Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for nonacog gamma

Proprietary Product Name: Rixubis

Sponsor: Baxter Healthcare Pty Ltd

First round: May 2013

Second round: October 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ABR	Annualised bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
aPTT	Activated partial thromboplastin time
AUC	Area under the plasma concentration versus time curve
$AUC_{0\text{-}72\ h}$	Area under the plasma concentration versus time curve from 0 to 72 hours post-infusion
$AUC_{0\text{-}\infty}$ or $AUC_{0\ \text{-inf}}$	Area under the plasma concentration versus time curve from time 0 to infinity
BDS	Bulk Drug Substance
BE	Bleeding episode
BU	Bethesda Unit
CHO	Chinese hamster ovary
CIC	Circulating immune complexes
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CRM	Cross-reacting material
CRT	Case report tabulation
CTM	Clinical Trial Material
DIC	Disseminated intravascular coagulation
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EC	Ethics committee

Abbreviation	Meaning
ED	Exposure day
EDCS	Electronic data capture system
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ER	Emergency room
FAS	Full Analysis Set
FDP	Finished Drug Product
FIX	Factor IX
GCP	Good clinical practice
GP	General practitioner
h	Hour(s)
HAV	Hepatitis A virus
anti-HBs	Antibody to hepatitis B surface antigen
anti-HBc	Antibody to hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRP	Horseradish peroxidase
HR QoL	Health-related quality of life
hs-CRP	High-sensitive C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
iCSR	Interim clinical study report
Ig	Immunoglobulin

Abbreviation	Meaning
INR	International normalised ratio
IP	Investigational product
IR	Incremental recovery
ITI	Immune tolerance induction
IU	International units
IVRS	Interactive Voice Response System
LSO	Last subject out
MRT	Mean residence time
MRL	Master Randomisation List
NOAEL	No observable adverse event level
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PTP	Previously treated patients
SAE	Serious adverse event
SAER	Serious adverse event report
SIC	Subject identification code
SOC	System organ class
SPC	Summary of product characteristics
STD	Standard deviation
SWFI	Sterile water for injection
TAT	Thrombin anti-thrombin
T1/2	Elimination phase half-life
VAS	Visual analog scale
V_{ss}	Volume of distribution at steady state

1. Clinical rationale

1.1. Haemophilia B

Haemophilia B, or congenital Factor IX (FIX) deficiency, is an X-chromosomal-linked bleeding disorder with an incidence of approximately one in 30,000 live male births. Haemophilia B is the second most common type of haemophilia and is five times rarer than haemophilia A. The World Federation of Hemophilia (WFH) reported a worldwide prevalence of 399,000 subjects with haemophilia, of which there are an estimated 80,000 patients with haemophilia. In approximately 30 precent of haemophilia B cases, there is no family history of the disorder and the condition is the result of a spontaneous gene mutation.

FIX is a vitamin-K-dependent coagulation factor that belongs to the class of serine proteases. Maturation of FIX requires the sequential cleavage of the signal peptide and the pro-peptide, giving rise to the mature FIX zymogen with a length of 415 amino acids and a molecular weight of 57 kDa. The synthesis of FIX takes place in the hepatocytes, from where it is secreted into the circulation. Before secretion, the protein is subjected to substantial posttranslational processing as well as phosphorylation and sulfation. The physiological plasma concentration of FIX is 1 IU/mL, which equals about 5 µg/mL. Severely diminished or absent levels of circulating FIX in haemophilia B result from impaired synthesis caused by major defects in gene structure (large deletions, insertions, frame-shifts, and nonsense mutations) or from the rapid destruction of unstable defective FIX molecules. In contrast, missense mutations are often associated with aberrantly expressed FIX molecules that can be detected immunologically (cross-reactive material [CRM(+)]) but exhibit reduced activity in coagulation-based assays.

Historically, haemophilia patients were only treated when they had bleeding episodes (on-demand). One of the main reasons on-demand treatment has been used is the high cost and limited supply of FIX products. However, it has become known that treatment of severe haemophilia with frequent, periodic prophylactic FIX infusions can have significant medical and quality of life benefits. On prophylaxis, adequate plasma levels of FIX for haemostasis are maintained, approximating a non-diseased state. Prophylaxis treatment started at a young age would facilitate a complete lack of bleeding episodes, maintain healthy joints, and can lead to functionally normal lives. Thus, prophylaxis is preferred over on-demand therapy as it prevents most of the irreversible long-term effects brought about by bleeding.

1.2. Rixubis

Rixubis is synthesised by a recombinant Chinese Hamster Ovary (CHO) cell clone in suspension culture which co-expresses rFIX and recombinant human wild-type Furin [rFurin], a proteolytic enzyme which facilitates complete cleavage of the FIX Propeptide.1 The CHO cell culture medium is a chemically defined medium developed by Baxter, and the downstream process does not use monoclonal antibodies for the purification. No materials of human or animal origin are employed in the manufacture, purification, or formulation of the final product, thus reducing the risk of transmission of adventitious agents.

Rixubis has structural and functional characteristics comparable to those of endogenous FIX. Furthermore, studies demonstrate that the structure, identity, purity, potency, and functional integrity of Rixubis are comparable to those of a commercial rFIX. The polypeptide sequence of Rixubis is identical to that of a commercial rFIX and the post-translational modifications are comparable. The purity and specific activity (in units of clotting activity per mg of total protein) of Rixubis are within the same range as that found for a commercial rFIX.

Properly processed plasma-derived products are considered virally safe, but the discovery of any new human pathogen (such as West Nile virus, SARS and blood-borne prions) leads to apprehension within the haemophilia community. Due to the absence of exposure to any

human-derived proteins during manufacturing and formulation, Rixubis has an inherently improved viral safety profile compared with plasma derived FIX products.

Cell-bank derived recombinant products still carry viral risks related to the use of non-human sources in their manufacturing, so potential viral transmission is still a concern. Filters with nominal pore sizes in the nanometre range are well established tools for enhancing the virus safety margins but are intrinsically less successful for smaller viruses such as MMV which pass the 35-nm filter (or a nominal molecular weight cut off of 70,000 – 100,000 Da).

Although the development of both recombinant products (Rixubis and a commercially available rFIX) is comparable including purification by a chromatography process that does not require a monoclonal antibody step, the virus inactivation/removal procedures utilized during manufacturing are different. The purification process of a commercial rFIX consists of a virus-retaining membrane-nanofiltration step performed to retain molecules with molecular weights >70,000 Da (such as large proteins and viral particles). Unlike the commercial rFIX product, the manufacturing process of Rixubis includes two independent viral inactivation/reduction steps, that is, solvent/detergent treatment (used for clearance of enveloped viruses e.g. XMuLV)9 and 15 nm nanofiltration (providing a virus removal capacity for small non-enveloped viruses such as MMV, Reo-3 and prions).

With these two steps, the overall virus inactivation capacity of the Rixubis production process ensures very high safety margins of the final product against adventitious viruses.

> Comment: The rationale to develop a safer and effective replacement product to treat Haemophilia B is an acceptable rationale. The clinical evaluator is unable to comment on the additional viral safety claimed to be provided by the two step purification of Rixubis compared to the one stage membrane nanofiltration step used in purification of the commercial rFIX.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The clinical dosser documented a full clinical development program of pharmacology, efficacy and safety studies except for biopharmaceutical studies that were modified.

The submission contained the following clinical information:

- The pharmacokinetics (PK) of Factor VIII (FVIII) and FIX concentrates are generally accepted as a surrogate for haemostatic efficacy. Kinetics of Rixubis after a single dose, and after at least 30 EDs were evaluated in the completed pivotal Phase I/III Study 250901. In the ongoing Phase III surgery Study 251002, pre-surgical PK parameters were assessed only in subjects undergoing major elective surgery who did not undergo PK assessment in Study 250901.
- No population PK (PopPK) analyses were submitted.
- The pivotal study was Study 250901, a Phase I/III prospective, controlled, multicentre study evaluating PK, efficacy, safety, and immunogenicity in previously treated patients with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) Haemophilia B.
- Dose-finding studies were not done. The dose was determined The selection of dose regimens in this study is based on pre-clinical PK, pharmacodynamics (PD), single and repeated dose in vivo toxicity studies, as well as the standard human clinical dose for BeneFIX, the only other recombinant FIX in clinical use, and on regulatory agency guidelines.

- Study 251002 was a Phase III, prospective, multicentre study evaluating efficacy and safety in previously treated patients with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) haemophilia B undergoing surgical or other invasive procedures.
- An Integrated Analysis of Safety (ISS) for Rixubis was provided in which the safety of Rixubis was integrated across the complete and ongoing studies in terms of adverse events (AEs), and the risk of developing FIX inhibitors in previously treated patients (PTPs) assessed.

2.2. Paediatric data

The submission did not include paediatric data. The proposed indications exclude children under 12 years of age. A trial in children (Study 251101) is ongoing.

2.3. Good clinical practice

In both studies, the study protocol, informed consent form, and all amendments were reviewed and approved by the Independent Ethics Committee (IEC) of each participating institution. The study was conducted in accordance with the Study Protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements. Written informed consent was obtained from each patient and/or their legally authorised representative before entering into the study according to applicable regulatory requirements and ICH GCP.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each PK topic.

Table 1 Submitted PK studies 1

PK topic	Subtopic		Study ID
PK in healthy adults	General PK	Single dose	NA
		Multi dose	NA
	Bioequivalence†	Single dose	NA
		Multi-dose	NA
	Food effect		NA
PK in special populations	Target population §	Single dose	Study 250901
		Single dose	Study 251002
	Hepatic impairment		NA
	Renal impairment		NA

PK topic	Subtopic		Study ID
	Neonates/infants/children < 12 years		NA
	Elderly		NA
Genetic/gender-related PK	Males versus females		NA
PK interactions			NA
Population PK analyses	Healthy subjects		
	Target population		
	Other		

* Indicates the primary aim of the study.
† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

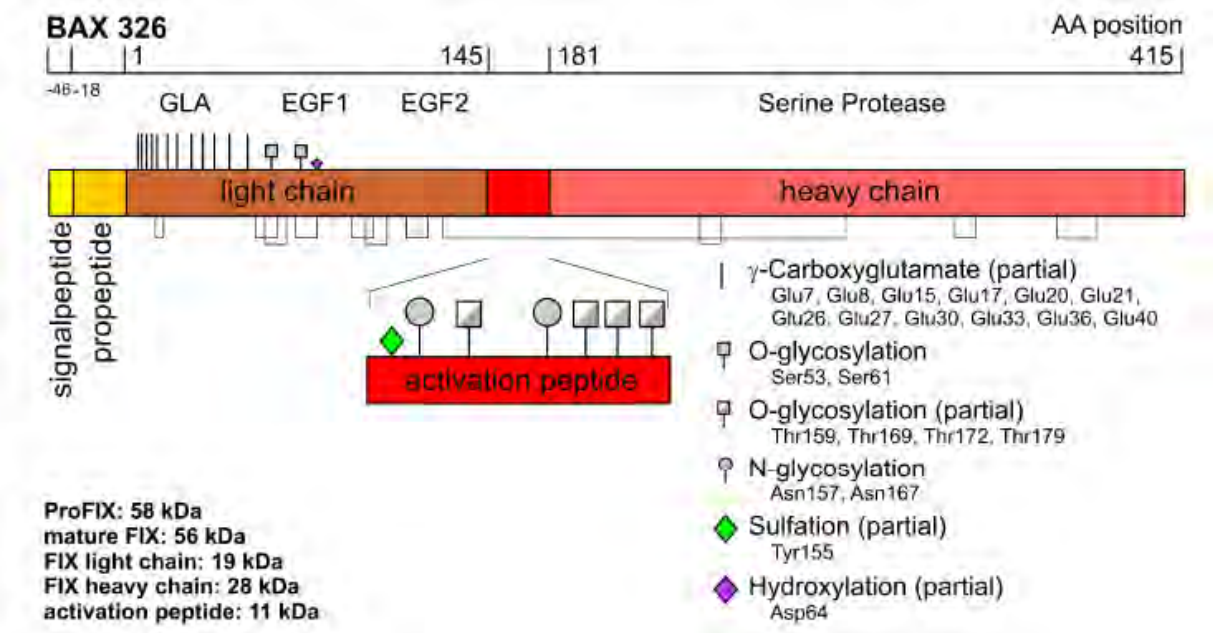
The information in the following summary is derived from conventional PK studies unless otherwise stated.

3.2.1. Physicochemical characteristics of the active substance

Structure: The structure of the molecular is shown in Figure 1. Mature BAX 326 consists of 415 amino acids, folded in a three dimensional structure containing the N-terminal Gla-domain, two domains resembling epidermal growth factor (EGF1 and EGF2) and the serine protease domain. During activation, the single chain molecule is proteolytically cleaved after Arg145 and Arg180 resulting in the light chain and the heavy chain part, held together by one disulfide bond.

The molecular formula for the peptide backbone of BAX 326, including the 12 Gla residues and 11 disulfide bonds is: $C_{2053}H_{3114}N_{558}O_{665}S_{25}$. The theoretical average molecular mass for the protein backbone of mature FIX according to the above formula is 47,054 Da. The average molecular mass for the BAX 326, expressed in the CHO cell system and purified by the described process is 54,300 Da. As in other vitamin K-dependent proteins, posttranslational modifications take place and include proteolytic cleavage, Ala148 polymorphism, formation of disulfide bonds, O-glycosylation, N-glycosylation, carboxylation, hydroxylation, and sulfation.

Figure 1: Structure of Rixubis



In human plasma, two naturally occurring allo forms of FIX are known to exist with Thr148 being present in 80% of the normal human population and Ala148 in the remaining 20%. BAX 326 represents the Ala148 allelic form. FIX binds multiple calcium ions at low-affinity and high-affinity sites located mainly in the Gla domain. Calcium ions are required for activation and for the function of Factor IXa in the tenase complex, which converts Factor X to Factor Xa.

Biological Activity: During the coagulation cascade, activated FIX catalyses the activation of Factor X. This reaction is greatly enhanced in the presence of Ca++, phospholipid and activated Factor VIII. Furthermore Factor IXa can also activate Factor VII in the presence of Ca++. The principal physiologic inhibitor of Factor IXa is anti-thrombin III by forming a 1:1 complex with Factor IXa.

3.2.2. Pharmacokinetics in the target population

3.2.2.1. Bioequivalence of clinical trial and market formulations

Analyses additional to those of the primary and secondary PK endpoints in the pivotal trial were prepared for the Full Analysis Set (FAS) comparing the PK parameters:

1. within subjects before and after switching clinical trial material (CTM), and
2. between subjects who received one versus the other type of CTM.

Twenty-seven (27) out of 28 subjects in Part 1 received pilot scale material and 23 out of 25 subjects in Part 3 received commercial scale material. The comparison was performed in the 22 subjects who received both pilot (Part 1) and commercial (Part 3) Rixubis product. The Part 1/Part 3-ratio of PK parameters showed that higher AUC, IR and C_{max} values were observed with the commercial product. The Part 1/Part 3-ratio of MRT, half-life and CL demonstrated very similar values for both pilot and commercial products. Incremental Recovery (IR) over time determined at 30 minutes post-infusion was assessed separately for subjects who received Rixubis pilot product and subjects who received Rixubis commercial product. Mean and median IR values were comparable for pilot and commercial product.

3.2.2.2. Bioequivalence to relevant registered products

The bioequivalence of Rixubis and a registered rFIX product, Benefix, was the primary PK endpoint of the PK section (Part 1) of the pivotal trial, Study 250901, and has been summarised in Table 2.

To assess PK equivalence of Rixubis and the commercial rFIX, the 90% confidence interval (CI) for the difference of the mean natural logarithms of $AUC_{0\text{-}72h\ /dose}$ between the two groups was calculated for the Per Protocol Analysis Set (PKPPAS) as well as for the Full Analysis Set (PKFAS) as randomised. To establish the equivalence in $AUC_{0\text{-}72h\ /dose}$ with a Type I error of 5%, the calculated two-sided 90% CI for the ratio had to be contained completely within the margins of equivalence defined as 80% to 125%. The results for the PKPPAS and the PKFAS are shown in Table 2 and Table 3 respectively.

Table 2: Bioequivalence results PP Analysis Set

Parameter	Least Squares Geometric Mean BAX326	Least Squares Geometric Mean BeneFIX	Ratio of Geometric Mean (BAX326/BeneFIX)	90% CI of Ratio[a]
$AUC_{0\text{-}72h}$ /Dose [IU·hr/dL : IU/kg]	13.97	13.14	1.063	(1.03, 1.09)
$AUC_{0\text{-}inf}$ /Dose [IU·hr/dL : IU/kg]	15.89	15.07	1.054	(1.01, 1.10)
$AUC_{0\text{-}72h}$ [IU·hr/dL]	1042.45	983.13	1.060	(1.03, 1.09)
$AUC_{0\text{-}inf}$ [IU·hr/dL]	1185.95	1126.85	1.052	(1.01, 1.10)

[a] Bioequivalence will be established if 90% C.I. of ratio is contained completely in the margins of equivalence of 0.8 to 1.25.
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Table 3: Bioequivalence results Full Analysis Set 1

Parameter	Least Squares Geometric Mean BAX326	Least Squares Geometric Mean BeneFIX	Ratio of Geometric Mean (BAX326/BeneFIX)	90% CI of Ratio[a]
$AUC_{0\text{-}72h}$ /Dose [IU·hr/dL : IU/kg]	13.90	13.14	1.058	(1.03, 1.09)
$AUC_{0\text{-}inf}$ /Dose [IU·hr/dL : IU/kg]	15.77	15.01	1.051	(1.01, 1.09)
$AUC_{0\text{-}72h}$ [IU·hr/dL]	1045.01	1005.11	1.040	(0.97, 1.11)
$AUC_{0\text{-}inf}$ [IU·hr/dL]	1186.70	1146.70	1.035	(0.97, 1.11)

[a] Bioequivalence will be established if 90% C.I. of ratio is contained completely in the margins of equivalence of 0.8 to 1.25.
[generated by 250901_csra_pk.sas]

Comment: PK equivalence of Rixubis and BeneFIX was demonstrated, as the 90% CI for $AUC_{0\text{-}72h\ /dose}$ and for $AUC_{0\text{-}72\ h}$ in both the Per Protocol and Full Analysis Sets was contained completely within the margins of equivalence defined as 80% to 125%.

3.2.2.3. Secondary pharmacokinetic endpoints in pivotal study

A further objective of Part 1 of the study was to assess the PK parameters of Rixubis and compare them with those of BeneFIX. The secondary PK endpoints were $AUC_{0\text{-}\infty}$/dose (area under the plasma concentration versus time curve from time 0 to infinity), MRT (mean residence time), CL (clearance), IR, T1/2 (elimination phase half-life) and Vss.

The results for AUC values for the two products were shown in the tables above. Table 4 shows the AUC values for Part 3 as well and presents the results for the other parameters for the Full Analysis Set. The results were not significantly different from those of the Per Protocol Analysis which are not shown in this evaluation.

The objective of Part 3 of the study was to re-evaluate the PK parameters for BAX 326 in the subjects who participated in Part 1 after a period of six months of treatment (26 ± 1weeks), in which they had accumulated at least 30 EDs, and to compare these parameters with those determined in Part 1. Twenty-three (23) subjects are included in the PKPPAS and 25 subjects are included in the PKFAS for Part 3. Individual graphs were included in the Study Report showing FIX activity levels versus time in Parts 1 and 3 of the study with each preparation.

