dose per infusion data have been recalculated (Table 6). In subjects prescribed routine prophylaxis, doses per infusion are calculated separately for routine prophylaxis, treatment of breakthrough bleeds, and for "other" uses.

Table 7. Summary of Dose Administration (Dose per Infusion, IU/kg) by prescribed treatment regimen and reason for infusion (Efficacy, evaluable population study 3090A1-301-WW)

Treatment Regimen	Statistic	Reason for Infusion[a]		
		Routine Prophylaxis	On-Demand	Other[b]
On-demand (n=4)	N[c]		25	
	Mean		93.14	
	SD		22.99	
	Median		105.2	
	Minimum		52.6	
	Maximum		113.3	
Routine prophylaxis (n=22)	N[c]	784	70	12
	Mean	63.72	69.56	112.02
	SD	19.09	22.41	62.14
	Median	57.6	58.2	82.75
	Minimum	27.9	27.5	55.9
	Maximum	164.5	115.2	187.2

a. Data are presented for all infusions except those given for PK/recovery evaluations.
b. Other includes preventative treatment for pain or before travel, or before, during, or after surgical procedures.
c. Number of infusions.
Source: Compounds/PF-05/PF-05208755/Clinical/Summary/Tables and Figures/Pediatric Response Aug 2012/median doses

Twenty (20) bleeding episodes were reported in 4 patients on an on-demand regimen, 4 patients, resulting in a bleed rate of 1.279 bleeding episodes per month; of these, 5 bleeding episodes were spontaneous (0.32 spontaneous bleeding episodes per month) and 15 were due to injury (0.959 injury-related bleeding episodes per month). Investigators changed the treatment regimen of 4 patients to routine prophylaxis.

Table 8. Summary of Treated Bleeding Episodes by Patient, During On-Demand Treatment in All Patients (Study 3090A1-301-WW)

Subj. No.	On-demand Dose	Days on Regimen	Number of Bleeding Episodes by Type			Infusions Needed to Resolve Bleeding Episodes	
			Spontaneous	Due to Injury	Total Bleeds	Total No. Infusions	Total Dose (IU/kg)
1360/110[a]	*50 IU/kg*	*178*	*0*	*1*	*1*	*1*	*90.1*
491/120	75 IU/kg	34	0	1	1	1	85.5
1241/160[a]	*33.1 IU/kg*	*52*	*0*	*0*	*0*	*0*	*0*
1253/170	100 IU/kg	122	0	6	6	9	989.3
1359/180[a]	*35−40 IU/kg*	*339*	*0*	*1*	*1*	*1*	*32.3*
1357/191	60 IU/kg	18	0	0	0	0	0
	60 IU/kg	68	4	0	4	4	226.8
	100 IU/kg	134	1	4	5	8	410.3
1255/232	50 IU/kg	93	0	4	4	4	316.7

Subj. No.=subject number.
a. Subjects in italics included only in safety and intent-to-treat population, not in efficacy evaluable population.
Source: dia_251od/18MAR08

Two patients underwent surgical procedures (circumcision and port-a-catheter insertion) during the study. BeneFIX administered by bolus infusion in the surgical setting was effective in restoring and maintaining haemostasis in both patients. There were no bleeding episodes during postoperative prophylaxis. Estimated blood loss (EBL) during the surgeries was minimal, and there was no postoperative blood loss. No blood transfusions were required.

Consumption of Factor IX:

Of the 22 patients receiving prophylaxis doses, 9 (40.9%) received BeneFIX once per week, 12 (54.5%) patients received doses twice per week, and 1 (4.5%) received doses once or twice per week. In general, the higher doses were given once per week (median 73.2 IU/kg per infusion) and the lower doses were given twice per week (median 56.4 IU/kg). For patients prescribed a prophylactic regimen, the average routine doses ranged from 42 IU/kg once per week and 33 IU/kg twice per week to 87 IU/kg twice per week and 100 IU/kg once or twice per week. Only 1 patient routinely received doses less than 40 IU/kg per infusion (ie, 33 IU/kg twice per week).

Although the investigator prescribed a routine prophylaxis regimen of once or twice weekly doses that were generally in the range of 50 to 100 IU/kg per infusion, the investigator adjusted the dose and frequency of administration according to clinical needs, which sometimes resulted in doses that appeared as "outliers." The range of prophylaxis doses that were administered routinely was 31.9 to 111.5 IU/kg. The extremes of the range of 27.9 to 187.2 IU/kg can be explained by 2 subjects with outlier doses. The lower dose of 27.9 IU/kg was received once by a subject (301-1359-182) who had been receiving 55.9 IU/kg once per week. After receiving his scheduled prophylaxis dose a day early because of a spontaneous bleed, the dose of 27.9 IU/kg was administered 2 days later and classified by the investigator as routine prophylaxis, although it was likely given as an on-demand treatment in response to that bleed. This subject received his usual dose 5 days later and then continued to receive 55.9 IU/kg once per week.

