



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BeneFIX

International non-proprietary name: NONACOG ALFA

Procedure No. EMEA/H/C/000139/II/0131

Note

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



Assessment Timetable / Steps taken for the assessment

Timetable	Dates
Start of procedure:	23 March 2015
PRAC Rapp AR	5 May 2015
CHMP Rapp AR	5 May 2015
PRAC Outcome	7 May 2015
CHMP members comments	11 May 2015
Request for supplementary information	21 May 2015
CHMP Rapporteur's assessment report:	29 September 2015
CHMP Members comments	12 October 2015
Updated Rapporteur's assessment report:	15 October 2015
Opinion:	22 October 2015

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1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 4 March 2015 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2, 5.1, and 5.2 of the SmPC in order to update the posology with once-weekly prophylaxis regimen. The RMP is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

The variation proposes amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

1.2. Rationale for the proposed change

The MAH recently completed two studies (3090A1-400-WW and B1821010) of BeneFIX which evaluated the relative safety and efficacy of 2 prophylaxis regimens versus on-demand treatment and of one prophylaxis regimen versus on-demand treatment, respectively. Data from these studies are provided with the present variation application to support amending section 4.2, Posology and method of administration and section 5.1 Pharmacodynamic properties of the Summary of Product Characteristics (SmPC) to add the 100 IU/kg once-weekly prophylaxis regimen. Proposed changes to Section 5.2 Pharmacokinetic properties are based on additional PK data for reformulated BeneFIX from Study 3090A1-304-WW (B1821038).

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

The MAH recently completed two studies for BeneFIX evaluating the relative safety and efficacy of prophylaxis regimens versus on-demand treatment. Study 400 was previously submitted within a Type II variation on 02 September 2011 in support of a proposed addition for a once-weekly regimen for prophylaxis to SmPC sections 4.2 and 5.1. However, a major objection remained unsolved and the variation was withdrawn by the MAH. The results of study 1010 were previously submitted in accordance with Article 46 of the Paediatric Regulation (EC) No 1901/2006 (P46 144).

The possibility to reduce the frequency of infusions in long term prophylaxis from twice-weekly to once weekly would be a relevant improvement for haemophilia patients. Currently there are multiple attempts to increase the half-life of different coagulation factor concentrates to enable such a dosing regimen.

No new safety concerns have been detected from the submitted study results apart from potentially insufficient protection from bleedings. It is therefore considered to be a pragmatic approach to inform physicians treating haemophilia about once weekly regimen acknowledging that this schedule cannot be recommended in general, however it could be an option for some of the patients. Therefore updated sections 5.1 and 5.2 of the SmPC are considered approvable.

It has to be noted however that submitted data have not addressed convincingly the question, whether it

is possible to maintain FIX:C levels in subjects with severe haemophilia B who represent the target population for long term prophylaxis within a range which protects them from bleedings during the entire dosing interval of seven days (168 hours) with doubled dose but the same half-life of 18 hours. Deficiencies have been identified in relation to the choice of study population, the duration of treatment and statistical analysis. Pharmacokinetic characterisation in the provided studies was limited: no PK-calculation based on in-patient FIX-activity levels according to the Clinical Guideline has been submitted and neither of the studies determined Benefix half-life. With an anticipated half-life of 18 hours (results of earlier studies) reported for BeneFIX it has to be assumed that FIX levels would return to pre-infusion levels after 72 hours.

Therefore an update of the SmPC section 4.2. Posology and method of administration: '*In other clinical studies BeneFIX was administered as 100 IU/kg once weekly, which may be an option for some patients (see section 5.1).*' is considered not approvable.

The benefit-risk balance of BeneFIX remains positive.

Scientific discussion for the EPAR

In this variation the MAH updated the Product Information with data from two open-label studies in which BeneFIX was found to be safely administered at 100 IU/kg once-weekly. However, the half-life of the product and the limited pharmacokinetic study data for the once-weekly regimen do not allow recommending this regimen in general for long-term prophylaxis in severe haemophilia B patients.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 5.1 of the SmPC with information on once-weekly administration of BeneFIX based on two open label studies. The RMP has been updated accordingly. Additionally, section 5.2 has been updated with new pharmacokinetic information. The MAH also introduced minor editorial changes throughout the PI.

☒ is recommended for approval.

The requested variation leads to amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

4. Scientific discussion

4.1. Introduction

BeneFIX (nonacog alfa, rFIX) is a recombinant DNA-based protein therapeutic that has structural and functional characteristics comparable to endogenous factor IX. Recombinant coagulation factor IX is a glycoprotein that is secreted by genetically engineered mammalian cells derived from a Chinese hamster ovary (CHO) cell line. Marketing authorization in the EU was first granted under exceptional circumstances in 1997. In May 2010 the Commission decided, that there were no remaining grounds for the marketing authorization to remain under exceptional circumstances.

BeneFIX is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Haemophilia B is a sex-linked hereditary disorder of blood coagulation characterized by decreased levels of factor IX and may result in profuse bleeding into joints, muscles, or internal organs, either spontaneously or as a result of accidental or surgical trauma. Replacement of factor IX allows for temporary correction of the factor deficiency and the attendant bleeding tendencies.

The dosage and duration of the substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding episode, on age and clinical condition of the patient and on factor IX recovery. In general, the required dosage in International Units (IU) is calculated using a formula that takes into account patient body weight, the desired percentage increase in circulating factor IX, and the average observed recovery. Estimation of the required dosage of rFIX can be based on the empirical finding that 1 IU factor IX per kg body weight raises the plasma factor IX activity, on an average, by 0.8 IU/dl. However, pharmacokinetics have to be assessed regularly in each patient and posology has to be adjusted accordingly.

BeneFIX is available in five dosage strengths (250 IU, 500 IU, 1,000 IU, 2,000 IU and 3000 IU per vial); the powder is to be reconstituted with 5 ml sodium chloride solution for injection. It is a single-use product for intravenous administration. For long-term prophylaxis in severe haemophilia B, BeneFIX is usually administered every 3 to 4 days.

Two clinical studies were submitted by the MAH (see Table 1) to support once-weekly prophylaxis with 100 IU/kg BeneFIX. These two studies (3090A1-400-WW, hereafter referred to as study 400, and B1821010, hereafter referred to as study 1010) of BeneFIX evaluated the relative safety and efficacy of 2 prophylaxis regimens versus on-demand treatment and of one prophylaxis regimen versus on-demand treatment, respectively. Data from these studies are provided with the present variation application to support amending section 4.2, Posology and method of administration, section 5.1 Pharmacodynamic properties and section 5.2 Pharmacokinetic properties, of the Summary of Product Characteristics (SmPC) to add the 100 IU/kg once-weekly prophylaxis regimen.

Proposed changes to Section 5.2 Pharmacokinetic properties are based on relevant additional PK data for reformulated BeneFIX from Study 3090A1-304-WW (B1821038). These data replace earlier PK data from the previous formulation included in that section.

Study 3090A1-400-WW was previously submitted in a Type II variation in 02 September 2011 in support of a proposed addition for a once-weekly regimen for prophylaxis to SmPC sections 4.2 and 5.1. This application was withdrawn, as the duration of treatment in Study 400 alone (4 months) did not meet the Clinical Guideline for FIX requirements (ie, 6 months).

Table1. BeneFIX Clinical Development Program

Study ^a	Study Dates (Site of Conduct)	Study Significance	Study Design	Patient Population	No. Subjects ^b
New Studies for This Submission					
B1821002 (3090A1-400-WW)	2007-2010 (Global)	SE comparison of on-demand treatment with 2 prophylaxis (50 IU/kg twice-weekly and 100 IU/kg once-weekly) regimens of recombinant factor IX (BeneFIX)	• Open-label, 4-period study • 16-week on-demand period • Random assignment to 1 of 2 prophylaxis regimens for 16 weeks (treatment A: 100 IU/kg once per week <u>or</u> treatment B: 50 IU/kg twice per week). • 8-week on-demand period • Crossover to the alternate prophylaxis treatment for 16 weeks. • Dosing with BeneFIX during the on-demand treatment periods, as well as treatment of any bleeding episodes occurring during the prophylaxis periods, at the discretion of the investigator.	Male subjects, aged 6 years to 65 years with moderately-severe or severe haemophilia B (FIX:C ≤2%).	50
B1821010	2011-2014 (Global)	SE comparison of once-weekly 100 IU/kg prophylaxis regimen of BeneFIX with on-demand treatment Factor IX recovery studies at the start of the on-demand period and at the start and end of the prophylaxis period.	• Multicenter, open-label, 2-period study • 6-months on-demand treatment • 12-months prophylaxis with 100 IU/kg once-weekly • On-demand BeneFIX infusions during the prophylaxis period were permitted to treat acute bleeding events.	Male PTPs, aged 12 years to 65 years with moderately severe to severe haemophilia B (FIX:C ≤2%)	25

Abbreviations: BE=bioequivalence; BI=bolus infusion; CI=continuous infusion; FIX=factor IX; FIX:C=factor IX plasma activity; IU=international unit; No.=number; pdFIX=plasma-derived factor IX; PK=pharmacokinetics; PR=pulse replacement; PTPs=previously treated patients; PUPs=previously untreated patients; SE=safety and efficacy.

a. Presented by study initiation date. The 3090A1 study numbers for Studies C9408-21, C9407-21, and [C9417-21](#) surgery were assigned after completion of the respective CSRs and, therefore, are not included in the CSRs.

b. Number of subjects who received ≥1 infusion of study drug.

4.2. Clinical Pharmacology aspects

Study B1821010

Factor IX activity was determined at the local laboratory for plasma samples collected at Visit 1 and at the central laboratory for pre- and post-dose sample taken on Day 1 (Visit 2), Week 26 (Visit 4), and Week 78 (Visit 8), .

FIX:C measured 30 minutes after administration of 100 IU/kg BeneFIX was approximately twice that observed after administration of 50 IU/kg.

Their mean $\pm$ standard deviation (SD) recovery values are shown in Table 4.

Table 4 Factor IX Recovery in Study 1010 (IU/dL per IU/kg)

	Day 1 (50 IU/kg) (n = 24)	Week 26 (n = 24)	Week 78 (100 IU/kg) (n = 24)
Mean $\pm$ SD	0.77 $\pm$ 0.18	0.87 $\pm$ 0.21	0.70 $\pm$ 0.21
Min, max	0.48, 1.12	0.52, 1.23	0.39, 1.17

SD = standard deviation.

Source: [Study 1010 CSR Table 14.3.4.2.](#)

The mean FIX recovery for pediatric subjects (N=5) was 0.64 $\pm$ 0.08 (IU/dL)/(IU/kg) at Visit 2, 0.74 $\pm$ 0.17 (IU/dL)/(IU/kg) at Visit 4, and 0.72 $\pm$ 0.09 (IU/dL)/(IU/kg) at Visit 8.

Study 3090A1-400-WW

A modified FIX recovery study was performed once at the start of each prophylaxis period (study week 16 [visit 4] and study week 40 [visit 7]). After a minimum of 72 hours since the previous BeneFIX dose administration blood samples for determination of FIX:C were collected immediately before BeneFIX infusion and, when assessing recovery, at 30 minutes ($\pm$ 5 minutes) after the start of this infusion.

Blood samples for determination of FIX:C were also collected once during each prophylaxis period, at study week 24 (visit 5) and study week 48 (visit 8) at least 72 hours after the previous dose administration in order to assess the trough FIX:C. For both FIX recovery and trough measurements, FIX:C was assessed at the local laboratory using the one-stage clotting assay.

In this study, incremental recovery observed after administration of doses of 50 IU/kg or 100 IU/kg were consistent with what has been reported previously for the pharmacokinetics of factor IX. Following 50 IU/kg and 100 IU/kg regimens, the mean $\pm$ SD recovery measured were consistent between dosing regimens: 0.93 $\pm$ 0.31 and 0.91 $\pm$ 0.35 IU/dL/IU/kg respectively. As expected, the mean $\pm$ SD concentration measured 0.5 hours after dosing increased in a dose proportional manner and were 49.9 $\pm$ 16.1 and 91.5 $\pm$ 28.9 IU/dL for the respectively.

The summary statistics are shown in Table 5 below. One subject (011-001101) was observed to have low C0.5hr with correspondingly low recovery on both occasions. The reason for this is unknown; it is possible that there was a problem with dose administration, sample collection, and/or the presence of neutralizing antibodies to BeneFIX. However, despite the low recovery, the subject did respond to treatment. Response to treatment (ie, primary efficacy endpoint) was evaluated in Study 400 by comparison of the ABR during weekly prophylaxis treatment with BeneFIX 50 IU/kg twice weekly and 100 IU/kg weekly.

Assessor's comment

The MAH provided the requested details on the study participant. Clinically, a treatment effect was measurable. The low recovery values cannot be explained.

Table 5 **FIX:C and Recovery during Prophylactic BeneFIX Dosing in Subjects with Haemophilia B**

	C_{0hr} (IU/dL)	$C_{0.5hr}$ (IU/dL)	Recovery (IU/dL/IU/kg)	C_{trough} (IU/dL)
50 IU/kg (n=41)				
Mean	3.57	49.9	0.93	6.38
SD	3.11	16.1	0.31	4.63
Min	0	0.6	0.002	0.3
Median	3	49.9	0.9	5
Max	14	83	1.51	27
100 IU/kg (n=43)				
Mean	3.10	91.5	0.91	6.31
SD	2.19	28.9	0.35	5.41
Min	0	1.12	0.011	0.04
Median	2.7	95.1	0.93	4.9
Max	10	146	2.32	24

Source: /Final: Clinical R&D/Pharmacokinetic Anova and Graphs/BeneFIX/400/Statistical Pharmacokinetic Documentation

Abbreviations: C_{0hr} = the FIX:C measured before administration of the recovery dose; $C_{0.5hr}$ = the FIX:C measured after administration of the recovery study dose; C_{trough} = FIX:C measured at least 72 hours after previous dose; SD = standard deviation; min = minimum; max = maximum

Assessor's comment

Pre-infusion plasma levels of FIX (C_{0h}) and their increase at 30 minutes after start of BeneFIX infusion ($C_{0.5h}$) have been measured once at the start of each prophylaxis period for determination of recovery. Although at least 72 hours had passed since the previous FIX administration during the preceding on-demand treatment period, the pre-infusion FIX:C was in most subjects higher than awaited for a population with the inclusion criterion of moderate-severe and severe haemophilia B. This is a concern regarding the assessment of efficacy, see there.

FIX concentrations increased dose-proportionally when doubling the single dose from 50 IU/kg to 100 IU/kg; incremental recovery remained unchanged. Half-life was not determined, but anticipated as being approximately 18 hours (see CSR section 6.2).

Subjects Excluded From Pharmacokinetic Evaluation

A total of 250 FIX:C values were reported in 47 individuals. Although all individual FIX:C values that were reported are presented, recovery could not be determined if either the C_{0h} or the $C_{0.5h}$ was not reported. Recovery was not assessed for subjects 015-001501 (100 IU/kg), 016-001602 (50 IU/kg), 018-001802 (100 IU/kg), 018-001803 (50 IU/kg), 018-001808 (100 IU/kg), 019-001906 (50 IU/kg), 020-002001 (100 IU/kg), 025-002502 (100 IU/kg), 027-002701 (50 IU/kg), 028-002802 (50 IU/kg), 029-002901 (50 IU/kg), and 032-003203 (50 IU/kg) (see Supportive Tables 15.53 and 15.54).

Trough Concentration Results

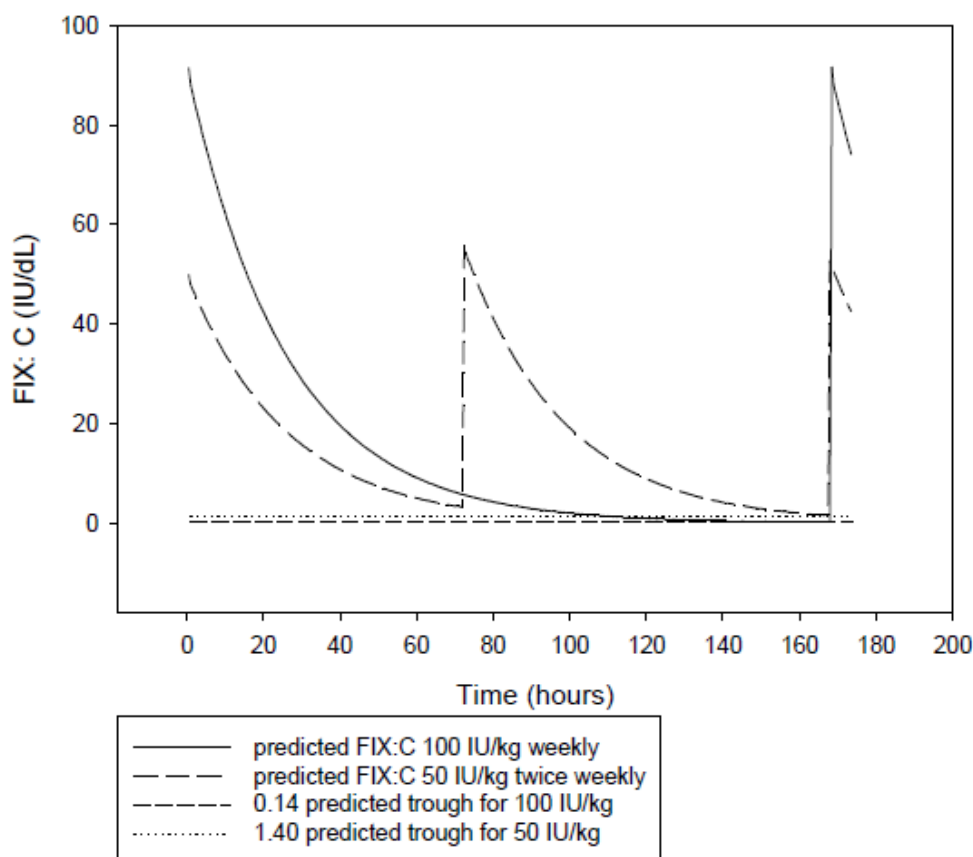
Trough FIX:C data are shown in CSR Supportive Tables 15.53 and 15.54, as well as in Table 2. No difference could be detected between the mean C_{trough} observed for the same doses. Despite the longer time between doses, which would predict lower C_{trough} following 100 IU/kg once per week, the observed C_{trough} values were similar between doses. This may reflect the fact that the time of sample collection could be any time after at least 72 hours post dose, and sample collection was not at the same time as the true lowest concentration.

Assessor's comment

Long term replacement therapy is intended to provide FIX concentrations which are sufficiently high to protect from bleedings, also at their lowest values. In this study trough FIX:C was measured once during each prophylaxis regimen. As written in CSR section 11.5 'Pharmacokinetic conclusions': "... the time of blood sampling for trough level measurement could be any time after at least 72 hours post dose, and sample collection was not at the same time as the true lowest concentration". So in fact, the reported values are no "trough", meaning lowest values immediately before next dosing.

Figure 1 below is a revision of the FIX:C simulation from the previous variation, using the observed mean C_{0.5hr} for the respective doses and assuming a 1-compartment elimination model with a half-life of 18 hours. In this simulation, the C_{0.5hr} values are in agreement with the observed concentrations, but the concentrations at the end of the dosing interval are very low, due to the assumption of a monoexponential model. It does, however, reasonably predict the concentrations observed at least 72 hours after dosing, when the "trough" concentrations were to be collected.

Figure 1. Simulated FIX:C After BeneFIX Prophylaxis Regimens of 50 IU/kg Twice Weekly or 100 IU/kg Once Weekly



Assessor's comment:

The MAH revised the simulation of factor IX concentrations as requested. The revised Figure 1 above shows a simulated predicted trough level for 100 IU/kg given every 7 days of 0.14 IU/dL and of 1.40 IU/dL for the regular 50 IU/kg twice weekly regimen. As demonstrated in the simulation, the proposed 100 IU/kg once weekly regimen is not able to maintain a protective factor IX level throughout the dosing interval. During the last 2 to 3 days of the treatment interval, patients' factor IX levels are as low as if they were without substitution therapy. This corresponds to the clinical finding that bleedings occurred more often in the late phase of the treatment interval: 12/52 bleeds during 0-72 hrs and 40/52 bleeds during 72-168 hours after administration of 100 IU/kg (Table 5 of AR). The once weekly posology seems inadequate.