Table 4: PK Parameters for Parts 1 and 3 for Pivotal Study (Full Analysis Set)

PK Parameter	Statistic	Part 1: BAX326	Part 1: BeneFIX	Part 3: BAX326	Ratio in BAX326 (Part 1/Part 3)
$AUC_{0\text{-}72h}$ /Dose [IU·hr/dL : IU/kg]	N	28	28	25	25
	Mean (Std)	14.25 (3.18)	13.45 (2.94)	15.57 (3.23)	0.92 (0.10)
	Median	14.25	13.42	15.98	0.93
	Q25 ; Q75	10.89 ; 16.16	11.48 ; 15.15	12.83 ; 17.24	0.86 ; 1.00
	Min ; Max	9.51 ; 21.57	8.57 ; 20.63	9.52 ; 21.13	0.72 ; 1.09
$AUC_{0\text{-}inf}$ /Dose [IU·hr/dL : IU/kg]	N	28	28	25	25
	Mean (Std)	16.08 (3.29)	15.32 (3.28)	17.50 (3.73)	0.93 (0.10)
	Median	15.99	15.18	17.51	0.93
	Q25 ; Q75	12.98 ; 17.64	13.18 ; 17.22	14.68 ; 20.63	0.89 ; 0.98
	Min ; Max	10.97 ; 23.48	9.99 ; 22.84	10.59 ; 24.21	0.67 ; 1.15
$AUC_{0\text{-}72h}$ [IU·hr/dL]	N	28	28	25	25
	Mean (Std)	1074.40 (251.68)	1039.08 (277.25)	1164.92 (250.33)	0.93 (0.14)
	Median	1085.05	1030.41	1213.32	0.93
	Q25 ; Q75	795.31 ; 1185.75	805.04 ; 1162.24	960.58 ; 1287.95	0.86 ; 0.98
	Min ; Max	696.07 ; 1576.55	650.08 ; 1827.68	753.85 ; 1626.81	0.67 ; 1.27
$AUC_{0\text{-}inf}$ [IU·hr/dL]	N	28	28	25	25
	Mean (Std)	1212.96 (261.58)	1180.41 (295.15)	1308.99 (287.69)	0.94 (0.14)
	Median	1235.63	1146.33	1317.57	0.94
	Q25 ; Q75	974.19 ; 1303.43	987.51 ; 1339.45	1071.10 ; 1445.01	0.89 ; 0.99
	Min ; Max	825.51 ; 1749.44	747.72 ; 1945.28	838.24 ; 1863.77	0.63 ; 1.33
IR at C_{max} [IU/dL : IU/kg]	N	28	28	25	25
	Mean (Std)	0.87 (0.21)	0.77 (0.20)	0.95 (0.24)	0.93 (0.11)
	Median	0.87	0.74	0.94	0.97
	Q25 ; Q75	0.76 ; 0.99	0.66 ; 0.90	0.80 ; 1.17	0.86 ; 1.00
	Min ; Max	0.53 ; 1.35	0.44 ; 1.27	0.52 ; 1.38	0.66 ; 1.12
C_{max} [IU/dL]	N	28	28	25	25
	Mean (Std)	66.65 (16.51)	60.39 (18.10)	73.24 (18.97)	0.93 (0.15)
	Median	67.40	56.70	72.50	0.92
	Q25 ; Q75	56.35 ; 74.70	49.45 ; 70.05	64.70 ; 88.10	0.89 ; 0.95
	Min ; Max	41.70 ; 100.30	33.60 ; 109.80	38.50 ; 106.30	0.62 ; 1.23
Half-life [hr]	N	28	28	25	25
	Mean (Std)	26.34 (9.18)	27.09 (9.01)	24.67 (6.99)	1.14 (0.38)
	Median	24.58	25.72	23.67	1.05
	Q25 ; Q75	20.51 ; 28.92	21.56 ; 29.44	19.37 ; 28.96	0.93 ; 1.43
	Min ; Max	15.83 ; 52.34	17.59 ; 64.29	15.50 ; 42.20	0.55 ; 2.21
MRT [hr]	N	28	28	25	25

PK Parameter	Statistic	Part 1: BAX326	Part 1: BeneFIX	Part 3: BAX326	Ratio in BAX326 (Part 1/Part 3)
	Mean (Std)	30.56 (7.01)	31.68 (7.04)	29.38 (4.36)	1.06 (0.20)
	Median	28.47	30.22	29.02	1.00
	Q25 ; Q75	26.32 ; 32.18	27.37 ; 34.64	27.17 ; 31.24	0.96 ; 1.16
	Min ; Max	22.25 ; 47.78	23.10 ; 60.70	21.32 ; 37.52	0.74 ; 1.66
CL [dL/(kg·hr)]	N	28	28	25	25
	Mean (Std)	0.0648 (0.0136)	0.0682 (0.0147)	0.0599 (0.0140)	1.09 (0.13)
	Median	0.0625	0.0659	0.0571	1.07
	Q25 ; Q75	0.0567 ; 0.0772	0.0581 ; 0.0761	0.0485 ; 0.0681	1.03 ; 1.12
	Min ; Max	0.0426 ; 0.0912	0.0438 ; 0.1001	0.0413 ; 0.0945	0.87 ; 1.49
V_{ss} [dL/kg]	N	28	28	25	25
	Mean (Std)	2.01 (0.74)	2.16 (0.66)	1.75 (0.45)	1.14 (0.21)
	Median	1.74	1.95	1.64	1.11
	Q25 ; Q75	1.54 ; 2.22	1.75 ; 2.47	1.43 ; 1.92	1.02 ; 1.29
	Min ; Max	1.10 ; 3.94	1.19 ; 3.92	1.12 ; 2.72	0.80 ; 1.61
Dose [IU/kg]	N	28	28	25	NA
	Mean (Std)	75.32 (3.90)	77.42 (15.29)	74.81 (3.29)	NA
	Median	74.43	75.26	75.60	NA
	Q25 ; Q75	72.84 ; 76.92	73.24 ; 76.71	73.40 ; 76.51	NA
	Min ; Max	71.27 ; 91.38	65.45 ; 153.92	64.48 ; 79.40	NA

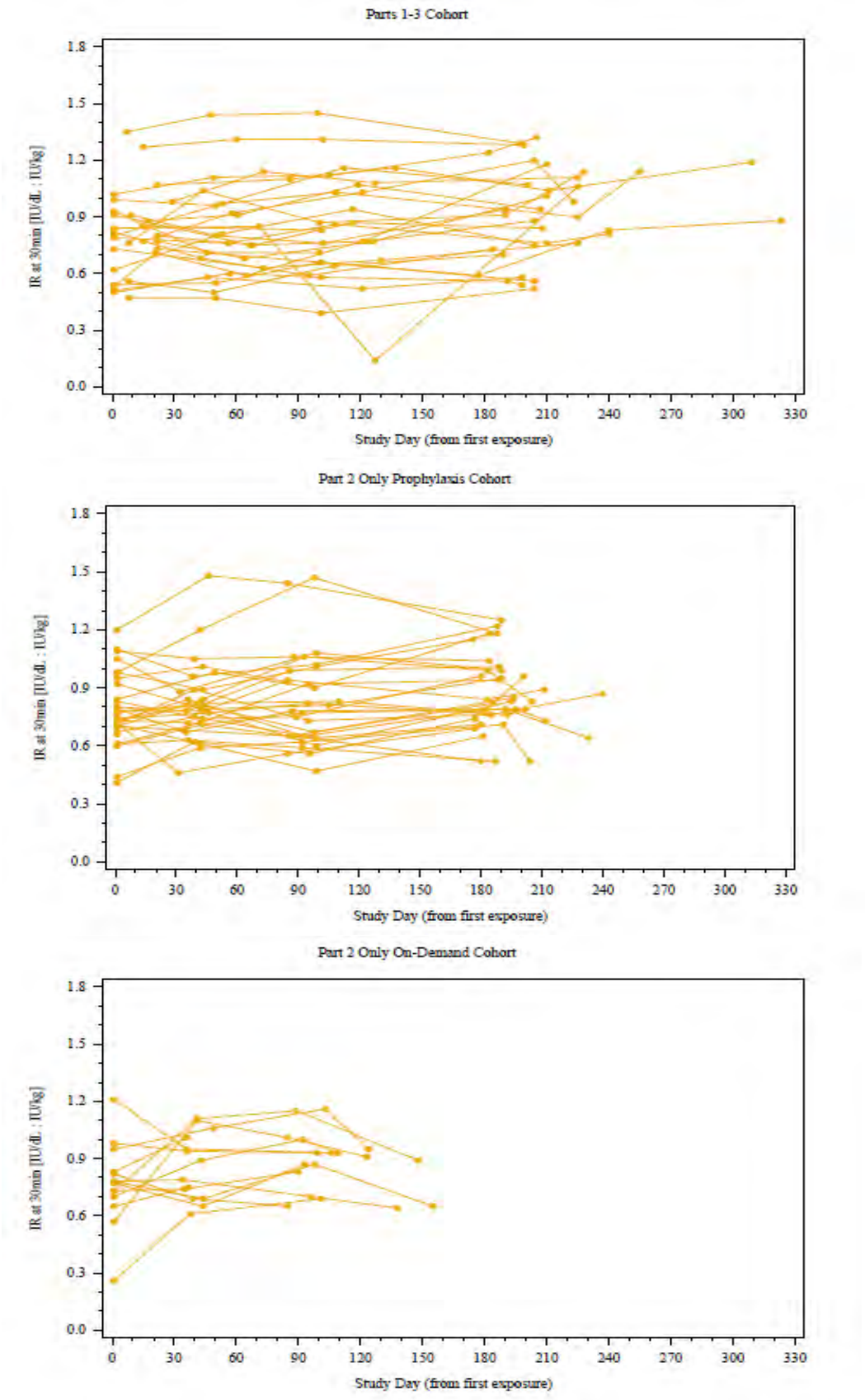
[generated by 250901_csra_pk.sas]

The subjects in Part 3 were those who participated in Part 1, and who after that received treatment for a period of six months (26 ± 1weeks), in which they had accumulated at least 30 EDs. No differences were seen between the PK parameters of Rixubis and BeneFIX, except that the study report notes that the IR at C_{max} was higher for Rixubis than for the commercial rFIX, with median values (in IU/dL : IU/kg) of 0.88 for Rixubis and 0.73 for the commercial rFIX in the PKPPAS (n=25) and median values of 0.87 for Rixubis and 0.74 for the commercial rFIX in the PKFAS (n=28). Mean values (± STD) were 0.87 ± 0.22 for Rixubis and 0.76 ± 0.20 for the commercial rFIX in the PKPPAS and 0.87 ± 0.21 for Rixubis and 0.77 ± 0.20 for the commercial rFIX in the PKFAS. In Part 3, median and mean IR of Rixubis at C_{max} was 0.93 and 0.95 ± 0.25, respectively.

> Comment: No statistical comparison was performed for the above PK findings, which were descriptive only, so that the difference in the values for the IR was not statistically tested for significance. Taking two STDs from the mean values in each case gives ranges of 0.45 to 1.29 for Rixubis and 0.37 to 1.17, so the difference is unlikely to be significant.

Incremental Recovery (IR) in the Pivotal Trial: IR [IU/dL: IU/kg] at C_{max} was defined as (C_{max} - C_{pre}-infusion)/Dose, where C_{max} was determined as the highest concentration achieved within one hour after infusion. IR over time was assessed for Rixubis in the FAS at the following time points at 30 minutes post-infusion: on Exposure Day (ED) 1 in Part 1/Part 2 (n=73), at Week 5 in Part 2 (n=71), at Week 13 in Part 2 (n=64), at Week 26 in Part 3/Part 2 (n=52), and at study completion/termination (n=17). Both median and mean values remained constant over time, with median IR values of 0.78, 0.79, 0.83, 0.88 and 0.89 at the respective time points listed above, demonstrating that the average incremental FIX recovery was consistent over time. Mean values (± STD) were 0.79 (0.20), 0.83 (0.21), 0.85 (0.25), 0.89 (0.21) and 0.87 (0.20), respectively. The median changes in IR, calculated from ED 1, were 0.03 at Week 5, 0.075 at Week 13, 0.06 at Week 26 and 0.12 at completion/termination. IR values at 30 minutes post-infusion are displayed graphically for each cohort (that is, Parts 1-3 Cohort, Part 2 Prophylactic Cohort, Part 2 On-Demand Cohort) in Figure 2.

Figure 2: Incremental Recovery at 30min for Rixubis Full Analysis Set



3.2.2.4. PK section of surgery study 251002

In Surgery Study 251002, pre-surgical PK parameters were available for seven subjects in the FAS (of whom six underwent major and one underwent minor surgery).

The seven subjects for whom pre-surgical PK parameters were calculated from PK assessments in the surgery study received a mean (STD) dose of 75.75 (2.52) IU/kg of Rixubis (range: 71.80-78.79 IU/kg). The mean (STD) values (+ range) of the individual PK parameters were:

- $AUC_{0\text{-}72\ h}$/dose (IU hour/dL : IU/kg): 19.77 (7.88) (range: 14.46-37.26)
- $AUC_{0\text{-}inf}$/dose (IU hour/dL : IU/kg): 21.74 (8.94) (range: 16.62-41.73)
- MRT (hour): 25.58 (4.56) (range: 18.57-31.16)
- CL (dL/[kg hour]): 0.0503 (0.0124) (range: 0.0240-0.0602)
- IR at 30 minutes (IU/dL : IU/kg): 1.06 (0.35) (range: 0.71-1.73)
- C_{max} (IU/dL): 82.06 (26.93) (range: 56.80-134.40)
- T½ (hour): 21.50 (4.98) (range: 14.85-28.61)
- Vss (dL/kg): 1.28 (0.39) (range: 0.69-1.87)

For a further six subjects, PK parameters were available from the assessment in the pivotal study. For two of the six subjects, additional IR (at 30 minutes) values were available from the continuation study.

3.2.2.5. Comparison of PK results from the pivotal study 250901 and the surgery study 251002

No statistical comparison of PK data between Pivotal Study 250901 and Surgery Study 251002 was performed.

Table 5 shows the PK parameters calculated in Study 250901 (PKPPAS and PKFAS) and in Study 251002. The Summary of Clinical Pharmacology states that no conclusions can be drawn, since the sample sizes are very different (25 [PKPPAS] and 28 [PKFAS] subjects in Study 250901 vs. 7 subjects in Study 251002).

> Comment: The clinical evaluator agrees that a meaningful statistical comparison is not possible between the results of the two studies, not only because of the small numbers in Study 251002, but because of the large values of the SD in the values for the PK parameters (for example, for IR at 30 minutes, 25% in the pivotal study and 33% in the surgical Study). The studies were not powered to make this comparison. This is unfortunate because the comparison is important as the data in Table 5 below suggests some differences could be statistically different if larger numbers of patients were studied. For example, in the FAS of each study the C_{max} and AUC values for Rixubis in the surgery study were greater (+30% to +45%) than in the pivotal study while the Vss was about 40% lower.
>
> Also disturbing is the error in the table below, from the Summary of Clinical Pharmacology which stated that the IR at 30 minutes for Rixubis in the pivotal study was not calculated for PKFAS. However the CSR of the pivotal trial gives these results for a number of time periods including 30 minutes after first exposure (see Figure 2). This comparison between the studies is that the IR at 30 minutes for Rixubis in the pivotal study was 0.79±0.20 and 1.06±0.35 in the surgery study, and the highest value in the latter was 1.73, more the two SDs greater than the mean in the pivotal study. However, although these differences may be statistically significant in a properly powered study, it is unlikely that they would be clinically significant.

Table 5: PK Parameters Calculated in Studies 250901 and 251002

PK Parameter	Study 250901 PKPPAS, n=25 BAX326 Mean + Range	Study 250901 PKPPAS, n=25 Commercial rFIX Mean + Range	Study 250901 PKFAS, n=28 BAX326 Mean + Range	Study 250901 PKFAS, n=28 Commercial rFIX Mean + Range	Study 251002 n=7 BAX326 Mean + Range
Dose for PK assessment	74.69 ± 2.37 IU/kg 71.27-79.38 IU/kg	74.83 ± 2.51 IU/kg 70.12-80.00 IU/kg	75.32 ± 3.90 IU/kg 71.27-91.38 IU/kg	77.42 ± 15.29 65.45-153.92	75.75 ± 2.52 IU/kg 71.80-78.79 IU/kg
$AUC_{0\text{-}72\ h}$/dose (IU hr/dL : IU/kg)	14.31 ± 3.23 9.51-21.57	13.45 ± 3.05 8.57-20.63	14.25 ± 3.18 9.51-21.57	13.45 ± 2.94 8.57-20.63	19.77 ± 7.88 14.46-37.26
$AUC_{0\text{-}inf}$/dose (IU hr/dL : IU/kg)	16.17 ± 3.28 10.97-23.48	15.39 ± 3.41 9.99-22.84	16.08 ± 3.29 10.97-23.48	15.32 ± 3.28 9.99-22.84	21.74 ± 8.94 16.62-41.73
MRT (hr)	30.82 ± 7.26 22.25-47.78	32.24 ± 7.16 25.40-60.70	30.56 ± 7.01 22.25-47.78	31.68 ± 7.04 23.10-60.70	25.58 ± 4.56 18.57-31.16
CL (dL/[kg hr])	0.0644 ± 0.0133 0.0426-0.0912	0.0681 ± 0.0153 0.0438-0.1001	0.0648 ± 0.0136 0.0426-0.0912	0.0682 ± 0.0147 0.0438-0.1001	0.0503 ± 0.0124 0.0240-0.0602
IR at 30 min (IU/dL : IU/kg)	Not calculated for PKPPAS	Not calculated for PKPPAS	Not calculated for PKFAS	Not calculated for PKFAS	1.06 ± 0.35 0.71-1.73
IR at C_{max} (IU/dL : IU/kg)	0.87 ± 0.22 0.53-1.35	0.76 ± 0.20 0.44-1.27	0.87 ± 0.21 0.53-1.35	0.77 ± 0.20 0.44-1.27	Not done
C_{max} (IU/dL)	66.22 ± 15.80 41.70-100.30	58.24 ± 15.83 41.70-100.30	66.65 ± 16.51 41.70-100.30	60.39 ± 18.10 33.60-109.80	82.06 ± 26.93 56.80-134.40
$T_{1/2}$ (hr)	26.70 ± 9.55 15.83-52.34	27.87 ± 9.22 17.59-64.29	26.34 ± 9.18 15.83-52.34	27.09 ± 9.01 17.59-64.29	21.50 ± 4.98 14.85-28.61
V_{ss} (dL/kg)	2.02 ± 0.77 1.10-3.94	2.20 ± 0.69 1.19-3.92	2.01 ± 0.74 1.10-3.94	2.16 ± 0.66 1.19-3.92	1.28 ± 0.39 0.69-1.87

3.2.3. Pharmacokinetics in other special populations

3.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

Not done.

3.2.3.2. Pharmacokinetics in subjects with impaired renal function

Not done.

3.2.3.3. Pharmacokinetics according to age

The studies and the requested indication limit the patients' age to 12 years or more. A study in paediatric patients (Study 251101) is in progress.

3.2.4. Pharmacokinetic interactions

3.2.4.1. Pharmacokinetic interactions demonstrated in human studies

While no interactions of Rixubis with other administered substances was investigated, interactions of Rixubis with the immune system in possible production of antibodies and with the coagulation system in producing thrombotic products are important and will be considered in the Safety section of this evaluation.

3.3. Evaluator's overall conclusions on pharmacokinetics

The clinical evaluator's conclusions are that in the pivotal Study 250901:

- PK equivalence of Rixubis and the commercially available rFIX was confirmed.
- The PK parameters analysed for Rixubis and the commercial rFIX (IR, C_{max}, half-life, MRT, CL and Vss) were comparable.
- Repeated in vivo recovery testing for up to 26 weeks demonstrated that the mean incremental FIX recovery was consistent over time.
- Rixubis half-life remained constant in Part 3.
- The comparison of Rixubis pilot product used in Part 1 and Rixubis commercial product used in Part 3 (Part 1/Part 3-ratio) showed that higher AUC, IR and C_{max} values were

observed with the commercial product. The Part 1/Part 3-ratio of MRT, half-life and CL demonstrates very similar values for both pilot and commercial products.

For surgery Study 251002:

- Pre-surgical PK parameters ($AUC_{0\text{-}72\ h}$/dose, $AUC_{0\text{-}inf}$/dose, C_{max}, and IR at 30 minutes) calculated for seven subjects in the FAS, were higher than those in the pivotal study, while the values for MRT, CL, T½and Vss were lower.
- Although a comparative study that was properly powered may have shown these differences to be statistically significant, they are unlikely to be clinically significant.

4. Pharmacodynamics

The PD characteristics of rFIX are intrinsic to its therapeutic action and are measured by the FIX activity after administration. These measurements also form the PK and Efficacy properties of the compound.

5. Dosage selection for the pivotal studies

The calculation of the required dose of rFIX is based on the empirical finding that 1 IU rFIX activity per kilogram of body weight is expected to increase the circulating level of FIX by 0.9 IU/dL of plasma (0.9% of normal) (range from 0.5 to 1.4 IU/dL) in patients (≥ 12 years). Using this assumption, the method to calculate the doses to be used in the pivotal trial was the use of a formula provided in the core SPC for human plasma derived and recombinant coagulation FIX products that is also consistent with the SPC of the comparator rFIX.

Due to the wide range of inter-individual differences in incremental recovery (as demonstrated by individual subject values), it was recommended to base the calculation for the initial estimated dose on the patient's individual incremental recovery using serial FIX activity assays. Doses administered were to be titrated to the patient's clinical response and individual PK, in particular incremental recovery and half-life.

> Comment: As the latter data would not be routinely available in medical practice, the dosing in the Product Information (PI) may need to reflect this. The sponsor should comment and advise on this issue (see Clinical Questions).

6. Clinical efficacy

6.1. Prophylaxis, treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B.

6.1.1. Pivotal efficacy study

6.1.1.1. Study 250901

6.1.1.1.1. Study design, objectives, locations and dates

Study 250901 was a Phase I/III prospective, controlled, multicentre study evaluating the PK, efficacy, safety, and immunogenicity of rFIX (Rixubis) in PTPs with severe or moderately severe haemophilia B. The study began on 29 July 2011 and finished on 3 May 2012.

Subjects were enrolled at investigative sites in Russia (17), Poland (15), Bulgaria (10), Ukraine (10), Romania (eight), Colombia (five), and Japan (five) Brazil (four), Chili (four), Czech Republic (two), UK (two), Argentina (two), Sweden (one), and Spain (one). No adjustments for race or

ethnic factors have been planned as there is no evidence that the effect of FIX products is affected by differences in race or ethnicity.

The study was in three parts each of which had a different design. Part 1 was a PK study and was discussed above. The three parts are, however, connected as shown in Figure 3.

Part 2 was an open-label, uncontrolled study of the haemostatic efficacy, safety, immunogenicity and Health Related Quality of Life (HR QoL) of Rixubis over six months with twice weekly prophylactic infusions with Rixubis or at least 50 Exposure Days (Eds) to Rixubis, whichever occurred last, in 60 subjects in order to have 50 evaluable subjects (prophylactic cohort).

Part 3 was an open-label, uncontrolled repeat PK study with Rixubis (single dose of 75 ± 5 IU/kg) in the subjects who participated in Part 1 and had been treated for 26 ± 1 weeks in Part 2, having accumulated at least 30 EDs to Rixubis. Thrombotic markers were also assessed at specified time points.