The higher dose of 187.2 IU/kg was received by a subject (301-491-121) on 4 occasions related to insertion and removal of a peripherally inserted central catheter (PICC) line, rather than for routine prophylaxis. This patient's routine dose had been 93.6 IU/kg per week; he received routine doses of 86.4 IU/kg per week after the procedure. In another case of occasional high prophylaxis doses, a subject's (301-490-120) dose was doubled (to 164.5 and 148.9 IU/kg on separate occasions) because he was going to be travelling and would not receive the next dose for a month.

Of the 5 patients on prophylaxis who had spontaneous bleeds, all except one received routine doses once per week. One patient was scheduled to receive routine doses of 82 IU/kg each week, but did not always comply with that regimen; he had missed doses before the spontaneous bleed and received infusions only once within 2-week and 4-week intervals. For 2 patients, the routine doses were approximately 56 to 58 IU/kg once per week. The patient who received 57.6 IU/kg twice per week had a spontaneous bleed within 3 days of a series of bleeds due to injury. The fifth patient had a spontaneous bleed during routine prophylaxis with 109 IU/kg once per week. BeneFIX consumption has been calculated to clarify the reasons for infusions and amount received, and is shown in Table 9 and Table 10 for consumption per year and per month, respectively. In subjects prescribed routine prophylaxis, doses per infusion are calculated separately for routine prophylaxis, treatment of breakthrough bleeds during prophylaxis, and for other uses, such as preventative treatment for pain or before travel, or before, during, or after surgical procedures.

Table 9. Summary of Annual BeneFIX Consumption (IU/kg) by Prescribed Treatment Regimen and Reason for Infusion (Efficacy Evaluable Population, Study 3090A1-301-WW)

Treatment Regimen	Statistic	Reason for Infusion[a]		
		Routine Prophylaxis	On-Demand	Other[b]
On-demand (n=4)	Mean		1769.9	
	SD		1399.52	
	Median		1150.8	
	Minimum		918.5	
	Maximum		3859.7	
Routine prophylaxis (n=22)	Mean	4606.8	758.5	389
	SD	1849.42	950.55	362.2
	Median	4699.7	466.7	217.7
	Minimum	2052.7	70.6	159
	Maximum	8161.6	3907.1	1028.2

a. Data are presented for all infusions except those given for PK/recovery evaluations.
b. Other includes preventative treatment for pain or before travel, or before, during, or after surgical procedures.
Source: Compounds/PF-05/PF-05208755/Clinical/Summary/Tables and Figures/Pediatric Response Aug 2012/annual consumption

Table 10. Summary of Monthly BeneFIX Consumption (IU/kg) by Prescribed Treatment Regimen and Reason for Infusion (Efficacy Evaluable Population, Study 3090A1-301-WW)

Treatment Regimen	Statistic	Reason for Infusion [a]		
		Routine Prophylaxis	On-Demand	Other[b]
On-demand (n=4)	Mean		145.4	
	SD		114.95	
	Median		94.5	
	Minimum		75.4	
	Maximum		317	
Routine prophylaxis (n=22)	Mean	378.4	62.3	32
	SD	151.9	78.07	29.75
	Median	386	38.3	17.9
	Minimum	168.6	5.8	13.1
	Maximum	670.4	320.9	84.5

a. Data are presented for all infusions except those given for PK/recovery evaluations.
b. Other includes preventative treatment for pain or before travel, or before, during, or after surgical procedures.
Source: Compounds/PF-05/PF-05208755/Clinical/Summary/Tables and Figures/Pediatric Response Aug 2012/monthly consumption

The mean (±standard deviation, SD) FIX consumption for routine prophylaxis doses in the 22 evaluable patients was 4606.8 (±1849.4) IU/kg per year and 378.4 (±151.9) IU/kg per month.

2.2.3.2. Supportive study

Ongoing **Study 3090A1-4406** is a pharmacovigilance evaluation of BeneFIX conducted in Germany and Austria. This is a non-interventional study to monitor patients treated with BeneFIX. The study commenced in February 2008. In order to obtain long-term results for patients regularly treated with BeneFIX the extension of the study without any predefined study end or maximum number of patients is planned.

Objective of this study is the long-term evaluation of the safety and efficacy profile of BeneFIX in usual healthcare settings.

Since February 2008, a total of 58 patients have been recruited in **study 3090A1-4406**. Nine (9) of them were <6 years of age at the time of enrollment and 4 of these 9 were PUPs. The median follow-up was 32.5 months. The data cutoff for this information is 31 August 3011.

At baseline, 5 of these 9 children received prophylaxis, while 4 received an on-demand regimen. One child received a non-specified regimen. Subsequently, 2 of the children who were initially utilizing on-demand therapy changed to a prophylactic regimen.

Eight (8) children on prophylaxis experienced a total of 6543 observation days; 102 bleeding events occurred; the majority was soft tissue bleeds. In 4 of the 9 patients <6 years of age, an average of fewer than 2 injections was required to control a bleeding episode.