Anti-CHO Antibodies

The incidence of anti-CHO antibodies was similar to what was observed in the survey of samples from normal healthy volunteers during the validation of the assay. Testing for anti-CHO antibodies was performed in 50 subjects on a total of 99 occasions. Twenty-one subjects (42%) tested positive on at least 1 occasion. While most subjects who tested positive did so on both occasions studied, 3 subjects tested positive at week 0 and were negative at week 56 and one subject tested negative at week 0 and positive at week 56.

Assessor's comment

CSR Listing 15.52 of Anti-CHO Lab results demonstrates, that the testing on anti-CHO antibodies revealed in most cases similar results for the titers measured at screening and in week 56 of treatment, either both negative or both positive. So no concern derives from that.

Study B1821010+ Study 3090A1-400-WW**Residual FIX:C Observed**

Early studies of FIX:C half-life of 18 hours led to guidelines for designing of PK studies limiting sampling to 50 to 72 hours after dose administration. During studies of extended half-life factor IX replacement products, PK samples were collected up to 96 hours after dosing and a longer estimate for FIX:C half-life (33 hours) after BeneFIX administration emerged (3). Assuming a peak FIX:C of 80 IU/dL after a dose of 100 IU/kg, the residual FIX:C after 5 half-lives (~ 1 week, 168 hours), would be expected to be approximately 2.5 IU/dL; assuming linearity of PK, the residual FIX:C after a 50 IU/kg dose would be approximately 1.25 IU/dL.

Assessor's comment

A subgroup of 22 participants in the study of Powell et al, mentioned above, completed a baseline pharmacokinetic assessment. It is important to point out that the terminal half-life was 33.8 hours and the half-life, calculated on the basis of the traditional 48-hour pharmacokinetic sampling schedule, was 17.04 hours (95% CI, 15.89 to 18.26), which is similar to previously reported 48-hour-data. The time to reach a factor IX level of 1 IU/dL (1%) was 5.1 days (95% CI, 4.6 to 5.7).

These data do not support an addition of a once-weekly 100 IU/kg prophylaxis regimen.

Neither Study 1010 nor 400 were designed to collect data to allow an assessment of FIX activity half-life after administration of BeneFIX. All subjects in these studies had recovery assessed on at least 3 occasions following at least a 72-hour washout since previous doses of factor IX replacement. These data were used in a post hoc analysis of residual FIX:C observed a week after dosing. All subjects enrolled in Studies 400 and 1010 had moderately severe or severe haemophilia, so it would be anticipated that their FIX:C would be ≤ 2 IU/dL if sufficient time had passed since previous doses. Of particular interest are the FIX:C collected approximately one week (144 to 192 hours) after a previous dose (Appendix Table 1). Of these 47, 30 show FIX:C greater than 2 IU/dL (minimum [min] - maximum [max] of 2.13 – 11.4 IU/dL) and thus are consistent with the longer half-life described by Powell et al, which in turn would provide PK justification for the observed efficacy of once-weekly dosing.

Assessor's comment

The pre-infusion FIX:C in study 400 was in most subjects higher than awaited for a population with the inclusion criterion of moderate-severe and severe haemophilia B. In study 1010 16 Patients had severe haemophilia B and 9 patients had moderate severe haemophilia B.

But the data of all patients in both studies were used in the post hoc analysis. Therefore, the results are questioned with regard to once-weekly dosing in severe haemophilia B patients.

Valid calculation of Factor IX activity half-life is considered to be crucial when intending extension of the dosage-interval. Lack of such reliable complete PK-data including previous dosage and pre-dose values considered to be a significant gap. Furthermore, reliable endogenous FIX-levels for each patient are required for assessment of PK- and efficacy-results.

Population Pharmacokinetic Analysis

The population PK model for FIX activity after BeneFIX administration was updated, from a previously developed model, using a pooled dataset from the first 8 studies and was evaluated with a pooled dataset from Study 1010 and Study 400.

Table 6 Clinical Studies Included in Population Pharmacokinetic Model Development

Pfizer Protocol Number	Previous Protocol Number(s)	Study Description	Number of Subjects with FIX Activity Observations	BeneFIX Dose used for PK
B1821031	3090A1-200 C9408-21 3090A1-201 C9407-21	Three part study: segment 1: crossover pharmacokinetic comparison of BeneFIX versus plasma-derived coagulation factor IX; segment 2: 24-month open label treatment period to assess the efficacy of BeneFIX; segment 3: assessment of efficacy and safety of BeneFIX for surgical prophylaxis	56	50 IU/kg
B1821032				
B1821033	3090A1-202 C9417-21	Phase 2/3 safety and efficacy study of surgical prophylaxis in PTP	9	50 IU/kg

B1821034	3090A1-300 C9418-21	Phase 3 safety and efficacy study in PUP	61	50 IU/kg
B1821035	3090A1-301 C0105-21	Phase 3 study in children less than 6 years of age	25	75 IU/kg
B1821036	3090A1-302 C0124-21	Phase 3 study in PTP	23	75 IU/kg
B1821037	3090A1-303 C9623-21	Phase 1/2 in Japanese PTP	3	50 IU/kg
B1821038	3090A1-304	Phase 3 in PTP (modified BeneFIX formulation)	24	75 IU/kg

PK = pharmacokinetics; PTP = previously treated patients; PUP = previously untreated patients.

Source: PMAR Table 1, Table 7.

The final model was a 2-compartment model, parameterised using clearance (CL), central volume of distribution (V1), peripheral volume of distribution (V2), intercompartmental clearance (Q), and effect of normalised weight as a power function on each parameter. Inter-occasional variability on CL and V1 showed significant decreases in the objective function and, therefore, were included in the model. A correlation between V2 and Q was also included. The effect of study on residual error was evaluated. Inclusion of separate parameters for Studies C9407-21/C9408-21 (θ_{11}) and 3090A1-300-WW (θ_{12}) and the all other studies (θ_5) was found to be significant. Age was not found to be a significant covariate when weight was included in the model.

Table 7 Parameter Estimates for Final Population Pharmacokinetic Model

$CL_{ij} = \theta_1 \times \left(\frac{WT_i}{70} \right)^{\theta_7} \times e^{\eta_{CL_i} + \kappa_{CL_{ij}}}$ $V1_{ij} = \theta_2 \times \left(\frac{WT_i}{70} \right)^{\theta_8} \times e^{\eta_{V1_i} + \kappa_{V1_{ij}}}$ $V2_i = \theta_3 \times \left(\frac{WT_i}{70} \right)^{\theta_9} \times e^{\eta_{V2_i}}$ $Q = \theta_4 \times \left(\frac{WT_i}{70} \right)^{\theta_{10}} \times e^{\eta_{Q_i}}$		Residual Error $Y_{ijk} = F_{ijk} + w_{ijk} \cdot \varepsilon_{ijk}$ $w_{ijk} = \theta_6^2 + \theta_p^2 \cdot F_{ijk}^2$ where Y_{ijk} denotes the observed FIX:C for the ith individual in occasion j at time t_k, F_{ijk} denotes the corresponding predicted FIX:C based on the PK model, and θ_6 and θ_p denote the standard deviations of additive and proportional residual errors, respectively C9407-21 & C9408-21: $\theta_p = \theta_{11}$ 3090A1-300-WW: $\theta_p = \theta_{12}$ Other Studies: $\theta_p = \theta_5$	
Parameter	Estimate (RSE%)	Parameter	Estimate (RSE%)
CL (dL/hr, θ_1)	5.51 dL/hr (2.2%)	Inter Individual Variability (IIV)	
V1 (dL, θ_2)	97.7 dL (4.0%)	IIV _{CL} (CV%)	25.6% (18.9%)
V2 (dL, θ_3)	46.2 dL (4.1%)	IIV _{V1} (CV%)	23.2% (10.2%)
Q (dL/hr, θ_4)	5.77 dL/hr (12.6%)	IIV _{V2} (CV%)	35.7% (13.7%)
Power on CL (θ_7)	0.799 (3.6%)	IIV _Q (CV%)	69.1% (17.6%)
Power on V1 (θ_8)	0.881 (3.9%)	ρ_{Q-V2}	0.481
Power on V2 (θ_9)	1.02 (9.9%)	Interoccasion Variability (IOV)	
Power on Q (θ_{10})	0.741 (22.1%)	IOV _{CL} (CV%)	24.7% (14.3%)
		IOV _{V1} (CV%)	18.9% (8.6%)

η -shrinkage	η_{CL} : 20.2%, η_{V1} : 14.9%	Residual Variability: Proportional error	
	η_{V2} : 30.8%, η_Q : 25.8%		
ε -shrinkage	13.0%		
		C9407-21 & C9408-21 (θ_{11})	0.122 (5.4%)
		3090A1-300-WW (θ_{12})	0.260 (11.7%)
		Other studies (θ_5)	0.117 (16.2%)
		Additive error (θ_6)	0.614 IU/dL (8.4%)

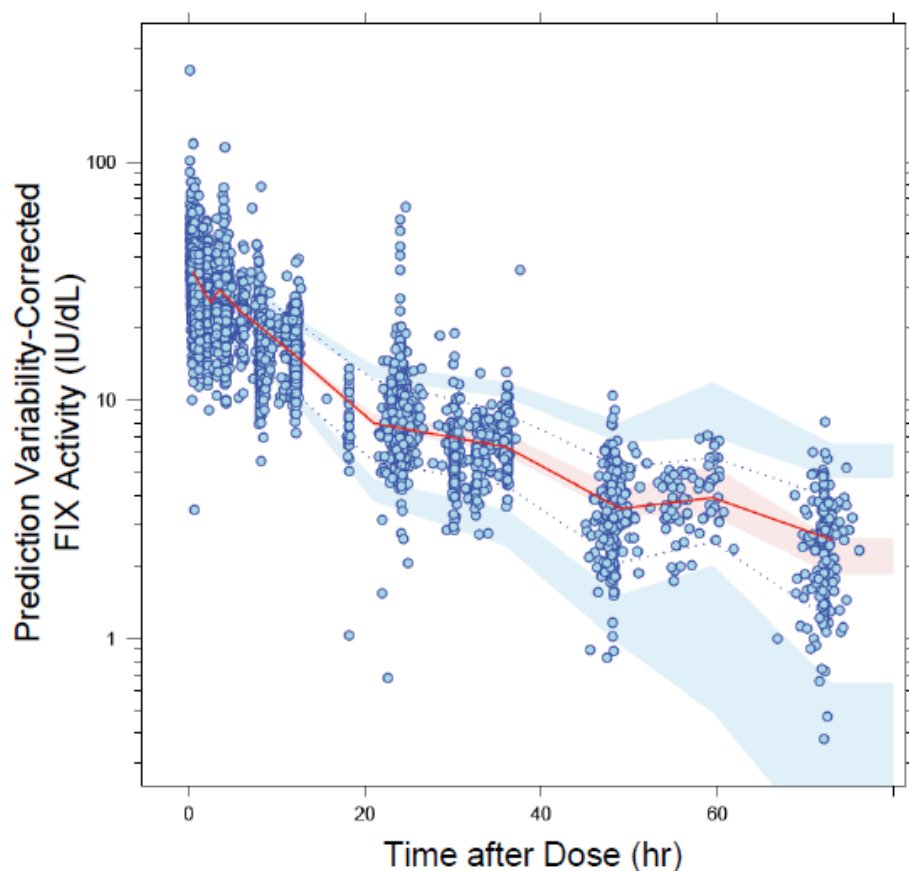
RSE% for IIVs and IOVs (CV%) were obtained by using delta method. [RSE% for IIVs and IOV (CV%)=SE(ω^2)/2 ω^2 x 100]

Source: [PMAR Table 15](#).

Abbreviations: CV=coefficient of variation, dL=deciliter, dL/hr=deciliter/hour, IIV=Inter Individual Variability; IOV=Interoccasion Variability; ρ_{Q-V2} =correlation between Q and V2, RSE=relative standard error

The plot for the visual predictive checks from the final model is shown in **Figure 1**. There was no overt bias in the final model and model performance was considered adequate.

Figure 3 Visual Predictive Checks (VPC) from the Final Model (Prediction and Variance Corrected)



Open circle: observation

Solid red line: observed median

Dashed blue lines: 10th and 90th percentile of the observed concentration-time profiles

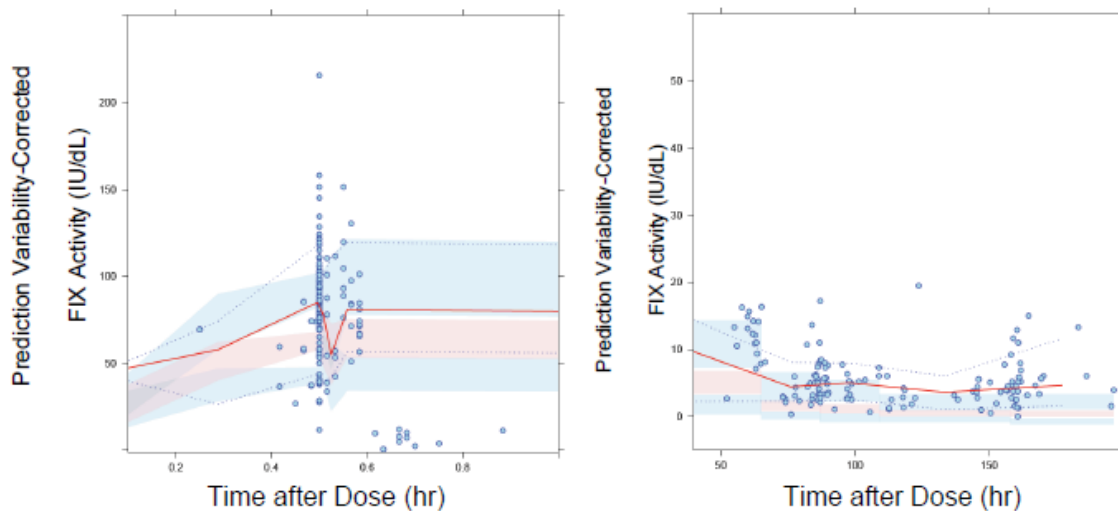
Red field: the areas covering 95% confidence intervals of the median of the simulated profiles

Blue field: the areas covering 95% confidence intervals of the 10th and the 90th percentile of the simulated profiles

Source: [PMAR Figure 5](#).

When datasets of identical design to Studies 1010 and 400 were simulated using the final parameter estimates from the model, actual observations from the studies were higher than the simulated values as may be seen in Figure 2, both immediately after dose administration (left figure) as well as up to a week after dosing (right figure).

Figure 4 Visual Predictive Checks (VPC) from the Final Model Immediately after and Later after Dosing (Prediction and Variance Corrected: B1821002 (Study 400) and B1821010)



Source: PMAR Figure 7

Abbreviations: hr=hours, IU/dL=international units per deciliter

Open circle: observation

Solid red line: observed median

Dashed blue lines: 10th and 90th percentile of the observed concentration-time profiles

Red field: the areas covering 95% confidence intervals of the median of the simulated profiles

Blue field: the areas covering 95% confidence intervals of the 10th and the 90th percentile of the simulated profiles

The positive bias observed immediately after dosing, may reflect the difference in subjects included in the study. The mean recovery observed in Study 400 was higher than had been reported in other studies and, thus, the higher observed than model-predicted FIX activity shortly after dosing is consistent with this result.

The bias observed during the 50 to 200 hour period after dosing may be a result of the longer half-life of FIX:C after BeneFIX administration (33 hours), which has come to light in studies of extended half-life products in which BeneFIX was a PK comparator (Powell et al). It was observed when the model was applied to the data collected in Studies 400 and 1010 because they uniquely collected samples approximately 1 week after previously administered doses.

Assessor's comment:

As mentioned by the applicant neither study 400 nor study 1010 were designed to collect data to allow for a definitive assessment of the FIX activity half-life after administration of BeneFIX. Instead of real measurements, the MAH provided a simulation of FIX:C over time.

Thus, although there are observations that are in line with the idea of a half-life longer than claimed on data from early studies, a definite proof of a longer half-life of FIX activity after administration of BeneFIX is still open.

Based on the observation of a possibly longer half-life one might critically reconsider the population PK model for FIX activity following BeneFIX administration. On one hand the ETA-shrinkages for V2 (30.8%) and Q (25.8%) from the final popPK model are relatively high [2.5.3.4, Table 2], indicating a lack of data to provide robust individual parameter estimates regarding V2 and Q. On the other hand, comparing the data on FIX activity in studies 400 and 1010 to the model simulated profiles, a bias (i.e. higher values than simulated based on the final popPK model which could be due to a longer half-life) is to be observed, questioning the validity of the model for data from these 2 studies. The applicant attributes this bias to possible study differences (i.e. differences in included subjects between studies 400 & 1010), but further investigations, taking study effects for studies 400 and 1010 respectively into account, were not performed.

Furthermore, meaningful PK-data containing maximum- and trough-levels in the late phase of the treatment –interval (measured values in respective patients) are considered to be essential. The MAH should perform additional long-term PK investigations regarding the FIX activity following BeneFIX administration.

In study 400 mean peak values of 49.9 IU/dL (after infusion of 50 IU/kg) and 91.5 IU/dL (after infusion of 100 IU/kg) were found. With an anticipated half-life of 18 hours reported for BeneFIX it is assumed that FIX levels return to pre-infusion levels after 72 hours.

4.2.1. Discussion

FIX concentrations increased dose-proportionally when doubling the single dose from 50 IU/kg to 100 IU/kg, incremental recovery remained unchanged between the two prophylactic regimens in study 400.

Recovery values observed in Study 400 (0.91 ± 0.35 IU/dL/IU/kg and 0.93 ± 0.31 IU/dL/IU/kg for the 100 IU/kg and 50 IU/kg doses respectively) were higher than the recovery observed in Study 1010 (0.77 ± 0.18 IU/dL/IU/kg). The MAH stated that Individual recovery values do vary and so the higher values observed in Study 400 may simply reflect random chance.

In study 400, Pre-infusion plasma levels of FIX (C0h) and their increase at 30 minutes after start of BeneFIX infusion (C0.5h) have been measured once at the start of each prophylaxis period for determination of recovery. Although at least 72 hours had passed since the previous FIX administration during the preceding on-demand treatment period, the pre-infusion FIX:C was in most subjects higher than awaited for a population with the inclusion criterion of moderate-severe and severe haemophilia B. In study 1010 only 5 patients had severe haemophilia B and 20 patients had moderate severe haemophilia B. But recovery data of all patients in both studies were used in the post hoc analysis. Therefore, the results are questioned with regard to once-weekly dosing in severe haemophilia B patients.

Half-life was not determined, neither in study 400 nor in study 1010, but anticipated as being approximately 18 hours (results of earlier studies of BeneFIX). The MAH refers to a study of Powell et al, which published a FIX:C half-life of 33 hours after BeneFIX administration. A subgroup of 22 participants in this study completed a baseline pharmacokinetic assessment. It is important to point out that the terminal half-life was 33.8 hours and the half-life, calculated on the basis of the traditional 48-hour pharmacokinetic sampling schedule, was 17.04 hours (95% CI, 15.89 to 18.26), which is similar to previously reported 48-hour-data. The time to reach a factor IX level of 1 IU/dL (1%) was 5.1 days (95% CI, 4.6 to 5.7). Therefore, these data do not support an addition of a once-weekly 100 IU/kg prophylaxis

regimen. In study 400 mean peak values of 49.9 IU/dL (after infusion of 50 IU/kg) and 91.5 IU/dL (after infusion of 100 IU/kg) were found. With an anticipated half-life of 18 hours reported for BeneFIX it is assumed that FIX levels return to pre-infusion levels after 72 hours.

No PK-calculation based upon in-patient FIX-activity levels according to the Clinical Guideline has been submitted. Instead the MAH provided a simulation of FIX:C over time.

Thus, although there are observations that are in line with the idea of a half-life longer than claimed on data from early studies, a definite proof of a longer half-life of FIX activity after administration of BeneFIX is still open.