Changes in the conduct of the study or planned analyses:

There were seven amendments to the study protocol, with three global amendments and four local amendments specific to the US and/or Japan, although no patients were entered from the US. Five were entered from Japan. Each amendment contained a number of changes but most were minor. The more substantial that altered the study design were as follows:

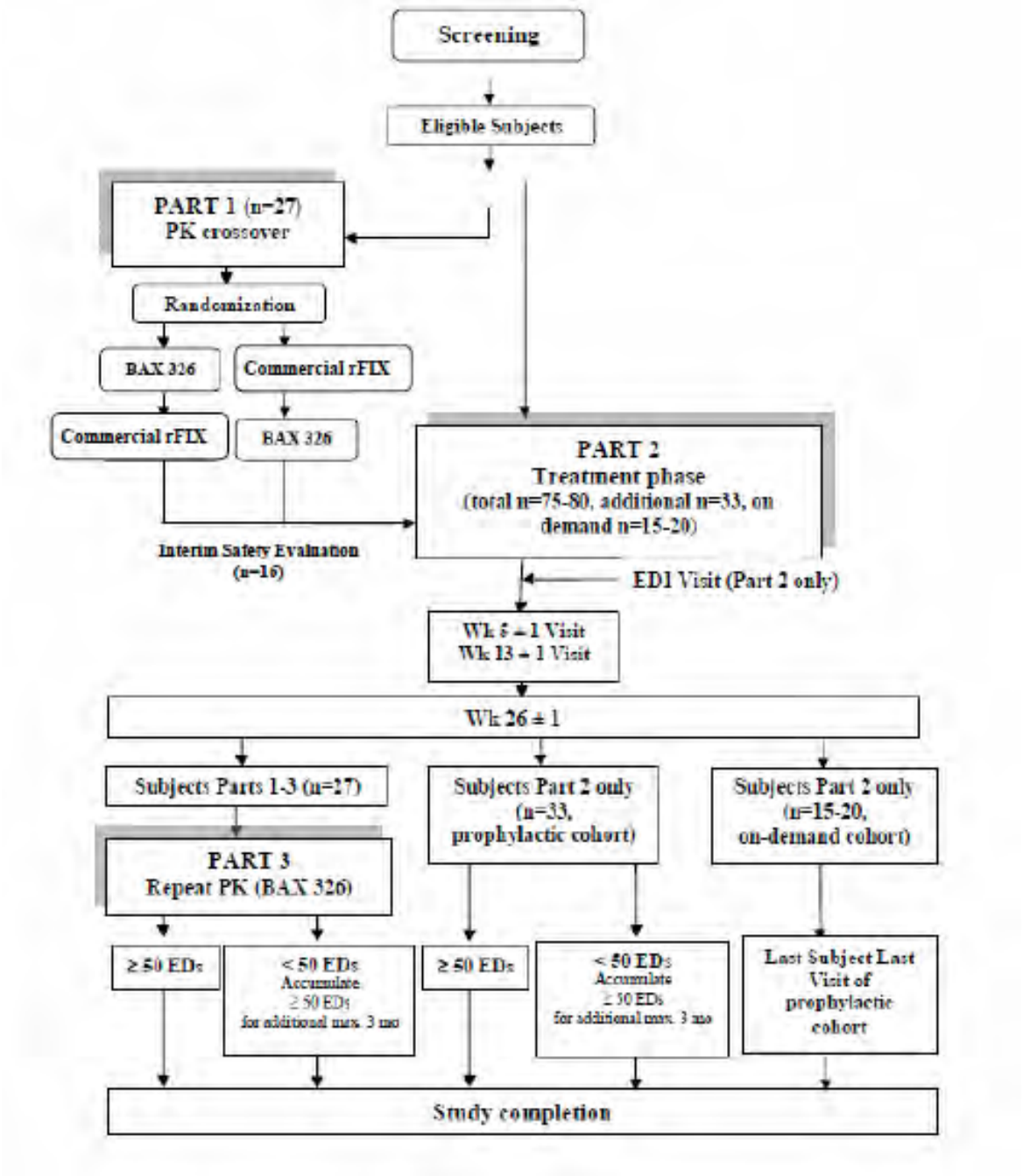
Amendment 1: 5 July 2010 (global): The sample sizes for Parts 1 and 3 were reduced from n = 30 to n = 27 by reducing the drop-out from four to one subject (in order to reduce the overall number of potential drop-outs from four to one); the number of subjects to be enrolled in Part 2 was increased from n = 30 to n = 33 to account for the reduction of the sample size in Part 1 and to maintain the overall sample size of n = 60 in Part 2; and a third interim safety review was added which was to be performed after 24 subjects (20 evaluable) had completed Part 2 of whom 16 subjects had also completed Parts 1 and 3, and had been evaluated for haemostatic efficacy, safety, and immunogenicity for a period 50 EDs or six months, whichever occurred last.

Amendment 2: 16 July 2010 (specific to US and Japan): Per request of the US FDA and the Japanese PMDA, Part 2 of the study was not to start before the safety data of the first 16 subjects who had completed Part 1 had been analysed and the proposed dose to be used in Part 2 had been confirmed. The data were to be evaluated by the DMC.

Amendment 3: 3 May 2011 (global):

1. An additional cohort of 15 to 20 subjects was added to Part 2 of the study. These subjects were to receive on-demand treatment with Rixubis until the last subject of the prophylactic cohort completed the study. The other 60 PTPs (54 evaluable) in Part 2 would receive twice weekly prophylactic infusions over six months, or 50 EDs, whichever occurred last. The total sample size was therefore increased from 60 up to 75-80 PTPs. The two cohorts are described as ‘prophylactic cohort’ and ‘on demand cohort’. The reason for adding an on-demand cohort was to ensure sufficient data on the haemostatic efficacy of Rixubis in the treatment of BEs.
2. The upper acceptable limit of the International Normalised Ratio (INR) in the eligibility criteria was increased from 1.2 (upper limit of normal as defined by the central laboratory) to 1.4 to account for the fluctuating INR values between 1.1 and 1.4, in particular in subjects with hepatitis.

Figure 3: Design of Pivotal Study 250901



3. Although the required minimum wash-out period prior to the PK infusions in Parts 1 and 3 and prior to all study visits in Part 2 was five days, it was added that a washout period of seven days would be preferable to ensure that the baseline FIX activity level was reached.
4. The following subject participation periods for the respective cohorts (prophylactic and on-demand) were added:
   - Prophylactic cohort: eight to 12 months for subjects taking part in Parts 1, 2 and 3; approximately seven to 10 months for subject taking part in Part 2 only (unless prematurely discontinued)
   - On-demand cohort: approximately two to 10 months, depending on when the subject is enrolled.

Amendment 5: 12 Jan 2012: As this amendment was specific to the USA from which no subjects were entered, it is not presented here.

Amendment 6: 2 March 2012 (global): The sample size for the third interim safety review was increased from 24 to 50 subjects (as suggested by FDA).

Amendment 7: 2 March 2012 (Japan): This was as for Amendment 6.

Change to the planned analyses:

The only change was that from Amendment 6, the increase in numbers from 24 to 50 in the third interim safety review.

Part 2: Design:

6.1.1.1.2. Inclusion and exclusion criteria

Inclusion criteria:

- Diagnosis of severe (FIX level < 1%) or moderately severe (FIX level ± 2%) haemophilia B (based on the one stage activated partial thromboplastin time [aPTT] assay), as tested at screening at the central laboratory
- 12 to 65 years of age at time of screening
- Previous treatment with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 150 EDs (based on the subject's medical records)
  - If a subject did not have a verifiable, documented history of 150 EDs, s/he could be enrolled if the following two requirements were met (Please note: This inclusion criterion was not valid for the US and Japan)
    i. there were 100-150 EDs to any FIX product (plasma-derived or recombinant FIX concentrate(s), cryoprecipitate, or fresh frozen plasma) that are not fully documented, and
    ii. s/he had participated in the Immunine Protocol 050901 and accumulated either at least 50 EDs to Immunine or a total of at least 150 EDs to a plasma-derived and/or recombinant FIX concentrate prior to enrolment.]
- No evidence of a history of FIX inhibitors (based on the subject's medical records)
  - [If a verifiable, documented history was unavailable, the subject could be enrolled if s/he had participated in Study 050901 for at least 50 EDs to Immunine prior to enrolment. Please note: This inclusion criterion was not valid for the US and Japan]
- For subjects receiving prophylactic treatment in Part 2: willingness to receive prophylactic treatment over a period of six months
- For subjects receiving on-demand treatment in Part 2: subject had ≥ 12documented BEs requiring treatment within 12 months prior to enrolment and willingness to receive on-demand treatment for the duration of participation in this study

Exclusion criteria:

- History of FIX inhibitors with a titre ≥ 0.6 BU (as determined by the Nijmegen modification of the Bethesda assay or the assay employed in the respective local laboratory) at any time prior to screening.
- Detectable FIX inhibitor at screening, with a titre ≥ 0.6 BU as determined by the Nijmegen modification of the Bethesda assay in the central laboratory.
- Abnormal renal function (serum creatinine > 1.5 times the upper limit of normal).

- Severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalised Ratio (INR) > 1.4, hypoalbuminaemia, portal vein hypertension including presence of otherwise unexplained splenomegaly and history of oesophageal varices.
- Active hepatic disease with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > five times the upper limit of normal.

6.1.1.1.3. Study treatments

Part 2 (prophylactic cohort): 50 IU/kg (ranging from 40-60 IU/kg, which could be increased up to 75 IU/kg, if necessary) twice weekly for a period of six months or for at least 50 EDs to Rixubis (whichever occurred last).

Part 2 (on-demand cohort): BEs were treated according to a dosing guidance provided in the study protocol.

Part 2 (both cohorts): A dose of 75 ± 5 IU/kg of Rixubis was given at each of the study visits during Part 2 to assess FIX incremental recovery (IR).

Part 3: Patients were treated with a single dose of Rixubis of 75 ± 5 IU/kg.

6.1.1.1.4. Efficacy variables and outcomes

Outcomes were based on the following main efficacy variables, which were recorded by the subject, the subject's legal representative (for home treatment) or by authorised, qualified personnel at the participating site (for hospital-based treatment in case of a BE):

- Location of bleed, such as., joint, soft tissue, muscle, body cavity, intracranial, other
- Type of bleed, such as., spontaneous, injury, unknown
- Severity of bleed, such as, minor, moderate, major, life/limb threatening
- Date and time of onset of bleed
- Date and time of each infusion of Rixubis required to achieve adequate haemostasis
- Date and time of resolution of BE
- Type and number of analgesics required
- Overall clinical efficacy rating according to the rating scale as described in Table 6,at 12 ± 1 and 24 ± 1 hours post-treatment and/or at resolution of bleed, if prior to the 12 ± 1 or 24 ± 1 hour post-treatment time-point.

Table 6: Rating Scale for Treatment of Bleeding Episodes

Excellent	Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

Details pertaining to all home treatments for each bleed, including response to treatment, were to be recorded by study subjects in subject diaries provided by the Study Sponsor. At each study visit the Investigator was to review, together with the subject, the response to treatment and

evaluate the haemostatic efficacy rating based on the four point rating scale shown in the above table.

The primary haemostatic efficacy outcomes were:

1. Annualised rate of bleeding episodes (ABR)
2. Treatment of Bleeding Episodes
3. Analysis of Consumption of Rixubis

6.1.1.1.5. Method of assigning subjects to treatment groups and blinding

After the eligibility of the subject had been confirmed, the investigator requested patient randomisation via the Interactive Voice Response System (IVRS) for those subjects participating in Parts 1 and 3. The subject randomisation number was assigned based on the master randomisation list (MRL). Eligible subjects were randomised to receive one of the following two PK infusion sequences:

1. Rixubis followed by BeneFIX or
2. BeneFIX followed by Rixubis, with equal allocation in study Part 1. Using a centralised block randomisation scheme ensured that the number of subjects in each infusion sequence was balanced.

Baxter Global Pharmacovigilance has had access to the MRL. The investigator was to be provided with access only in the event of an emergency requiring unblinding of a study subject. No unblinding was necessary during the course of the study.

Subjects and investigators were only blinded in the crossover PK assessment in Part 1 of the study; Parts 2 and 3 of the study were unrandomised and open label.

6.1.1.1.6. Analysis populations

The FAS was to comprise all subjects who received at least one infusion during the study. The analysis for the haemostatic efficacy endpoints, that is,, analysis of annualised bleed rate, analysis of treatment of BEs and analysis of consumption of Rixubis, was to be performed on the FAS.

6.1.1.1.7. Sample size

The method of determining the sample size for the PK study (Part 1) to be 26 evaluable patients was given in the PK section.

Part 2: Sample size consideration for inhibitor formation:

With the sample size of 50 subjects, the upper limit of the 95% CI of the rate of subjects with an inhibitor is less than 10% if none or one subject develops inhibitors in the study. In order to allow for a 10% dropout rate, a total of about 60 subjects participated in Part 2.

Part 2: Sample size consideration for treatment of bleeding episodes:

An additional cohort of 15-20 subjects was enrolled to evaluate the haemostatic efficacy of BAX 326 in the treatment of bleeding episodes in subjects receiving on demand treatment only.

6.1.1.1.8. Statistical methods

Handling of Missing, Unused, and Spurious Data: For subjects with multiple screening visits resulting in multiple values, the most recent screening visit was used for analysis. If any data was not used in statistical analysis, the reasons were documented, for example, biological implausibility. If a subject's weight was missing from any infusion record, the subject's last recorded weight was used to calculate the weight-adjusted dose. Handling of findings data reported with "<" or ">" symbols were addressed as they arose. For FIX activity levels reported

as below the limit of detection (< 1%), 0.5 (a value halfway between zero and one) was imputed for summary purposes, graphical presentations, and IR calculation.

Analysis of Annualised Bleed Rate: ABR during prophylaxis (twice-weekly) and on-demand treatment in Part 2 was calculated as (Number of bleeding episodes/observed treatment period in days) * 365.25. The treatment period on prophylaxis was defined as time between the first and the last prophylactic infusions and ABR on prophylaxis was calculated for subjects having received a minimum of three months of prophylactic treatment with BAX 326. The treatment period for surgery was excluded from the bleed rate calculation.

ABR during Part 2 was summarised by bleeding site (joint/non-joint) and cause (spontaneous /injury) in each of the treatment groups. Treatment duration, subject's own historical on-demand ABR (if applicable), and the compliance to prophylactic treatment was also summarised. A subject-level listing was followed. Target joints were explored by summarising improved, worsened, unchanged target joints from screening visit, and new target joints developed during the study. It was summarised for prophylaxis and on-demand treatment separately in a table and a subject level listing was also provided.

Analysis of Treatment of Bleeding Episode: The efficacy of bleeding treatment of BAX 326 was summarised. It included overall haemostatic efficacy rating at resolution of bleed, and the number of infusions and total weight-adjusted dose per bleeding episode, by anatomical site (joint/non-joint), cause (spontaneous/injury), severity (minor, moderate, major, and life/limb-threatening), and treatment regimen (prophylaxis and on-demand treatment). The overall haemostatic efficacy rating performed prior to resolution of bleed and at the 12 ± 1 hour and 24 ± 1 hour from the first infusion of bleeding treatment was also analysed as exploratory endpoints. The number of bleeding episodes beginning within 24 and 48 hours of prophylactic infusion as exploratory endpoint was also calculated. A listing for all bleeding episodes including haemostatic efficacy ratings at different time points was provided.

Analysis of Consumption of BAX 326: Product consumption of BAX 326 was summarised as average number of infusions and average weight-adjusted consumption per month, and average weight-adjusted consumption per event (for a prophylactic infusion and a bleed).

Evaluation of Quality of Life: For all scores, paired t-tests were employed to evaluate mean change from baseline at Week 26 ± 1 follow-up. Additional descriptive analyses assessing changes in HRQOL scores between the prophylaxis cohort with the on-demand cohort were to be performed.

Health Resource Use: The analysis of the health resource use data was descriptive in nature. The total number of hospitalisations, ER visits, office visits and days missed from work/school were reported. Additional analyses were to include mean hospitalisations per subject, mean length of stay, and mean days missed from work/school.

6.1.1.1.9. Participant flow

Number of Participants Planned: Twenty seven (27) subjects (26 evaluable) in Parts 1 and 3 + an additional 33 subjects in Part 2 (60 in total, 54 evaluable) were to receive prophylactic treatment and up to 15-20 subjects in Part 2 were to receive on-demand treatment, producing a total of 75-80 subjects.

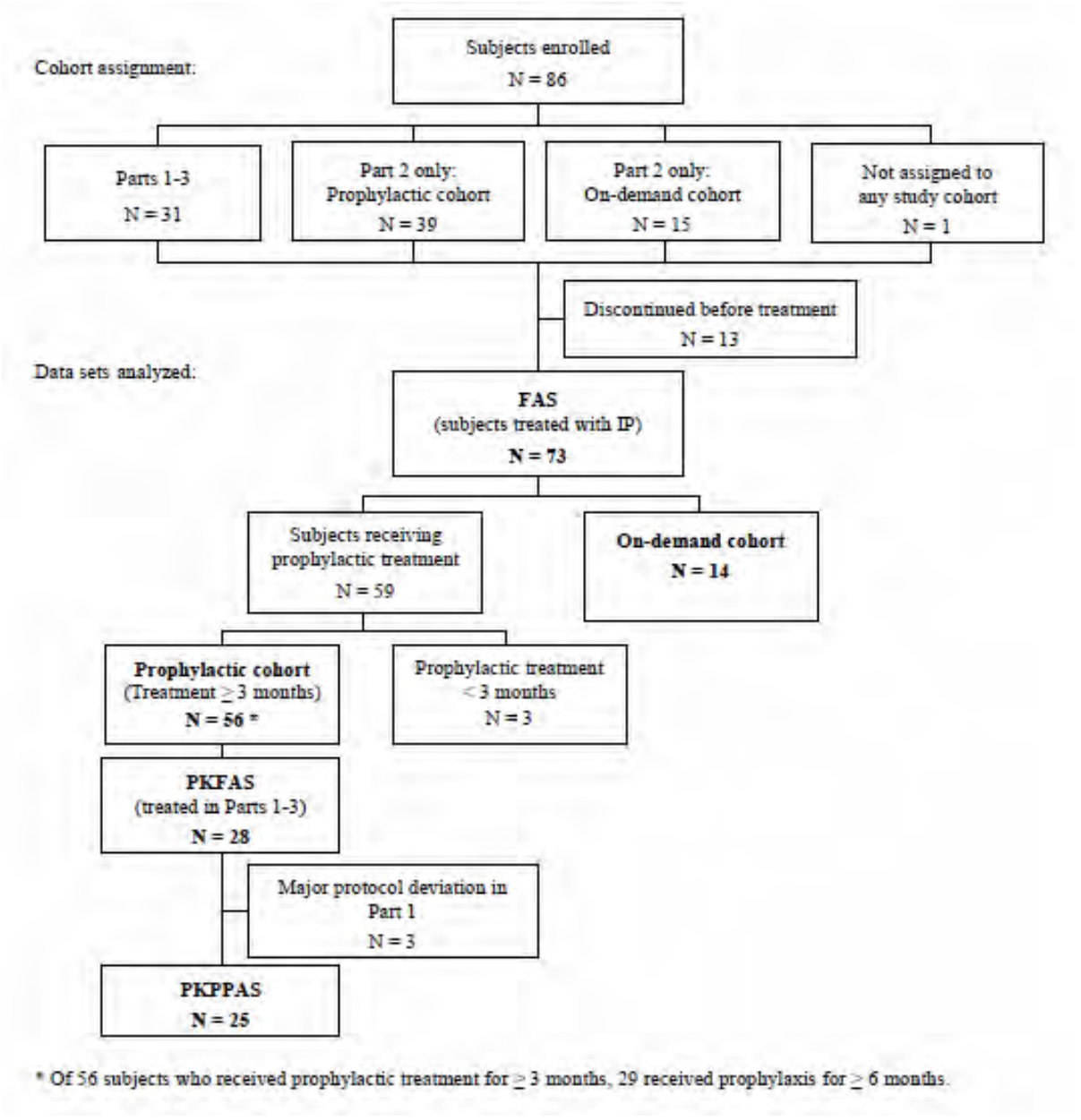
Analysed:

- PKPPAS: 25 subjects
- PKFAS: 28 subjects
- FAS: 73 subjects
- Prophylactic cohort (subjects who received at least three months of prophylactic treatment): 56 subjects

- 29 subjects received at least six months of prophylactic treatment
- On-demand cohort: 14 subjects

The disposition of patients is shown in the following figure (Figure 4).

Figure 4: Disposition of Patients in Pivotal Study 250901



Discontinuations: Thirteen (15.1%) of 86 enrolled subjects discontinued the study before treatment (see above table). One subject discontinued due to an AE (Subject 150002: suicide attempt), two subjects were screen failures, and seven subjects discontinued on their own accord. A further four of 86 enrolled subjects discontinued the study after treatment. One was based on a physician decision (for right ureteral calculus). Three subjects were discontinued when the sponsor closed one study site – the Hospital do Apoio de Brasilia SAIN - Lote 04 - Unidade de Coagulopatias Asa Norte - Brasilia, Distrito Federal 72.620-000, Brazil.

6.1.1.1.10. Major protocol violations/deviations

The Study Report of the Pivotal Study, states "A total of 369 deviations were reported during the study. Of these, 37 were considered major deviations, the majority of which concerned IP

administration. Individual subject deviations are listed". No other comment was made in the Study Report.

None of the Summary of Clinical Efficacy, the Summary of Clinical Safety, or the Clinical Overview mentioned Protocol Deviations.

> Comment: Two unsuccessful requests were made to the sponsor to arrange and justify the large numbers of protocol deviations that included contradictions in classification, as well as safety and efficacy issues. A new listing of major deviations was provided that attempted to group the deviations by type, but again without comment or explanation. Consequently the clinical evaluator evaluated the deviations as follows. This has led to a number of questions that the sponsor will need to address in a satisfactory manner before indications one and two can be recommended for approval (see questions for sponsor in Clinical Questions).

Evaluator's summary and review of protocol deviations in the pivotal trial summary of relevant numbers:

Number of patients in the PK FAS: 28 (PK PPAS, n=25) [Parts 1 and 3 of pivotal study].

Number randomised in Part 2: 73. (Prophylactic treatment = 59; treatment on demand = 14).

Note that the same patients in the PK section continued in Part 2, so the total unique patient population was 73.

Total number of protocol deviations = 369. (Major= 37[36]. Minor = 332[333] as classified).

> Comment: The number of major deviations was stated in the Study Report above to be 37 but only 36 are listed, so 36 is the number considered here. Although the average of protocol deviations per patient was 369/73 or 5.0 per patient, this has little meaning (except for the high number), since some individual patients had multiple deviations. What follows then is a summary of the patients who had major and minor deviations. Also described is the same type of deviation as major in some cases and minor in others. This contradiction requires explanation by the sponsor, so the true number of major and minor deviations awaits the review of the sponsor's explanation.