2.2.3.3. Discussion and conclusion on clinical efficacy

Of the 25 patients who were in the safety and ITT analyses of study 3090A1-301, 22 were evaluable for efficacy. The 3 patients who were not included in the efficacy evaluable population subset were the patients who received BeneFIX only as on-demand treatment. The 4 remaining patients of the 7 who were initially prescribed on-demand treatment subsequently were changed to a prophylaxis regimen; these patients were included in the efficacy evaluable population. Two of those patients who were originally prescribed on-demand treatment and who later received BeneFIX as prophylaxis also underwent a surgical procedure.

No relevant on-demand treatment was therefore documented in study 3090A1-301. Consequently, the SmPC should only include a generalised dosage recommendation for on-demand treatment.

If clinical efficacy of on-demand treatment is aimed to be included in the SmPC, FIX-consumption should be reflected as “IU/kg per event” (which means per bleeding episode), according to the currently valid Clinical Guideline. Therefore, the inclusion of “median dosage per infusion…” under section 4.2 of the SmPC is not supported. However, database of 4 subjects who all switched to prophylaxis is not considered to be a valid basis for reflection in the SmPC. Therefore, we propose to include There is limited documentation of on-demand treatment in paediatric patients less than 6 years of age treated with BeneFIX into SmPC-section 4.2 “Paediatric population”.

Despite limited documentation, relevant differences in dosing “authentic” bleeds in an on-demand setting versus “break-through” bleeds under prophylaxis have been documented: Median infusion-dose was 105 IU/kg for bleeds in an on-demand setting and 58 IU/kg for bleeds under prophylaxis. However, differentiated reflection of this issue in the SmPC is considered to be premature due to the following reasons: (1) the numbers do not reflect dosage per bleed as requested by the Clinical Guideline and might therefore be misleading and (2) data-base is insufficient.

The database even for subjects on prophylaxis is considered to be limited. However, mean dose of routine prophylaxis with standard deviation might be of interest for the user due to relevant deviation

from the dose recommended for adults. Thus, it is suggested to include “Mean dosage (±standard deviation) for routine prophylaxis was 63.72 (±19.09) IU/kg” in section 4.2 Paediatric population as indicated in the SmPC-document.

The MAH substantiate basis of dosage-recommendation and subsequent documentation of high dosages with reference to NHS guidelines. These dosages (mean 63.7) are in general notably above the usual doses of 20-40 IU/kg (aimed at adults) in the Core-SPC and mainly derived from experience with pdFIX products. These results are reflected in section 4.2 of the SmPC.

No data for continuous infusion treatment have been provided.

The on-going pharmacovigilance study 3090A1-4406 – as study 301 – currently reflects a rather low number of subjects overall (9); even lower (1-2) is the number of subjects on an on-demand regimen.

2.2.4. Clinical safety

2.2.4.1. Introduction

To demonstrate clinical safety, the final results of Study 3090A1-301-WW (hereafter referred to as Study 301) have been provided.

To further support the findings of Study 301, the Marketing Authorisation Holder (MAH) has compiled substantial data from MAH-sponsored non-interventional trials (several of which are completed post-approval commitments):

- Study 3090A-101039 (hereafter referred to as Study 101039), a Prospective Registry of European Patients Receiving BeneFIX for Usual Use, was performed to evaluate the safety of BeneFIX in the usual care setting (with a focus on events of special circumstances [ESC]) and enrolled 33 patients <6 years of age. A final report was submitted on 03 February 2010.
- A global retrospective study (Protocol 3090A-101657 [Study 401]; hereafter referred to as Study 101657), previously submitted on 04 March 2008, which contains data from 86 patients <6 years of age including 61 patients <2 years of age.
- A confirmatory global retrospective study (Protocol 3090A-100938; hereafter referred to as Study 100938), also previously submitted on 30 June 2002, which contains data from 65 patients <6 years of age including 5 patients <2 years of age. Both retrospective studies compared the frequency of class II and III allergic reactions and FIX inhibitor development in patients taking plasma-derived FIX products with that of patients taking BeneFIX.
- Study 3090A1-4406 (hereafter referred to as Study 4406), Pharmacovigilance Evaluation of BeneFIX, is an ongoing study being conducted in Germany and Austria. Currently, 9 patients <6 years of age have been enrolled.

In addition in the UK, the United Kingdom Haemophilia Centre Doctors’ Organisation (UKHCDO) National Haemophilia Database has followed patients treated with BeneFIX since 1995 and contains data on 163 patients <6 years of age through 31 March 2010.

Supportive data:

Study 101039, was a Prospective Registry of European Patients Receiving BeneFIX in a Usual Care Setting. This open-label, non-interventional, multicentre, prospective observational cohort study evaluated the overall safety of original or reformulated BeneFIX in adult or paediatric patients with haemophilia B, under routine medical practice with specific focus on the product-specific events of

ESCs: (1) LETE (less than expected treatment effect), (2) inhibitor development, (3) thrombotic events, (4) red blood cell agglutination, and (5) allergic events.