Based on the observation of a possibly longer half-life one might critically reconsider the population PK model for FIX activity following BeneFIX administration. On one hand, the ETA-shrinkages for V2 (30.8%) and Q (25.8%) from the final popPK model are relatively high [2.5.3.4, Table 2], indicating a lack of data to provide robust individual parameter estimates regarding V2 and Q. On the other hand, comparing the data on FIX activity in studies 400 and 1010 to the model simulated profiles, a bias (i.e. higher values than simulated based on the final popPK model which could be due to a longer half-life) is to be observed, questioning the validity of the model for data from these 2 studies. The applicant attributes this bias to possible study differences (i.e. differences in included subjects between studies 400 & 1010), but further investigations, taking study effects for studies 400 and 1010 respectively into account, were not performed.

Furthermore, meaningful PK-data containing maximum- and trough-levels in the late phase of the treatment –interval (measured values in respective patients) are considered to be essential. The MAH should perform additional long-term PK investigations regarding the FIX activity following BeneFIX administration.

4.3. Clinical Efficacy aspects

4.3.1. Methods

Study B1821010

‘A Multicenter, Open-Label Study to Compare On-Demand Treatment to a Prophylaxis Regimen of Nonacog-Alfa (BeneFIX) in Subjects with Moderately Severe to Severe Haemophilia B (FIX:C $\leq$ 2 %)’

The phase III study was performed between September 2011 and April 2014 in 15 centers from 9 countries world-wide.

Objective(s):

Primary objective: to demonstrate that a prophylaxis regimen of BeneFIX reduces the ABR compared to on-demand treatment only, in subjects with moderately severe to severe haemophilia B.

The secondary objective: to describe the safety and efficacy of BeneFIX when administered for prophylaxis at a dose of 100 IU/kg once weekly.

Assessor’s comment:

In general, the primary objective of comparing annual bleed rates (ABR) under on-demand versus prophylaxis-regimen is questioned: Clinical support for Extension of the dosing interval mainly requires proof of protection in the late phase of the treatment interval in severely affected haemophilia patients. ABR in an on-demand treatment setting mainly reflects bleeding-pattern of the respective population but does not serve as adequate comparator for a "new" prophylaxis regimen.

Subjects were eligible to participate in this study, if they had a documented history of moderately-severe or severe haemophilia B (FIX:C $\leq 2\%$), were males aged 12 to 65 years, with at least 100 exposure days to FIX products and had a minimum of 12 bleeding episodes, 6 of which were joint bleeds, in the 12 months before screening.

Period 1 On-Demand Treatment

In the on-demand treatment period, bleeding events were treated at the discretion of the investigator using the study drug according to the locally approved BeneFIX label or the BeneFIX Core Data Sheet. The dose prescribed by the investigator was to be based on the subject's body weight (as measured at the most recent study visit according to the study procedures) and nominal vial potency. On-demand treatment was defined as the administration of study drug at the time of an acute bleeding event.

In the prophylaxis regimen period, subjects were to administer the prophylaxis dose once weekly. The interval between prophylaxis infusions was intended to be 7 days. The prophylaxis dose was to be approximately 100 IU/kg, rounded to the closest vial strength. The dose was to be prepared using the subject's body weight (as measured at the most recent study visit according to the study procedures) and actual vial potency (prior to approval of Amendment 1, dated 28 September 2011) or nominal potency of the study drug (after approval of Amendment 1).

If a bleeding event occurred during the prophylaxis period, the subject was to infuse study drug on demand at a dosage determined by the investigator according to the locally approved BeneFIX label or the BeneFIX Core Data Sheet to treat the acute bleeding event. The subject was to return to the once-weekly regularly scheduled prophylaxis dosing regimen as soon as possible at the discretion of the investigator.

Concomitant treatment with FIX concentrates other than the study drug was prohibited during the treatment phase from Visit 2 (Enrollment) to Visit 8 (Study Completion), unless clinically indicated.

Except for FIX concentrates, there were no other restrictions on the subject's regular medication. Analgesics, as well as other therapy considered necessary for the subject's well-being during the study were permissible at the discretion of the investigator.

Study design

```

graph LR
    S[Screening] --> OT[On-Demand Therapy]
    OT --> PT[Prophylaxis Therapy]
    T4[4 Weeks] --> S
    T6[6 Months] --> OT
    T12[12 Months] --> PT
    D1[Dose is at the investigator's discretion] --> OT
    D2[100 IU/kg once a week] --> PT
  
```

The flowchart illustrates the study design progression. It starts with 'Screening' at '4 Weeks', leading to 'On-Demand Therapy' at '6 Months'. 'On-Demand Therapy' leads to 'Prophylaxis Therapy' at '12 Months'. Above 'On-Demand Therapy' is a box stating 'Dose is at the investigator's discretion'. Above 'Prophylaxis Therapy' is a box stating '100 IU/kg once a week'.

Outcomes/endpoints

Primary efficacy endpoint:

annualized number of bleeding episodes calculated using the following formula:

$$\text{ABR} = \text{number of bleeds} / (\text{days on treatment period} / 365.25)$$

The number of bleeds for the ABR calculation included all bleeds requiring treatment with FIX product during the time on treatment.

Secondary efficacy endpoint:

1. response to on-demand treatment with BeneFIX for all bleeds as assessed by the subject/caregiver or investigator/qualified designee using a 4-point response scale.
2. Number of BeneFIX Infusions Used to Treat Each Bleed
3. Number of Breakthrough (Spontaneous/Non-traumatic) Bleeds within 48 Hours of a Prophylaxis Dose of BeneFIX
4. Average Infusion Dose and Total Factor Consumption
5. Incidence of Less than Expected Therapeutic Effect (LETE)
6. LETE in the On-Demand Setting
7. LETE in the Prophylaxis Setting
8. LETE – Low Recovery

Participant flow

A total of 32 subjects were screened for the study, 7 subjects were withdrawn during the screening period, and 25 subjects enrolled and completed the study.

Table 2: Summary of Subject Disposition

Subject Disposition	Total Number of Subjects
Screened	32
Withdrawn During the Screening Period	7
Enrolled	25
Treated	25
Discontinued	0
Study Completed	25

Source: [Section 14.1, Table 14.1.1](#)

Five paediatric subjects (i.e., less than 18 years of age) were screened, enrolled, and completed the study.

Study 3090A1-400-WW

'A multicenter, open-label study to compare on-demand treatment with 2 prophylaxis regimens of recombinant coagulation factor IX (BeneFIX) reformulated drug product (rFIX-R) in subjects with severe haemophilia B'

The phase IV study was performed between May 2007 and October 2010 in 18 centers in Canada, USA, Europe and Russian Federation.

Objective(s):

Primary objective: to evaluate efficacy and safety of BeneFIX infused as two prophylaxis regimens (100 IU/kg once weekly and 50 IU/kg twice weekly) compared with BeneFIX administered in an on-demand regimen only.

Secondary objectives: to evaluate and compare efficacy, safety, and patient-reported outcomes of 2 BeneFIX prophylaxis regimens, as well as patient-reported outcomes between the prophylaxis regimens and the first on-demand regimen.

Study participants

Subjects were eligible to participate in this study, if they had a documented history of moderately-severe or severe haemophilia B (FIX:C $\leq$ 2%), were males aged 6 to 65 years, and had a minimum of 12 bleeding episodes, 6 of which were joint bleeds, in the 12 months before screening.

Treatment

The 50 IU/kg twice-weekly dosing regimen employed in Study 400-WW was selected based on the results of pivotal Study 3090A1-304-WW (reformulated BeneFIX), where subjects utilizing prophylaxis infused a median dose of 51.7 IU/kg (range 13.9 to 184.2 IU/kg), given as 2 or more infusions per week. This dose is also within the range and frequency (ie, 40-100 FIX units/kg two to three times weekly) recommended by the Medical and Scientific Advisory Committee (MASAC) of the National Haemophilia Foundation (NHF)¹, a United States-based advocacy organization.

[1 Medical and Scientific Advisory Committee MASAC Recommendation Concerning Prophylaxis (Regular Administration of Clotting Factor Concentrate to Prevent Bleeding) (Document #179), 03 November 2007]

Assessor's comment

Median dose of 52 IU/twice weekly is not in accordance with the EMA-approved SmPC (40 IU/kg at 3-4 days intervals).

The 100 IU/kg alternative, once-weekly prophylaxis regimen in Study 3090A1-400-WW was derived by doubling the twice-weekly dose, so that the same total factor IX dose in IU/kg is delivered over the same period, given, however, in 1 infusion rather than in 2 infusions.

The dose for the prophylaxis regimen was either 50 IU/kg twice weekly or 100 IU/kg once weekly based on nominal vial potency. Subjects utilizing on-demand therapy were treated at a dose prescribed at the discretion of the investigator. If a bleeding episode occurred during the prophylaxis period, the subject was to infuse BeneFIX at a dosage determined by the investigator. The assigned prophylaxis regimen was then to be resumed as soon as possible, at the discretion of the investigator and subject.

Subjects were given vials containing 250 IU and/or 2000 IU (nominally) of BeneFIX.

Prior and concomitant therapy

At the screening visit, reasonable efforts were made to determine all relevant treatments (ie, pharmacologic and non-pharmacological treatments, including non-prescription medications) received by

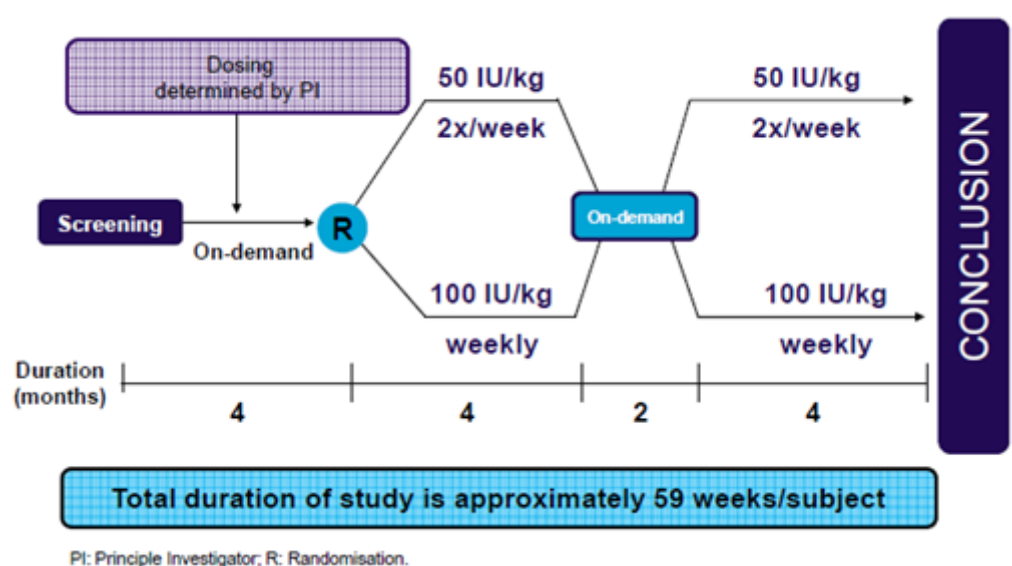
the subject within 30 days before administration of the study drug. Use of prestudy medications (other than FIX concentrates) continued unchanged. Analgesic agents, as well as other therapy considered necessary for the subject's well-being during the study, could have been given at the discretion of the investigator. During each prophylaxis period, subjects could treat any bleeding episode with BeneFIX, at the discretion of the investigator. Concomitant treatment with any FIX product other than BeneFIX was prohibited during this study.

Assessor's comment

According to Clinical Study Report (CSR) Supportive Table 15.16 'Number (%) of subjects reporting prior non-study medications' only 19 out of the 50 patients enrolled reported the use of blood coagulation factor IX within the 30 days before study treatment. It is questioned whether all patients enrolled had moderate – severe or severe haemophilia B.

Study design

Figure 2 BeneFIX Study 400-WW - Study Design



Outcomes / endpoints

Primary efficacy endpoint:

The annualized bleed rate (ABR) or number of bleeds per year:

$ABR = \text{number of bleeds} / (\text{days on treatment regimen} / 365.25)$

Information regarding bleeding episodes was collected with electronic subject diaries.

Secondary efficacy endpoints:

1. Amount and quality of sleep measured by a Sleep Diary after hemarthrosis
2. Acute pain scale after hemarthrosis (Brief Pain Inventory BPI)
3. Time lost from work or school after hemarthrosis (Health-Related Productivity Questionnaire Diary)
4. General health status (Short Form-36. Health Survey [SF-36] questionnaire)

Participant flow

Of the 58 subjects screened, 50 subjects were enrolled (47 randomized, 41 (82%) completed).

Table 3 Study 400-WW Subject Disposition – ITT Population

Characteristic	n (%)			
	Pre-Randomization N = 3 ^a	BeneFIX		Total N = 50
		100 IU/kg/ 50 IU/kg N = 22	50 IU/kg/ 100 IU/kg N = 25	
Screened	11	22	25	58
Enrolled	3 (100.0)	22 (100.0)	25 (100.0)	50 (100.0)
Randomized	0	22 (100.0)	25 (100.0)	47 (94.0)
Study Completed	0	19 (86.4)	22 (88.0)	41 (82.0)
Early Discontinued	3 (100.0)	3 (13.6)	3 (12.0)	9 (18.0)
Reasons for Conclusion				
Adverse Event	0	0	1 (4.0)	1 (2.0)
Protocol Violation	0	1 (4.5)	0	1 (2.0)
Subject Request	2 (66.7)	0	0	2 (4.0)
Discontinuation of Study by Sponsor	0	0	0	0
Lost to Follow-up	0	0	1 (4.0)	1 (2.0)
Other	1 (33.3)	2 (9.1)	1 (4.0)	4 (8.0)

Abbreviations: ITT = intent-to-treat; N = number of subjects beginning the treatment period; n = number of subjects in each category within a treatment period.

a. Three (3) subjects were enrolled and received study drug in the first on-demand period, but were never randomized.

4.3.2. Results

Study B1821010

Analysis of Efficacy

Primary Efficacy Endpoint of Annualized Bleed Rate

The mean ABR ($\pm$ SD) for the prophylaxis period was 3.6 ± 4.6 (median: 2.0) and was significantly lower ($p < 0.0001$) than the mean ABR for the on-demand period of 32.9 ± 17.4 (median: 33.6).

Table 8: Annualized Bleed Rate by Treatment Period

Statistic	Annualized Bleed Rate (ABR)		
	On-Demand ^a (Number of Bleeds = 417)	Prophylaxis ^b (Number of Bleeds = 90)	Difference ^c
N	25	25	25
Mean	32.9	3.6	29.3
SD	17.4	4.6	15.8
Median	33.6	2.0	31.4
Min, Max	6.1, 69.0	0.0, 13.8	6.1, 60.7
95% CI	25.7, 40.1	1.7, 5.6	22.8, 35.8
p-value ^d			<0.0001

Source: [Section 14.2, Table 14.2.4.1](#)

ABR = annualized bleed rate; CI = confidence interval; min = minimum; max = maximum; N = number of subjects in each treatment period; SD = standard deviation

^a For the on-demand period,

ABR = Number of bleeds / (Date of enrollment until the day before date of Visit 4 / 365.25).

^b For the prophylaxis period,

ABR = Number of bleeds / (Date of Visit 4 until the day before date of Visit 8 / 365.25).

^c Difference = On-demand period ABR minus prophylaxis ABR.

^d p-value: comparing the ABR between on-demand and prophylaxis using the paired t-test.

Annualized Bleed Rate for Pediatric Subjects

Table 9 Annualized Bleed Rate and Total Infusions in Pediatric Subjects

Subject #	On-Demand Period			Prophylaxis Period		
	Number of Bleeds	Annualized Bleed Rate ^a	Total Number of Infusions Needed for Resolution	Number of Bleeds	Annualized Bleed Rate ^a	Total Number of Infusions Needed for Resolution
10031001	37	69.0	38	8	8.2	8
10171002	21	43.8	21	10	9.8	10
10261002	18	35.0	36	13	13.3	22
10311001	12	24.4	12	2	2.0	2
10381001	27	54.2	31	9	8.9	11

Source: [Section 14.2, Table 14.2.2.1.1](#) and [Table 14.2.2.2.1](#)

^a Annualized bleed rate = Number of bleeds / (Days on treatment period / 365.25).

Number of Breakthrough/Spontaneous Bleeds and Time to Spontaneous Bleeds During the Prophylaxis Period

Table 10 Summary of Bleeds

	Treatment		
	On-Demand (N = 25)	Prophylaxis (N = 25)	Total (N=25)
N	25	25	25
Mean (SD) duration of period (weeks)	26.3 (1.3)	52.2 (1.8)	78.5 (1.2)
n (%) of subjects with no bleed of any kind	0	9 (36.0)	0
n (%) of subjects with a bleed of any kind	25 (100.0)	16 (64.0)	25 (100.0)
n (%) of subjects with a spontaneous bleed	21 (84.0)	13 (52.0)	21 (84.0)
n (%) of subjects with a traumatic bleed	18 (72.0)	13 (52.0)	22 (88.0)
n (%) of subjects with a bleed at 'joint'	25 (100.0)	12 (48.0)	25 (100.0)
n (%) of subjects with a bleed at 'soft tissue/muscle'	14 (56.0)	4 (16.0)	17 (68.0)
n (%) of subjects with a bleed at 'other'	7 (28.0)	8 (32.0)	11 (44.0)

Source: [Section 14.2, Table 14.2.12](#)

n = number of observations; N = number of subjects who had participated in the period; SD = standard deviation

Note: (N=25) represents the number of subjects in the safety population.

A subject may be counted more than once if a subject has bleeding episodes at multiple sites.

Thirteen subjects (52.0%) experienced 64 spontaneous bleeds during the prophylaxis period. Three subjects experienced 1 spontaneous bleeding episode each within 48 hours of a previous prophylaxis infusion. The MAH stated that all of these bleeding episodes were associated with confounding factors and were not considered occurrences of LETE.

4 subjects experienced 2-5 spontaneous bleeding episodes each within >48 - ≤72 hours of a previous prophylaxis infusion.

The majority of spontaneous bleeds in the prophylaxis period (47 of 64 bleeds, 73.4%) occurred >72 hours from the previous prophylaxis infusion.

Assessor's comment

The prophylactic treatment regimen leads to statistically significant lower annualized bleed rates (ABR) compared to on-demand treatment. The primary efficacy endpoint of the study has been met.

7 out of 25 (28%) patients experienced multiple spontaneous bleeding episodes within 72 hours of a previous prophylaxis infusion. In addition, the presented data show, that a considerable number of subjects (12/25, 48%) experienced bleeds after 4 or 5 days despite being on the proposed once-weekly prophylaxis regimen and received additional on-demand treatment.

Mean Infusion Dose and Total Factor IX Consumption

There was a cumulative total of 1923 infusions for 25 subjects over the entire study; with a mean number of infusions ($\pm$ SD) per subject of 50.0 ± 2.0 (median: 50) for prophylaxis treatment, 26.0 ± 18.0 (median: 24) for on-demand treatment, and 2 ± 1 (median: 1) infusions for preventative treatment (N=6) (safety population). These infusion numbers do not include the infusions for the recovery studies which occurred at Visit 2 in the on-demand period and at Visits 4 and 8, the start and end of the prophylaxis period. A total of 73 infusions were administered for the recovery studies.

The mean dose by weight per infusion was 99 ± 2 IU/kg (median: 99 IU/kg, range: 93-104 IU/kg) for prophylaxis infusions and 40 ± 9 IU/kg (median: 42 IU/kg, range: 20-54 IU/kg) for on-demand infusions. The majority of infusions administered in response to a bleeding episode were between the doses of 30 to 50 IU/kg (527 out of 659 infusions, 80.0%), and of those, 453 infusions resulted in an "Excellent" or "Good" response to the infusion.

The annualized mean TFC by weight per subject was 4985 ± 233 IU/kg for prophylaxis infusions administered during the 12-month prophylaxis period and 707 ± 519 IU/kg for on-demand infusions administered during the entire 18 months of the study. During the same timeframes, the monthly TFC by weight per subject was 415 ± 19 IU/kg for prophylaxis infusions and 59 ± 43 IU/kg for on-demand infusions.

For the recovery studies, the annualized mean TFC by weight per subject was 152 ± 27 IU/kg.