Number of patients with a minor or major deviation: 69 (95% of total patient population)

Number with a major deviation: 17 (23%)

Number with a minor deviation: 52 (71%)

Number with a single major deviation; eight; with two major deviations: five; with three major deviations, three; with five major deviations; two. These patients often had large numbers of minor deviations as well. For example patient 230002 had three major and 15 minor, and patient 150004 had five major and six minor deviations.

Number with two or more major deviations: 10 (14% of total population; 56% of all major deviations).

Of the 51 patients with minor deviations, 37 (73%) had no major deviation.

> Comment: The number of deviations that are acceptable in any clinical trial is not agreed. The FDA and the EMA do not state an acceptable figure. Some authors have argued that a trial is of doubtful reliability if the incidence of protocol deviations exceeds 10% of patients in the trial[1]. By any standards, when the incidence of major deviations is 23%, as in the present pivotal trial, the integrity of the trial is called into question, and requires an explanation from the sponsor.

[1] Pocock SJ. 1983. In: Clinical Trials: A Practical Approach. John Wiley & Sons New York, Protocol Deviations; pp. 176–186

Types of major deviations:

Error in Administration of Investigational Product: 31 of total of 36

Protocol Procedure not done: Two

Protocol Schedule not followed: One

Other: Two

> Comment: Administration errors (major deviations) occurred repeatedly in some patients. Two patients had one error; eight had two errors each; one had three errors; and two had five errors each. It is disturbing that the same drug administration error occurred in the same patient repeatedly in some of these cases. The "Other" deviations were one case (020001) in which a patient's consent seems to have been obtained before the consent form was approved (Sponsor needs to clarify). The other (140002) was a mistake using the wrong version of the consent form.

Significance of protocol deviations in the pivotal trial:

The significance of the deviations with respect to safety and to data analysis will depend on a review of the sponsor's response to questions on the specific deviations.

Discussion:

Definitions: The terms 'protocol deviation' and 'protocol violation' are not used separately in international guidelines such as those of the EMA and the FDA. The FDA defines 'protocol deviation' as "….any change, divergence, or departure from the study design or procedures defined in the protocol." and 'important protocol deviation' as a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being"[2].

The NHMRC guidelines to clinical trials uses the term 'protocol violation', defined as "…. a failure to comply with the study protocol as approved by the Ethics Committee. A violation is a serious non-compliance with the protocol that can result in the exclusion of a participant or their results in the study, participant refusal to be part of the study, and in some cases a charge of research misconduct. 'Protocol deviation' is a less serious non-compliance with the approved study protocol and in some cases may be considered as a "breach of the Code", that is the Australian Code for the Responsible Conduct of Research, NHMRC, 2007."

The present application uses the terms "major" and "minor" [protocol] deviations without definition. The usual definitions are that a major deviation is one that may impact on subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study. A minor deviation is one that does not impact subject safety, compromise the integrity of study data and/or affect subject's willingness to participate in the study. The clinical evaluator used these terms and definitions in this assessment.

GCP, Clinical Trial Guidelines and Protocol Deviations: The guidelines for GCP and the ICH guidelines for the conduct and reporting of clinical trials both consider major protocol deviations as potential safety risks to patients, as well as possibly compromising efficacy analyses. To comply with these guidelines, the clinical trial protocol must clearly set out procedures for identifying, recording and reporting protocol deviations. Investigators must be informed and responsible, and the site monitors must carefully review and check the identification, recording and reporting of the deviations. The trial manager also must take actions to prevent the same deviations from occurring.

[2] Patricia Holobaugh. FDA:CBER: Reporting information regarding the falsification of data. <http://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM283427.pdf>, Accessed 21/4/2013

Comment: The protocol of the pivotal study provides appropriate procedures for the management of protocol deviations, including the responsibility of investigators and monitors, but the Statistical Analysis Plan, and the reporting in the Study Report, the study Summaries and the Clinical Overview are all inadequate. The problems therefore may have been with poorly trained and informed investigators, faulty monitoring or both. An attempt will be made to assess this problem, and its possible effect on the trial's safety and efficacy analyses on review of the sponsor's response to the questions in Clinical Questions in this report.

6.1.1.1.11. Baseline data

The patient population was different in a number of ways from that of Australia haemophiliacs. These differences were addressed in the submission with reference to haemophilia B and its treatment, as follows:

'The countries in which the highest number of subjects were enrolled (Russia, Poland, Bulgaria, Ukraine) are considered upper middle income countries, in which the reported number of IUs of FIX used has increased over a recent seven year observation period. Some adults with severe haemophilia B in these geographies historically had limited access to FIX product and comprehensive haemophilia care. This may impact response to therapy compared to persons with pristine joints and access to early prophylaxis. However, all subjects had at least 150 previous exposure days (EDs) to a FIX product before enrolment or in situations where the 150 EDs could not be documented by the treating investigator, alternatively the subject could have previously participated in Baxter Immunine Study 050901 (conducted with a plasma-derived FIX product Immunine, manufactured by Baxter). This ensured that all subjects had over 50 EDs to a FIX concentrate and, at least 150 EDs to a FIX containing product. There were 34 subjects enrolled in the Immunine study who then advanced into the pivotal study. The most frequently reported previous FIX product used (in 15.1% of subjects) was the plasma-derived FIX product Immunine, manufactured by Baxter. FIX antigen levels were ≥ 1% in the majority of subjects (69.9%), with levels ≥ 40 % in 30.1% of subjects. Thirty-nine (53.4%) subjects had a FIX activity level < 1%; while 34 (46.6%) had a FIX activity level of 1-2%.'

Comment: The single US site 'initiated' (University of California at San Diego Medical Centre) did not enter any patients.

The demographics of patients in the pivotal trial were as follows:

All analysed subjects were male. The median age of all 73 subjects in the FAS was 33 years (range 12-59 years); there were three paediatric subjects aged 12, 13, and 15 years. Most subjects were white (83.6%); the rest were Japanese (6.8%), Latin American/Mestizo (6.8%), Black or African American (1.4%) and Arabic (1.4%). Thirty nine (53.4%) subjects had a FIX activity level < 1%; while 34 (46.6%) subjects had a FIX activity level of 1-2%. FIX antigen levels were ≥ 1% in the majority of subjects (69.9%), with levels ≥ 40 % in 30.1% of subjects.

A missense mutation was diagnosed in 45.2% of subjects through genetic testing, followed by a nonsense mutation in 19.2%. The majority of subjects (87.7%) had arthropathy at screening; one to two target joints were present in 41.1% of subjects; 12.3% of subjects had three to four target joints and a further 12.3% of subjects had > four target joints. Only 13 (17.8%) of subjects had received prophylactic treatment prior to enrolment, whereas 27 (37%) had received on-demand treatment only and the remainder (33 subjects, 45.2%) both. The most frequently reported previous FIX product used (in 15.1% of subjects) was the plasma-derived FIX product Immunine, manufactured and marketed by Baxter.

Comment: 'Target joint' was defined as one in which there had been ≥ four bleeds in the six months prior to study entry. The relatively large number of "target joints" – more than three in 30% of patients, suggests as indicated above that many of the study population had not received state of the art care before study entry, and their response

may have therefore been compromised. The efficacy in Australian patients may therefore be greater.

6.1.1.1.12. Results for the primary efficacy outcome

The FAS comprised all 73 subjects who were exposed to IP. Within the FAS, subjects were further analysed by the type of treatment they received in Part 2:

- Prophylactic treatment (n=59)
  - Subjects with ≥ three months of prophylaxis (n=56)
  - Subjects with ≥ six months of prophylaxis (n=29)
- On-demand treatment (n=14)

1. Annualised rate of bleeding episodes:

Prophylactic Treatment: A total of 56 subjects received prophylaxis twice weekly for at least three months. All subjects on prophylaxis had 50 or more EDs to Rixubis during the study (mean number of EDs was 58.3 [± 8.0]; 29 subjects received at least six months of prophylactic treatment.

The mean ABR in the prophylactic cohort (n=56) was 4.26 (SD ± 5.80; median: 1.99), [Table 7]. There was no difference in the ABR for BEs that occurred spontaneously (1.72) and those due to injury (1.70); 0.84 were of unknown cause.

> Comment: The large difference between the mean and median values is accounted for by the high SD values of the mean and that 43% of subjects had no bleeds during the period, reducing the mean value. No direct comparison of this efficacy outcome for prophylactic and on-demand treatment was provided, nor was any required to show efficacy under the EMEA Guidelines[3]. The PI for a commercially available rFIX (BeneFIX) administered at a similar dose for a similar time gives the ABE as 3.1 bleeds per year (whether median or mean, not stated), with 65% of subjects not having a spontaneous bleed while on prophylaxis.

On-Demand Treatment: Among the 14 subjects in the on-demand cohort of the FAS, who all had bleeds, the mean ABR was 33.87 (± 17.37) and the median ABR 26.98 (range: 12.9-73.1) [Table 7]. This was slightly higher than the mean and median of these subjects' own historical on demand bleed rates, which were 24.50 (± 13.65) and 17, respectively, with a range of 12 - 56. The mean rate of joint bleeds in the on-demand cohort was 29.88 (± 16.05) in the study versus 3.99 (± 5.26) for non-joint bleeds. The rate of spontaneous bleeds was higher (mean: 19.85 ± 12.90) than the rate of bleeds caused by injury (mean: 10.58 ± 13.58) [Table 7].

[3] Committee for Propriety Medicinal Products (CPMP). 2000. Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX Products. London. CPMP/BPWG/1561/99.

Table 7: Annualised Bleeding Rate by Treatment Regimen (FAS)

Treatment	Statistic	Site		Cause			All
		Joint[a]	Non-Joint[b]	Spontaneous	Injury	Unknown	
Prophylaxis[c]	N	56	56	56	56	56	56
	Mean (Std)	2.85 (4.25)	1.41 (2.87)	1.72 (3.26)	1.70 (2.80)	0.84 (2.64)	4.26 (5.80)
	Median	0.00	0.00	0.00	0.00	0.00	1.99
	Q25 ; Q75	0.0 ; 4.5	0.0 ; 2.0	0.0 ; 2.0	0.0 ; 2.1	0.0 ; 0.0	0.0 ; 6.5
	Min ; Max	0.0 ; 21.5	0.0 ; 10.7	0.0 ; 15.6	0.0 ; 10.7	0.0 ; 12.7	0.0 ; 23.4
On-Demand	N	14	14	14	14	14	14
	Mean (Std)	29.88 (16.05)	3.99 (5.26)	19.85 (12.90)	10.58 (13.58)	3.44 (8.13)	33.87 (17.37)
	Median	26.98	1.18	16.63	6.51	0.00	26.98
	Q25 ; Q75	18.1 ; 37.9	0.0 ; 7.2	14.1 ; 23.6	0.0 ; 9.9	0.0 ; 3.5	25.3 ; 42.4
	Min ; Max	8.6 ; 60.2	0.0 ; 14.8	0.0 ; 47.3	0.0 ; 39.3	0.0 ; 30.4	12.9 ; 73.1

[a] Major joints: wrist, elbow, shoulder, hip, knee, ankle
[b] Soft tissue, muscle, body cavity, intracranial and other
[c] Subjects received a minimum of 3 months of prophylactic treatment with BAX326.
[generated by 250901_csra_effic.sas]

Comment: The PI for BeneFIX gives the ABR for on-demand treatment as 21.8 bleeds a year, although the number of subjects was small (n=6). The Study Report states, "As expected, these results show that ABRs were lower in subjects who received prophylactic treatment than in subjects who received on-demand treatment. While the ABRs of spontaneous BEs and BEs caused by injury were comparable in the prophylactic cohort (means of 1.72 and 1.70, respectively), there was a great difference between the ABR of spontaneous BEs (mean: 19.85) and BEs caused by injury (mean: 10.58) in the on-demand cohort. However, a statistical comparison between the prophylactic and the on-demand cohort was not performed due to the baseline differences between the two study populations with regard to ABR prior to enrolment".

2. Treatment of Bleeding Events: The results are shown in Table 8.

Table 8: Characteristics of all bleeding episodes by site and cause

Parameter	Category/ Statistic	Site				Cause		
		Target Joint[a] N = 107 n (%)	Non-Target Joint[a] N = 90 n (%)	All Joint[a] N = 197 n (%)	Non-Joint[b] N = 52 n (%)	Spontaneous N = 130 n (%)	Injury N = 90 n (%)	Unknown N = 29 n (%)
Number of Infusions per Bleed	1	65 (60.7)	57 (63.3)	122 (61.9)	31 (59.6)	84 (64.6)	50 (55.6)	19 (65.5)
	2	26 (24.3)	21 (23.3)	47 (23.9)	11 (21.2)	29 (22.3)	24 (26.7)	5 (17.2)
	>=3	16 (15.0)	12 (13.3)	28 (14.2)	10 (19.2)	17 (13.1)	16 (17.8)	5 (17.2)
Hemostatic Efficacy at Resolution of Bleed	Excellent	53 (49.5)	32 (35.6)	85 (43.1)	17 (32.7)	51 (39.2)	40 (44.4)	11 (37.9)
	Good	46 (43.0)	57 (63.3)	103 (52.3)	34 (65.4)	75 (57.7)	45 (50.0)	17 (58.6)
	Fair	5 (4.7)	0 (0.0)	5 (2.5)	0 (0.0)	2 (1.5)	2 (2.2)	1 (3.4)
	None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not Reported	3 (2.8)	1 (1.1)	4 (2.0)	1 (1.9)	2 (1.5)	3 (3.3)	0 (0.0)
Total Dose per Bleed [IU/kg]	N	107	90	197	52	130	90	29
	Mean (Std)	80.3 (54.0)	81.8 (60.9)	81.0 (57.1)	94.5 (64.3)	75.9 (50.3)	91.2 (62.5)	96.2 (77.0)
	Median	56.5	59.0	56.5	68.7	52.3	70.0	56.5
	Q25 ; Q75	48 ; 97	46 ; 97	47 ; 97	50 ; 130	45 ; 92	48 ; 116	51 ; 108
	Min ; Max	26 ; 278	25 ; 372	25 ; 372	34 ; 350	26 ; 243	25 ; 350	39 ; 372

Abbreviation: N = Number of bleeds treated with BAX326
Only infusions required until resolution of bleed are considered.
[a] Major joints: wrist, elbow, shoulder, hip, knee, ankle
[b] Soft tissue, muscle, body cavity, intracranial and other
[generated by 250901_csra_effic.sas]

Table 9: Characteristics of all bleeding episodes by bleeding severity

Parameter	Category/ Statistic	Minor N = 71 n (%)	Moderate N = 163 n (%)	Major N = 15 n (%)	All N = 249 n (%)
Number of Infusions per Bleed	1	56 (78.9)	92 (56.4)	5 (33.3)	153 (61.4)
	2	9 (12.7)	46 (28.2)	3 (20.0)	58 (23.3)
	>=3	6 (8.5)	25 (15.3)	7 (46.7)	38 (15.3)
Hemostatic Efficacy at Resolution of Bleed	Excellent	45 (63.4)	53 (32.5)	4 (26.7)	102 (41.0)
	Good	25 (35.2)	102 (62.6)	10 (66.7)	137 (55.0)
	Fair	0 (0.0)	4 (2.5)	1 (6.7)	5 (2.0)
	None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not Reported	1 (1.4)	4 (2.5)	0 (0.0)	5 (2.0)
Total Dose per Bleed [IU/kg]	N	71	163	15	249
	Mean (Std)	66.11 (52.98)	87.85 (58.24)	124.00 (67.03)	83.83 (58.82)
	Median	48.38	65.76	116.28	62.29
	Q25 ; Q75	36.8 ; 70.3	48.4 ; 104.7	55.8 ; 178.9	48.0 ; 98.3
	Min ; Max	25.7 ; 349.6	25.5 ; 372.1	47.2 ; 277.6	25.5 ; 372.1
Estimated FIX Increase from First Treatment [IU/dL]*	N	71	163	15	249
	Mean (Std)	36.72 (11.41)	40.17 (12.75)	46.09 (12.21)	39.55 (12.51)
	Median	34.94	37.92	43.50	37.25
	Q25 ; Q75	29.3 ; 43.9	31.5 ; 48.5	37.9 ; 50.8	31.0 ; 48.5
	Min ; Max	20.6 ; 86.9	12.0 ; 78.0	30.6 ; 81.8	12.0 ; 86.9

Abbreviation: N = Number of bleeds treated with BAX326
Only infusions received until resolution of bleed are considered.
* Defined as the dose [IU/kg] from the first infusion of bleeding treatment multiplied by the most recent incremental recovery at 30 minutes post-infusion of BAX326 prior to the infusion [IU/dL /IU/kg]
[generated by 250901_cura_effic.sas]

Number of infusions per bleeding event: Of the total of 249 BEs, the majority (153; 61.4%) were treated with one infusion. Fifty-eight (23.3%) BEs were treated with two infusions, and 38 (15.3%) BEs were treated with more than three infusions (Table 9). Of 197 joint bleeds, 122 (61.9%) were treated with one infusion and 47 (23.9%) were treated with two infusions. The number of infusions needed to treat bleeds into target joints [as defined at screening] non-target joint BEs, and non-joint BEs were similar. The majority of spontaneous bleeds and bleeds caused by injury were also treated with one infusion (64.4% and 55.6%, respectively).

Minor and moderate bleeds were mostly treated with one infusion only (78.9% and 56.4%, respectively). Seven of 15 major bleeds (46.7%) were treated with more than three infusions.

Total weight-adjusted dose per bleeding event by site and cause: The mean total dose per bleed was 83.83 ± 58.82 IU/kg (median: 62.29 IU/kg, range: 25.5-372.1 IU/kg). The highest mean dose (94.5 ± 64.3 IU/kg) was administered for non-joint bleeds. A mean dose of 81.0 (± 57.1) IU/kg (median: 56.5 IU/kg) was administered for joint bleeds.

A higher mean dose was administered for bleeds caused by injury (91.2 ± 62.5 IU/kg; range: 25-350 IU/kg) than for spontaneous bleeds (75.9 ± 50.3 IU/kg; range: 26-243 IU/kg) (Table 8 and Table 9). Three bleeds in three subjects were treated with more than 300 IU/kg each.

> Comment: The difference in the doses for each of injury and spontaneous bleed groups is unlikely to be statistically or clinically significant for the following reasons: the large values of the SD relative to the mean values; the similar values of the doses for the Q75 populations in each of the groups, injury and spontaneous bleeds (116 and 92

respectively); and two of the three patients who needed a dose greater than 300IU/kg were in the 'injury' group, the third being in the 'unknown' group.

Total weight-adjusted dose per bleeding event by severity and treatment regimen: The mean estimated initial FIX increase for all bleeds from the first treatment was 39.55 ± 12.51 IU/dL (median: 37.25 IU/dL; range: 12.0-86.9 IU/dL). As expected, the highest estimated FIX increase was noted for 15 major BEs, with a mean of 46.09 ± 12.21 IU/dL (median: 43.50 IU/dL; range: 30.6-81.8 IU/dL). However, this was still at the lower end of the range of proposed required FIX levels. The mean FIX increase for minor bleeds was 36.72 ± 11.41 IU/dL (median: 34.94 IU/dL; range: 20.6-86.9 IU/dL) and 40.17 ± 12.75 IU/dL (median: 37.92 IU/dL; range: 12.0-78.0 IU/dL) for moderate bleeds; these were within the recommended required FIX levels (Table 9). Of a total of 249 BEs in the FAS, 115 occurred during prophylactic treatment and 134 in the on-demand cohort (Table 10).

Comment: Neither the Clinical Overview nor the Study Report discussed or compared these two sets of data, although both sets were listed for analysis in the Statistical Analysis Plan. A comparison (Table 10) shows that for all patients in the prophylaxis and on-demand groups, many more infusions per bleed were needed in the former (> 3, 31% compared with 2%), while the median total dose per bleed was roughly half in the on-demand group (97 compared with 48 IU/kg).

Table 10: Characteristics of all bleeding episodes by treatment regimen

		Prophylaxis			On-Demand		
Parameter	Category/ Statistic	FIX <1% N = 50 n (%)	FIX 1-2% N = 65 n (%)	All N = 115 n (%)	FIX <1% N = 99 n (%)	FIX 1-2% N = 35 n (%)	All N = 134 n (%)
Number of Infusions per Bleed	1	23 (46.0)	26 (40.0)	49 (42.6)	75 (75.8)	29 (82.9)	104 (77.6)
	2	13 (26.0)	17 (26.2)	30 (26.1)	22 (22.2)	6 (17.1)	28 (20.9)
	>=3	14 (28.0)	22 (33.8)	36 (31.3)	2 (2.0)	0 (0.0)	2 (1.5)
Hemostatic Efficacy at Resolution of Bleed	Excellent	14 (28.0)	15 (23.1)	29 (25.2)	56 (56.6)	17 (48.6)	73 (54.5)
	Good	35 (70.0)	45 (69.2)	80 (69.6)	39 (39.4)	18 (51.4)	57 (42.5)
	Fair	1 (2.0)	3 (4.6)	4 (3.5)	1 (1.0)	0 (0.0)	1 (0.7)
	None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not Reported	0 (0.0)	2 (3.1)	2 (1.7)	3 (3.0)	0 (0.0)	3 (2.2)
Total Dose per Bleed [IU/kg]	N	50	65	115	99	35	134
	Mean (Std)	113.5 (80.0)	115.5 (62.9)	114.6 (70.5)	58.7 (27.5)	53.7 (19.6)	57.4 (25.7)
	Median	88.2	98.3	97.1	51.6	48.4	48.4
	Q25 ; Q75	51 ; 153	62 ; 150	52 ; 153	39 ; 70	47 ; 57	39 ; 70
	Min ; Max	25 ; 372	41 ; 311	25 ; 372	26 ; 186	34 ; 97	26 ; 186

Abbreviation: N = Number of bleeds treated with BAX326
Only infusions required until resolution of bleed are considered.
[generated by 250901_csra_effic.sas]

Efficacy rating at resolution of bleed: Haemostatic efficacy at resolution of bleed was rated 'excellent' in 41.0% and 'good' in 55.0% of all treated BEs (total of 96.0%). Only 2.0% of bleed treatments were rated as 'fair', and none had a rating of 'none'. For the remaining 2.0%, no efficacy ratings were provided (Table 9). The treatment in the on-demand group was rated as excellent twice as often as in the prophylactic group (55% compared with 25% (Table 10).