All European patients who began treatment with original or reformulated BeneFIX for haemophilia B were eligible for participation in the Registry. Reformulated BeneFIX is a modified isotonic formulation with increased ionic strength relative to original BeneFIX.

Data collection of this Registry differs from an interventional trial by patients being not pre-selected based on custom tailoring. The treating physician collected a patient's medical data prospectively and retrospectively, and from reviews of medical records. At enrollment the patient's family history of haemophilia B, inhibitors and allergy to FIX, demographic information, the baseline FIX activity level, and Bethesda assay for inhibitor were recorded. In the absence of any structured visit schedule, the investigator reviewed each patient's medical records, typically every quarter, to obtain any relevant safety information not collected through other means (eg, verbal communication with patient). In addition to ESCs (serious or non-serious), all product-related non-serious AEs and all SAEs were to be reported to the sponsor. Non-serious AEs definitely or probably unrelated to BeneFIX were not collected or reported for this Registry.

The primary objective of two **Global Retrospective Studies (101657 and 100938)**, which were post-approval commitment studies, was to estimate the frequency of class II and III allergic reactions in association with the administration of any coagulation factor IX (FIX) concentrate. The secondary objective was to compare the frequency of class II and III allergic reactions occurring with plasma-derived FIX (pdFIX) to recombinant FIX (BeneFIX) and to evaluate the occurrence of inhibitor formation in these patients.

Study 101657 used a retrospective, multicenter design. It was conducted in patients with haemophilia B in North America and Europe, who had their first FIX infusion between 01 January 1991 and 31 December 2003. This study involved a medical chart review of eligible patients; no study medication was provided and no prospective interventional procedures were performed. Demographic, treatment, and safety data were collected. Efficacy assessments were not included in this protocol.

While a formal analysis of Study 101657 was not conducted separately for children aged <6 years of age, the study included 86 patients <6 years of age of which 61 patients were <2 years of age. Thus, 47.8% of the patient population included in this study was <6 years old.

Study design and entry criteria for Study 100938 were similar to those in Study 101657.

Ongoing Study 4406; Pharmacovigilance Evaluation in Germany and Austria is a non-interventional study to monitor patients on routine treatment with BeneFIX. The study commenced in February 2008. In order to obtain long-term results for patients regularly treated with BeneFIX, the study protocol did not include any predefined study end or maximum number of planned patients.

The objectives of this study are the long-term evaluation of the safety and efficacy profile of BeneFIX in usual healthcare settings. Since February 2008, 58 patients have been recruited in this study. Nine (9) of them were <6 years at the time of enrollment and 4 of these 9 were previously untreated patients (PUPs). The median follow-up was 32.5 months.

The **UK National Haemophilia Database (NHD)** has, since its inception in 1969, collected national statistics on the treatment, complications, and causes of death of patients with bleeding disorders. The NHD gathers data from all 67 haemophilia centres in the UK.

In February 2011, Pfizer requested a report from the UK National Haemophilia Database regarding the UK use of BeneFIX in children <6 years of age. Topics of particular interest were:

· Number of patients <6 years of age treated with BeneFIX either in the most recent available calendar year or overall

· Consumption data – in IU/kg

· Any available data on bleeding episodes such as number of treatments needed to control bleeds

· Reported (serious) adverse events

· Additional safety data, if available

Extent of exposure:

Study 301 enrolled 25 children below the age of 6 years. Of those 25 children, 1 patient (301-1241-160) received one ED but was not eligible for participation in the study All the other patients received study treatment for ≥6 months. Of these 24 children, 10 received >50 EDs; 5 received 40-50 EDs; 7 received 30-40 EDs; and 2 received <30 EDs. Two of 24 patients were excluded from the efficacy analysis. Overall, more than 1000 EDs were applied during the course of this study.

Supportive data:

Overall, 193 patients <6 years of age received FIX treatment in MAH-sponsored studies. In addition, 163 patients <6 years of age were included in the UK National Haemophilia Database (1995-2010); however, the latter numbers include patients recruited to BeneFIX clinical trials. According to Table 3 of the Clinical overview, overall 123 of 136 registered patients with severe hemophilia B were treated with BeneFIX.

Characteristics of the study population:

Study 301

In Study 301, (100%) patients were male and predominantly Caucasian (72%). Median age was 2 years (range, 0.6 to 4 years). Previously treated patients (PTPs) as expected were older, weighed more, and were taller. Demographic and baseline characteristics for the 25 treated patients are summarized below in Table 10:

Table 10. Study 301 – Summary of Demographics and Baseline Characteristics by Patient Exposure Days