Incidence of Less-Than-Expected Therapeutic Effect (LETE)

Two successive "No Response" ratings after BeneFIX infusions did not occur in any subject in the on-demand setting. Therefore out of 507 bleeding episodes (safety population), no bleeds met LETE criteria in the on-demand setting and the observed incidence rate of LETE in the on-demand setting was 0.0%.

In the prophylaxis setting, 3 subjects were identified as having spontaneous bleeding episodes within 48 hours after a regularly scheduled prophylaxis dose of BeneFIX. Confounding factors included the bleed being in a target joint identified at the start of the study (Subjects 10171004 and 10521002) and inadequate dose and deviation in prescribed prophylaxis regimen before the bleed (Subject 10221002). These circumstances discount these bleeding episodes as occurrences of LETE. Out of a total of 1254

routine prophylaxis infusions, no bleeding episodes met the criteria for LETE in the prophylaxis setting and the observed incidence rate of LETE was 0.00%.

No occurrences of LETE were reported following infusion of BeneFIX for the FIX recovery studies.

Study 3090A1-400-WW

Primary Efficacy Results

The primary efficacy endpoint for the study was the annualized bleed rate (ABR); Table 11 describes the data for the intent-to-treat (ITT) population in the study.

Routine dosing statistically significantly reduced ABR when compared with on-demand therapy. Both traumatic and spontaneous bleed rates were lower after routine dosing compared to the on-demand periods.

Table 11 BeneFIX Study 400-WW - Comparison of Annualized Bleed Rates between First On-demand and Each Prophylaxis Regimen and between Prophylaxis Regimens - ITT Population

Characteristic	BeneFIX Treatment					
	OD1 N = 50	100 IU/kg N = 44	50 IU/kg N = 44	100 IU/kg - OD1 N = 44	50 IU/kg - OD1 N = 43	100 IU/kg - 50 IU/kg N = 43
ABR						
Fixed Effects						
LS Mean	35.1	4.6	2.6	-30.5	-32.5	2.0
95% CI	28.8 – 41.4	2.1 – 7.2	-0.1 – 5.3	-36.5 – -24.5	-38.5 – -26.6	-1.2 – 5.2
p-value ^a				<0.0001	<0.0001	0.2167

a. p-values based on model including terms for treatment regimen (OD1, OD2, 50 IU/kg, and 100 IU/kg), treatment sequence, and the interaction of these terms with repeated measures on subjects.

Abbreviations: ITT = intent-to-treat; N = number of patents; OD = on-demand; ABR = annualized blood rates; CI = confidence interval; LS = least squares.

Source: /CSR table ABR4DIFF-ITT

Assessor's comment

Both prophylactic treatment regimens lead to statistically significant lower annualized bleed rates (ABR) compared to on-demand treatment. There is no statistically significant difference in ABR between the 50 IU/kg twice weekly and the 100 IU/kg once weekly prophylactic schedule. The applicant concludes that the primary efficacy endpoint of the study has been met.

However, there is a concern regarding the selection of study population. The ABR of 35.1 bleeds per year during the initial on-demand phase represents a population of 2-3 bleeds per month. However, only 19 out of 50 subjects used factor IX concentrates within the 30 days prior to study treatment. Such numbers are considered to be conflicting. It is not clear, whether the remaining 31 subjects did not have any bleeds during the 30 days prior to study treatment or whether they had bleeds but no access to factor IX products.

Further doubts on the severity of haemophilia B in the study population arise from factor IX determinations. Supportive Tables 15.53 and 15.54 'Individual FIX:C observed during 50 IU/kg twice weekly' and '...during 100 IU/kg once weekly', respectively, provide the results of the recovery testing (C_{0h} , $C_{0.5h}$, total dose, weight, in vivo recovery, and C_{trough}). It is noted, that baseline FIX:C (C_{0h}) was in the majority of subjects >2%. The assessor prepared the following summarizing table:

Table 4 Individual FIX:C (C0h) observed at start of prophylaxis periods

FIX:C	Subjects before first 50 IU/kg prophylaxis (N=40) ^a	Subjects before first 100 IU/kg prophylaxis (N=42) ^a
≤ 2%	15	16
>2% - 5%	15	19
>5%	10	7

^a Number of subjects with C_{0h} measurement

Derived from CSR 3090A1-400-WW Supportive Tables 15.53 and 15.54

According to this table, only 15 out of 40 subjects ready to receive 50 IU/kg (37.5%) and 16 out of 42 subjects awaiting 100 IU/kg (38.1%) had a FIX activity ≤2%, which defines moderate-severe and severe haemophilia B and was an inclusion criterion. More than 60% of the subjects were at the start of their prophylactic treatment periods in a situation of moderate or mild haemophilia B. It is current knowledge, that individuals with moderate haemophilia B seldom have spontaneous bleeding and subjects with mild haemophilia B (FIX:C >5%-30%) normally do not have spontaneous bleeding episodes, at all. The concern is, whether efficacy of the proposed prophylactic regimen has been investigated in the appropriate study population for which long-term prophylaxis is indicated i.e. with severe haemophilia B. The MAH is requested to comment.

As already requested above, baseline FIX activity levels before start of the first on-demand treatment period would be of major interest. The MAH is asked whether the inclusion criterion 'history of moderate-severe or severe haemophilia B' was verified by measuring a FIX:C ≤2% at screening and to provide that data.

Table 12 Summary of Time from Start of Previous Test Article Infusion to Start of New Bleed during Prophylaxis Treatment – ITT Population

CHARACTERISTIC	TIME DIFFERENCE n (%)							
	≤ 24 HR	> 24 - 48 HR	> 48 - 72 HR	> 72 - 96 HR	> 96 - 120 HR	> 120 - 144 HR	> 144 - 168 HR	> 72 HR
Type of Bleed	8	9	24	17	14	6	4	46
Spontaneous	6 (75.00)	5 (55.56)	18 (75.00)	12 (70.59)	13 (92.86)	4 (66.67)	3 (75.00)	33 (71.74)
Trauma	2 (25.00)	4 (44.44)	6 (25.00)	5 (29.41)	1 (7.14)	2 (33.33)	1 (25.00)	13 (28.26)
Treatment	8	9	24	17	14	6	4	46
PR 50 BW	6 (75.00)	8 (88.89)	15 (62.50)	2 (14.29)				6 (13.04)
PR 100 QW	2 (25.00)	1 (11.11)	9 (37.50)	17 (100.00)	12 (85.71)	6 (100.00)	4 (100.00)	40 (86.96)

Source: Cabinets/Compounds/PF-05/PF-05208755/Clinical/TV/3090A1-400/Tables and Figures/CSR

Assessor's comment

Table 12 presents the number of bleedings after dosing and with respect to the prophylaxis-regimen. It can be concluded that the occurrence of bleedings is related to the actual FIX plasma level. However, superiority of one regimen cannot be derived from this presentation due to the different dosage.

The majority of bleeds within 72 hours after dosing occurred in the 50 IU/kg group, i.e. 29 bleeds versus 12 bleeds within 72 hrs after 100 IU/kg. Due to the different dosing intervals of the prophylactic regimens, later occurring bleedings cannot be compared.

Secondary Efficacy Results: Patient-Reported Outcomes

Data on pain, sleep, and days lost from work/school were recorded in the diary at 24 and 48 hours after the onset of each joint bleeding episode. Additional data on health status were collected at the end of the 16-week on-demand period, and at the end of each prophylaxis period using the Short Form-36 (SF-36) Health Survey.

Sleep Diary

The amount and quality of sleep was measured by a sleep diary, which was completed by the subjects at 24 and 48 hours after each incidence of hemarthrosis. The question in the sleep diary for each of those time points referred to the amount and quality of their sleep "last night." Thus, the data for 24 hours refers to sleep within the 24-hour period after the bleeding episode (first night) and the data for 48 hours refers to sleep within the second 24-hour period after the bleeding episode (second night).

The analyses were done for all bleeding episodes for which a completed sleep diary was available (rather than per subject), for each of the treatment regimens: during the first on demand regimen, during treatment with 100 IU/kg once weekly, during treatment with 50 IU/kg twice weekly, or during the second on-demand regimen. For each treatment regimen, the mean of all the mean differences (ie, the sleep diary scores for the second night minus those for the first night after the bleeding episode) are presented, along with the standard deviation, 95% confidence intervals, and p-values based on those mean differences. The row for mean contains the same data as for mean differences. Note that the total number of bleeding episodes for Table 9-4 was 837, rather than 831 used for Table 9-6, because the latter table did not include bleeds ≥ 7 days after infusion and only included 1 bleed per day.

Overall, there were no meaningful differences in sleep variables across treatment regimens. There was a statistically significant increase (from 7.4 to 7.8 hours) in the amount of time slept and a statistically significant decrease (0.4) in the number of sleep interruptions, from the first night to the second night after the bleed event for each treatment regimen, except for the second on-demand period. Self-reported sleep quality decreased by 0.3 points (on a 1 to 5 scale) from the first to second night after the bleed event.

Brief Pain Inventory (BPI)

Subjects were required to complete the BPI following a joint bleed. At 24 hours post-bleed 27.2% of subjects reported pain. None of the parameters captured by the BPI appeared to differ meaningfully across treatment regimens.

Health-Related Productivity

The amount of work missed did not appear to differ meaningfully across regimens at either time point (24 or 48 hours) for any category of work performed. Subjects reported a meaningful subjective impact on their work (on average, a 20%-25% degree of impairment) at 24 hours.

SF-36 Questionnaire (Health Survey Short Form-36 questionnaire)

Using the norm-based scoring for the SF-36, a score of 50 represents the mean for the US population, with a standard deviation of 10 points. The role-physical and pain domains showed statistically and clinically significant improvements in both prophylaxis regimens relative to the on-demand regimen. The scores at the end of the 50 IU/kg period also showed statistically significant improvements compared with the on-demand period in the vitality scores and role-emotional domains, although the magnitude of the change in vitality may not be clinically meaningful. None of the other domains showed statistically significant change.

Other Efficacy Parameters

Number of Infusions for Resolution of Bleeds by Location

Across all locations, 78.0% (648 of 831 bleeds) resolved with a single infusion of BeneFIX. Most joint (77.7%) and soft tissue/muscle bleeds (81.4%) resolved with 1 BeneFIX infusion. Similarly, the majority of multiple site bleeds were also treated with a single BeneFIX infusion (80.0%). Five (5) joint bleeds required >4 infusions of BeneFIX for resolution.

Time between Bleed Onset and Prior Prophylaxis Infusion

The majority of spontaneous bleeds (33 of 62 bleeds; 53.2%) occurred >72 hours from the prior prophylaxis infusion, which includes both treatment periods (50 IU/kg twice weekly and 100 IU/kg once weekly). In the 100 IU/kg treatment period, of the 52 observed bleeds (including spontaneous and traumatic bleeds), 12 occurred in the first 72 hours after a prophylaxis dose. In the 50 IU/kg treatment period, of the 35 observed bleeds (including spontaneous and traumatic bleeds), 29 occurred in the first 72 hours after a prophylaxis dose.

Consumption of BeneFIX

The median numbers of exposure days per subject (with corresponding minimum and maximum values) were 16.0 (1.0 to 38.0 days, 100 IU/kg once weekly) and 28.5 (1.0 to 44.0 days, 50 IU/kg twice weekly). The median cumulative doses were 104,030 IUs per subject for the 100 IU/kg group (2500 to 231,280 IU) and 105,042 IUs per subject for the 50 IU/kg group (3500 to 216,340).

Study B1821010 and Study 3090A1-400-WW

ABRs pooled by regimen for Study 1010 and Study 400 for prophylaxis with BeneFIX are presented in Table 13. For the pooled data, once-weekly prophylaxis using 100 IU/kg BeneFIX (mean $\pm$ SD: 4.1 $\pm$ 8.4) provided efficacy, in terms of ABR, comparable to twice-weekly prophylaxis at 50 IU/kg (mean $\pm$ SD: 2.8 $\pm$ 5.7). Likewise, the pooled prophylaxis ABR data for Study 1010 and Study 400 by regimen, type of bleed (aetiology) and location of bleed (site type), provided comparable efficacy for 50 IU/kg twice-weekly and 100 IU/kg once-weekly.

Table 13 Annualised Bleed Rate for BeneFIX Prophylaxis, Pooled for Study 1010 and Study 400

Characteristic	Prophylaxis Regimen	
	100 IU/kg QW	50 IU/kg BW
Annualised Bleed Rate		
N	69	43
Mean	4.1	2.8
Standard Deviation	8.4	5.7
Median	1.0	0.0
Min, Max	0.0, 50.5	0.0, 24.1

Source: [SCE in-text Table 6](#).

Abbreviations: N=number of subjects; Min=minimum; Max=maximum.; BW=twice weekly; QW=once weekly

Post Hoc Poisson Sensitivity Analysis of BeneFIX ABR for Study 1010 and Study 400

The results from the Poisson regression model analysis, as well as the previously reported paired t-test results for the efficacy population in BeneFIX Study 1010 are shown in Table 14.

Table 14 Study 1010 - Analysis of Annualised Bleed Rate Using Poisson Regression Mixed Model in Efficacy Population

	Regimen		
	Estimated ABR and 95% CI		Ratio of Estimated ABRs 95% CI
	OD (N=25)	RP100 QW (N=25)	Chi-square test p-value OD/ RP100 QW
Poisson Regression Mixed Model	33.09 (27.03, 40.51)	3.61 (2.23, 5.84)	9.17 (5.99, 14.06) p< 0.0001
Previously reported paired t-test results	32.9 (25.7, 40.1)	3.6 (1.7, 5.6)	p<0.0001

Source: Compounds/PF-05/PF-05208755/Clinical/Summary/Tables and Figures/Poisson 400 and 1010 - Oct 2014/
TABLEY for Poisson Regression Mixed Model - Analysis of ABR using Poisson Regression Model - Efficacy
Population and SCE in-text Table 1 for Previously reported paired t-test results
Abbreviations: ABR=annualized bleed rate, CI=confidence interval, N=number of subjects, OD=on-demand,
RP=routine prophylaxis; QW=once weekly.

The pairwise comparison of regimens from the Poisson model gave similar results as the paired t-test which is that the prophylaxis regimen had statistically significantly lower ABR than the on-demand regimen.

The results from the Poisson regression model analysis, as well as the previously reported ANOVA results for the intent-to-treat (ITT) population in BeneFIX Study 400 are shown in Table 15.

Table 15 Study 400 - Analysis of Annualised Bleed Rate Using Poisson Regression Mixed Model in ITT Population

	Estimated ABR and 95% CI			Ratio of Estimated ABR, 95% CI and (chi-square) test p-value		
	OD1 (N=49)	RP100 QW (N=44)	RP50 BW (N=43)	OD1/ RP100 QW	OD1/ RP50 BW	RP100 QW/ RP50 BW
Poisson Regression Mixed Model	34.85 (29.43, 41.27)	4.21 (2.27, 7.80)	2.63 (1.39, 4.97)	8.28 (4.66, 14.72) p<0.0001	13.26 (7.12, 24.67) p<0.0001	1.60 (0.74, 3.48) p=0.2357
Previously reported ANOVA model	35.1 (28.8, 41.4)	4.6 (2.1, 7.2)	2.6 (-0.1, 5.3)	p<0.0001	p<0.0001	p<0.2167

Source: Compounds/PF-05/PF-05208755/Clinical/Summary/Tables and Figures/Poisson 400 and 1010 - Oct 2014/
TABLEX updated for Poisson Regression Mixed Model - Analysis of ABR using Poisson Regression Model - ITT
Population and SCE in-text Table 4 for Previously reported ANOVA model.
Abbreviations: ABR=annualized bleed rate, ANOVA=analysis of variance, BW=twice weekly, CI=confidence interval,
ITT=intent-to-treat; N=number of subjects, OD=on-demand, QW=once weekly.

The pairwise comparison of regimens from the Poisson model gave similar results as the ANOVA model which is that both the prophylaxis regimens had statistically significantly lower ABR than the first on-demand regimen, and the ABR of the prophylaxis regimens were not significantly different from each other.

Treatment Failure Post Hoc Analysis

A post hoc survival curve analysis was performed using the Kaplan-Meier technique comparing 100 IU/kg once-weekly and 50 IU/kg twice-weekly. Prophylaxis data (ie, individual data for spontaneous bleeds from the prophylaxis periods) for the two regimens were pooled from Study 400 and Study 1010, and failure for this analysis was defined as having two spontaneous joint bleeds during the prophylaxis regimen. If a second spontaneous joint bleed for a subject occurred during the regimen treatment period, the date of this bleed was used; otherwise, the subject was considered censored on the date of the end

of that regimen treatment period. Each prophylaxis period in Study 400 was approximately 4 months in duration, and approximately 12 months for the 100 IU/kg once-weekly period in Study 1010. Days were counted from the first prophylactic dose of the regimen until either the failure date or censoring date. Subjects from Study 400 with data for both prophylaxis regimens were included in both the 100 IU/kg once-weekly and 50 IU/kg twice-weekly regimen treatment periods.

The probability of failure by Day 60 and by Day 120 is reported for each regimen, and the null hypothesis of equal survivor functions for the two regimens was tested using the Chi-square (log-rank) test statistic.

Forty-three (43) of the 47 subjects randomised in Study 400 contributed data for the 50 IU/kg twice-weekly regimen. Data from 44 of the 47 subjects randomised in Study 400 and all 25 subjects from Study 1010 were pooled for a total of 69 subjects for the 100 IU/kg once-weekly regimen.

The probability of failure (ie, having 2 spontaneous joint bleeds) by Day 60 is 11.6% for the 100 IU/kg once-weekly regimen, and 7.0% for the 50 IU/kg twice-weekly regimen. By Day 120, the probability of failure is 14.6% for the 100 IU/kg once-weekly regimen, and 9.8% for the 50 IU/kg twice-weekly regimen.

Survival curve analysis of time from start of the regimen until second spontaneous joint bleed comparing 100 IU/kg once-weekly with 50 IU/kg twice-weekly using the Kaplan-Meier technique showed no significant difference between regimens ($p=0.42$, Chi-square [log-rank] test).

4.3.3. Discussion

The primary objective of this study 1010 was to demonstrate that a routine prophylaxis regimen of BeneFIX reduces the ABR compared to on-demand treatment, in subjects with moderately severe to severe haemophilia B. The secondary objective was to describe the safety and efficacy of BeneFIX when administered for prophylaxis at a dose of 100 IU/kg once weekly.

The prophylactic treatment regimen leads to statistically significant lower annualized bleed rates (ABR) compared to on-demand treatment. The applicant concludes that the primary efficacy endpoint of the study has been met. All sensitivity analyses supported the results of the primary endpoint and suggest that the significantly lower ABR in the prophylaxis period was not due to a seasonal effect. In addition, the mean ABR was lower in the prophylaxis period than in the on-demand period when summarized separately by bleed etiology (spontaneous and traumatic) and bleed location (joint, soft tissue/muscle, and other).

Nonetheless, the primary objective of comparing annual bleed rates (ABR) under on-demand versus prophylaxis-regimen is questioned: Clinical support for Extension of the dosing interval mainly requires proof of protection in the late phase of the treatment interval in severely affected haemophilia patients. ABR in an on-demand treatment setting mainly reflects bleeding-pattern of the respective population but does not serve as adequate comparator for a "new" prophylaxis regimen.

7 out of 25 (28%) patients experienced multiple spontaneous bleeding episodes within 72 hours of a previous prophylaxis infusion. In addition, the presented data show, that a considerable number of subjects (12/25, 48%) experienced bleeds after 4 or 5 days despite being on the proposed once-weekly prophylaxis regimen and received additional on-demand treatment.

Primary efficacy endpoint of study 400 was the Annualized Bleeding Rate (ABR). Both prophylaxis regimens showed better efficacy compared with the on-demand regimen: 35.1 annualized bleeds in the initial on-demand treatment period compared to 4.6 (100 IU/kg once weekly) and 2.6 (50 IU/kg twice weekly). Between the two prophylaxis regimens no statistically significant difference in the ABR was found. Thus the primary objective has been met. However, significance of this finding is questioned.

Secondary objectives in terms of patient-reported outcomes provided in part some results, but their clinical relevance is not further discussed at this place.

Factor IX levels (FIX:C) measured after administration of BeneFIX were dose proportional and the FIX recovery was similar after administration of both 50 IU/kg and 100 IU/kg.