Treatment of bleeding episodes with Rixubis pilot and commercial product: During the pivotal study, clinical material was changed from pilot to commercial final drug product (FDP). An in vitro comparability study demonstrated that the change in manufacturing facility and decrease in NaCl content had no influence on the structure or function of rFIX. The biopharmaceutical similarity between pilot and commercial Rixubis was evaluated by a descriptive comparison of PK. Here the efficacy parameters in of each product in the pivotal trial are presented.

The efficacy parameters 'number of infusions per bleed', 'haemostatic efficacy at resolution of bleed' and 'total dose per bleed' have been analysed for 25 bleeds that were treated with Rixubis pilot product only, for 182 bleeds treated with Rixubis commercial product only and for 42 bleeds treated with both pilot and commercial product. Due to the difference in numbers of bleeds analysed per group, it was not possible to draw any meaningful conclusions from the results. However, 96.0% of bleeds treated with pilot product only and 96.7% of bleeds treated with commercial product had efficacy ratings of 'excellent' or 'good'. In comparison, 92.8% of bleeds treated with both types of CTM rated the efficacy at resolution of bleed as 'excellent' or 'good'. The mean total dose per bleed was 92.7 ± 55.9 IU/kg in the pilot product group and 73.1 ± 49.0 IU/kg in the commercial product group, compared with 124.9 ± 78.9 IU/kg in the group treated with both pilot and commercial product.

> Comment: The actual results do not support equal efficacy of the two products (see Table 11). The data show that the percentage of subjects requiring three or more infusions per bleed were greater in the pilot group (24% compared with 8%), and the median and mean doses per bleed (median 74 compared with 56IU/kg) were also greater in the pilot group. These results suggest the commercial preparation was more effective than the pilot material. The ratings at resolution of the bleeds were similar, but this would be expected after more of the pilot material was used than of the commercial material as shown by the data to achieve the clinical result. I conclude that there is a strong suggestion that the commercial material was more active than the pilot material. If so, there would be no regulatory concern because the commercial material was the more effective.

Table 11: Comparison of Pilot and Commercial Rixubis in treating BEs

Parameter	Category/ Statistic	Treated with Pilot Only N = 25 n (%)	Treated with Commercial Only N = 182 n (%)	Treated with Both Pilot and Commercial N = 42 n (%)
Number of Infusions per Bleed	1	12 (48.0)	125 (68.7)	16 (38.1)
	2	7 (28.0)	42 (23.1)	9 (21.4)
	>=3	6 (24.0)	15 (8.2)	17 (40.5)
Hemostatic Efficacy at Resolution of Bleed	Excellent	9 (36.0)	84 (46.2)	9 (21.4)
	Good	15 (60.0)	92 (50.5)	30 (71.4)
	Fair	1 (4.0)	2 (1.1)	2 (4.8)
	None	0 (0.0)	0 (0.0)	0 (0.0)
	Not Reported	0 (0.0)	4 (2.2)	1 (2.4)
Total Dose per Bleed [IU/kg]	N	25	182	42
	Mean (Std)	92.7 (55.9)	73.1 (49.0)	124.9 (78.9)
	Median	74.3	56.0	103.3
	Q25 ; Q75	48 ; 97	44 ; 90	51 ; 157
	Min ; Max	47 ; 240	25 ; 350	45 ; 372

Abbreviation: N = Number of bleeds treated with BAX326
Only infusions required until resolution of bleed are considered.
[generated by 250901_csra_add1.sas]

3. Analysis of Consumption of Rixubis:

An overview of Rixubis consumption by type of treatment is provided in Table 12 and Table 13.

Table 12: Consumption of Rixubis per Subject. FAS Pivotal Study

Parameter	Statistic	Parts 1-3 and Part 2 Only: Prophylaxis	Part 2 Only: On-Demand	All
Total Consumption [IU]	N	59	14	73
	Sum	11,609,436	804,354	12,413,790
Total Consumption [IU/kg]	N	59	14	73
	Sum	166,208	11,772	177,980
Consumption per Month [IU/kg]	N	59	14	73
	Mean (Std)	356.1 (61.3)	166.6 (64.2)	319.7 (97.0)
	Median	347.8	167.3	333.6
	Q25 ; Q75	320 ; 396	102 ; 234	280 ; 376
	Min ; Max	159 ; 516	92 ; 266	92 ; 516
Number of Infusions per Month	N	59	14	73
	Mean (Std)	6.9 (1.0)	3.1 (1.2)	6.1 (1.8)
	Median	6.7	2.7	6.6
	Q25 ; Q75	6 ; 7	2 ; 4	6 ; 7
	Min ; Max	3 ; 10	2 ; 5	2 ; 10

[generated by 250901_csra_ex.sas]

Table 13: Consumption of Rixubis per Event per subject, FAS Pivotal Study

Parameter	Statistic	Prophylactic	Bleeding Treatment[a]
Consumption per Event [IU/kg]	N	59	47
	Mean (Std)	49.5 (4.8)	93.2 (41.3)
	Median	50.5	87.1
	Q25 ; Q75	46 ; 52	56 ; 125
	Min ; Max	40 ; 63	34 ; 210

[a] Only infusions required until resolution of bleed are considered.
[generated by 250901_csra_ex.sas]

All 73 subjects included in the FAS, consumed a total of 12,413,790 IU or – in terms of weight-adjusted consumption – 177,980 IU/kg. In the group consisting of Part 1-3 subjects and subjects from the prophylactic cohort in Part 2 (n=59), the total consumption was 11,609,436 IU or 166,208 IU/kg. In the on-demand cohort of Part 2 (n=14), the total consumption was 804,354 IU or 11,772 IU/kg. Median consumption per month was 347.8 IU/kg (mean: 356.1 ±61.3 IU/kg) in the Part 1-3 subjects and prophylactic cohort (n=59) and 167.3 IU/kg (mean: 166.6 ±64.2 IU/kg) in the on-demand cohort of Part 2 (n=14). By contrast, all 73 subjects in the FAS had a median consumption of 333.6 IU/kg per month (mean: 319.7 ± 97.0 IU/kg).

The median number of infusions administered per month in the Part 1-3 subjects and prophylactic cohort (n=59) was 6.7 (mean: 6.9 ± 1.0) while it was only 2.7 (mean: 3.1 ± 1.2) in the on-demand cohort (n=14). No separate results are provided for 'number of infusions' and 'weight-adjusted consumption' per year. However, 'number of infusions per year' and 'weight-adjusted consumption per year' are equivalent to the respective results per month multiplied by 12. Weight-adjusted consumption of Rixubis has been analysed by event per subject, that is, for prophylactic treatment and for treatment of bleeds until resolution of bleed. The median consumption of Rixubis was 50.5 IU/kg (mean: 49.5 ± 4.8 IU/kg) for prophylactic treatment and 87.1 IU/kg (mean: 93.2 ± 41.3 IU/kg) for treatment of bleeds.

> Comment: For actual consumption figures that relate to a comparison of cost effectiveness of treatment, the relevant figures are the total consumption/kg per month and the number of infusions per month. The former shows that approximately twice as much Rixubis was used in the prophylaxis group, which also received 2.5, as many infusions per month as the on-demand group.

The consumption per event (Table 12) is more difficult to interpret. As shown in Table 11, the consumption of Rixubis for each subject in the prophylaxis group per month was 347.8 IU/kg and for the on-demand group 167.3. In the former group there were a median of 1.99 bleeds a year and in the latter 26.98 (Table 6). The consumption per event per subject per month would therefore be:

- 347.8 divided by (1.99/12) = 2097.3IU/kg for the prophylactic group; and
- 167.3 divided by (26.98/12) = 376.2IU/kg for the on-demand group, that is, 5.6 times lower.

The figures in Table 13, based on the footnote, were based on only infusions required from the start to the conclusion of each bleed, and did not consider the Rixubis used in prophylaxis between bleeds. Interestingly only these figures were quoted in the Clinical Overview.

6.1.1.2. Results for other efficacy outcomes

The following exploratory analyses were also performed:

1. Haemostatic efficacy rating by time at which the rating occurred:

As an exploratory endpoint, the haemostatic efficacy rating after treatment with Rixubis was analysed by the time at which the rating occurred, that is, at 12 hours and at 24 hours from the first infusion with Rixubis. Of a total of 148 BEs with available efficacy ratings at the 12-hour timepoint, the majority were 'fair' (59; 39.9%), followed by 'good' (58; 39.2%), 'none' (19; 12.8%) and 'excellent' (12; 8.1%). Of 59 BEs with efficacy ratings available for the 24-hour time point, the majority were 'good' (25; 42.4%), followed by 'fair' (24; 40.7%), 'none' (9; 15.3%) and 'excellent' (1; 1.7%)

Comment: These results contrast, as expected, with those ratings at resolution of the bleed (Table 6, Table 9 and Table 10). More detailed information regarding 25 subjects who needed three or more infusions to treat a bleed and who had exploratory efficacy ratings of 'none' prior to resolution of bleed (two subjects in the on-demand and 23 in the prophylactic cohort) was presented for each subject.

2. Occurrence of BEs within Day 1 to 5+ of prophylactic infusion:

As an additional exploratory endpoint, the occurrence of BEs within Day 1 to 5+ of prophylactic infusion was analysed. The time from last prophylactic infusion until occurrence of a BE was available for 122 of a total of 249 BEs. The calculations were based on a total of 2690 prophylactic infusions and a total of 59 subjects who received prophylactic treatment. Most BEs (36) occurred within 48 and 72 hours of prophylactic infusion (rate of 1.34 BEs per total number of prophylactic infusions); 34 BEs occurred within 24-48 hours of prophylactic infusion (rate of 1.26). Most spontaneous BEs (of a total of 50 spontaneous BEs for which time from last prophylactic infusion is available) also occurred within 48-72 hours of prophylactic infusion, whereas joint bleeds mostly occurred within 24-48 hours (of a total of 83 joint bleeds for which time from last prophylactic infusion is available). This suggests that 50% of BEs that occurred within 24 hours of prophylactic infusion were spontaneous BEs, and that spontaneous BEs accounted for a third of the BEs that occurred within 24-48 hours and for a third of BEs that occurred within 48-72 hours of prophylactic infusion. However, the data available were insufficient to draw any reliable conclusions.

3. Health-Related Quality of Life (HR QoL) and the use of health resources:

Another exploratory efficacy outcome was an assessment of HR QoL and the use of health resources. The assessment of HR QoL, based on four questionnaires, and the capture of health resource use were performed by a named member of study site staff. For subjects aged 12 to 16, the Haemo-QOL, PedsQL, EQ-5D, VAS Pain Scale, and health resource utilisation were measured. For subjects aged 17 and older, the HaemAQOL (adult version), SF-36, EQ-5D, VAS Pain Scale, and health resource utilisation were measured.

Comment: Detailed descriptions of the questionnaires were provided, but are not included in this evaluation.

Results: HR QoL**:** The study assessed all Short Form Health Survey (SF-36v2) domains. The SF-36v2 is a valid and reliable measure of HR QoL that is comprised of eight domains and two summary scores (Table 14).

Table 14: Mean Change inSF-36v2 Health Domain Scores – Prophylaxis Group

SF-36v2 Health Domain	N	Mean Change	95% Confidence Interval
Physical Component Score	52	2.60	(0.45, 4.75)
Mental Component Score	52	2.01	(-1.10, 5.12)
Physical Functioning Score	53	0.68	(-1.39, 2.74)
Role-Physical Score	53	3.47	(0.67, 6.26)
Role-Emotional Score	53	0.37	(-2.87, 3.60)
Bodily Pain Score	53	3.45	(0.71, 6.19)
Mental Health Score	52	2.44	(-0.71, 5.58)
Vitality Score	52	2.46	(-0.53, 5.45)
Social Functioning Score	53	2.78	(-0.19, 5.75)
General Health Score	53	2.20	(-0.06, 4.47)

*Positive change values are in the favorable direction

HR QoL endpoints were only exploratory; the study was not powered for these endpoints. Significant improvements (defined as $p < 0.05$) between baseline and follow-up at approximately six months were observed in the Physical Component Score ($p = 0.0189$) and the Bodily Pain ($p = 0.0146$) and Role Physical ($p = 0.0162$) domains of the SF-36 in addition to the EQ-5D VAS Score ($p = 0.005$). All other measures of HR QoL did not show significant changes over the course of the study in the subjects on prophylaxis. No significant differences in HR QoL were reported by the on-demand patients between baseline and follow-up.

Comment: The clinical evaluator agreed that no conclusions can be drawn from these data. They do indicate what possible endpoints would be worth a properly powered study to demonstrate benefit.

4. Comparison of annualised bleeding rate from the pivotal trial with historical controls:

The ABR resulting from twice-weekly prophylactic treatment with Rixubis in the pivotal Study 250901 (interim analysis of 56 subjects treated for at least three months) was compared to the ABR of patients from a historical control treated on-demand using a meta-analytic literature-based approach. Twelve studies published from 1976 to 2011 with a total of 276 haemophilia B patients treated on-demand with FIX for an average of 19.6 months were included.

The endpoint of the meta-analysis was the ABR during FIX on-demand treatment of haemophilia B patients. Two studies were retrospective and the rest prospective. Of the prospective studies, two were randomised crossover trials. Ten of the 12 studies were multicentre investigations, and three enrolled at least 50 patients receiving on-demand treatment. Three studies were paediatric studies in children less than five years of age and nine studies included older patients. Baseline FIX was ≤ 2% in all patients of nine studies. One study evaluated PUPs, while five studies evaluated PTPs. Prior treatment was unspecified for the remaining six studies. For three studies, it was indicated that treatment on-demand was administered before switching to prophylaxis. Enrolment in one study was limited to patients with ≥ 12 bleeds in the preceding 12-month period. A prior bleeding rate criterion was not specified in patient selection for the other included studies.

For the 12 included studies, ABR varied from 7.2 to 33.4 bleeds per patient-year, displaying significant heterogeneity (I^2 = 91.8%, p < 0.001).

The ABR resulting from twice-weekly treatment with Rixubis (4.2) in pivotal Study 250901 was significantly lower (79% reduction, p<0.001) than the mean ABR of 20.0 for on-demand treatment in a historical control group.

> Comment: The heterogeneity of the studies in the meta-analysis is apparent from the above description and confirmed by a p value of < 0.001. Although the study report claimed that "No significant differences were detected in ABR between retrospective and prospective studies, earlier and recent studies, patients of average age below five years and older patients, or studies enrolling patients exclusively with ≤ 2% FIX and those with > 2% in some patients, any conclusion from a comparison of the ABRs should be taken with caution.

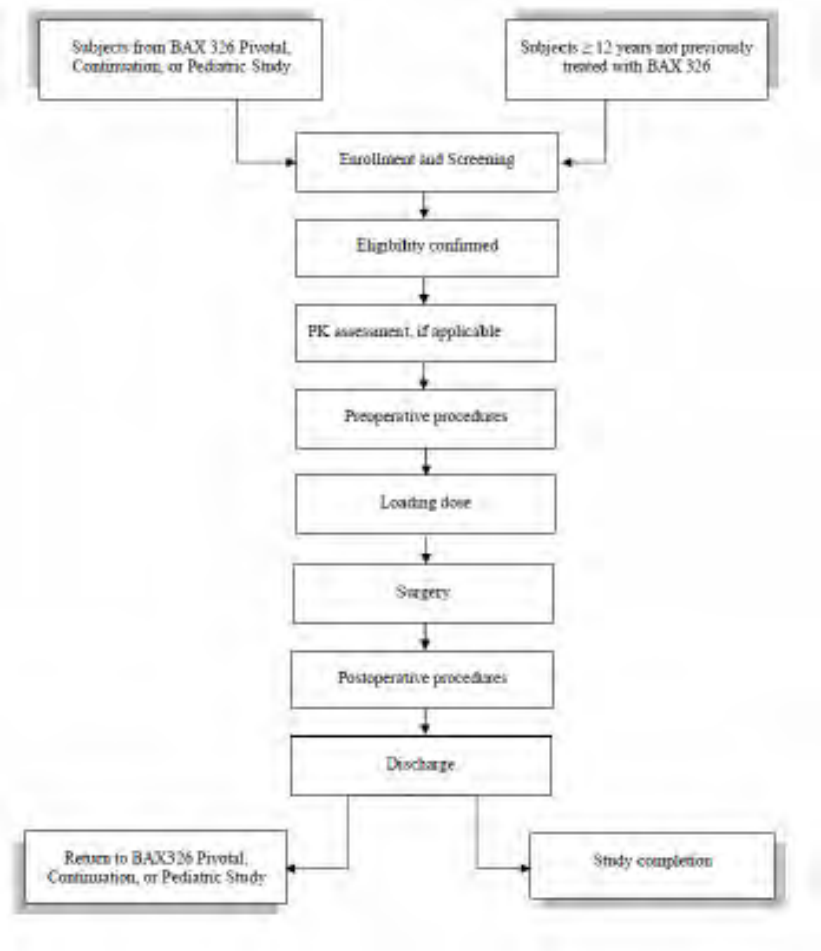
6.1.1.3. Surgery study 251002

6.1.1.3.1. Study design, objectives, locations and dates

Study 251002 was a Phase III, prospective, open-label, uncontrolled, multicentre study designed to evaluate the haemostatic efficacy and safety of Rixubis in approximately 30 subjects with severe or moderately severe haemophilia B undergoing major and minor surgical, dental or other invasive procedures. The overall study design is illustrated in Figure 5.

The objectives of the study were to evaluate the haemostatic efficacy and safety of Rixubis in the peri- and postoperative setting. The study was carried out at five centres – two in Russia, one in Poland, one in Bulgaria and one in the Ukraine. The study was administered centrally by the Department of Global Clinical Research & Development at Baxter Innovations GmbH (Vienna, Austria) and Baxter Healthcare Corporation (Westlake Village, CA, US). The study began on 19 December, 2011 and is ongoing (anticipated duration three years). This interim analysis was based on the complete data of 14 subjects. Data cut-off was performed after 13 surgeries, of which ten were major surgeries, had been completed per protocol.

Figure 5: Design of Study 251002



Changes in the conduct of the study or planned analyses:

Changes to the conduct of the study: There were two amendments to the original study protocol of the 21 March 2011, the first of which was a global amendment and the second a local amendment specific to the UK. Some involved the participation of paediatric patients that are not in the present interim analysis. The main changes relevant to the present study are as follows:

Amendment 1 (11 Oct 2011): The occurrence of thrombotic events was added as a safety endpoint and the determination of the occurrence of thrombotic events added as a study objective.

Amendment 2 (19 Oct 2011; UK only): The only change was a rewording of the study stopping rules as requested by the regulatory authority in the UK (MHRA).

Changes to the Planned Analyses**:** There were no changes from the planned analyses.

6.1.1.3.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria were similar to those in the first pivotal study, Study 251009 with the following exceptions:

Inclusion criteria:

- Subject is participating in either the Rixubis Pivotal Study (#250901), the Rixubis Continuation Study (#251001) or the Rixubis Paediatric Study (#251101) requiring an emergency or elective major or minor surgical, dental, or other invasive procedure, and

continues to meet eligibility criteria as outlined in the Rixubis pivotal, continuation, or paediatric study.

For newly entering subjects, that is, subjects not participating in any other Rixubis clinical study, the following main inclusion criteria applied:

- Subject requires elective major surgery

Exclusion criteria:

For newly entering subjects who did not participate in any other Rixubis clinical study, the following main exclusion criteria applied:

- Subject requires emergency surgery (Only subjects participating in the Rixubis pivotal, continuation or paediatric study were eligible for emergency surgery).

6.1.1.3.3. Study treatments

Pre-surgical pharmacokinetics: Pre-surgical PK was assessed in subjects undergoing major elective surgery who did not undergo a PK assessment in the pivotal study. The following parameters will be assessed: $AUC_{0\text{-}72\,h}$/dose, total AUC/dose, MRT, CL, IR, T1/2, and Vss.

Treatment: Rixubis. The dose was to be tailored to raise FIX concentration to 80%-100% of normal for major surgeries and to 30%-60% of normal for minor surgeries.

Dosage form: Lyophilised powder and solvent to add for injection. It was not stated whether the pilot or the commercial formulations were used.

Dosage frequency: Following the loading dose(s) with Rixubis, subjects received Rixubis as a bolus infusion. The regimen was to be determined by the intensity and duration of the haemostatic challenge and the institution's standard of care. The following frequency of doses was recommended:

- **Minor surgeries:** approximately every 24 hours for at least one day until healing was achieved.
- **Major surgeries:** every eight to 24 hours to maintain pre-infusion target plasma FIX levels of 80-100% until adequate wound healing, then therapy for at least another seven days to maintain a pre-infusion FIX activity of 30-60% (IU/dL).

Duration of treatment: Duration of participation per subject depended on the type of surgery and the intensity and duration of the haemostatic challenge, consistent with the study site's standards of care for surgical management of haemophilia B patients.

6.1.1.3.4. Efficacy variables and outcomes

The main efficacy variables were:

Haemostatic efficacy rating: The haemostatic efficacy of Rixubis was assessed intra-operatively, postoperatively and on the day of discharge, using ratings of 'excellent', good', 'fair' and 'none', defined as follows:

1. Intra-operatively:

The intra-operative haemostatic efficacy was to be assessed by the operating surgeon according to the criteria shown below. The rating was to reflect the intraoperative blood loss as compared to the expected amount of blood loss estimated preoperatively for the type of procedure in a thermostatically normal individual. Table 15 defines the ratings used.