		PUP	MTP	PTP	TOTAL[a]
Age Category, n (%)	Neonate (Birth – 1 Month)	0	0	0	0
	Infant (2 Months – 2 Years)	1 (100%)	5 (83%)	9 (50%)	15 (60%)
	Children (3 – 12 Years)	0	1 (17%)	9 (50%)	10 (40%)
Age (years)	N	1	6	18	25
	Mean	0.6	1.8	2.8	2.4
	Median	0.6	1.5	2.5	2.0
	SD		1.2	1.0	1.2
	Range	0.6-0.6	0.9-4.0	1.2-4.0	0.6-4.0
Sex, n (%)	Male	1 (100%)	6 (100%)	18 (100%)	25 (100%)
	Female	0	0	0	0
Race, n (%)	Asian	0	1 (17%)	0	1 (4%)
	Black	1 (100%)	1 (17%)	1 (6%)	3 (12%)
	Caucasian	0	4 (67%)	14 (78%)	18 (72%)
	Hispanic	0	0	0	0
	Other			3 (17%)	3 (12%)
Weight (kg)	N	1	6	17	24
	Mean	8.2	12	15.9	14.6
	Median	8.2	10.9	16.0	15.1
	SD		3.3	3.0	3.7
	Missing	0	0	1	1
	Range	8.2-8.2	9.2-17.5	10.0-20.0	8.2-20.0
Height (cm)	N	1	4	18	23
	Mean	70.0	90.8	97.2	94.9
	Median	70.0	90.7	96.7	95.0
	SD		11.2	10.9	12.0
	Missing	0	2	0	2
	Range	70.0-70.0	78.0-103.8	78.0-113.0	70.0-113.0

Abbreviations: MTP = minimally treated patient; N=number; PTP=previously treated patient; PUP=previously untreated patient; SD=standard deviation.

a. Exposure days code: PUP is 0 exposure days, MTP is <20 exposure days, PTP is ≥20 exposure days.

Source: Study 301 CSR.

Supportive data:

Registry population of **Study 101039** (Prospective Registry of European Patients Receiving BeneFIX in a Usual Care Setting) consisted of 203 (93.1%) male patients, and 15 (6.9%) female patients with haemophilia B. The majority of patients were Caucasian. The mean age of male patients was 30.1 years (range <1-79 years) and for female patients, 41.1 years (range 3-76 years). Data from all patients who received at least 1 dose of BeneFIX were included in the safety analyses. Of the enrolled patients, 66 (30.3%) were paediatric patients (defined as less than 18 years of age at screening); 33 (15.1%) were less than 6 years of age at screening.

Global Retrospective Study **101657** included 180 patients. 86 (47.8%) patients were <6 years of age including 61 (33.9%) patients <2 years of age. Patients ranged in age from 2.4 to 82.6 years at the time of consent or assent. 177 were male and 154 were Caucasian. All but 1 patient was alive at the time of the review. Of the 180 patients reviewed 7 (3.89%) were noted to have had a class II or III allergic reaction to a FIX product.

Global Retrospective Study **100938** included 234 patients. 65 (27.8%) were <6 years of age including 5 (2.1%) patients <2 years of age. Patients ranged in age from 1 to 91 years Most of the patients were Caucasians.

2.2.4.2. Results

Complete AE information was reported for Study 301; however, information for the supportive studies is generally limited to ESCs (events of special circumstances), which include LETE (less than expected therapeutic effect), inhibitor development, thrombotic events, red blood cell agglutination, and allergic events.

In **Study 301** 23 of 25 patients (92%) had at least 1 TEAE (Treatment emergent adverse event). The most frequent TEAEs (≥10%) reported in this study were fever and infection (14, 56% each); rhinitis (12, 48%); cough increased (10, 40%); vomiting (9, 36%); accidental injury (8, 32%); rash (6, 24%); and laboratory test abnormal, diarrhoea, conjunctivitis, and otitis media (3 [12%] each), which are events frequently reported in this patient population.

Related TEAEs were laboratory test abnormal and rash (2, 8% each); and allergic reaction, urticaria, FIX inhibition, local reaction to procedure, and cough increased (1, 4% each). No related TEAEs were reported during the surgical periods. No patient had a life-threatening TEAE

One (1) of 25 patients (4%) had a severe TEAE of FIX inhibition considered related to BeneFIX. A summary of the patient narrative is provided below:

A 7 months old African American with severe haemophilia B (FIX-activity <1%) was the only PUP within study 301. Recovery at screening was 38.1%. His first treatment exposure was for surgical intervention (circumcision) and he remained on on-demand therapy of 60 IU/kg/injection. On 13th ED he experienced increased cough, urticarial and rash 15 minutes after infusion for treatment of a spontaneous bleed. Symptoms resolved after administration of an oral antihistamine. According to the investigator, this event was definitely related to BeneFIX and judged to be allergic-type reaction. Low-titer inhibitor of 2.3 and 2.4 BU was detected 21 days after the event. Post-allergic testing of IgG1, IgG2 and IgG3 antiFIX antibodies was also significantly positive. The patient continued on BeneFIX; the prescribed dose was increased from 60 to 100 IU/kg/infusion and antihistamines and/or corticosteroids were administered prior to study drug infusions. Inhibitor-testing changed to borderline or negative, subsequently. Final recovery was 29.7%.

Nine (9) of 25 patients (36%) had at least 1 treatment-emergent haemophilia event (TEHE).