Regarding efficacy of such high-dosage-regimen, a major concern derives from the selection of study population. Long-term prophylactic treatment with BeneFIX is only indicated in subjects with severe haemophilia B. In study 400, as verified by the FIX baseline levels (C0h) at the start of each of the two prophylaxis periods, more than 60% of the subjects had FIX:C >2%, indicating only moderate or mild haemophilia B. According to the Supportive Tables 15.53 and 15.54, only 7 out of 40 subjects ready to receive 50 IU/kg (17.5%) and 8 out of 42 subjects awaiting 100 IU/kg (19%) had a FIX activity <1%, which defines true severe haemophilia B.

According to the Listing 16.2.8.1.4, in study 1010, 5 out of 25 subjects (20%) had a FIX activity <1%.

It is therefore unknown, whether the newly proposed prophylactic regimen of 100 IU/kg once weekly would be able to provide sufficient FIX levels and protection from bleedings over the complete 7 days interval in subjects with severe haemophilia B, which might benefit from long-term prophylaxis.

In addition to that concern, no reliable trough level measurements of FIX activity are provided for the 100 IU/kg once weekly period. Blood samples for trough level assessments were taken any time after at least 72 hours after the last dose and are therefore meaningless for this treatment group with dosing intervals of 7 days.

Real trough levels 7 days after the previous and immediately before the next 100 IU/kg dose administration are considered to be relevant. It is thus unclear, whether a single 100 IU/kg infusion is able to substitute the lacking factor IX during the entire 7 days period between dosings.

4.4. Clinical Safety aspects

Study B1821010

Adverse Events

Overall, 24 out of 25 subjects (96.0%) experienced a total of 348 AEs (haemophilia-related and non-haemophilia-related).

Eleven subjects (44.0%) experienced a total of 95 haemophilia-related AEs .

Five subjects (20.0%) experienced a total of 6 SAEs.

There were no AEs that led to discontinuation from the study, no medically important events, and no deaths were reported.

Table 16: Overview of Adverse Events

Category	Number (%) of Subjects Experiencing Event(s)			Total Number of Events
	On-Demand N=25	Prophylaxis N=25	Total N=25	
Any adverse events	16 (64.0)	24 (96.0)	24 (96.0)	348
Treatment-emergent adverse event	16 (64.0)	24 (96.0)	24 (96.0)	325
Serious adverse events	1 (4.0)	4 (16.0)	5 (20.0)	6
Adverse events causing discontinuation from study	0	0	0	0
Medically important events	0	0	0	0
Deaths	0	0	0	0

Source: [Section 14.3](#), [Tables 14.3.1.1.1](#), [14.3.1.2](#), [14.3.1.3.1](#), [14.3.2.1](#), and [14.3.2.2.1](#), and [Appendix 16.2.7](#), [Listing 16.2.7.7](#)

Note: Subjects with adverse events that started in the on-demand treatment period and continued into the prophylaxis treatment period were only counted in the on-demand and total column summaries.

Twenty-four subjects experienced a total of 325 TEAEs.

Eleven subjects (44.0%) reported a total of 77 haemophilia-related TEAEs. The most commonly reported haemophilia-related TEAEs by SOC were in the Musculoskeletal and connective tissue disorders and were reported in 8 subjects (32.0%). The most commonly reported haemophilia-related TEAEs by preferred terms included Arthralgia in 6 subjects (24.0%) and Joint swelling in 5 subjects (20.0%). Local swelling (General disorders and administration site conditions SOC) was reported in 3 subjects (12.0%).

Table 17: Number (%) Subjects Reporting Treatment-Emergent Haemophilia-Related Adverse Events

System Organ Class Preferred Term	On-Demand N=25 n (%)	Prophylaxis N=25 n (%)	Total N=25 n (%)	Total Number of Events
Any Adverse Event	7 (28.0)	10 (40.0)	11 (44.0)	77
Musculoskeletal and connective tissue disorders	6 (24.0)	8 (32.0)	8 (32.0)	67
Arthralgia	5 (20.0)	5 (20.0)	6 (24.0)	26
Joint swelling	3 (12.0)	2 (8.0)	5 (20.0)	7
Arthritis	1 (4.0)	1 (4.0)	1 (4.0)	10
Bone pain	0	1 (4.0)	1 (4.0)	1
Joint range of motion decreased	1 (4.0)	1 (4.0)	1 (4.0)	16
Musculoskeletal pain	1 (4.0)	1 (4.0)	1 (4.0)	2
Neck pain	0	1 (4.0)	1 (4.0)	1
Pain in extremity	1 (4.0)	1 (4.0)	1 (4.0)	4
General disorders and administration site conditions ^a	1 (4.0)	4 (16.0)	4 (16.0)	6
Local swelling	1 (4.0)	3 (12.0)	3 (12.0)	5
Pain	0	1 (4.0)	1 (4.0)	1
Gastrointestinal disorders	0	1 (4.0)	1 (4.0)	2
Gingival bleeding	0	1 (4.0)	1 (4.0)	2
Renal and urinary disorders	1 (4.0)	0	1 (4.0)	1
Haematuria	1 (4.0)	0	1 (4.0)	1
Skin and subcutaneous tissue disorders	0	1 (4.0)	1 (4.0)	1
Skin warm	0	1 (4.0)	1 (4.0)	1

Source: Section 14.3, Table 14.3.1.3.2

n = Number of subjects reporting an event; N = Number of subjects in each treatment period

Note: MedDRA (version 17.0) coding dictionary applied. Subjects with adverse events that started in the on-demand treatment period and continued into the prophylaxis treatment period were only counted in the on-demand and total column summaries.

^aIn General disorders and administration site conditions SOC, the preferred term 'Oedema peripheral' which occurred in 2 subjects in the IA was re-coded to 'Local swelling' for the final analysis.

24 subjects (96.0%) reported 248 non-haemophilia TEAEs. The most commonly reported non-haemophilia-related TEAEs by SOC were in the Infections and infestations SOC in 16 subjects (64.0%), the Injury, poisoning and procedural complications SOC in 15 subjects (60.0%), and in the Nervous system disorders SOC in 10 subjects (40.0%). The most commonly reported preferred terms occurring in 5 or more subjects included Headache (9 subjects, 36.0%), Upper respiratory tract infection, Inappropriate schedule of drug administration, Toothache (6 subjects each, 24.0%), and Pharyngitis and Pyrexia (5 subjects each, 20.0%).

The number of subjects reporting non-haemophilia-related TEAEs by SOC in the prophylaxis period and

the on-demand period was similar except for the Injury, poisoning and procedural complications SOC which included study medication dosing/administration errors for subjects in the prophylaxis period only, and in the Nervous system disorders SOC where 9 subjects in the on-demand period and only 4 subjects in the prophylaxis period reported TEAEs.

Adverse Events in the Paediatric Population

The 5 paediatric subjects enrolled in the study experienced a total of 79 AEs. All 5 paediatric subjects experienced AEs in the Infections and infestations SOC with Upper respiratory tract infection being reported in the most subjects (4 subjects). Four paediatric subjects reported AEs in the Injury, poisoning and procedural complications SOC including events related to study medication errors occurring in 3 subjects and Head injury occurring in 2 subjects. In the Musculoskeletal and connective tissue disorders SOC,

20 events of Arthralgia were reported in 3 paediatric subjects.

Two paediatric subjects, Subject 10171002 and Subject 10261002, experienced SAEs of Varicella and Pain, respectively. Both SAEs were considered not related to study drug and the subjects recovered. See Section

Adverse Events Related to Study Medication

Three subjects experienced a total of 10 TEAEs considered related to the study drug by the investigator. Subject 10171001 experienced mild events of Malaise (1 event) and Throat irritation (4 events) during the on-demand period that resolved without treatment.

Subject 10261004 experienced Diabetes mellitus, Hyperlipidemia, and Periodontitis (2 events) during the prophylaxis period; all of which were considered mild in intensity and treated with concomitant medication. Subject 10351001 experienced a severe SAE of Blood pressure decreased which required treatment and was considered related to the study drug by the investigator.

Deaths, Serious Adverse Events, and Other Significant Adverse Events

No deaths were reported in this study.

Five subjects (20.0%) reported a total of 6 SAEs. Five of the 6 SAEs were considered not related to study drug and 1 SAE was considered related to study drug by the investigator.

Two of the SAEs (Varicella and Pain) occurred in pediatric subjects.

Development of FIX Inhibitor

Samples for FIX inhibitor were collected at Visits 1, 4, and 8.

None of the 25 subjects developed FIX inhibitor during the study as confirmed by local and central laboratory analysis.

Thrombogenicity

No thrombotic events were reported during the study.

Samples for assessing D-Dimer and TAT laboratory biomarkers for thrombosis were collected pre-dose and 30 minutes post-dose at Visit 2 and at the start of the prophylaxis period (Visit 4). Incremental changes in D-Dimer and TAT results observed in some subjects were not associated with any clinical thrombotic event or TEAE.

D-Dimer and TAT results were available for 11 subjects at Visit 2 and for 21 subjects at Visit 4. Test results are noted as "cancelled" or no data are listed for subjects who completed these visits before approval of

Protocol Amendment 1.

Study 3090A1-400-WW

The safety of BeneFIX was determined using the following assessments: monitoring of AEs, withdrawals due to AEs, concomitant medications, physical examinations, vital signs, and laboratory determinations.

No deaths were reported in the study; 1 subject discontinued treatment due to a serious adverse event (SAE) (worsening of left knee arthropathy and left knee replacement). A total of 7 SAEs were reported for 5 unique subjects. All of these SAEs were considered to be not related to BeneFIX by the investigator and the medical monitor.

Four (4) events of interest (Events with Special Circumstances [ESC]) were specifically monitored during the study: development of FIX inhibitors, potential allergic-type manifestations, thrombogenicity, and red blood cell (RBC) agglutination. These ESCs are listed in the BeneFIX Risk Management Plan and are monitored closely in all clinical studies conducted with BeneFIX. The investigators were trained to report ESC to the MAH in the same time frame as an SAE. There were no reports of ESC or other events associated with BeneFIX during this study.

Treatment-emergent AEs (TEAEs) occurring in $\geq 5\%$ of subjects during any treatment period are presented in Table 6. Thirty (30 [60%]) subjects reported at least 1 TEAE. The most frequently reported TEAEs within a treatment period were headache, arthralgia, pain, and infection. Headache was reported more frequently in subjects during the 100 IU/kg prophylaxis regimen. None of these TEAEs were assessed as related to BeneFIX by the investigator. Only 1 TEAE in Study 400-WW was assessed as related to BeneFIX by the investigator; 1 subject experienced a TEAE (injection site reaction [burning during injection]) that was reported in all 4 treatment periods and for nearly all injections; this TEAE was of mild severity, resolved without treatment. There were 4 subjects who reported a total of 8 TEAEs considered "severe." None of these events were considered related to

BeneFIX, none were reported during the 100 IU/kg prophylaxis regimen, and none required that the subjects discontinue participation in the study.

TEAEs reported in Study 400-WW are consistent with events previously reported in the BeneFIX annual reassessments and PSURs. The adverse reactions observed in Study 400-WW are also consistent with those described provided in the BeneFIX SmPC.

Table 18 BeneFIX Study 400-WW - Summary of Treatment-Emergent Adverse Events Reported in $\geq 5\%$ Subjects in Any Treatment Period – ITT Population

Body System ^a Adverse Event	BeneFIX Treatment				Total N = 50
	OD1 N = 50	100 IU/kg N = 44	50 IU/kg N = 44	OD2 N = 43	
Any Adverse Event	21 (42.0)	14 (31.8)	14 (31.8)	14 (32.6)	30 (60.0)
Body As A Whole					
Headache	3 (6.0)	6 (13.6)	2 (4.5)	2 (4.7)	8 (16.0)
Pain	2 (4.0)	1 (2.3)	3 (6.8)	1 (2.3)	5 (10.0)
Infection	1 (2.0)	3 (6.8)	1 (2.3)	1 (2.3)	4 (8.0)
Musculoskeletal System					
Arthralgia	5 (10.0)	4 (9.1)	2 (4.5)	2 (4.7)	6 (12.0)

a. Adverse events are presented with in descending order of the total population within body system.

Source: CSR table AE4-T-AE

Abbreviations: ITT = intent-to-treat; OD = on-demand

One or more episodes of headache were reported for 8 (16%) subjects during Study 3090A1- 400-WW. Headache was reported for 3 (6.0%) subjects during the first on-demand period, 6 (13.6%) subjects during prophylactic treatment with 100 IU once weekly, 2 (4.5%) subjects during prophylactic treatment with 50 IU twice weekly, and 2 subjects (4.7%) during the second on-demand period. By comparison, in Studies 302 and 304, in which the doses received were generally lower than 100 IU/kg, the overall frequency of headache was 26% and 29%, respectively.

Infusion rates were not recorded for Study 3090A1-400-WW, and although dates and times of infusion were recorded, only the dates of treatment-emergent adverse events (TEAEs) were recorded. For 4 subjects, a single instance of headache was reported on a day when there was no infusion of FIX; for 2 other subjects, multiple instances of headache were reported, and the start dates for headache were not associated with days of infusions. Multiple instances of headache were reported for 2 additional subjects, of which 1 report for each subject occurred on the day of an infusion.

All cases of headache were mild, none led to withdrawal from the study, none were judged by the investigator to be related to treatment, and all resolved. Headache is an expected adverse event for BeneFIX, which is listed in the product labeling as an uncommon ($\geq 0.1\%$ to $\leq 1\%$) adverse reaction, and the incidence of headache in Study 400 was not greater than in prior studies of BeneFIX (eg, 304) in which the doses were generally lower than those in Study 400.

Assessor's comment

Except for headache, no differences between the treatment groups became apparent from the numbers of subjects experiencing Treatment Emergent Adverse Events (TEAE) (CSR Table 15.42, summarized in Table 6 above). Since this is a cross-over study, all subjects went through each of the four treatment periods. It is therefore of note, that 13.6% of subjects experienced headache while on BeneFIX 100 IU/kg prophylaxis compared to only 4.5% of subjects while in the 50IU/kg twice weekly prophylaxis period and 6.0% / 4.7% (on-demand). The MAH provided details on the events of headache. No timely relation to the infusion of BeneFIX was observed.

The monitoring of events of interest or "Events with Special Circumstances" (ESC) is acknowledged: development of FIX inhibitors, hypersensitivity reactions, thrombotic events, and red blood cell agglutination. No such event was reported.

Thrombotic Events and Laboratory Markers of Activation of Blood Coagulation

Laboratory markers of activation of blood coagulation were not measured in Study 400.

However in Study 1010 and several other studies, BeneFIX doses of approximately 100 IU/kg or higher were administered and coagulation markers were measured in these studies.

In clinical studies of BeneFIX, 110 subjects received a total of 2973 infusions of BeneFIX that were approximately 100 IU/kg or higher. The number of subjects in each study and the number of infusions received are summarised in Table 19.

Table 19 Summary of Subjects Receiving at Least One Dose of Approximately 100 IU/kg
No. Subjects With Coagulation Marker Data

Study	No. Subjects	No. Infusions	TAT	D-dimer	F1+2	FPA
301	8	71	8	8	8	NA
302	7	28	7	7	7	NA
304	9	123	9	9	9	NA
400	45	811	NA	NA	NA	NA
1010	25	1923	21	21	NA	NA
Surgery ^a	16	17	NA	NA	6	6
Total	110	2973	45	45	30	6

Abbreviations: F1+2=prothrombin fragment 1 + 2; FPA=fibrinopeptide A; NA=not applicable/not done; No.=number; TAT=thrombin-antithrombin III.

a. "Surgery" includes subjects from the surgery study C9417-21 and patients needing surgery in Studies C9407-21 and C9408-21.

No thrombotic events were reported in any of the 110 subjects receiving approximately 100 IU/kg or higher in these studies.

4.4.1. Discussion

Four areas of events of interest necessitating special vigilance had been identified for BeneFIX: development of FIX inhibitors, potential allergic-type manifestations, thrombogenicity, and red blood cell (RBC) agglutination. No such events were reported during the course of this clinical study.

However, doubling the single dose of BeneFIX to 100 IU/kg as proposed with this application theoretically increases especially the thrombogenic risk. .

In order to investigate a potentially increased thrombogenic risk in patients with severe haemophilia B after receiving BeneFIX 100 IU/kg , intravascular coagulation markers were measured in study 1010, but not in study 400.

The MAH reported that in clinical studies with BeneFIX, 85 subjects received a total of 1050 infusions of BeneFIX of approximately 100 IU/kg or higher. In 30 of these subjects receiving 230 infusions of approximately 100 IU/kg or greater coagulation marker tests were performed without clinically significant differences to baseline values.

High levels of factor IX increase the risk of venous thrombosis. Van Hylckama Vlieg et al [1] found a 2- to 3-fold increased risk for individuals who have factor IX levels above 129 IU/dL compared with individuals having factor IX levels below this cutoff. When administering rFIX 100 IU/kg, FIX levels in this range have been found in the present studies. Although these high levels would only be transient and rapidly declining, the thrombogenic risk may be real. This should be considered when proposing such dosing for a long-term prophylactic treatment.

In addition, the results of the investigations of Ameri et al [2] should be considered, who demonstrated a close association between elevated circulatory factor IX levels in mice with thrombosis as well as myocardial fibrosis.

At the point of current investigation, thrombogenic risk of a high-dose (100 IU/kg) prophylaxis regimen has not been addressed although it is considered to be relevant at least in patients at risk according to current scientific publications. Safety data in patients > 65 years – representing a respective risk population are missing. The possible impact of missing (safety) data in patients >65 years of age – who are at higher risk for thromboembolic events – in view of the proposed higher treatment doses should be discussed.

Since BeneFIX is dosed in relation to body weight, overweight subjects would be exposed to extremely high single doses of factor IX, e.g. up to 14,000 IU in the present study. For such high doses, there is little clinical experience. The MAH is asked to discuss theoretical risks, mainly thrombogenicity, when administering such high doses of factor IX.

It is further noted, that headache occurred more frequently during the 100 IU/kg prophylaxis period compared to the other treatment periods. The MAH provided details on the events of headache. No timely relation to the infusion of BeneFIX was observed.

4.5. Risk management plan

The MAH submitted an updated RMP version with this application.

☒ The content of the updated RMP proposed by the MAH contains the following elements: the MAH performed minor editorial changes across the RMP document. He further took opportunity to update patient exposure and safety data:

Safety concerns

Table 20: Summary of the Safety Concerns

Summary of Safety Concerns	
Important identified risks	Inhibitor development Less than expected therapeutic effect (LETE) Allergic reactions Thrombogenicity
Important potential risks	Medication errors/product confusion
Missing information	Risks in paediatric patients Risks in elderly patients ≥ 65 years of age Risks in women, including pregnant and lactating women Risks in patients with organ system impairment (<u>eg.</u> hepatic or renal)

Considering the data in the safety specification, the safety concerns listed by the MAH are appropriate.

Assessor's comment

Off- note: In response to the last PSUR assessment report (PSUR22) the MAH agreed to add the following information into "missing information" section:

"Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent used in aPTT potency tests".

Pharmacovigilance plan

In contrast to the previous RMP version (version 8) the MAH has stated that no studies are ongoing or planned (category 1-3) in the post-authorization PhV development plan.

Table 21 Table of Completed Studies / Activities from the Pharmacovigilance Plan

Study Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date of Submission of Final Study Report
3090X1-4403, Post marketing surveillance to observe safety and efficacy of BeneFIX in patients with haemophilia B.	This non- interventional study in Korean patients assessed safety and efficacy of original or reformulated BeneFIX during usual care setting with the following overall objectives: Detect SAEs and Adverse Drug Reactions (ADRs), detect unexpected AEs and ADRs that were not included in precaution of local product document, observe already known ADRs, observe nonserious ADRs, detect other information on safety and efficacy.	Capture all adverse events (AEs) with a causal relationship with BeneFIX; Serious AEs (SAEs) or unexpected non-serious AEs with a causal relationship with BeneFIX; all events of particular interest and all other notifiable information; subjective evaluation of safety of the patient at each visit	Completed	Final CSR dated 14 November 2012 was submitted to EMA on 4 December 2012.
3090X1-4409 (B1821007), Prospective observational study of reformulated BeneFIX (France)	Primary: Collect safety data on reformulated BeneFIX used under routine clinical practice conditions in France. Secondary: Collect data on the clinical course of patients treated with reformulated BeneFIX and on the ease of use of reformulated BeneFIX.	Capture all adverse events (AEs) with a causal relationship with BeneFIX; Serious AEs (SAEs) or unexpected non-serious AEs with a causal relationship with BeneFIX; all events of particular interest and all other notifiable information; subjective evaluation of safety of the patient at each visit	Completed, CSR not yet available	A final CSR will be available in April 2015.