Table 15: Criteria for assessing intraoperative efficacy

Rating	Criteria
Excellent	Intraoperative blood loss was less than or equal to that expected for the type of procedure performed (≤ 100%)
Good	Intraoperative blood loss was up to 50% more than expected for the type of procedure performed (101 – 150%)
Fair	Intraoperative blood loss was more than 50% of that expected for the type of procedure performed (> 150%)
None	Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of FIX concentrate

2. Postoperatively

   a. **At drain removal**: The postoperative haemostatic efficacy was also assessed by the operating surgeon, at the time of drain removal. The ratings reflected the volume in drain as compared to the volume estimated preoperatively for the type of procedure performed in a thermostatically normal individual. The rating criteria are shown in Table 16.

Table 16: Criteria for assessing efficacy at time of drain removal

Rating	Criteria
Excellent	Volume in drain was less than or equal than that expected for the type of procedure performed (≤ 100%)
Good	Volume in drain was up to 50% more than expected for the type of procedure performed (101% - 150%)
Fair	Volume in drain was more than 50% of that expected for the type of procedure performed (> 150%)
None	Uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of FIX concentrate

   b. **Postoperatively at Day 3**: In the case of major surgery and where no drain was employed, the postoperative haemostatic efficacy was assessed by the operating surgeon on postoperative Day 3 (approximately 72 hours postoperatively). The ratings (see Table 17) were to reflect how postoperative homeostatic efficacy with Rixubis compared with haemostasis for the type of surgical procedure in a thermostatically normal individual.

Table 17: Criteria for assessment at 72 hours postoperatively

Rating	Criteria
Excellent	Postoperative hemostasis achieved with BAX 326 was as good or better than that expected for the type of surgical procedure performed
Good	Postoperative hemostasis achieved with BAX 326 was probably as good as that expected for the type of surgical procedure performed
Fair	Postoperative hemostasis with BAX 326 was clearly less than optimal for the type of procedure performed but was maintained without the need to change the FIX concentrate
None	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of FIX concentrate

3. Day of discharge:

On the day of discharge from hospital, the homeostatic efficacy was assessed by the investigator, the haemophilia physician. The rating criteria were the same as for postoperative Day 3 (see above).

Primary efficacy outcomes:

> Comment: No primary efficacy outcome(s) was defined in the Study Report or the Clinical Overview. The Synopsis of the study, not the Study Report itself, gave the primary and secondary objectives of the study. These were the same as the latter (secondary objectives as stated) were the endpoint variables used to assess the primary objective, homeostatic efficacy, as described above. The clinical evaluator assumed that all the above outcomes are primary. Those that appear to be secondary are shown below as "other". The above results were presented using descriptive statistics. Comparison with other efficacy data was not part of the primary outcome.

Other efficacy outcomes included:

- The summary of average daily and total weight-adjusted consumption of Rixubis per subject using descriptive statistics. Units and amount (in mL) of blood product transfused were presented descriptively.
- A record of the number of units and amount of blood product transfused.
- Pre- and post-infusion FIX activity levels summarised descriptively for the perioperative period.
- A subject-level listing (which additionally includes associated aPTT results) as well as figure of factor level and dose versus time.

Note: The PK analysis from those patients on whom such studies were carried out in this study were described in the PK section to this evaluation.

6.1.1.3.5. Randomisation and blinding methods

Given the nature of the study, these were not applicable.

6.1.1.3.6. Analysis populations

The FAS was to comprise all subjects exposed to IP and who provided data suitable for the homeostatic efficacy analysis.

> Comment: 'Data suitable for the homeostatic efficacy analysis' was not defined in either the study report or the statistical analysis plan.

The PAS was to comprise subjects in the FAS who do not have major protocol deviations that are associated with efficacy endpoints or serious breaches of protocol. The PK population was described previously.

6.1.1.3.7. Sample size

The sample size was not based on statistical considerations and was determined by the number of subjects participating in Rixubis Pivotal (250901), Rixubis Continuation (251001) and Rixubis Paediatric (251101) studies, who were undergoing major or minor elective or emergency surgical, dental or other invasive procedures. Approximately 30 elective or emergency surgical, dental or other invasive procedures were to be performed in approximately 30 subjects. At least ten of the procedures must be major surgeries in ten unique subjects. Additional subjects not participating in any of these studies may also be enrolled.

The interim analysis presented here was based on the complete data of 14 subjects. Data cut-off was performed after 13 surgeries, of which ten were major surgeries, had been completed per protocol.

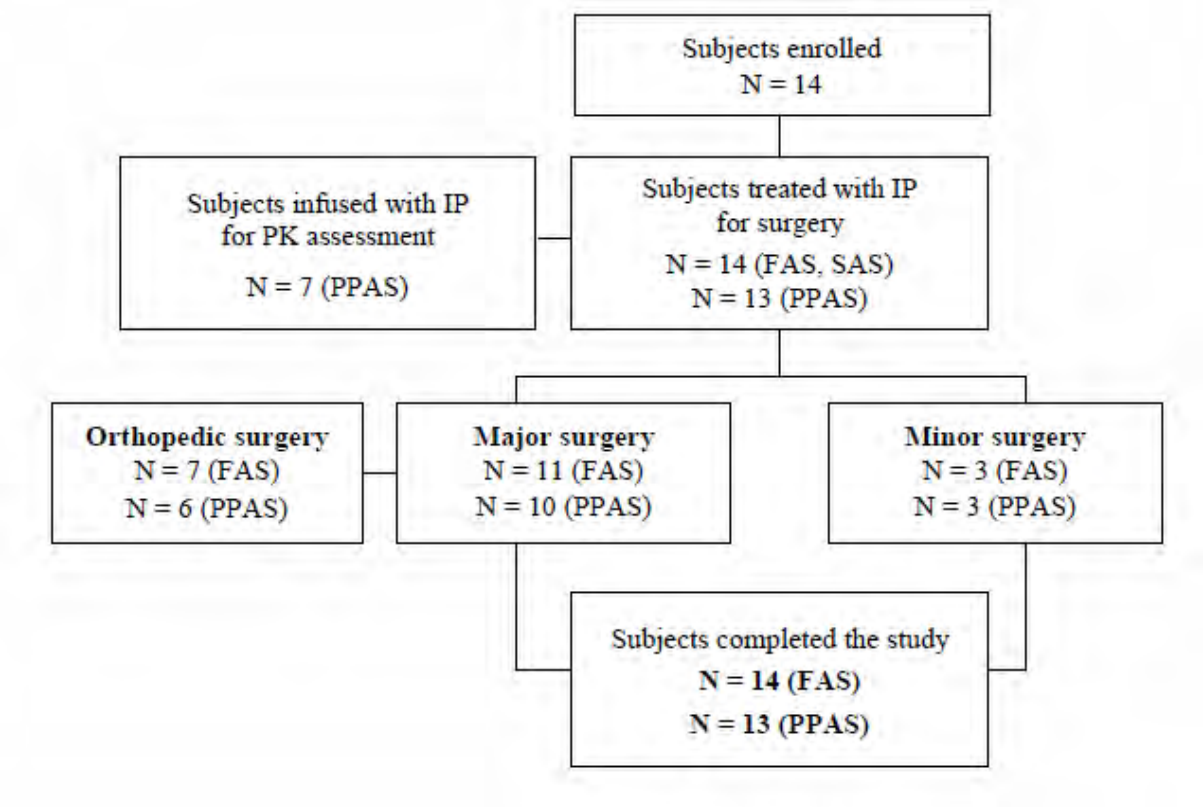
6.1.1.3.8. Statistical methods

The statistical methods were descriptive and the same as the description of the methods for assessing homeostatic efficacy (see above). The only additional information in the SAP was the handling of missing, unused or spurious data as follows – "Missing data is to be reported as missing. No technique is to be employed to adjust for missing data….. In case of excessive or unexplained bleeding, back-up testing for FIX activity is permitted at the central laboratory. However, if back-up testing is done in the absence of excessive or unexplained bleeding, only the results of the planned testing will be considered for analysis."

6.1.1.3.9. Participant flow

Patient disposition is shown in Figure 6. In the Figure, IP stands for Investigational Product.

Figure 6: Flow Chart for Surgical Study 251002



6.1.1.3.10. Major protocol violations/deviations

Most protocol deviations were minor. Major deviations were reported for seven subjects. The majority of these were of the category 'procedure not done' (such as, local laboratory result missing). The most serious deviation, which was a local breach of GCP and the protocol, assessed as 'serious' by the Sponsor, was committed by an investigator who performed major surgery (total hip replacement) despite knowing that the FIX results from the local laboratory were unreliable and who based postoperative IP dosing and FIX monitoring on aPTT only. For this reason, this subject (Subject 260003) was not included in the PPAS.

> Comment: The listing of protocol deviations confirms these conclusions. The one serious violation that potentially affected the patient's safety is described above.

6.1.1.3.11. Baseline data

All 14 subjects were male, white and ≥ 16 years of age. The youngest subject was 19 and the oldest was 54 years old at time of consent. The mean study duration (STD) was 44.5 (27.4) days in the PPAS (n=13) and 42.5 (27.3) in the FAS and SAS (n=14 in both); range: 4-93 days.

Eleven subjects had severe haemophilia B, with a FIX level < 1%, and three subjects had moderately severe haemophilia B, with a FIX level 1-2%. FIX antigen levels were < 1% in six (42.9%) subjects and ≥ 1% in 8 (57.1%) subjects, with levels ≥ 40% in five (35.7%) subjects. Gene mutations were diagnosed in ten subjects; seven had a missense, two a nonsense and one a frameshift mutation.

All 14 subjects had arthropathy at screening. All 14 subjects had a history in the haematopoietic/lymphatic and musculoskeletal categories, due to the disease under investigation in this study (haemophilia B) and a diagnosis of haemophilic arthropathy. All 14 subjects also had a history of hepatitis A, B and/or C.

6.1.1.3.12. Results for the primary efficacy outcome

The surgical procedures are described in Table 18, and the results for the primary efficacy outcomes in Table 19.

Table 18: Description of Surgery. Study 251002 FAS

Subject ID	Start/End Datetime of Hospitalization	Start/End Datetime of Surgery	Surgery Name	Surgery Type	Anesthesia Type	Drain Planned?	Drain Placed?	Postop Day of Drain Removal
010001	2012-04-19T08:30 2012-05-02T13:20	2012-04-20T10:50 2012-04-20T11:50	Removal Of The Nail Residual From Intramedullary Nailing Of Left Femur Fracture	Major / Orthopedic	General	No	Yes	1
010002	2012-01-12T09:30 2012-01-27T13:15	2012-01-13T12:30 2012-01-13T14:30	Joint Replacement	Major / Orthopedic	General	Yes	Yes	3
010004	2012-04-23T08:30 2012-05-08T14:00	2012-04-25T09:30 2012-04-25T13:50	Left Knee Replacement	Major / Orthopedic	General	Yes	Yes	3
070001	2012-02-13T09:59 2012-03-02T15:00	2012-02-15T09:38 2012-02-15T11:00	Total Left Knee Replacement	Major / Orthopedic	General	Yes	Yes	3
070002	2012-02-17T07:37 2012-02-24T10:30	2012-02-17T10:20 2012-02-17T10:41	Maxillary Third Molar Tooth Extraction	Major / Dental	Local	No	No	NA
070003	2012-05-28T10:36 2012-06-08T12:00	2012-05-29T09:45 2012-05-29T10:25	Excision Of Neurofibroma	Major / Other: Surgical Excision Of Tumor From Soft Tissue	General	Yes	Yes	2
150001	2012-05-15T07:00 2012-05-31T12:00	2012-05-15T09:30 2012-05-15T10:45	Hernioplastica (Left Side)	Major / Abdominal	General	No	No	NA
150002	2012-04-24T07:30 2012-05-02T12:00	2012-04-24T09:45 2012-04-24T10:15	Extraction Of 1st Upper Molar (Left Side) And 2nd Lower Molar (Left Side)	Minor / Dental	Local	No	No	NA
180001	2012-06-25T10:50 2012-07-06T14:00	2012-06-26T13:00 2012-06-26T15:00	Open Synovectomy	Major / Orthopedic	General	No	No	NA
180003	2012-07-11T10:30 2012-07-26T14:00	2012-07-13T12:00 2012-07-13T13:30	Hernioplastic	Major / Abdominal	General	No	No	NA
260001	2012-05-11T06:56 2012-05-31T15:00	2012-05-16T10:00 2012-05-16T12:15	Total Knee Replacement	Major / Orthopedic	General	Yes	Yes	1
260002	2012-04-16T11:50 2012-04-25T10:10	2012-04-18T14:25 2012-04-18T14:50	Extraction Of Upper 1st Molars (Both Left And Right)	Minor / Dental	General	No	No	NA
260003	2012-04-18T09:43 2012-05-04T11:00	2012-04-24T09:55 2012-04-24T11:40	Total Hip Replacement	Major / Orthopedic	General	Yes	Yes	1
260005	2012-05-23T09:00 2012-05-24T12:00	2012-05-23T11:10 2012-05-23T11:20	Intraarticular Injection	Minor / Other: Intraarticular Infusion	NA	No	No	NA

Table 19: Actual and Predicted Average and Maximum Blood Loss FAS

Subject ID	Surgery Name	Surgery Type	Period	Actual [mL]	Average Predicted [mL]	Maximum Predicted [mL]
010001	Removal Of The Nail Residual From Intramedullary Nailing Of Left Femur Fracture	Major / Orthopedic	Intraoperative	20	100	200
			Postoperative	810	600	800
010002	Joint Replacement	Major / Orthopedic	Intraoperative	1100	500	1100
			Postoperative	800	400	800
010004	Left Knee Replacement	Major / Orthopedic	Intraoperative	500	500	1100
			Postoperative	500	450	600
070001	Total Left Knee Replacement	Major / Orthopedic	Intraoperative	300	300	600
			Postoperative	1100	400	1000
070002	Maxillary Third Molar Tooth Extraction	Major / Non-Orthopedic	Intraoperative	10	10	15
070003	Excision Of Neurofibroma	Major / Non-Orthopedic	Intraoperative	50	50	100
			Postoperative	11	1	11

Subject ID	Surgery Name	Surgery Type	Period	Actual [mL]	Average Predicted [mL]	Maximum Predicted [mL]
150001	Hernioplastica (Left Side)	Major / Non-Orthopedic	Intraoperative	10	30	50
150002	Extraction Of 1st Upper Molar (Left Side) And 2nd Lower Molar (Left Side)	Minor / Non-Orthopedic	Intraoperative	2	3	5
180001	Open Synovectomy	Major / Orthopedic	Intraoperative	100	60	100
180003	Hernioplastic	Major / Non-Orthopedic	Intraoperative	20	20	20
260001	Total Knee Replacement	Major / Orthopedic	Intraoperative	500	500	1000
			Postoperative	1000	500	1000
260002	Extraction Of Upper 1st Molars (Both Left And Right)	Minor / Non-Orthopedic	Intraoperative	3	10	20
260003	Total Hip Replacement	Major / Orthopedic	Intraoperative	700	500	1000
			Postoperative	1270	400	1000

Comment: The table shows that 11 subjects had major surgery (seven orthopaedic, two abdominal and one dental surgery and one excision of neurofibroma) and three had minor surgery (two dental surgeries and onw intraarticular infusion). Note that the two abdominal surgical procedures were both herniorraphies. The PI for the rFIX product (BeneFIX) marketed in Australia gives clinical data for that product based on a study of 28 haemophilia B patients undergoing 36 surgical procedures including liver

transplantation, splenectomy, inguinal hernia repair, orthopaedic procedures, calf debridement and complicated dental extraction.

Intraoperative blood loss

In the PPAS (n=13), the mean intraoperative blood loss was 201.2 mL (range: 0-1100 mL). As expected, blood loss was higher in major (n=10) than in minor (n=3) surgeries (mean of 261.0 versus 1.7 mL) and was highest in orthopaedic (n=6) surgeries (420.0 mL, range: 20-1100). In terms of actual versus predicted average/maximum intraoperative blood loss, actual blood loss during major surgery largely matched the predicted blood loss: 6/11 major surgeries matched the average predicted blood loss, 2/11 matched the maximum predicted blood loss, 2/11 were below the average predicted blood loss, and 1/11 (not included in the PPAS due to major protocol deviation) was between the average predicted and maximum predicted blood loss. For all three minor surgeries, actual intraoperative blood loss was below the average predicted blood loss.

Comment: For major surgery, in eight of 11 procedures the actual blood loss was below or the average of that predicted.

Postoperative blood loss

A total of seven subjects, who all had major surgery (six orthopaedic, one non-orthopaedic), had a drain placed. In the six subjects in the PPAS who had a drain placed, the mean postoperative blood loss was 703.5 mL (range: 11-1100 mL). Blood loss was slightly higher in orthopaedic surgeries (n=5; mean: 842.0 mL, range: 500-1100 mL). In terms of actual versus predicted average/maximum postoperative blood loss, actual blood loss was mostly higher than or equal to the maximum predicted blood loss: 4/7 major surgeries with drain placement were above the maximum predicted blood loss (including one surgery that is not part of the PPAS), 2/7 met the maximum predicted blood loss, and 1/7 was between the average predicted and maximum predicted blood loss. When analysing the four major surgeries with an actual postoperative blood loss exceeding the maximum predicted blood loss, FIX levels on postoperative Days 1-3 ranged between 34.3-40% for Subject 010002 (joint replacement) and between 40-56% for Subject 260003 (total hip replacement). The latter was excluded from the PPAS since the principal investigator (PI) dosed the patient according to aPTT values. In both patients, the drain was removed on postoperative Day 3. For Subject 010001 (removal of residual nail from intramedullary nailing of left femur fracture), the postoperative actual blood loss exceeded the maximum predicted blood loss by 10 mL (810 versus 800 mL). The subject's pre-infusion FIX levels were within the recommended range (84.5-91%). However, the initially predicted blood loss did not take into account the use of a tourniquet, and it was only decided intra-operatively to place a drain which was removed on postoperative Day 1. The PI was then asked to retrospectively predict blood loss, taking into account the use of a tourniquet and the drain. Subject 070001, who underwent a total knee replacement, had FIX levels ranging from 55.6-81.1%. The drain was removed on postoperative Day 3; the postoperative actual blood loss exceeded the maximum predicted by 100 mL (1100 versus 1000 mL).

Comment: In four of the seven major surgical procedures in which drains were placed, the postoperative blood loss exceeded the predicted maximum. In the four cases, the FIX levels postoperatively were below the levels recommended in the study protocol (34% to 81%).

Haemostatic efficacy assessment

All surgeries included in the intraoperative assessment (n=13 in the PPAS, n=14 in the FAS) had a rating of 'excellent'. At drain removal, 50% of the ratings were 'excellent' and 50% were 'good' (3/6 subjects in the PPAS and 3/7 subjects in the FAS had a rating of 'excellent', and /6 subjects in the PPAS and 4/7 subjects in the FAS had a rating of 'good'). On postoperative Day 3, all six surgeries in the PPAS/FAS where no drain was employed (including four major surgeries), had a rating of 'excellent'. At discharge from hospital, most of the ratings were 'excellent' and the

rest were 'good': 11/13 (84.6%) subjects in the PPAS and 11/14 (78.6%) subjects in the FAS (with eight major surgeries) had a rating of 'excellent' and 2/13 subjects in the PPAS and 3/14 subjects in the FAS (with two and three major surgeries, respectively) had a rating of 'good'.

> Comment: Note that the ratings were those of the surgeons who had carried out the surgery.

6.1.1.3.13. Results for other efficacy outcomes

Rixubis consumption

Total Rixubis consumption in terms of total units was 1,241,820 IU in the PPAS (n=13) and 1,338,100 IU in the FAS (n=14). Throughout the study, subjects in the PPAS (n=13) received a total of 16,390 IU/kg. Ten subjects who underwent major surgery received a total of 15,043 IU/kg. Six subjects who underwent orthopaedic surgery received a total of 10,423 IU/kg, and three subjects with minor surgery received a total of 1,347 IU/kg. For ten major surgeries in the PPAS, the mean daily doses of Rixubis from the day of surgery until postoperative Day 11+ were 187.5, 134.9, 130.6, 119.9, 125.9, 109.3, 106.9, 91.1, 96.7, 95.1, 90.6 and 81.3 IU/kg. The mean daily doses administered in six subjects with orthopaedic surgeries in the PPAS from the day of surgery until postoperative Day 11+ were 199.7, 131.6, 131.0, 134.3, 150.7, 124.9, 123.7, 115.9, 113.6, 111.6, 104.9 and 88.1 IU/kg.

During the intraoperative period, the mean weight-adjusted dose in the PPAS was 188 IU/kg range: 134-296 IU/kg) for major surgery (n=10), 200 IU/kg (range: 147-296 IU/kg) for orthopaedic surgery (n=6) and 132 IU/kg (range: 55-203 IU/kg for minor surgery (n=3). During the postoperative period, the mean weight-adjusted dose in the PPAS was 1,264 IU/kg (range: 415-2,965 IU/kg) for major surgery (n=10), 1,487 IU/kg (range: 829-2,965 IU/kg) for orthopaedic surgery (n=6) and 291 IU/kg (range: 55-601 IU/kg) for minor surgery (n=3).

Blood product use

Three subjects in the PPAS and four subjects in the FAS, who all underwent major (orthopaedic surgery) received blood product transfusions, either in the form of packed red blood cells or fresh frozen plasma (FFP). The mean volume transfused was 558.7 mL in the PPAS (range: 520-600 mL). In the FAS, the mean volume transfused was 725.3 mL during the intraoperative period (range: 520-1225 mL) and 575 mL during the postoperative period.

Bleeding episodes

No bleeding episodes were reported.

6.1.2. Other efficacy studies

Not applicable.