No deaths were reported in the study.

In **Study 101039,** a Prospective Registry of European Patients Receiving BeneFIX in a Usual Care Setting, 6 (9.1%) 7 of 66 paediatric patients experienced ESCs (events of special circumstances) that were considered either probably, possibly or definitely related to BeneFIX. Four (12.1%) of 33 patients less than 6 years of age experienced 5 of these ESCs.

The reported ESCs for all paediatric patients were LETE (3 events in 3 patients), allergic events (3 events in 3 patients, 1 of whom also experienced inhibitor development). The patient with inhibitor development was 11 months old with severe haemophilia B, no previous history of inhibitor development, and unknown FIX gene defect. The patient developed a high–titer (10.3 BU) inhibitor after 10 EDs and a subsequent life threatening allergic reaction immediately after the administration of BeneFIX, which led to BeneFIX and study discontinuation. Under rVIIa and immune-tolerance-therapy the inhibitor was considered to be resolved after 1 month as documented with negative Bethesda assays and antibody screen.

Baseline FIX activity was available for 216 subjects; of those subjects, 65 were <18 years of age, and 33 of those subjects were <6 years of age. Table 7 shows the numbers of paediatric subjects in Study 101039 by category of baseline FIX activity. The percentages of subjects with severe, moderate, and mild haemophilia were roughly equal in all subjects and within the 2 age categories.

Table 11. Number (%) of Subjects in Study 101039 by Age Group and Severity of Haemophilia

Haemophilia Severity (Baseline FIX Activity)	Subjects <6 Years of Age	Subjects <18 Years of Age	All Subjects
Severe (<1%)	12 (36.4)	19 (29.2)	72 (33.3)
Moderate (1% to 5%)	12 (36.4)	25 (38.5)	79 (36.6)
Mild (>5%)	9 (27.2)	21 (32.3)	65 (30.1)
Total	33	65	216

FIX=factor IX.
Source: 3090A-101039 CSR-78609, Table 7-3, Supportive Table 14.4.

During Study 101039, 16 subjects had events of special circumstance that were judged by the investigator to be at least possibly related to treatment; 6 of these were paediatric subjects (<18 years of age), and of those subjects, 4 were aged <6 years. One of these subjects had more than 1 event of special circumstance (allergic reaction and inhibitor development). An additional paediatric patient (aged 17 years) had a lack of drug effect that was considered to be definitely not related to BeneFIX.

Table 12 lists the paediatric (<18 years of age) subjects who had one or more treatment-related events of special circumstance while receiving BeneFIX in Study 101039, categorized by severity of haemophilia at baseline. All of these subjects had severe or moderate haemophilia B at baseline. The results are consistent with previous data that show that subjects with more severe haemophilia are more likely to have inhibitor development or allergic reactions. Subject narratives for the 4 subjects aged <6 years are presented.

Table 12. Paediatric Subjects Who Had Treatment-Related Events of Special Circumstance in Study 101039, by Severity of Haemophilia

Haemophilia Severity (Baseline FIX Activity)	Subject Number	Event	Age at Screening (yr)
Severe (<1%)			
	004001	Hypersensitivity/allergic reaction	13
	034001	Hypersensitivity/allergic reaction	<1
	171009	Inhibitor development Hypersensitivity/allergic reaction	<1
Moderate (1% to 5%)			
1%	050001	Lack of effect	1
3%	050002	Lack of effect	9
1%	163002	Lack of effect	<1

Source: 3090A-101039 CSR-78609, Table 9-2, Supportive Tables 14.4 and 14.12.

In study **3090A-101657**, of the 180 patient charts reviewed, 7 (3.89%) were noted to have had a class II or III allergic reaction to a FIX product. Of the 180 patients in the study, 86 (47.8%) patients were <6 years of age including 61 (33.9%) patients <2 years of age.

Of the 163 patients taking BeneFIX, 3 (1.84%) had an inhibitor to FIX develop (95% CI, 0% to 3.9%). Of the 88 patients taking pdFIX products, 4 (4.55%) developed an inhibitor (95% CI, 0.19% to 8.90%). Two (2) additional patients had inhibitors for whom causality to a specific FIX product could not be assigned. Of the 9 patients with FIX inhibitor, 5 patients had class II or III allergic reactions and 4 patients did not. There were no reports of thrombogenicity. Of note, patients who received both pdFIX and BeneFIX during the study period were counted in both groups.

The combined data review (protocols **3090A-101657 and 3090A-100938**) included data of 414 patients, of whom 328 had received BeneFIX and 248 had received pdFIX products.

Of the 328 patients taking BeneFIX, 7 (2.13%) had a class II or III allergic reaction (95% CI, 0.57 to 3.70%). Of the 248 patients taking pdFIX products, 10 (4.03%) had a class II or III allergic reaction (95% CI, 1.58 to 6.48%). Of the 328 patients taking BeneFIX, 6 (1.83%) developed an inhibitor (95% CI, 0.38 to 3.28%). Of the 248 patients taking pdFIX products, 15 (6.05%) developed an inhibitor (95% CI, 3.08 to 9.02%). In study 3090A- 100938 there were no reports of thrombosis.