B1821010 Multicenter, open-label study to compare on-demand treatment to a prophylaxis regimen of NONACOG-ALFA (BeneFIX) in subjects with moderately severe to severe haemophilia B (FIX:C ≤2%)	Primary: Demonstrate that a prophylaxis regimen of BeneFIX reduces the Annualized Bleeding Rate (ABR) compared to on-demand treatment in subjects with moderately-severe to severe haemophilia B. Secondary: Describe the safety and efficacy of BeneFIX when administered for prophylaxis at a dose of 100 IU/kg once weekly.	Medically important events.	Completed	Final CSR 18 September 2014
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*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Assessor's comment

Agreed

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures

Assessor's comment

Agreed

Risk minimisation measures

5.3 Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Inhibitor development	Summary of Product Characteristics (SmPC) and Package Leaflet	None
Less than expected therapeutic effect (LETE)	SmPC and Package Leaflet	None
Allergic reactions	SmPC and Package Leaflet	None
Thrombogenicity	SmPC and Package Leaflet	None
Medication errors /product confusion	SmPC and Package Leaflet and by distinctive packaging.	None
Risks in: Paediatric patients	SmPC and Package Leaflet	None

The proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Assessor's comment

Agreed

Elements for a public summary of the RMP

The MAH performed minor editorial changes in all parts of the RMP. In addition tables in part 6, section 6.2.6 and 6.2.7. "Planned Post Authorisation Development Plan" have been amended according to the changes in part III, section 3.5 "Summary of the Pharmacovigilance Plan".

The summary of updates to the RMP over time has been updated appropriately.

Version	Date	Safety Concerns	Comment
9.0	20 February 2015	Updated to include data from completed Study B1821010.	Four ongoing studies previously listed as Additional PhV activities were removed, since these studies are not PASS or specific safety studies for the EU. These studies will continue to monitor safety data and assess risks.

Annexes

The annexes have been updated appropriately regarding this type II variation procedure.

Assessor's comment

Off-note: In response to the last PSUR assessment report (PSUR22) the MAH agreed to update the BeneFIX SmPC to the new version of the Core-SmPC Guideline, effective on 01 April 2015 by adding the following warning in section 4.2:

"When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. This is of importance particularly when changing the laboratory and/or reagents used in the assay."

The amendment to SmPC by a type II variation was submitted on 10April 2015.

Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

4.6. Changes to the Product Information

The MAH proposed changes to the Product Information (PI) in section 4.2, 5.1 and 5.2 In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

5. Request for supplementary information

Based on the review of the data on safety and efficacy within this procedure, this type II variation **is not approvable** since “major objections” have been identified, which preclude a recommendation for this variation at the present time. The major objections relate to pharmacokinetics and efficacy and are provided below.

In addition, satisfactory answers must be given to the “other concerns”.

5.1. Major objections

Clinical aspects

Pharmacokinetics

1. The lack of meaningful PK-data is of major concern, since they are considered to be essential in order to support the claimed dosage regimen. The validity of the final population PK model is questioned, because of higher values observed from present studies in comparison to simulated values gained from the final model. The lack of data on in-patient trough levels for those on 100 IU/kg once a week combined with the experienced bleeds after 4 or 5 days all strongly suggest that once weekly posology is inadequate.

Especially in patients with severe haemophilia B and/or high bleeding tendency for whom long-term prophylaxis might be indicated, the weekly prophylaxis regimen is thus not supported by clinical data. A treatment recommendation cannot be given and it should be removed from the SmPC, section 4.2 Posology and method of administration to section.

Clinical efficacy

2. The primary objective (study 1010) of comparing annual bleed rates (ABR) under on-demand versus prophylaxis-regimen is questioned: Clinical support for Extension of the dosing interval mainly requires proof of protection in the late phase of the treatment interval in severely affected haemophilia patients. ABR in an on-demand treatment setting mainly reflects bleeding-pattern of the respective population but does not serve as adequate comparator for the “new” prophylaxis regimen.
3. In study 400, according to their FIX:C levels, more than 60% of the subjects were at the start of their prophylactic treatment periods in a situation of moderate or mild haemophilia B, in the face of a general sufficient washout interval. No factor IX activity was measured at baseline. Concerns relate to the choice of study population, to the efficacy analysis population, and to the duration of study treatment.

Additionally, in study 1010 only 20% of subjects had a FIX activity <1%, which defines true severe haemophilia B and 48% of subjects experienced spontaneous bleeds after 4 or 5 days.

The MAH is asked to comment on the concern, that efficacy has not been demonstrated in a population with true severe haemophilia B for which long term prophylaxis with BeneFIX would be indicated.

Other concerns

Clinical aspects

Clinical safety

4. Doubling the single dose of BeneFIX to 100 IU/kg as proposed with this application theoretically increases especially the thrombogenic risk.
 - a) It should also be considered, that BeneFIX is dosed in relation to body weight and overweight subjects would be exposed to extremely high single doses of factor IX. For such high doses, there is little clinical experience. Obesity itself serves as a risk-factor for thrombosis. The MAH is asked to discuss the theoretical thrombogenic risk when administering such high doses of factor IX.
 - b) The possible impact of missing (safety) data in patients >65 years of age – who are at higher risk for thromboembolic events – in view of the proposed higher treatment doses should be discussed.

SmPC

The details of the SmPC wording will be performed depending on the further approach.

6. Assessment of the responses to the request for supplementary information

6.1. Major objections

Clinical aspects

Pharmacokinetics

Question 1

The lack of meaningful PK-data is of major concern, since they are considered to be essential in order to support the claimed dosage regimen. The validity of the final population PK model is questioned, because of higher values observed from present studies in comparison to simulated values gained from the final model. The lack of data on in-patient trough levels for those on 100 IU/kg once a week combined with the experienced bleeds after 4 or 5 days all strongly suggest that once weekly posology is inadequate.

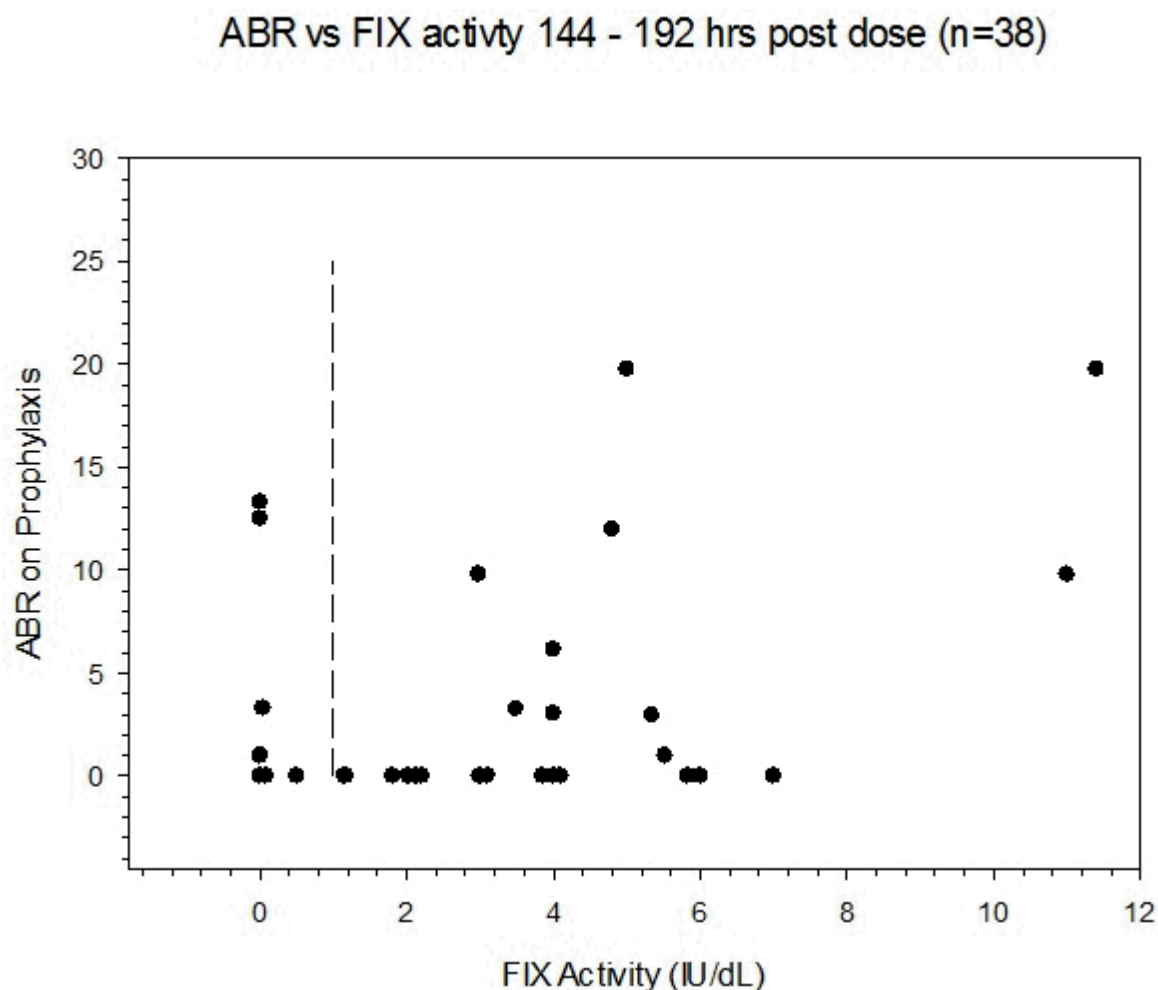
Especially in patients with severe haemophilia B and/or high bleeding tendency for whom long-term prophylaxis might be indicated, the weekly prophylaxis regimen is thus not supported by clinical data. A treatment recommendation cannot be given and it should be removed from the SmPC, section 4.2 Posology and method of administration to section.

Summary of the MAH's response

The MAH agrees that there are no new pharmacokinetics (PK) data available for factor IX (FIX) activity after the administration of BeneFIX 100 IU/kg once weekly dose. However here, the MAH is presenting new additional analysis of existing PK and pharmacodynamics (PD) data that are considered supportive of the proposed dosing regimen of 100 IU/kg once weekly.

The new post hoc analysis examines the relationship between residual FIX activity observed approximately 1 week (± 1 day) after administration of BeneFIX 100 IU/kg once weekly during Study 3090A1-400-WW and Study B1821010. As shown in Figure 1 among the 38 subjects with a FIX activity value collected at the time point of interest, the large majority, 76% (29/38) had FIX activity levels $> 1\%$. There was no apparent relationship between the level of residual FIX activity measured and the annualized bleeding rate (ABR) (Figure 1). Extravascular FIX binding has been proposed as one hypothesis for the discrepancy between PK and PD (Gui, 2002). Moreover, clinical experts in the field consider that PK is a somewhat less influential factor when determining an appropriate dosing regimen in haemophilia B. Berntorp et al, (2014) state that the “Clinical assessment of the frequency and severity of bleeds remain an important measure of the efficacy of treatment for haemophilia B and the role of PK-guided therapy remains to be established.”

Figure 1. Annualized Bleeding Rate vs Residual FIX Activity Measured Between 1



Source: lab1_rec_pre_pool

Note: Broken vertical line indicates 1% FIX activity (IU/dL).

In response to the second part of the question, the following should be considered. The development of the population PK model had two objectives. The first was to update a previously developed model, assessing the role of body weight among other covariates as being significant in explaining intersubject variability. The second objective was to simulate the study design of the studies presented above and compare the observations to what was predicted by the model. The first objective was achieved. Weight was identified as a significant covariate and the key parameters (clearance and volume of distribution) were consistent with previous analyses of the same data. Further, the population PK model was assessed for adequacy or goodness using current industry standards. There was no overt bias observed in the model and the model performance appeared to be adequate (CHMP, 2007).

It was in the evaluation of data collected in the present studies that, as noted, there was bias between the predictions from the model and the observations. Possible explanations for the biases were presented, including the fact that the FIX recovery observed in Study 3090A1- 400-WW was higher than in any other BeneFIX study and the sampling times post dose in Study B1821010 were longer than in other BeneFIX studies. Work is ongoing to understand the potential impact of including these data in the development of a model, but the conclusions from the model itself, the importance of weight on PK parameters, remain valid.

Post hoc stepwise logistic regression analyses have been conducted by the MAH in order to evaluate potential clinical factors that may be used to predict the response to treatment with BeneFIX 100 IU/kg once-weekly prophylaxis. Data from Studies 3090A1-400-WW and B1821010 were pooled, and two definitions of a responder were investigated. Using the first definition, in which a responder was defined as a subject with no spontaneous bleeds on the BeneFIX 100 IU/kg once-weekly prophylaxis regimen, yielded a model containing the subject's spontaneous annualised bleed rate (sABR) during the on-demand (OD) period as a predictor, with an estimated cut off point of 9.21 sABR during OD. A subject with sABR $\leq$ 9.21 during OD would likely 'respond' (ie, have no spontaneous bleeds) on this prophylaxis regimen. When a responder was defined as a subject with $\leq$ 3 sABR on this prophylaxis regimen, the model was very similar, and the estimated cut off was 18.3 sABR during OD. Based on the results of these models, the sABR during OD was associated with outcome and could potentially be used to predict which patients will respond. Targeting these cut off values of the sABR during OD could be considered in determining patients appropriate for prophylaxis treatment with BeneFIX 100 IU/kg once weekly.

Nijdam et al, (2014) recommend starting prophylaxis treatment with one to two infusions per week, and then increasing the regimen according to the bleeding tendencies of the patient. In addition, the MAH believes that those patients with poor venous access, or who are practically challenged adhering to a twice-weekly regimen, would benefit from a once weekly posology. Furthermore the MAH believes that the opportunity to administer BeneFIX once weekly (with the subsequent reduction in the number of infusions required per annum) would provide a significant advancement in the care and quality of life for patients with haemophilia B.

The MAH would like to propose wording in the Summary of Product Characteristics (SmPC) to indicate that the regimen could be of value for some patients that would require a decreased dosing frequency.

Originally submitted wording:

BeneFIX may be administered for long term prophylaxis against bleeding in patients with severe haemophilia B. In a clinical study for routine secondary prophylaxis the average dose for previously treated patients (PTP) was 40 IU/kg (range 13 to 78 IU/kg) at intervals of 3 to 4 days. In other clinical studies in moderately severe to severe haemophilia B (FIX:C $\leq$ 2%) PTPs, BeneFIX was administered as 100 IU/kg once weekly (see section 5.1).

Amended proposal:

BeneFIX may be administered for long term prophylaxis against bleeding in patients with severe haemophilia B. In a clinical study for routine secondary prophylaxis the average dose for previously treated patients (PTP) was 40 IU/kg (range 13 to 78 IU/kg) at intervals of 3 to 4 days.

In other clinical studies BeneFIX was administered as 100 IU/kg once weekly, which may be an option for some patients (see section 5.1).

Note that the statement 'In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary' was added in type II variation II-0133 with positive opinion on 23 July 2015.

Assessment of the MAH's response

There are no new pharmacokinetics (PK) data available for factor IX (FIX) activity after the administration of BeneFIX 100 IU/kg once weekly dose.

The MAH argues that efficacy of the 100 IU/kg once weekly prophylactic regimen would have been demonstrated, being better than on-demand treatment and comparable to the approved 50 IU/kg twice weekly prophylactic regimen. Demonstration of efficacy would overcome the necessity to investigate pharmacokinetics and that PK would be a somewhat less influential factor when determining an appropriate dosing regimen in haemophilia B. This is no acceptable profound scientific approach.

The MAH refers to a publication of Berntorp et al, (2014). However, the same publication states that “PK parameters are good surrogates for clinical efficacy and therefore PK should be used in haemophilia when dosing is determined. This is the only way to introduce evidence-based prophylaxis...”

This underlines the importance of PK which is mentioned and requested in the current “Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products” (21 July 2011 EMA/CHMP/BPWP/144552/2009)

The direct aim of a long-term prophylactic factor IX replacement therapy in deficient patients is to maintain protective factor IX levels. Secondary to this effect, a reduction of bleedings can be expected. Measurement of factor IX concentration in plasma is therefore the most direct and objective surrogate-parameter of a treatment effect.

Moreover, the final population PK model is still questioned. There was bias between the predictions from the model and the observations. The applicant attributes this bias to possible study differences (i.e. differences in included subjects between studies 400 & 1010), but further investigations, taking study effects for studies 400 and 1010 respectively into account, were not performed. Manolis et al, (2009) state that “the use of modelling and simulation could provide an additional degree of evidence, but is based on assumptions and, as such, should be supported by experimental data. It cannot and should not be used to replace data from well-conducted studies as primary degree of evidence.”

Meaningful PK-data containing maximum- and trough-levels in the late phase of the treatment –interval (measured values in respective patients) are considered to be essential. The MAH should provide results of additional long-term PK investigations regarding the FIX activity following BeneFIX administration.

Therefore, a statement in the SmPC regarding a weekly treatment regimen, as proposed by the applicant under section 4.2 Posology and method of administration cannot be endorsed.

Conclusion

Point not solved.

The lack of meaningful PK-data remains as a major concern, since they are considered to be essential in order to support the claimed dosage regimen. The lack of data on in-patient trough levels for those on 100 IU/kg once a week combined with the experienced bleeds after 4 or 5 days all strongly suggest that once weekly posology is inadequate to be a general SmPC recommendation.

Clinical efficacy

Question 2

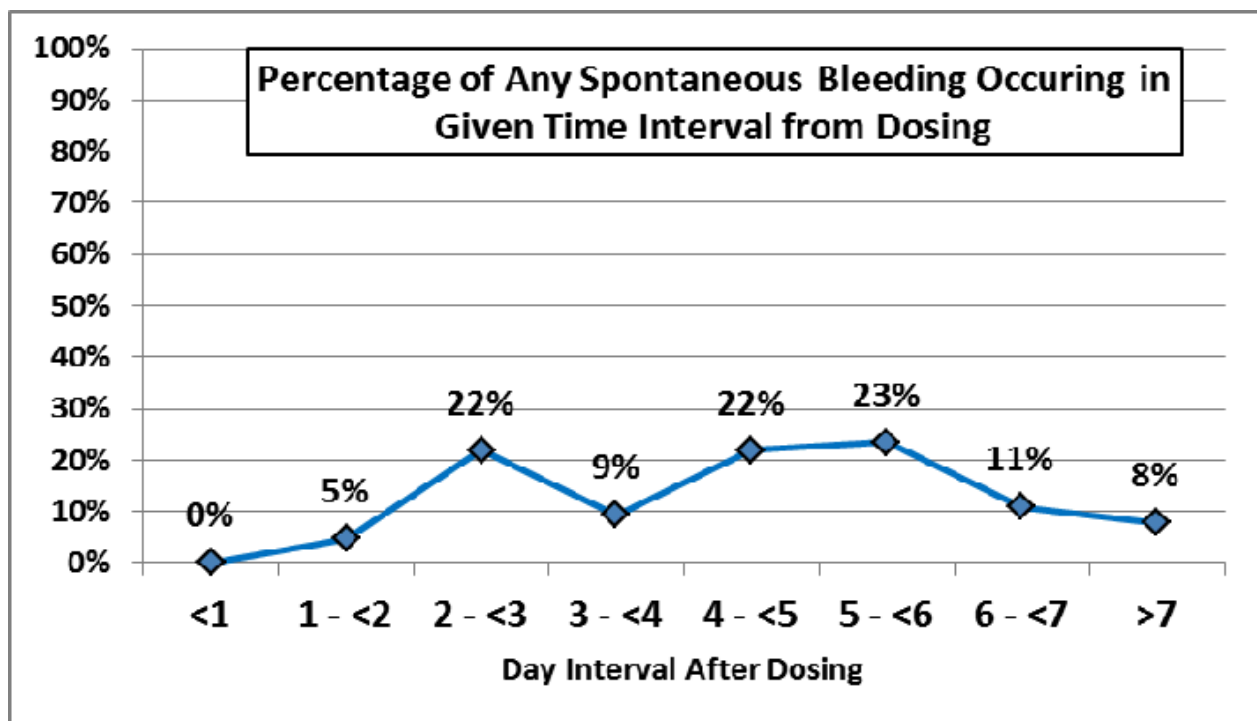
The primary objective (study 1010) of comparing annual bleed rates (ABR) under on-demand versus prophylaxis-regimen is questioned: Clinical support for Extension of the dosing interval mainly requires proof of protection in the late phase of the treatment interval in severely affected haemophilia patients. ABR in an on-demand treatment setting mainly reflects bleeding-pattern of the respective population but does not serve as adequate comparator for the “new” prophylaxis regimen.