6.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

Efficacy data were presented from Studies 250901 and 251002. Both studies included patients aged 12-65 years with severe (FIX level <1%) or moderately severe (FIX level 1-2%) haemophilia B who had previously been treated with FIX concentrates. In Surgery Study 251002, subjects underwent surgical, dental or other invasive procedures.

The Summary of Clinical Efficacy stated "A comparison of the efficacy results of Pivotal Study 250901 and Surgery Study 251002 is not possible due to the different types of treatment investigated in the two studies and the different efficacy measurements used. In Study 250901 subjects received IP for prophylactic or on-demand treatment, and ABR and treatment of bleeding episodes were the main efficacy parameters analyzed. HR QoL and health resource use were also measured. In Study 251002, subjects received IP in the peri- and postoperative setting and the main efficacy parameters analysed were intra- and postoperative blood loss and intra- and postoperative homeostatic efficacy as assessed by the operating surgeon and

investigator (homophile physician). Rixubis consumption and blood product use were also assessed."

> Comment: The Statistical Analysis Plan states that the operating surgeon was to assess homeostatic efficacy. No mention is made of any role of the investigator.

6.1.4. Evaluator's conclusions on clinical efficacy for indication 1

Pivotal Study 250901: The pivotal study of prophylactic and on-demand treatment with Rixubis showed the median ABR per patient was 27 in the on-demand group, and two in the prophylactic group, although no direct comparison could be made. Nevertheless the efficacy of prophylactic treatment in reducing the ABR compared to treatment on-demand was demonstrated. The efficacy was similar to that reported in the PI of a commercially available rFIX (BeneFIX) in Australia.

In the prophylaxis group, 30% of bleeding events (BEs) required more than three infusions, compared to only 1.5% of BEs in the on-demand group (Table 10). The same table showed the total dose per bleed in the prophylaxis group was twice that in the on-demand group. This was also shown for the total consumption of Rixubis/kg/month. Higher doses than the overall mean were needed for non-joint bleeds and for bleeds caused by injury. Dosage of FIX was increased more for major bleeds than for minor bleeds.

It follows that Rixubis is effective as prophylactic treatment to reduce the frequency of ABEs, and to treat them when they occur. Prophylactic treatment required twice the amount of Rixubis to achieve this result. No conclusions could be drawn from the QoL assessments that were underpowered. Patients were not asked in QoL assessments whether they preferred prophylactic to on-demand treatment.

Surgical Study 251002**:** The study showed that for major surgery in six of 11 patients treated with Rixubis, the treatment was effective in reducing intraoperative blood loss to an amount predicted for the average blood loss of a healthy matched individual. In two cases the loss was less and in two cases equal to the maximum predicted.

However in four of seven subjects, who all had major surgery with a drain placed, postoperative blood loss exceeded the maximum predicted blood loss. In these cases, the patients' FIX levels were suboptimal (34% to 81%) after FIX treatment.

Ratings for homeostatic efficacy were done by the operating surgeons, and so had the problem of potential bias. All intraoperative assessments were "excellent" as were 50% of those at drain removal. At hospital discharge, in the FAS, 78.6% (11 of 14) of ratings were "excellent" (see Table 15, Table 16 and Table 17).

The difficulty in recruiting for and conducting this type of study is acknowledged as well as the fact that the number of subjects and surgical procedures complied with the requirements of the CPMP Guidelines (at least five patients undergoing ten surgical procedures). However problems with the study were as follows:

1. The numbers of patients who had major surgery (n=11) and minor surgery (n=5) were small, given the intention had been to recruit a total of 30 subjects. This report is an interim analysis, but no clear reason is given for not waiting to complete the study.
2. The PK properties of Rixubis in seven patients studied differed from those in other patients in the pivotal study and no statistical comparison could be done. This may relate to the failure to obtain adequate FIX levels in patients in the post-operative period although a specified protocol was followed.
3. The postoperative blood loss at drain removal exceeded the maximum predicted in four of seven subjects who had major surgery.

4. The surgery called "major" included two cases of abdominal surgery, each for herniorraphy. This abdominal surgery does not compare to abdominal surgery such as liver transplantation or splenectomy for risk of blood loss, the latter two having been part of the assessment of a commercial rFIX product (BeneFIX) and reported in the PI for that product. As well, as shown in Table 18, one case of dental extraction was classed as major surgery and two other cases as minor.
5. All assessments of homeostatic efficacy were by the operating surgeon, so that bias was possible, although again this was according to recommendations of the CPMP Guidelines.

The clinical evaluator concluded that the efficacy results of the interim analysis of the surgical study need to be treated with caution and that the study should be completed and final results analysed to confirm those of the interim analysis.

7. Clinical safety

Because the clinical studies were similar in terms of Rixubis product, dosage and safety assessments, the safety data provided is combined and evaluated from the Integrated Summary of Safety (ISS), with reference to the individual study reports where indicated. The patient population is homogeneous except for the one paediatric study. Note that the requested indication does not include this paediatric population. A safety issue that would occur in this population and not in the adult population seems unlikely so the safety assessments have been combined. The characteristics of the treated subjects by study and age groups are given in Table 20, Table 21 and Table 22.

Table 20: Overall Subject Disposition by Age Group and Study

Study	Subjects Treated N	<6 yrs n (%)	6 - <12 yrs n (%)	12 - <16 yrs n (%)	³16 yrs n (%)
250901	73	0 (0.0)	0 (0.0)	3 (4.1)	70 (95.9)
251001	64	0 (0.0)	0 (0.0)	2 (3.1)	62 (96.9)
251002	16	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
251101	16	6 (37.5)	10 (62.5)	0 (0.0)	0 (0.0)
All[a]	91	6 (6.6)	10 (11.0)	3 (3.3)	72 (79.1)

[a] Unique subjects
[generated by 25_is2_safety.sas]

Table 21: Demographic and Baseline Characteristics: Continuous Data by Age Group

Parameter	Statistic	<6 yrs	6 - <12 yrs	12 - <16	³16 yrs	All
Age at Consent [years]	N	6	10	3	72	91
	Mean (Std)	3.33 (1.03)	9.80 (0.92)	13.33 (1.53)	35.22 (11.66)	29.60 (15.20)
	Median	3	10	13	34.5	29
	Q25 ; Q75	3 ; 4	9 ; 10	12 ; 15	24.5 ; 46.5	19 ; 43
	Min ; Max	2 ; 5	8 ; 11	12 ; 15	18 ; 59	2 ; 59
Weight [kg]	N	6	10	3	72	91
	Mean (Std)	17.00 (1.74)	32.40 (5.29)	43.13 (6.50)	71.66 (12.78)	62.80 (21.23)
	Median	17.15	33.1	43	70.5	65
	Q25 ; Q75	16 ; 17.5	29 ; 34.5	36.7 ; 49.7	62.55 ; 80.2	51.4 ; 79
	Min ; Max	14.5 ; 19.7	21 ; 39.55	36.7 ; 49.7	46.5 ; 102.5	14.5 ; 102.5
Height [cm]	N	6	10	3	72	91
	Mean (Std)	104.17 (5.91)	137.10 (5.93)	160.67 (10.41)	173.78 (6.54)	164.73 (20.90)
	Median	106.5	137.5	164	175	172
	Q25 ; Q75	99 ; 108	135 ; 140	149 ; 169	170 ; 178	164 ; 176
	Min ; Max	95 ; 110	128 ; 148	149 ; 169	152 ; 188	95 ; 188

[generated by 25_is2_safety.sas]

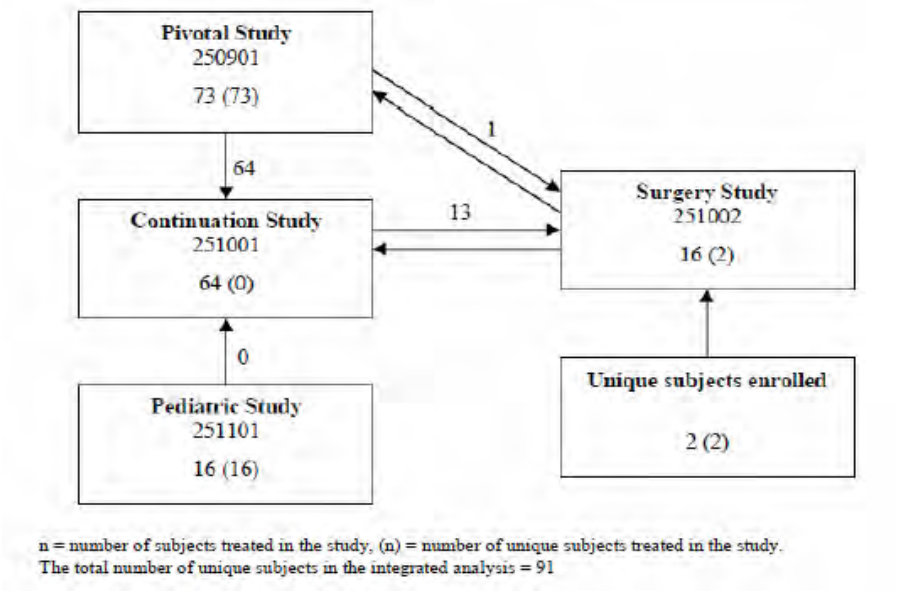
Table 22: Demographic and Baseline Characteristics: Categorical Data by Age Group

Parameter	Category	<6 yrs N = 6 n (%)	6 - <12 yrs N = 10 n (%)	12 - <16 N = 3 n (%)	³16 yrs N = 72 n (%)	All N = 91 n (%)
Gender	Male	6 (100.0)	10 (100.0)	3 (100.0)	72 (100.0)	91 (100.0)
	Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race	White	6 (100.0)	10 (100.0)	2 (66.7)	61 (84.7)	79 (86.8)
	Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
	Japanese	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.9)	5 (5.5)
	Native Latin American	0 (0.0)	0 (0.0)	1 (33.3)	2 (2.8)	3 (3.3)
	Mestizo	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)	2 (2.2)
	Arabic	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
Ethnicity	Not Reported	6 (100.0)	10 (100.0)	3 (100.0)	72 (100.0)	91 (100.0)
Gene Mutation	Missense	2 (33.3)	3 (30.0)	2 (66.7)	32 (44.4)	39 (42.9)
	Nonsense	0 (0.0)	0 (0.0)	0 (0.0)	14 (19.4)	14 (15.4)
	Splice Site	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.9)	5 (5.5)
	Deletion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
	Frameshift	0 (0.0)	1 (10.0)	0 (0.0)	1 (1.4)	2 (2.2)
	No Mutation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
	Not Reported	4 (66.7)	6 (60.0)	1 (33.3)	18 (25.0)	29 (31.9)
FIX Activity Level [%]	<1%	4 (66.7)	6 (60.0)	2 (66.7)	39 (54.2)	51 (56.0)
	1% - 2%	2 (33.3)	4 (40.0)	1 (33.3)	33 (45.8)	40 (44.0)

[generated by 25_is2_safety.sas]

The IAS has reported only on "unique" patients (n=91), so that the same patients in the different studies are not included more than once. Figure 7 shows these unique patients.

Figure 7 Flow of Subjects in Clinical Studies



n = number of subjects treated in the study, (n) = number of unique subjects treated in the study.
The total number of unique subjects in the integrated analysis = 91

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies 250901 and 251002

In the pivotal efficacy studies, the following safety data were collected:

- general AEs were assessed by the investigator for seriousness, severity and causal relationship to IP exposure as defined in the protocol. For each AE, the outcome (that is, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal) and action taken (that is, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn) was also to be recorded on the AE eCRF.

Recovering/resolving AEs were to be followed until resolution, medically stabilised, or 30 days after the study completion/termination visit, whichever came first.

- immunogenicity was assessed in terms of total binding and inhibitory antibodies to FIX and antibodies to CHO proteins and rFurin. These were measured at the timepoints shown in Table 23.

Table 23: Clinical Laboratory Assessments

Table 21.4-1
Clinical Laboratory Assessments[a]

Assessments	Screening Visit	Base-line	Part 1 for Infusions 1 and 2 (duration 2-4 weeks)		Part 2 Study Visits (duration 26 ± 1 weeks)				Part 3 (duration ~ 1 week)		Study Completion/Termination Visit[d]
			Pre-infusion	Post-infusion	ED 1[b]	Week 5 ± 1 ED: 10-15	Week 13 ± 1	Week 26 ± 1[c]	Pre-infusion	Post-infusion	
FIX activity	x										
FIX antigen	x										
Gene common/HLA genotype	x										
CD4 count	x										
HIV test and viral load, if positive	x							x[e]	x[e]		x
Hepatitis Serology	x							x[e]	x[e]		x
DNR	x										
Pregnancy Test	x										
FIX activity/ half-life pre/post FIX product		x[f]									
FIX recovery[g]					x	x	x	x			x
FIX activity/ PK[h]			x	x					x	x	
Hematology[i]	x			72 h		x	x	x	x	72 h	x
Clinical Chemistry[j]	x			72 h		x	x	x	x	72 h	x
Urinalysis[k]	x			72 h		x	x	x		72 h	x
Immunology[l]	x			72 h	x[m]	x[n]	x[n]	x[n]	x	72 h	x[n]
Thrombotic markers[o]	x		x	x[p]					x	x[p]	

a. At all assessments, subjects must not be actively bleeding. In addition to the assessments shown, clinical laboratory assessments should be performed whenever clinically indicated.
b. For subjects who participate in Part 2 of the study only.
c. If the subject is participating in Part 3 of the study, the subject will proceed directly to the Part 3 assessments.
If a subject is participating in Part 2 of the study only and has accumulated 50 EDs at the time of this visit, then this will be the subject's study completion visit if the subject has not accumulated 50 EDs, then the Week 26 assessments should be performed and a study completion/termination visit should be arranged within 3 months of this visit, by which time the subject should have accumulated 50 EDs.
d. At this visit subjects must have a minimum of 50 EDs and have been treated for at least 26 weeks.
e. If subject has accumulated 50 EDs by this visit.
f. For assessment of half-life: samples will be taken within 0.5 h before the start of the infusion, and at 0.5 h ± 5 minutes, 3 h ±10 minutes, and 24 h ± 2 h.
g. For assessment of recovery: samples will be taken within 0.5 h before the start of the infusion, and at 0.5 h ± 5 minutes after the infusion. FIX recovery is part of the PK assessments in Parts 2 and 3.
h. PK samples will be taken within 0.5 h before the start of the infusion, and at 0.25 h ± 5 minutes, 0.5 h ± 5 minutes, 1 h ± 5 minutes, 3 h ± 10 minutes, 6 h ±15 minutes, 9 h ± 30 minutes, 24 h ± 2 h, 30 h ± 2 h, 48 h ± 2 h, 60 h ± 2 h and 72 h ± 2 h following the infusion.
i. Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count.
j. Clinical chemistry assessments include: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose.
k. Urinalysis assessment: protein. Urinalysis should also be performed if inhibitors are detected.
l. Immunology assessments include: total binding and inhibitory antibodies to FIX, and antibodies to CHO protein and rFactor IX. If an inhibitory antibody with a Nijmegen titer ≥ 0.6 BU or total binding antibodies with a positive titer of 1:40 is detected, the test will be confirmed at the central laboratory within 2 weeks of study site notification. In either case the following additional tests will be performed: IgA, IgM, IgG subtypes, and hs-CRP; additional markers may be tested if applicable. If an inhibitor is suspected there may be additional testing for lupus anticoagulant/phospholipid antibodies, or FIX antibody testing with a different methodology. If a subject develops a severe allergic reaction or anaphylaxis: the following tests will be performed: hs-CRP, CIC-C1q and CIC-C3 (for circulating immune complexes), and IgE. Furthermore, Ig subtypes, inhibitory and total binding antibodies.
m. Immunology testing to be performed at least 3 days (72 h) after the first infusion of BAX 326.
n. Immunology testing to be performed at least 3 days (72 h) after the previous infusion of BAX 326 and before IP is administered at this visit.
o. Thrombotic markers include: thrombin-antithrombin III complexes (TAT), D-dimers, and prothrombin fragment 1.2.
p. Thrombotic marker assessments at 0.5 h ± 5 minutes, 3 h ± 10 minutes, 9 h ± 30 minutes, and 24 h ± 2 h following the infusion.

In brief, tests were as follows:

- The presence of FIX inhibitors was assessed according to the testing schedule shown in Table 23 using an assay based on the Nijmegen modification of the Bethesda method.
- The presence of total binding anti-FIX antibodies was determined by a validated in-house enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Ig antibodies (IgG, IgM and IgA) as detection antibodies. Test plasma samples were analysed for binding antibodies against the specific antigen in two steps. First, the sample was screened for antibodies and the titre of binding antibodies was determined (screening

assay). Second, the specificity of positive antibody results was confirmed (confirmatory assay). The ELISA assay is validated allowing an assay variability of ± 1 titre step. Therefore, differences ≤ 2 titre steps may be due to variability of the ELISA assay. As a result, the specificity of an antibody was confirmed if the competition assay showed an antibody titre that was reduced at least for three titre steps in comparison to the antibody titre detected in the screening assay. Therefore, it was not possible to confirm the specificity of antibodies in plasma samples that showed an antibody titre as low as 1:20 or 1:40. Accordingly, only plasma samples with an antibody titre of 1:80 or above could be evaluated in the confirmatory assays. Antibody titres of subject samples were only reported as positive, if specificity of the sample was shown in the confirmatory assay.

- The presence of binding antibodies to human furin proteins was determined by an inhouse ELISA employing polyclonal anti-human Ig antibodies (IgG, IgM and IgA). Antibody titres of subject samples were only reported as positive if specificity of the sample was shown in the confirmatory assay.
- Antibodies to CHO proteins were determined using a similar methodology to that used for detection of rFurin and FIX binding antibodies.
- the following seromarkers were tested at screening and at the study completion / termination visit: HIV: anti-HIV1+2, if HIV positive, the viral load will be determined; HAV: anti-HAV (IgG and IgM); HBV: HBsAg, anti-HBc and anti-Hbs ; HCV: anti-HCV If a seroconversion was observed following vaccination for hepatitis A and/or B before or during the course of the study, the vaccination was to be clearly documented. A seroconversion due to vaccination was not considered an AE. If a seroconversion was not attributable to a vaccination, additional confirmatory testing and a re-testing of the screening sample could be performed.
- The following thrombotic markers were tested at the central laboratory: TAT complexes; D-dimers; prothrombin fragment 1.2. Blood samples were to be drawn in all subjects at screening, and whenever clinically indicated. In addition, thrombotic markers were to be tested in the subjects taking part in the PK evaluation in Parts 1 and 3 at the following timepoints: 30 minutes prior to the Rixubis and BeneFIX infusions in Part 1 and 30 minutes prior to the Rixubis infusion in Part 3, and at 0.5 hours, 3 hours, 9 hours and 24 hours after the infusion.

Safety data at screening and baseline: Safety data were provided at the screening visit and at baseline, as shown in Table 23.

> Comment: The data collected as listed is self-explanatory or explained in footnote 'l' in the Table except for FIX antigen. This represents inactive FIX protein that retains FIX antigenicity, and is often associated with missense mutations, the incidence of which in this population was similar to the incidence of FIX antigen at screening.
>
> The sponsor needs to comment whether the presence of this antigenic material interferes with the other laboratory tests such as that for FIX activity or the detection of inhibitory antibodies to FIX.
>
> The relevance of the assay for antibodies to rFurin is assumed to be a measure of the patient's exposure and reaction to rFurin present in rFIX administered during previous treatments. rFurin is used as an activator to increase the yield of active FIX during purification. Similarly, because rFIX was purified from CHO cells, antibody formation to the proteins from these cells was also assessed at screening.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Dose-response and non-pivotal efficacy studies

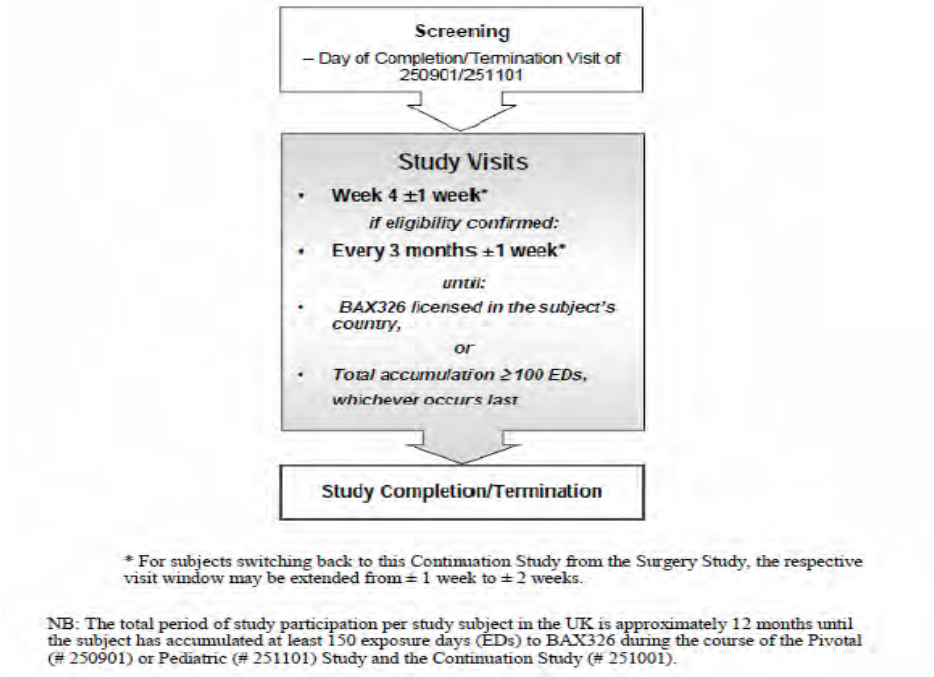
Not applicable.

Other studies evaluable for safety only

Continuation Study 251001: This ongoing continuation study was a prospective, open-label, multicentre, uncontrolled, Phase III study in up to 100 PTPs with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) haemophilia B, who had completed the Pivotal Study 250901 or the Paediatric Study 251101. Sixty four (64) subjects who completed the Pivotal Study 250901 were available for safety assessment only.