In the ongoing pharmacovigilance **study 4406** eight (8) AEs were reported in 3 of the 9 children <6 years (4 AEs on routine treatment, 3 in on-demand treatment for minor bleeding events, and 1 in surgical prophylaxis for phimosis surgery). There have been no reports of LETE, FIX inhibitor development, or allergic reactions with BeneFIX. No SAEs have been reported.

From the **UK National Haemophilia Database** a report was provided to the MAH.

Between 01 January 1995 and 31 March 2010, inhibitors were identified in 5 of 163 (3.1%) BeneFIX-treated patients <6 years of age at time of identification.

One anaphylaxis was reported. The patient was 8 months old at the time of the event. Inhibitor was reported as being present. The treatment during the year was BeneFIX and recombinant FVIIa.

2.2.4.3. Discussion and conclusion on clinical safety

The only data from an interventional study derive from study 301. However, supportive data were provided, based upon 193 subjects < 6 years of age. Due to the rareness of Haemophilia B and even less patients in small age-groups, these data might have to be accepted despite the fact that they cannot serve as a reliable basis for signal detection or frequency estimation.

One allergic reaction with clinically relevant inhibitor development after early surgery in the only included PUP has been reported from study 301. Allergic reactions are expected but occur more frequently in the PUP population than in the non-PUP population. Furthermore, the reporting rates of allergic events in patients below 6 years of age seem to be higher than in adults. This is included in the Paediatric sub-section 4.8 of the SmPC ("*Allergic reactions might be experienced more frequently in children than in adult*s").

The reporting of laboratory results as adverse events was done at the discretion of the investigator and did not necessarily reflect clinically relevant results or the most extreme out of-normal-range values. Laboratory results for TAT and D-dimer that were higher than the normal range were recorded sporadically during the course of the study, and occurred pre-dosing almost as often as at the 4-hour post-dose measurement.

Although the laboratory results are not consistent, it could be considered that the incremental increases for TAT or D-dimer express the activation of the coagulation system after the FIX infusion. These incremental increases do not necessarily reflect safety concerns; in Study 301, they were judged to be not clinically meaningful.

Furthermore, all cases of diarrhoea, vomiting and the majority of cases of cough increased and rash are considered “definitely not related” by the MAH.

The MAH has confirmed the assumption that severe haemophilia is associated with numerically more and more relevant Adverse Reactions. Consequently, when evaluating, presenting and rating such reactions, severity of haemophilia should always serve as concomitant information.

The presented data (retrospective chart-reviews) provide an overview on inhibitor-development and/or development of allergic reaction. Due to methodical reasons no valid comparison of the numbers is feasible. Statistically valid data regarding paediatric patients and the paediatric subgroup < 6 years of age are not expected from this data-source. However, no new safety signals have been detected.

The presented data from the UK National data-base are apparently generated in a cumulative way: According to a footnote in Table 3 of the Clinical Overview, “patients are reported in multiple years”. Furthermore, first entry of the amount of BeneFIX-use according to this database (Table 4) starts in 2005 and not in 1995 when first patients have been registered. This incongruence has not been explained. However, this database documents predominant use of BeneFIX in the UK in paediatric patients < 6 years of age. Further comprehensive information supporting safety or efficacy of Benefix is not expected from this source.

2.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 11 August 2013.

The annex II section related to the PSUR refers to the EURD list provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, which remains unchanged.

2.4. Update of the Product information

As a consequence of this new indication, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

4.2 Posology and method of administration

[…]

On demand treatment

One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma. Estimation of the required dose of BeneFIX can be based on the finding that one unit of factor IX activity per kg body weight is expected to increase the circulating level of factor IX, an average of 0.8 IU/dl (range from 0.4 to 1.4 IU/dl) in ~~adult patients (≥ 15 years). Pharmacokinetics have to be assessed regularly in each patient and posology has to be adjusted accordingly.~~patients ≥ 12 years (further information in section 5.2).

[…]

*Paediatric population*There ~~are insufficient data to recommend the use~~is limited documentation of ~~BeneFIX~~on-demand treatment and surgery in ~~children~~ paediatric patients less than 6 years of age~~.~~ treated with BeneFIX.

Mean dosage (± standard deviation) for prophylaxis was 63.7 (±19.1) IU/kg at intervals of 3 to 7 days. In ~~clinical studies, 57% of the paediatric~~younger patients ~~increased their~~, shorter dosage intervals or

higher doses ~~due to lower than expected recovery or to obtain sufficient therapeutic response or both, some to an average dose of >50 IU/kg. Therefore, close~~may be necessary. FIX consumption for routine prophylaxis in 22 evaluable patients was 4607 (± 1849) IU/kg per year and 378 (± 152) IU/kg per month.

[…]

4.8 Undesirable effects

[…]

Paediatric population

Allergic reactions might be experienced more frequently in children than in adults.There are insufficient data to provide information on inhibitor incidence in PUPs (see also section 5.1).