Summary of the MAH's response

The BeneFIX 100 IU/kg once-weekly prophylaxis regimen has been evaluated in comparison to a more frequent prophylaxis regimen and against on-demand treatment. It is important to note the consistent

efficacy shown in Study B1821010, a pivotal, prospective, 52-week trial of BeneFIX 100 IU/kg once weekly where 48% (12/25) of subjects experienced no spontaneous bleeds. Similarly, 48% of subjects experienced no traumatic bleeds while 52% (13/25) experienced no joint bleeds and 84% (21/25) experienced no soft tissue or muscle bleeds. Spontaneous bleeds with the once-weekly prophylaxis regimen occurred at varying daily rates and did not show a pattern with respect to timing post-dose (Figure 2), (Tortella et al, 2015). The efficacy of the BeneFIX 100 IU/kg once-weekly regimen has been published (Study 3090A1-400-WW, Valentino et al, 2014), and presented at international scientific meetings (Kavakli et al, 2014), therefore the MAH is proposing that this be reflected in the posology.

Figure 2. Plot of Spontaneous Bleed Rates versus Timing Post-Dose with the BeneFIX Once-weekly Prophylaxis Regimen.

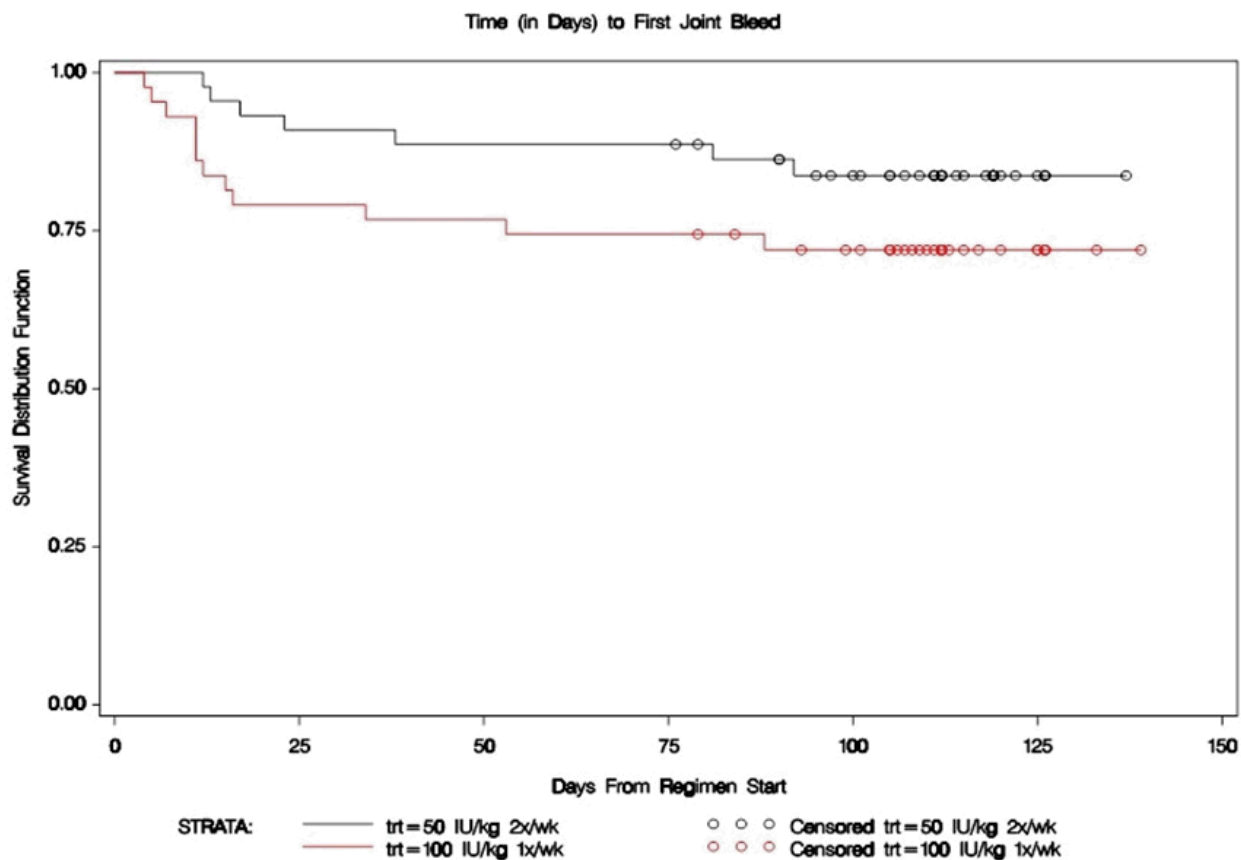


Source: Tortella et al, 2015

The BeneFIX once-weekly prophylaxis program was initiated in 2007, with Study 3090A1-400-WW (Study 400). The purpose of Study 400 was to evaluate the safety and efficacy of 2 BeneFIX prophylaxis regimens (50 IU/kg twice weekly and 100 IU/kg once weekly). In this study, the efficacy of the once-weekly prophylaxis regimen was superior to on-demand treatment with respect to the ABR, and was not different when compared with the twice weekly prophylaxis regimen.

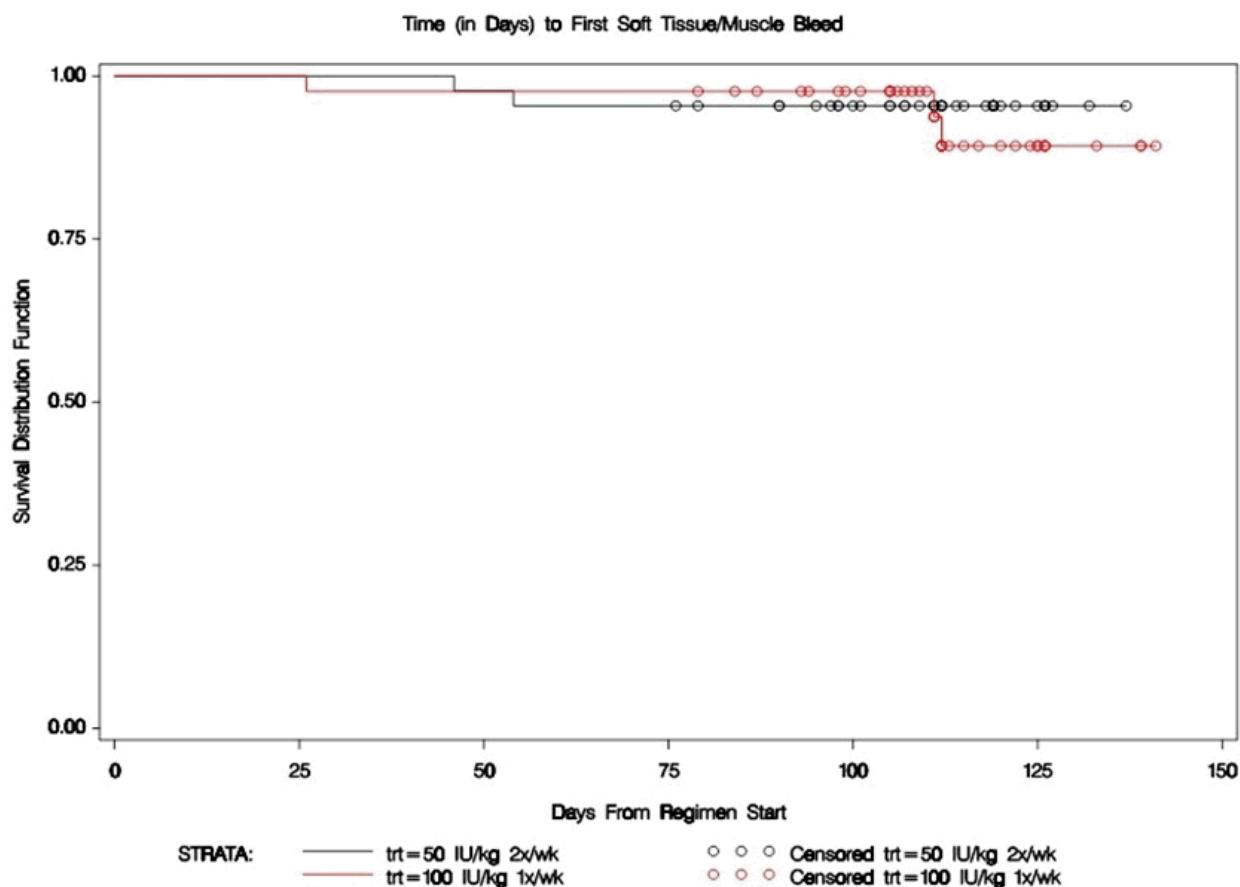
A post-hoc analysis of Study 400 was performed with the objective to evaluate the treatment failure (time until first spontaneous bleed) of both prophylaxis regimens. Survival curve analysis of time from start of regimen to first spontaneous bleed comparing 100 IU/kg once weekly with 50 IU/kg twice weekly using the Kaplan-Meier technique showed no significant difference in the timing or extent of either type of treatment failure. No statistical differences (Chi-squared [log-rank] analysis) were observed between the two regimens for both, joint bleeds ($p=0.14$), (Figure 3) and soft tissue/muscle bleeds ($p=0.61$), (Figure 4).

Figure 3. Comparison of BeneFIX 50 IU/kg (twice weekly) and 100 IU/kg (once weekly) Kaplan-Meier Plot, Time to First Joint Bleed (Study 3090A1-400- WW, n= 47)



Source: Rendo et al, 2013.

Figure 4. Comparison of BeneFIX 50 IU/kg (twice weekly) and 100 IU/kg (once weekly) Kaplan-Meier Plot, Time to First Soft Tissue/Muscle Bleed (Study 3090A1-400-WW, n=47)



The safety profile was similar across both doses (50 IU/kg twice weekly and 100 IU/kg once weekly); there was no impact on tolerability due to the increased dose (100 IU/kg once weekly). Based on these results, the 100 IU/kg once-weekly prophylaxis regimen for Study B1821010 was selected, based on the patient's convenience due to the reduction of the infusions. The MAH has conducted a confirmatory pivotal study, Study B1821010, that compared the safety and efficacy of a once-weekly prophylaxis (100 IU/kg) regimen versus an on-demand treatment regimen. Study B1821010 demonstrated a significant reduction of the ABR with 100 IU/kg once-weekly continuous prophylaxis in comparison to the on demand treatment. Studies 400 and B1821010 have reported a similar ABR rate with 100 IU/kg once-weekly continuous prophylaxis. The ability to dose at extended, weekly intervals is generally considered by physicians and patients to be a significant medical advancement in the treatment of haemophilia.

The once-weekly regimen becomes more meaningful in the context of the recently reported 33.8 hour half-life (geometric mean) for BeneFIX (Powell et al, 2013). Preclinical studies suggest the presence of extravascular factor IX bound to endothelial cells (Gui et al, 2002).

Assessment of the MAH's response

In study 1010, the primary objective of comparing annual bleed rates (ABR) under on-demand versus prophylaxis-regimen is questioned, because ABR in an on-demand treatment does not serve as adequate comparator for the "new" prophylaxis regimen.

The MAH stated that based on the results of study 400, the 100 IU/kg once-weekly prophylaxis regimen for Study1010 was selected, based on the patient's convenience due to the reduction of the infusions.

In study 400, both prophylactic treatment regimens (50IU/kg twice weekly and 100 IU/kg once weekly) lead to statistically significant lower annualized bleed rates (ABR) compared to on-demand treatment. There is no statistically significant difference in ABR between the 50 IU/kg twice weekly and the 100 IU/kg once weekly prophylactic schedule. The applicant concludes that the primary efficacy endpoint of the study has been met. But the duration of 16 weeks with the newly proposed dose regimen is of concern. According to the 'Guideline on clinical investigation of recombinant and human plasma-derived factor IX products' (EMA/CHMP/BPWP/144552/2009), for the assessment of clinical efficacy of factor IX in long-term prophylaxis, patients should be treated for 6 months and assessed for bleeding episodes, bleeding intervals and number of treatments.

Moreover, in study 400 efficacy has not been demonstrated in a population with true severe haemophilia B. (see MO 3)

Half-life was not determined, neither in study 400 nor in study 1010, but anticipated as being approximately 18 hours (results of earlier studies of BeneFIX). The MAH refers to a study of Powell et al, which published a FIX:C half-life of 33 hours after BeneFIX administration. A subgroup of 22 participants in this study completed a baseline pharmacokinetic assessment. It is important to point out that the terminal half-life was 33.8 hours and the half-life, calculated on the basis of the traditional 48-hour pharmacokinetic sampling schedule, was 17.04 hours (95% CI, 15.89 to 18.26), which is similar to previously reported 48-hour-data. The time to reach a factor IX level of 1 IU/dL (1%) was 5.1 days (95% CI, 4.6 to 5.7). Therefore, these data do not support an addition of a once-weekly 100 IU/kg prophylaxis regimen. In study 400 mean peak values of 49.9 IU/dL (after infusion of 50 IU/kg) and 91.5 IU/dL (after infusion of 100 IU/kg) were found. With an anticipated half-life of 18 hours reported for BeneFIX it is assumed that FIX levels return to pre-infusion levels after 72 hours.

Summarizing, demonstration of efficacy in the long-term prophylaxis with BeneFIX 100 IU/kg once weekly is not regarded sufficient. In study 400, concerns relate to the choice of study population, to the efficacy analysis population, and to the duration of study treatment. Therefore, study 400 can only be used as support and cannot replace an adequate study design in study 1010.

Conclusion

Point not solved.

Question 3

In study 400, according to their FIX:C levels, more than 60% of the subjects were at the start of their prophylactic treatment periods in a situation of moderate or mild haemophilia B, in the face of a general sufficient washout interval. No factor IX activity was measured at baseline. Concerns relate to the choice of study population, to the efficacy analysis population, and to the duration of study treatment.

Additionally, in study 1010 only 20% of subjects had a FIX activity <1%, which defines true severe haemophilia B and 48% of subjects experienced spontaneous bleeds after 4 or 5 days.

The MAH is asked to comment on the concern, that efficacy has not been demonstrated in a population with true severe haemophilia B for which long term prophylaxis with BeneFIX would be indicated.

Summary of the MAH's response

Inadequate washout was a potential issue in clearly identifying the severity of haemophilia in the subjects enrolled in Study 3090A1-400-WW (Study 400). At the time of the study conduct, the longer half-life of

FIX activity (33 hours), described by Powell et al, (2013) after BeneFIX administration was not appreciated. Subjects included in Study 400 could be moderately severe (FIX activity $\leq 2\%$) or severe (FIX activity $\leq 1\%$). Although it would be more rigorous to demonstrate this prior to inclusion in the study, any observation of FIX activity $\leq 2\%$ would be evidence that these subjects were appropriately enrolled. Per protocol, FIX activity was measured on 6 scheduled occasions over the duration of the study, before and after each recovery dose, and twice during the prophylaxis treatment, at least 72 hours after a previous dose. All of the available FIX activity data were examined and the lowest activity (ie, the lowest observation for each subject), along with the testing occasion, are shown below in Table 1 (Study 400) and Table 2 (Study B1821010 or Study 1010). Since FIX activity was evaluated by local laboratories, the reported precision varied. Twenty-eight of 45 subjects (62%) had FIX activity of severe or moderately severe, $\leq 2\%$.

Table 1. Lowest Individual FIX Activity for Subjects in Study 3090A1-400-WW

Subject Number	FIX activity (IU/dL)	Test
000101	3	Pre-50 IU/kg
000102	2	Pre-100 IU/kg
000302	3	Pre-50 IU/kg
000303	4	Pre-100 IU/kg
000304	3	Pre-50 IU/kg
000305	2	Pre-50 IU/kg
001101	0.04	Pre-100 IU/kg
001501	2	Pre-50 IU/kg
001504	2	Pre-100 IU/kg

001601	0.3	50 IU/kg trough
001602	0.8	Pre-100 IU/kg
001701	1	Pre-100 IU/kg
001801	2.2	Pre-100 IU/kg
001802	5.4	Pre-50 IU/kg
001807	1.7	Pre-100 IU/kg
001808	5.6	Pre-50 IU/kg
001809	1.7	Pre-50 IU/kg
001901	3.1	100 IU/kg trough
001902	2.6	50 IU/kg trough
001903	2.3	100 IU/kg trough
001904	1.4	Pre-100 IU/kg
001905	0.95	Pre-50 IU/kg
001906	2	Pre-100 IU/kg
002001	7	Pre-50 IU/kg
002002	9	Pre-50 IU/kg
002004	5	Pre-50 IU/kg
002301	0.58	Pre-50 IU/kg
002302	0.37	Pre-50 IU/kg
002303	0.19	100 IU/kg trough
002304	0.08	100 IU/kg trough
002305	0.49	Pre-50 IU/kg
002306	0.95	Pre-100 IU/kg
002307	2.61	Pre-100 IU/kg
002401	3	Pre-50 IU/kg
002502	1	Pre-50 IU/kg
002701	4	100 IU/kg trough

002801	0	Pre-50 IU/kg
002802	0	Pre-100 IU/kg
002901	1.3	Pre-100 IU/kg
003201	2	Pre-50 IU/kg
003401	5	Pre-50 IU/kg
033001	0.5	50 IU/kg trough
033002	1.81	Pre-50 IU/kg
033003	1.88	100 IU/kg trough
033004	0.78	Pre-100 IU/kg
Source: Tables 15.53 and 15.54 from CSR		

Similar evidence of low FIX activity was available for the subjects participating in Study B1821010 (Table 2). Twenty-three of 25 subjects (92%) have documented FIX activity below the limit of detection (<1%), demonstrating their severe disease status.

Table 2. Lowest Individual FIX Activity for Subjects in Study B1821010		
Subject Number	FIX activity (IU/dL)	Visit*
10021001	0	2
10031001	0	2
10111001	0	2
10171001	0	2
10171002	0	2
10171004	0	2
10221002	0	2
10221004	0	4
10221005	0	8
10261001	0	2
10261002	0	2
10261004	0	2
10271002	0	2
10281001	0	4 (day 179)
10281002	0	2
10281003	2.36	2
10311001	0	2
10351001	0	2
10361001	0	2
10361002	0	2
10371001	3.6	4
10381001	0	2
10481001	0	2
10521001	0	2
10521002	0	4
Source: Listing 16.2.8.1.7		
* visit 2 corresponds to study day 1; visit 4 corresponds to study visit at week 26 ± 2 weeks; and visit 8 corresponds to study completion which was at week 78 ± 2 weeks.		

The MAH respectfully requests clarification on how the assessor has derived a value of 48% in the statement “and 48% of subjects experienced spontaneous bleeds after 4 or 5 days”.

Based on the analysis of data (B1821010 Clinical Study Report, Supportive Table 14.2.3) performed by the MAH, 13 subjects reported a total of 64 episodes of spontaneous bleeding; 32% (8/25) subjects reported a spontaneous bleed “after day 4” (ie, on days 5, 6, or 7) at least once after a prophylaxis dose; 28% (7/25) subjects reported a spontaneous bleed “after day 5” (ie, on days 6, or 7) at least once after a prophylaxis dose.

The MAH would also like to provide some newly available supportive external registry data in this response. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) is an association of medical practitioners who work within the Haemophilia Centres of England, Scotland, Northern Ireland or Wales. The UKHCDO is required by the Department of Health to collect data on diagnosis, management and complications of bleeding disorders. This information is kept in the National Haemophilia Database. The attached analysis by Prof. Charles Hay (Personal Communication, 2015) describes the realworld- use of BeneFIX in severe haemophilia B patients (FIX $\leq 1\%$) as a once-weekly regimen as documented in the National Haemophilia Database. Patient-level data are provided as well as Prof. Hay' s interpretation of the data. The MAH would like to highlight that this supportive data provided by the UKHCDO has been provided in response to a request from the MAH. These data and its interpretation represent the opinion of Professor Hay and the MAH has had no input.

For both 2013 and 2014, 11 severe haemophilia B patients (10 patients, ≥ 18 years of age; 1 patient, < 18 years of age) were identified and confirmed by their centers as using BeneFIX once-weekly (please refer to Prof. Hay' s report for detailed information on the patient identification process). This corresponded to 11.5% of adults (≥ 18 yrs) and 2% of children (< 18 yrs) using Haemtrack (the UKHCDO electronic patient diary system) and reporting BeneFIX prophylaxis in 2013.

This group of patients was selected by UK clinicians for a once-weekly regimen for a number of reasons that include convenience for the patient, or because of poor venous access, or because they were unable to comply with more demanding twice weekly prophylaxis regimens.

In the cohort analysed by Professor Hay , once weekly prophylaxis appeared haemostatically effective, with an acceptably low median annualised bleed-rate of 3 in 2013 and 1 in 2014 despite the use of significantly lower weekly doses of BeneFIX than were reported by Valentino et al, (2014). The ABR reported with weekly prophylaxis was very similar to that reported for UK patients with severe haemophilia B using twice weekly prophylaxis whose median ABR in 2013 was 2.5 (IQR 0-10) and 2 (IQR 0.75-10) in 2014 (n= 42 and 48 respectively, selected using the same selection criteria).

In this analysis, the treatment appeared safe and no adverse events (including thrombosis, inhibitor development, poor efficacy event) were reported. The report concludes that there is a place for BeneFIX once-weekly prophylaxis and that many more patients may be suitable for this approach. This report demonstrates that BeneFIX as a once-weekly regimen has been used effectively and with a favourable safety profile in real-world clinical practice in a group of severe haemophila B patients (FIX $\leq 1\%$) in the UK in 2013 and 2014. Of particular interest are the two patients who had been poorly compliant with twice weekly prophylaxis or had refused twice weekly prophylaxis, and they have been found to be compliant with the BeneFIX once-weekly regimen.

Assessment of the MAH's response

The MAH clarified that at baseline no factor IX activity was measured in study 400. The MAH states that inadequate washout was a potential issue in clearly identifying the severity of haemophilia in the subjects enrolled in Study 400 and that the longer half-life of FIX activity (33 hours), described by Powell et al, (2013) after BeneFIX administration was “not appreciated”.

However, this can be excluded by checking Supportive Table 3.4 'Listing of infusion and bleed events for subjects in Study 400', which lists all factor IX administrations during the study. These listings show that in all but two cases the interval between last dosing and C0h measurement was at least 3 days, so the

washout interval was in general sufficient and the FIX level an innate one. In addition, the PK data of the longer half-life of FIX activity (33 hours), described by Powell et al, (2013) do not support an addition of a once-weekly 100 IU/kg prophylaxis regimen. (see Rapporteur's Assessment of MO 2).

The MAH submits new analyses of data about the lowest Individual FIX Activity for Subjects in Study 400. Thus, 17 of 45 subjects (38%) had FIX activity of moderate or even mild, $\geq 2\%$ and only 14 subjects (31%) had a FIX activity $< 1\%$.

The MAH presented the same analysis in a similar way for study 1010. Therefore, 23 of 25 subjects (92%) have documented FIX activity below the limit of detection ($< 1\%$).

For study 400 the concern remains that only a minority of the study population was affected by true severe haemophilia B, for study 1010 the point is resolved.

Please accept the apologies from Rapporteur regarding the statement "and 48% of subjects experienced spontaneous bleeds after 4 or 5 days" reflecting a typing error. Clarification: In study 1010, thirteen subjects (52.0%) experienced 64 spontaneous bleeds during the prophylaxis period. 8 out of these 13 subjects (32%) experienced spontaneous bleeds after 4 or 5 days, that means $>96\text{--}\leq 168$ hours. (see Supportive Tabel 14.2.3 "Number of spontaneous bleeding episodes by time between previous prophylaxis infusion and start of bleed - include subjects who had at least one bleed during the prophylaxis period").

Nevertheless, the bleeding rate achieved during this regimen cannot be regarded as sufficient, considering that prophylactic treatment would usually aim at a marked reduction in breakthrough bleeding frequency.

The MAH also provided external registry data. Those data are noted. However, it is also pointed out that the results derived from a very small population (11 severe haemophilia B patients). Overall, registry data could be supportive but do not replace long-term PK investigations regarding the FIX activity following BeneFIX administration.

Conclusion

Point partially solved.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Other concerns

Clinical aspects

Question 4

Doubling the single dose of BeneFIX to 100 IU/kg as proposed with this application theoretically increases especially the thrombogenic risk.

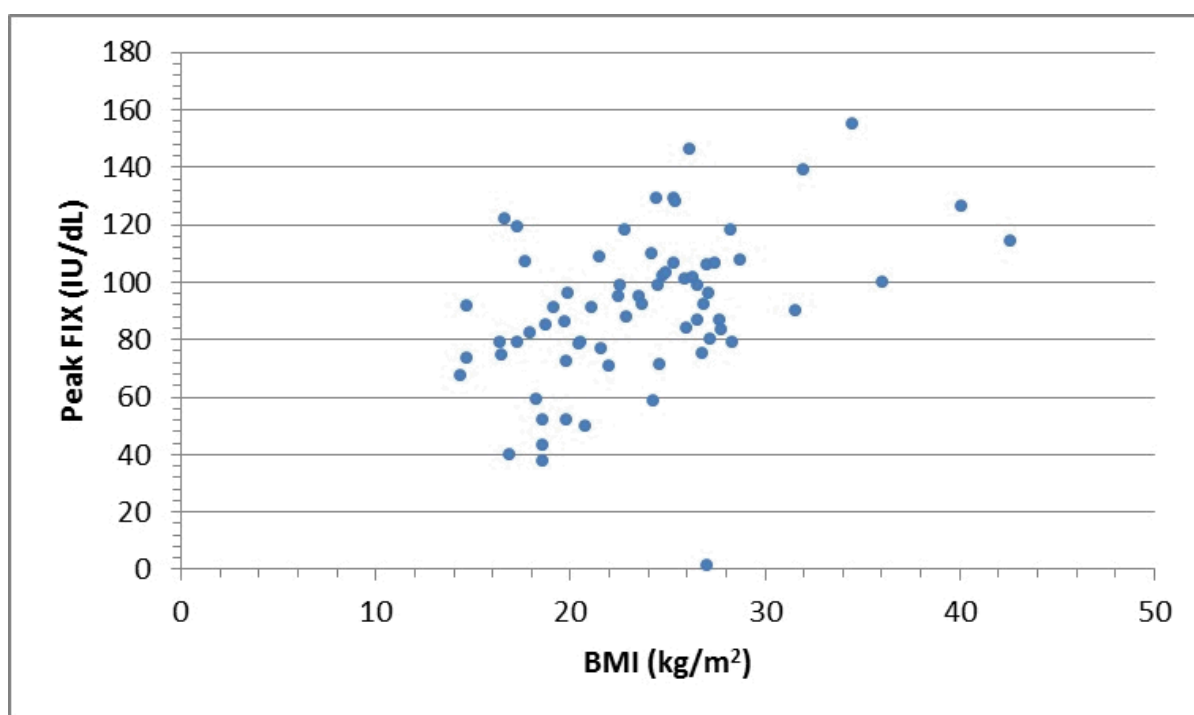
- a) It should also be considered, that BeneFIX is dosed in relation to body weight and overweight subjects would be exposed to extremely high single doses of factor IX. For such high doses, there is little clinical experience. Obesity itself serves as a risk-factor for thrombosis. The MAH is asked to discuss the theoretical thrombogenic risk when administering such high doses of factor IX.
- b) The possible impact of missing (safety) data in patients > 65 years of age – who are at higher risk for thromboembolic events – in view of the proposed higher treatment doses should be discussed.

Summary of the MAH's response

The MAH has previously provided data from clinical studies with BeneFIX, where 85 subjects received a total of 1050 infusions of BeneFIX of approximately 100 IU/kg or greater. Six subjects had body mass index (BMI) values of 30 to 43 kg/m² and would be classified as obese. In 30 of these subjects receiving 230 infusions of approximately 100 IU/kg or greater, coagulation marker tests were performed (see section 2.5.5.2.4, Clinical Overview for this application). Results showed no clinically significant differences from baseline values. There were no observed clinical manifestations of thrombotic events. A discussion of the theoretical thrombogenic risk when administering high doses of BeneFIX in obese patients is provided below.

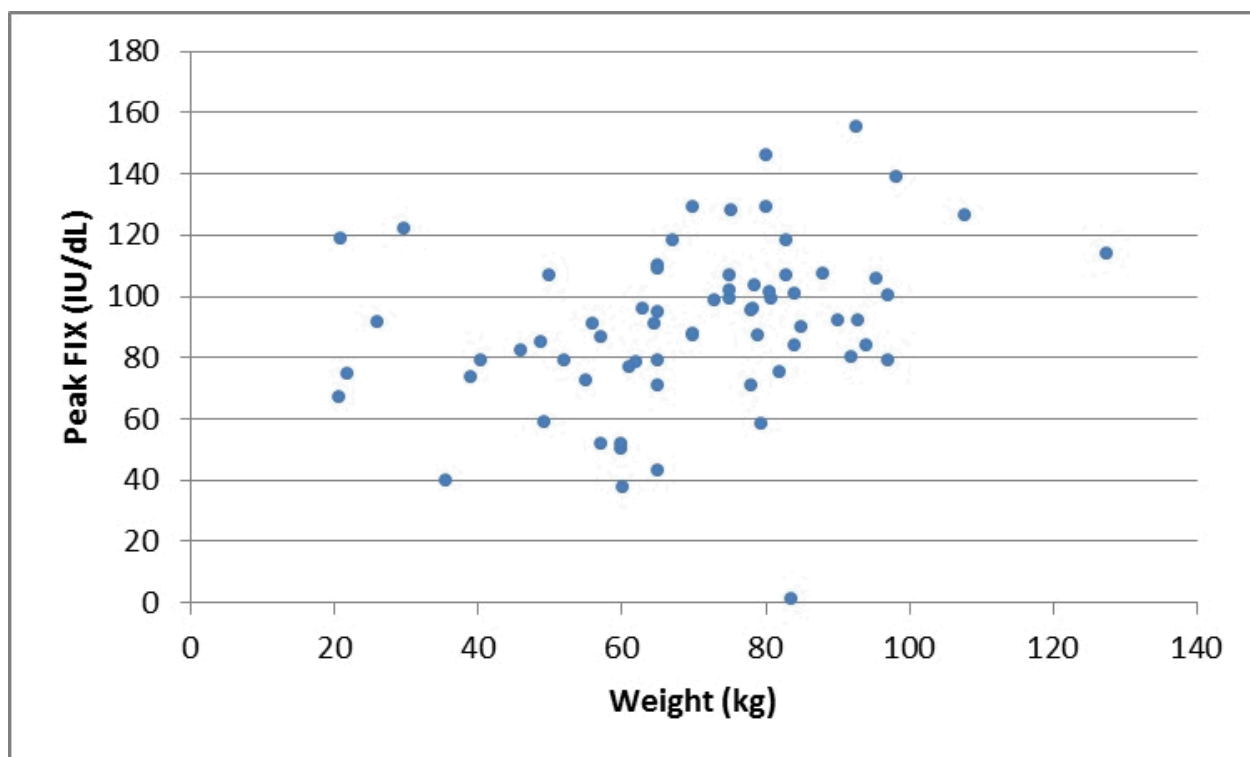
Peak FIX activity, collected 30 minutes after administration of BeneFIX 100 IU/kg, was measured in Study 400 and Study 1010. The potential relationship between peak FIX activity and bodyweight, and BMI were assessed and these data are presented in Figure 5 and Figure 6, respectively. Both analyses show a significant correlation, in that as weight and BMI increased, the peak FIX activity also increased, as has been reported previously for FVIII activity (Bjorkman et al, 2012). However, even among the heaviest individuals and those with the highest BMI, none of the FIX activity observed was above the upper limit of normal of most clinical laboratories (120 to 160 IU/dL for the laboratories used in Study 400). It should also be considered that FIX activities decrease from their peak steadily in patients with haemophilia because of their inability to synthesize replacement FIX, and therein are unlike individuals with normal coagulation factor production who have sustained FIX activities in the normal range.

Figure 5. FIX Peak versus Body Weight after Administration of BeneFIX 100 IU/kg (n=68)



Source: Listings for Demographic data and FIX activity. Note: The data for subject 4001101 were included although the peak observed after the 100 IU/kg dose was very low.

Figure 6. FIX Peak versus Body Mass Index (BMI) after Administration of BeneFIX 100 IU/kg (n=68)



Source: Listings for Demographic data and FIX activity. Note: The data for subject 4001101 were included although the peak observed after the 100 IU/kg dose was very low.

In consideration of the above analyses and the literature previously cited, Van Hylckama Vlieg et al, (2000) reported a 2- to 3-fold increased risk for individuals who have FIX levels above 129 IU/dL when compared with individuals having FIX levels below this cut-off. In the analysis presented above of peak FIX activity (collected 30 minutes after infusion of 100 IU/kg) 5/68 (7.4%) subjects analysed achieved peak FIX levels above the threshold of 129 IU/dL (these subjects had peak FIX activity values of 129, 129, 139, 146, and 155 IU/dL). Ameri et al, (2003) reported that transgenic mice with elevated circulatory FIX levels had increased risk of thrombosis, myocardial fibrosis and shorter life span. However, these are models of higher sustained plasma levels of FIX, unlike the transient FIX peak activity observed in patients with haemophilia following administration of FIX replacement therapy. Moreover, it is unclear if these published data in non-haemophiliac patients and in transgenic mice can be extrapolated to risks associated with the treatment of haemophilia patients.

In line with the FIX Core SmPC, the BeneFIX SmPC (as amended in variation II-0133) now includes within section 4.4 Special Warnings and Precautions for Use the statement “In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk” , in addition to information on thromboembolism and potential risk of thrombotic complications. Moreover, the BeneFIX SmPC now includes within section 4.2 Posology and Method of Administration the statement “Dose based on bodyweight may require adjustment in underweight or overweight patients” alerting the physician to the potential need to adjust dosage in underweight or overweight patients. In addition, section 4.2 advises the physician that “During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions” .

Lastly, within the Risk Management Plan thrombogenicity is an identified risk that is subject to ongoing routine pharmacovigilance.

In conclusion, based on the analyses presented within the context of this response, together with the data previously presented, the MAH considers that there is no evidence that obese patients would be placed at increased risk through administration of BeneFIX 100 IU/kg.

Experience with BeneFIX in patients >65 years is limited, as the elderly patients comprise approximately 2% of the total haemophilia A and B population, and approximately 1% of the total population with severe disease (Philipp, 2010). As already acknowledged by the assessor, this is a population for which information is missing, as also indicated within the approved Risk Management Plan (version 8.1, review completed with variation II-0133) and the Risk Management Plan revised in this application (version 9.0). Consequently, there are insufficient data upon which conclusions can be made in regards to the administration of BeneFIX 100 IU/kg to this population. However, in line with the FIX Core SmPC, the BeneFIX SmPC (amended in variation II-0133) now includes within section 4.4 Special Warnings and Precautions for Use, the statement "In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk", in addition to information on thromboembolism and potential risk of thrombotic complications.

Assessment of the MAH's response

Preclinical and clinical investigations regarding thrombogenicity were performed. The MAH reported that in clinical studies with BeneFIX, 85 subjects received a total of 1050 infusions of BeneFIX of approximately 100 IU/kg or higher. Six subjects had body mass index (BMI) values of 30 to 43 kg/m² and would be classified as obese. In 30 of these subjects receiving 230 infusions of approximately 100 IU/kg or greater coagulation marker tests were performed without clinically significant differences to baseline values. The MAH submits an analysis which assessed the potential relationship between peak FIX activity and bodyweight, and BMI. Even among the heaviest individuals and those with the highest BMI, none of the FIX activity observed was above the upper limit of normal of most clinical laboratories (120 to 160 IU/dL for the laboratories used in Study 400).

In line with the FIX Core SmPC, the BeneFIX SmPC (as amended in variation II-0133) now includes within section 4.4 Special Warnings and Precautions for Use the statement "In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk", in addition to information on thromboembolism and potential risk of thrombotic complications. Moreover, the BeneFIX SmPC now includes within section 4.2 Posology and Method of Administration the statement "Dose based on bodyweight may require adjustment in underweight or overweight patients" alerting the physician to the potential need to adjust dosage in underweight or overweight patients. In addition, section 4.2 advises the physician that "During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions".

The MAH confirmed that patients >65 years is a population for which information is missing. In line with the FIX Core SmPC, the BeneFIX SmPC (amended in variation II-0133) now includes within section 4.4 Special Warnings and Precautions for Use, the statement "In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk", in addition to information on thromboembolism and potential risk of thrombotic complications.

Conclusion

Point resolved.

SmPC aspects

The details of the SmPC wording will be performed depending on the further approach.

Summary of the MAH's response

Please see the revised wording proposed for SmPC section 4.2 under response 1b above. Changes originally proposed for Section 5.1 and 5.2 are as previously submitted and have not been amended. Note that the annexes now provided include the changes from procedure II- 0133 which reached positive CHMP opinion on 23 July 2015.

Assessment of the MAH's response

The MAH's response is not acceptable.

A treatment recommendation cannot be given and it should be removed from the SmPC, section 4.2 Posology and method of administration. Because of a variety of deficiencies, as outlined in the assessment report, presenting the study results in section 5.1 in the way as the MAH wishes is not acceptable.

However, it might be acceptable to give some information in SmPC section 5.1 on the use of this prophylactic regimen. A wording is proposed:

'In two open-label studies BeneFIX was found to be safely administered at 100 IU/kg once weekly. However, the short half-life of the product and the limited PK study data do not allow recommending this regimen in general for long-term prophylaxis in severe haemophilia B patients.'

If the MAH wishes to accept this proposal a revised PI including the proposed wording in section 5.1. should be submitted.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

Additional MAH's response submitted via EUDRALINK on 09th October 2015

The MAH has accepted the proposal made by Rapporteur to include some information in section 5.1 of the SmPC on the use of this prophylactic regimen. The MAH has submitted a revised product information with a proposal in section 5.1, which has been slightly modified to the proposal made by Rapporteur.

The following wording for section 5.1 is proposed by the MAH:

"In two open-label studies BeneFIX was found to be safely administered at 100 IU/kg once-weekly. However, the half-life of the product (see section 5.2) and the limited pharmacokinetic study data for the once-weekly regimen do not allow recommending this regimen in general for long-term prophylaxis in severe haemophilia B patients."

Conclusion

The above mentioned wording for section 5.1 of the SmPC as proposed by the Rapporteur and slightly modified by the MAH is acceptable.

The MAH should implement this change with a consolidated eCTD Sequence into the dossier.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

References

- a. van Hylckama Vlieg A, van der Linden IK, Bertina RM, Rosendaal FR. High levels of factor IX increase the risk of venous thrombosis. *Blood* 2000;95:3678-3682
- b. Ameri A, Kurachi S, Sueishi K, Kuwahara M, Kurachi K. Myocardial fibrosis in mice with overexpression of human blood coagulation factor IX. *Blood* 2003;101:1871-1873
- c. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in haemophilia B. *NEJM* 2013; 369: 2313–23.
- d. Berntorp E, Dolan G, Hermans C et al. Pharmacokinetics, phenotype and product choice in haemophilia B: how to strike a balance? *Haemophilia* 2014;20 (Suppl. 7):1–11.
- e. Manolis, Efthymios; Pons, Gérard (2009): Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. In: *British journal of clinical pharmacology* 68 (4), S. 493–501. DOI: 10.1111/j.1365-2125.2009.03484.x.