[…]

5.1 Pharmacodynamic properties

[…]

Paediatric population

Efficacy analysis in study 3090A1-301-WW was based on 22 evaluable paediatric subjects on prophylaxis regimen including 4 on-demand patients who shortly changed to prophylaxis. Two patients underwent surgical procedures (circumcision and port-a-catheter insertion). Safety analysis of 25 evaluable patients reflected a safety profile as expected. The only documented serious adverse event related with BeneFIX was reported from the only included PUP, who experienced hypersensitivity and inhibitor development.
~~There are insufficient data to recommend the use of BeneFIX in children less than 6 years of age.~~

5.2 Pharmacokinetic properties

[…]

A population pharmacokinetic model was developed using data collected in 73 patients aged 7 months to 60 years.The parameters estimated using the final 2-compartment model are shown in Table 2. Infants and children had higher clearance, larger volume of distribution, shorter half-life and lower recovery than adolescents and adults. The terminal phase has not been covered unambiguously due to lack of data beyond 24 hours in paediatric subjects < 6 years of age.

Table 2. Mean ± SD PK Parameters Based on Individual Bayes Estimates from Population PK Analysis

Age Group (years)	Infants <2	Children 2 to < 6	Children 6 to < 12	Adolescents 12 to < 18	Adults 18 to 60
Number of subjects	7	16	1	19	30
Clearance (mL/h/kg)	13.1 ± 2.1	13.1 ± 2.9	15.5	9.2 ± 2.3	8.0 ± 0.6
Vss (mL/kg)	252 ± 35	257 ± 25	303	234 ± 49	225 ± 59
Elimination half-life (h)	15.6 ± 1.2	16.7 ± 1.9	16.3	21.5 ± 5.0	23.9 ± 4.5
FIX increase (IU/dL per IU/kg)	0.61 ± 0.10	0.60 ± 0.08	0.47	0.69 ± 0.16	0.74 ± 0.20

Changes were also made to the PI to bring it in line with the current QRD template (version 8.2), which were accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Cyprus and Greece.

In Annex II and in the PL, the word “S.” has been changed to “San” in the address for manufacturer responsible for batch release.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Use of BeneFIX in paediatric subjects < 6 years of age is accepted medicinal practice as an alternative and in some European regions in favour of plasma-derived FIX-products.

Uncertainty in the knowledge about the beneficial effects

Documentation of use in the concerned age-group is limited despite more than 13 years of experience with BeneFIX on the market: Truncated PK-profile (documentation for not more than 24 hours, 2 post-infusional samples, only) and low number of documented subjects, contribute to uncertainty regarding dosage and safety.

The identified gaps have not been satisfactorily filled by a population pharmacokinetic evaluation due to additional lack of data in the age-group of 6 to 12 year old children.

Risks

Unfavourable effects

Risk-profile is assumed to correspond with that of older patients.

Uncertainty in the knowledge about the unfavourable effects

Due to low numbers of documented subjects in the respective age-group, risk profile has not been documented, comprehensively, and essentially relies on individual experience.

Benefit-risk balance

Importance of favourable and unfavourable effects

It is undoubted, that use of BeneFIX in the respective age-group is agreed by most of the treating physicians and specialised haemophilia centres. Therefore, restriction of indication in the respective paediatric subgroup does not reflect current use.

Discussion on the benefit-risk balance

For meeting the current therapeutic standard and simultaneously address the shortages of documentation, detailed SmPC adaptations have been suggested to most adequately reflect the identified lack of data for the respective age-group.

The overall benefit-risk balance of BeneFIX remains unchanged.

Recommendations

☒ The application for

Update of sections 4.2 and 5.1 of the SmPC to include information supporting the use of BeneFIX in children less than 6 years of age from Study 3090A1-301-WW and delete the statement that there are insufficient data to support the use of BeneFIX in this patient population. Section 5.2 of the SmPC was also revised to include additional pharmacokinetics parameters in children coming from a pop PK model. The MAH took the opportunity of this variation to bring the PI in line with the latest version of the QRD template (version 8.2) in particular the terms and order in which SOC are presented in section 4.8 of the SmPC. Finally, the MAH updated the contact details of representatives in member states.

is approvable since all remaining concerns have all been resolved.

Final Outcome

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 change:

Variation accepted		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

Extension of Indication to include a new patient population for BeneFIX:

Update of sections 4.2 and 5.1 of the SmPC to include information supporting the use of BeneFIX in children less than 6 years of age from Study 3090A1-301-WW and delete the statement that there are insufficient data to support the use of BeneFIX in this patient population. Section 5.2 of the SmPC was also revised to include additional pharmacokinetics parameters in children coming from a pop PK model. The MAH took the opportunity of this variation to bring the PI in line with the latest version of the QRD template (version 8.2) in particular the terms and order in which SOC are presented in section 4.8 of the SmPC. Finally, the MAH updated the contact details of representatives in member states.

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