The study design is shown in Figure 8.

Figure 8 Study Design of Study 251001



The treatment regimen with Rixubis was at the discretion of the investigator and consisted of either twice weekly prophylactic treatment with 50 IU/kg (range of 40-60 IU/kg, which could be increased to 75 IU/kg, in subjects ≥ 12 years of age; range of 40-80 IU/kg in paediatric subjects < 12 years); modified prophylaxis determined by the investigator; or on-demand treatment.

The total period of study participation per study subject varied and could be up to a maximum of 48 months, depending on the date of subject enrolment and the product licensure in the subject's respective country, and whether the subject accumulated a total of 100 EDs to Rixubis during the course of the Pivotal (# 250901) or Paediatric (# 251101) Study and the Continuation Study (# 251001). Thirteen subjects from Continuation Study 251001 underwent surgery in Surgery Study 251002 and then returned to Continuation Study 251001.

Study Clinical Study 251101: Phase I/III (Paediatric): This study was a Phase I/III, prospective, uncontrolled, multicentre study investigating the safety, immunogenicity, PK, homeostatic efficacy and HR QoL of Rixubis. The subjects will be dosed with twice weekly prophylactic infusions with a recommended dose of 50 IU/kg Rixubis twice weekly ranging from 40 to 80 IU/kg over six months or for at least 50 EDs, whichever occurs last, in 24 paediatric PTPs in order to have 20 evaluable subjects. Before the start of the six month prophylactic treatment period, a PK evaluation will be performed. There will be two cohorts of 12 subjects each, based on the age of the subjects: < six years and six to < 12 years. Within each cohort, subjects will be

randomised to one of two blood sampling sequences for the PK assessment to reduce the burden of frequent blood sampling on the individual subject. The overall duration of the study was to be approximately 18 months. The subject participation period was approximately eight months from enrolment to subject completion, unless prematurely discontinued. Safety assessments were carried out as described for the pivotal studies.

Clinical pharmacology studies as part of the pivotal trials: The pharmacology studies formed part of each pivotal trial and were discussed above. The safety data on these patients was included with those in each of the trials. One difference was that the patients in Part 1 (PK) of the pivotal Trial 250901 received commercial rFIX (BeneFIX) as well as Rixubis as follows: During Part 1, 13 subjects received one infusion with Rixubis followed by one infusion with BeneFIX, 14 subjects received one infusion with BeneFIX followed by one with Rixubis, and one subject received two infusions with Rixubis; overall exposure to Rixubis ranged from 12 to 83 days.

7.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

7.3. Patient exposure

In estimating drug exposure, one ED was defined as a calendar day (12:00 am to 11:59 pm) during which a subject received IP, regardless of the number of infusions or amount of product given during the day.

The number of subjects infused, number of infusions, total units administered, and total EDs according to study event (prophylaxis, treatment of bleeding episodes, PK assessments, prophylaxis, peri- and post-operative homeostatic management, or other, and all study events) were calculated overall and for each age group. The median, minimum, and maximum per-subject values were determined for each of these parameters.

Table 24: Summary of Exposure by Age Group

Parameter	Statistic	<6 yrs	6 - <12 yrs	12 - <16	≥16 yrs	All
Study Duration [months]	N	6	10	3	72	91
	Mean (Std)	3.02 (0.70)	3.72 (1.95)	13.57 (7.68)	13.54 (4.77)	11.77 (5.88)
	Median	3.14	3.17	17.05	13.72	13.11
	Q25 ; Q75	2.46 ; 3.65	2.89 ; 3.68	4.76 ; 18.89	10.60 ; 16.59	5.26 ; 13.80
	Min ; Max	2.00 ; 3.71	1.31 ; 8.51	4.76 ; 18.89	3.75 ; 25.23	1.31 ; 25.23
Exposure Days	N	6	10	3	72	91
	Mean (Std)	7.5 (3.9)	13.1 (14.4)	118.7 (83.5)	92.6 (67.5)	79.5 (54.4)
	Median	7.0	11.0	155.0	99.5	85.0
	Q25 ; Q75	4 ; 11	5 ; 25	21 ; 180	58 ; 128	25 ; 111
	Min ; Max	3 ; 13	3 ; 50	21 ; 180	8 ; 209	3 ; 209
Number of Infusions per Subject	N	6	10	3	72	91
	Mean (Std)	7.5 (3.9)	13.1 (14.4)	122.3 (89.4)	94.3 (67.8)	80.8 (55.0)
	Median	7.0	11.0	155.0	101.0	85.0
	Q25 ; Q75	4 ; 11	5 ; 25	21 ; 191	58 ; 128	24 ; 117
	Min ; Max	3 ; 13	3 ; 50	21 ; 191	8 ; 212	3 ; 212
Consumption [IU/kg] per Subject	N	6	10	3	72	91
	Mean (Std)	482.2 (256.3)	885.2 (914.2)	6720.1 (4882.1)	5157.6 (2762.0)	4416.6 (3104.4)
	Median	512.4	639.6	8202.2	5173.4	4653.0
	Q25 ; Q75	221 ; 604	207 ; 1346	1269 ; 10689	2994 ; 6855	1503 ; 6348
	Min ; Max	179 ; 864	169 ; 3195	1269 ; 10689	376 ; 13496	169 ; 13496
Number of Infusions for:						
Prophylactic	Sum	24	108	241	5,343	5,716
Bleed	Sum	1	3	109	769	882
PK	Sum	8	20	17	395	440
Surgery	Sum	NA	NA	NA	30	30
Other	Sum	12	20	NA	253	285
All	Sum	45	151	367	6,790	7,353
Consumption [IU] for:						
Prophylactic	Sum	27,052	200,156	587,008	19,999,527	20,813,743
Bleed	Sum	859	5,880	292,420	2,939,697	3,238,856
PK	Sum	10,511	50,466	57,619	2,142,292	2,260,888
Surgery	Sum	NA	NA	NA	200,294	200,294
Other	Sum	12,520	36,199	NA	1,274,371	1,323,090
All	Sum	50,942	292,701	937,047	26,556,181	27,836,871

[generated by 25_tt2_safety.sas]

Subjects participated in the Rixubis clinical program for a median of 13.11 months (range: 1.31 to 25.23 months). Subjects were treated with Rixubis for a median of 83 EDs (range: 3 to 209 EDs), with a median number of infusions of 85 (range: 3 to 212 infusions), and median consumption of Rixubis of 4653.0 IU/kg (range: 169 to 13496 IU/kg).

The 91 treated subjects received a total of 27,836,871 IU of Rixubis in 7353 infusions, including:

- 20,813,743 IU administered in 5716 infusions for prophylaxis
- 3,238,856 IU administered in 882 infusions for bleeding episodes
- 2,260,888 IU administered in 440 infusions for PK analysis
- 200,294 IU administered in 30 infusions for peri- and post-operative homeostatic management

· 1,323,090 IU administered in 285 infusions for "other" reasons

Comment: The median EDs of 83 and the median number of infusions (85) are small compared to those that would be received in a lifetime of treatment, and very small in the paediatric group. It should be remembered therefore that any adverse events detected in these studies would be those occurring in the short term. Longer term monitoring is recommended.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Integrated studies

AEs that occurred in the subjects included in this integrated analysis are summarized according to number, seriousness, severity, causality, and age in Table 25 and Table 26.

Table 25: Overview of AEs by Age Groups Irrespective of Relationship to Study Treatment

Seriousness of AE	Severity of AE	Relationship	<6 yrs N = 1 n (%)	6 - <12 yrs N = 3 n (%)	12 - <16 N = 2 n (%)	≥16 yrs N = 155 n (%)	All N = 161 n (%)
Serious	Mild	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
	Moderate	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
	Severe	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6)	4 (2.5)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6)	4 (2.5)
	Unknown	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.9)	6 (3.7)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.9)	6 (3.7)
Non-Serious	Mild	Not Related	1 (100.0)	1 (33.3)	2 (100.0)	113 (72.9)	117 (72.7)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	3 (1.9)
		Total	1 (100.0)	1 (33.3)	2 (100.0)	116 (74.8)	120 (74.5)
	Moderate	Not Related	0 (0.0)	2 (66.7)	0 (0.0)	30 (19.4)	32 (19.9)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	2 (66.7)	0 (0.0)	30 (19.4)	32 (19.9)
	Severe	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
	Unknown	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	2 (1.2)
	Total	Not Related	1 (100.0)	3 (100.0)	2 (100.0)	145 (93.5)	151 (93.8)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6)	4 (2.5)
		Total	1 (100.0)	3 (100.0)	2 (100.0)	149 (96.1)	155 (96.3)
Total			1 (100.0)	3 (100.0)	2 (100.0)	155 (100.0)	161 (100.0)

[generated by 25_as2_safety.sas]

Table 26: Overview of Subjects with AEs by Age Group

Seriousness of AE	Severity of AE	Relationship	<6 yrs N = 6 n (%)	6 - <12 yrs N = 10 n (%)	12 - <16 N = 3 n (%)	≥16 yrs N = 72 n (%)	All N = 91 n (%)
Serious	Mild	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
	Moderate	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
	Severe	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.2)	3 (3.3)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.2)	3 (3.3)
	Unknown	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.9)	5 (5.5)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.9)	5 (5.5)
Non-Serious	Mild	Not Related	1 (16.7)	1 (10.0)	2 (66.7)	37 (51.4)	41 (45.1)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)	2 (2.2)
		Total	1 (16.7)	1 (10.0)	2 (66.7)	37 (51.4)	41 (45.1)
	Moderate	Not Related	0 (0.0)	2 (20.0)	0 (0.0)	16 (22.2)	18 (19.8)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	2 (20.0)	0 (0.0)	16 (22.2)	18 (19.8)
	Severe	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
	Unknown	Not Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
		Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.1)
	Total	Not Related	1 (16.7)	3 (30.0)	2 (66.7)	42 (58.3)	48 (52.7)
		Related	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.2)	3 (3.3)
		Total	1 (16.7)	3 (30.0)	2 (66.7)	42 (58.3)	48 (52.7)
Total			1 (16.7)	3 (30.0)	2 (66.7)	42 (58.3)	48 (52.7)

[generated by 25_n2_safety.sas]

A total of 161 AEs were reported in 48 (52.7%) of the 91 subjects treated with at least one infusion of Rixubis. Of all treated subjects, 43 did not report an AE during their period of participation. Non-serious AEs (n=155) comprised the majority of all AEs and occurred in 48 (52.7%) subjects. The majority of non-serious AEs were mild or moderate events: 120 mild AEs in 41 (45.1%) subjects and 32 moderate AEs in 18 (19.8%) subjects. Of the 155 non-serious AEs, one in one (1.1%) subject was considered severe, and two AEs in one (1.1%) subject were of unknown severity.

Of the non-serious AEs, the majority were mild and unrelated (117/155) to Rixubis A summary of the number of AEs by age group follows:

- <6 years - one AE was non-serious, mild, and not related
- 6 to < 12 years - three AEs was non-serious, one mild, two moderate, all not related
- 12 to < 16 years – two AEs were non-serious, mild, and not related
- ≥ 16 years- 155 AEs in 42 subjects:
- six SAEs in five subjects

- 149 non-serious in 42 subjects (145 AEs not related)

A summary of non-serious AEs by MedDRA system organ class and preferred term was presented. The non-serious AEs by preferred term experienced by at least two subjects were as follows:

- Diarrhoea: six AEs in three subjects, considered not related
- Dyspepsia: two AEs in two subjects, considered not related
- Toothache: two AEs in two subjects, considered not related
- Pyrexia: five AEs in four subjects, considered not related
- Bronchitis: three AEs in three subjects, considered not related
- Gastroenteritis: three AEs in two subjects, considered not related
- Influenza: two AEs in two subjects, considered not related
- Nasopharyngitis: 14 AEs in eight subjects, considered not related
- Pharyngitis: five AEs in five subjects, considered not related
- Pneumonia: two AEs in two subjects, considered not related
- Rhinitis: two AEs in two subjects, considered not related
- Upper respiratory tract infection: four AEs in two subjects, considered not related
- Contusion: three AEs in two subjects, considered not related
- Procedural pain: three AEs in two subjects, considered not related
- Immunology test abnormal: 23 AEs in 17 subjects, considered not related
- Arthralgia: nine AEs in four subjects, considered not related
- Pain in extremity: three AEs in two subjects one AE of which was of unknown causality and conservatively considered related
- Headache: three AEs in three subjects, considered not related
- Cough: five AEs in three subjects, considered not related

The majority of the non-serious AEs appear to have been related to mild infections or gastrointestinal disease, abnormal immunology tests (antibodies of indeterminate specificity in assays for FIX or rFurin), or arthralgia, a well-described complication of haemophilia, and not related to IP.

7.4.1.2. Other studies

Not applicable.

7.4.2. Treatment-related adverse events (adverse drug reactions)

7.4.2.1. Integrated studies

Causally related: Of the 161 AEs reported for the subjects included in this integrated analysis, the only AEs rated as related to Rixubis by the investigator or the sponsor were four non-serious AEs in three (3.3%) subjects. One subject was reported to have a positive (and transient) rFurin antibody test result (1:80) and two AEs of dysgeusia in one subject were also reported. These three AEs were considered mild. One subject was reported to experience one AE of pain in extremity of unknown severity and causality, which was conservatively considered related. Three of the related AEs were reported in Pivotal Study 250901

- Dysgeusia: two AEs in one subject, both considered mild

- Pain in extremity: one AE (at one day after Rixubis infusion, unknown severity and unknown relatedness and therefore conservatively rated in this analysis as related).

One AE was reported in Continuation Study 251001:

- Development of positive rFurin antibodies, titre 1:80: one1 AE in one subject, considered mild

Temporally-associated AEs: Temporally-associated AEs were defined as any AE that began during or within 24 hours of infusion with IP, regardless of causality, and causally-associated AEs were all AEs assessed as related to IP (probable, possible, or AEs for which the investigator or sponsor's opinion of causality was missing or indeterminate). There were a total of 65 causally or temporally-associated AEs in 29 subjects with an incidence of 0.88% AEs/infusion. No causally-associated AEs occurred in more than one subject (and all are listed above). Temporally-associated AEs by preferred term which occurred in at least two subjects are as follows:

- Diarrhoea: four AEs in two subjects
- Pyrexia: three AEs in three subject
- Gastroenteritis: two AEs in two subjects
- Nasopharyngitis: two AEs in two subjects
- Pharyngitis: three AEs in three subjects
- Procedural pain: three AEs in two subjects
- Immunology test abnormal: nine AEs in seven subjects
- Headache: two AEs in two subjects

7.4.2.2. Other studies

Not applicable.

7.4.3. Immunogenicity

The following safety data were included with adverse events at the request of the Data Safety monitoring Committee.

7.4.3.1. Inhibitors to FIX

No subjects developed an inhibitory antibody to FIX with a titre ≥ 0.6 BU.

7.4.3.2. Total binding antibodies to FIX

None of the subjects developed treatment-related binding antibodies to FIX. Indeterminate titres were observed in 11 (12.1%) subjects.

7.4.3.3. Antibodies to rFurin

Over all the studies included in this ISS, indeterminate titres of antibodies to rFurin were observed in 11 (12.1%) subjects. In three of these subjects low antibody titre (1:20 or 1:40) was determined prior to exposure to IP. During the Pivotal Study, one subject (250901-010002) exhibited antibodies in the rFurin assay of indeterminate specificity and at a subsequent time point during the Continuation Study, this subject had an rFurin antibody assay result assessed as positive (a confirmed titre of 1:80) which was an increase in titre considered treatment-related. At the following sampling time points the rFurin antibody titre was classed as indeterminate (1:20), then negative and then indeterminate (1:20). The presence of binding antibodies to rFurin was considered not clinically significant by the investigators. Furthermore, a literature review did not reveal any reports suggesting a clinical impact of antibodies against rFurin.

7.4.3.4. Antibodies to chinese hamster ovary proteins

No subjects developed antibodies to CHO proteins.

7.4.4. Thrombotic events and severe allergic reactions

No thrombotic events or severe allergic reactions were reported in any subject in the integrated analysis.

7.4.5. Deaths and other serious adverse events

7.4.5.1. Integrated studies

There were no deaths. Two subjects were withdrawn due to an unrelated SAE requiring emergency treatment (following a road traffic accident in one subject, and intestinal surgery in one subject) with another FIX product rendering them ineligible for continuation of the Rixubis study. The subject who underwent emergency surgery could not, at that time, be included in Surgery Study (251002) as this study was not yet operational.

While eight SAEs are described in narratives in the Pivotal 250901 CSR, only the five SAEs, which occurred in four subjects during or after exposure to IP and within the cut-off date, were included in this integrated analysis. The two SAEs excluded, one concussion from a car accident, and the second a suicide attempt were patients either not randomised or not treated. An additional SAE occurred in one subject in Continuation Study 251001, resulting in a total of six SAEs reported in five (5.5%) subjects in this ISS. The six SAEs were as follows:

- Duodenal ulcer haemorrhage: one SAE in one subject (severe)
- Intestinal Obstruction: one SAE in one subject (severe)
- Cervical vertebral fracture: one SAE in one subject (severe)
- Traumatic haematoma: one SAE in one subject (severe)
- Convulsion: one SAE in one subject (moderate)
- Hepatitis B core antibody positive: one SAE in one subject (mild)

Four SAEs in three (3.3%) subjects were severe. One moderate SAE was reported in one (1.1%) subject and one mild SAE was reported in one (1.1%) subject. No SAEs were judged by the investigator or the sponsor to be possibly or probably related to Rixubis.

One SAE of convulsion, considered unrelated to IP, was also categorised as a temporally-associated AE (see comments, below).

> Comment: The SAEs reported in all studies require further evaluation. Narratives of each of the eight SAEs from the pivotal study were provided in the study Report, and another occurred in the Continuation Study 251001, reported in the ISS. The clinical evaluator discusses these in the following section.

Serious Adverse Events: As stated above, five of the eight SAEs in the pivotal study were included in the ISS. Exclusions of Subject 1 [car accident before randomisation) and Subject 3, a suicide attempt before any trial treatment was administered are appropriately excluded. The third case was Subject 2 with chronic persistent hepatitis from January 2002, who was found to be negative for HBs antigen in 2007, 2008 and 2010. On screening (4 August 2011) and at his completion visit (9 April 2012) he again tested positive for HBs antigen. However his screening test for Hepatitis core ABb that had been negative, was positive at the completion visit.

> Comment: The viral serology for Subject 2 at screening and at the end of study was as follows:

- HIV-1/2 Antibody: Non-Reactive / Non-Reactive
- Hepatitis B Core Total: Negative / Positive

- Hepatitis B Surface Antibody: Positive / Positive
- Hepatitis B Virus Surface Antigen: Negative / Negative
- Hepatitis C Virus Antibody: Positive / Positive
- IgM Ab to Hepatitis A Virus: Negative / Negative

The serology is consistent with the diagnosis of chronic persistent hepatitis, but the conversion of the HbcABb test is unexplained, but does not suggest any Hepatitis B infection during the trial. The patient's LFTs were not recorded as abnormal during the trial.

7.4.5.2. Other studies

Not applicable.

7.4.6. Discontinuation due to adverse events

7.4.6.1. Integrated studies

No discontinuations were reported.

7.4.6.2. Other studies

Not applicable.

7.5. Laboratory tests

Laboratory tests were done at screening (baseline) and at the following times:

- Part 1, Infusions 1 & 2: 72 hours post-infusion
- Week 5 ± 1 (10 to 15 EDs)
- Week 13 ± 1
- Week 26 ± (Part 2 only subjects)
- Part 3: Pre-infusion and 72 hours post-infusion
- And at study completion/termination, if it does not coincide with the Part 3/ Week 26 ± 1 visit.

7.5.1. Liver function

7.5.1.1. Integrated studies

At screening, the ALT values were normal in 73% of patients and at conclusion of the study, 71%, while the abnormal values were reported in 23% of patients at screening and 25% at completion. None were clinically significant.

Two events of elevated ALT of clinical significance were reported in one subject ≥ 16 years of age in the Surgical Study 251002, and was reported as an AE, but not causally related to the IP. Clinically Significant (CS) was defined as an abnormal value that constituted an AE [code #1] and the abnormal value was a symptom of or related to a disease that was already recorded as an AE [Code #2].

Comment: A majority of patients had past infections with Hepatitis B or C or both and a large number had chronic hepatitis with one or both viruses. No figures were given for the incidence of these conditions in the study reports but each patient's medical history was provided.

The one case above had both chronic hepatitis B and C. At screening his ALT was 142U/L (N 6 to 43), and 294U/L at completion of the study.

7.5.1.2. Other studies

Not applicable.

7.5.2. Kidney function

7.5.2.1. Integrated studies

No clinically significant abnormalities were reported.

7.5.2.2. Other studies

Not applicable.

7.5.3. Other clinical chemistry

7.5.3.1. Integrated studies

No clinically significant abnormalities were reported.

7.5.3.2. Other studies

Not applicable.

7.5.4. Haematology

7.5.4.1. Integrated studies

All clinically significant results were reported in two subjects ≥ 16 years of age:

- Erythrocyte mean corpuscular Hgb concentration (g/L) two cases in one subject
- Erythrocyte mean corpuscular volume (fL) three cases in one subject
- Erythrocytes (TI/L) four cases in two subjects
- Haematocrit four cases in two subjects
- Haemoglobin (g/L) four cases in two subjects

None of the clinically significant assessments were reported as AEs, but were all a symptom of, or related to, a disease that was already recorded as an AE (anaemia and haemorrhagic anaemia).

7.5.4.2. Other studies

Not applicable.

7.5.5. Vital signs

7.5.5.1. Integrated studies

Vital signs, physical findings, and other safety-related observations were evaluated. No vital sign measurements were considered clinically significant. Descriptive statistics of measurements of vital signs taken within 15 minutes prior to administration, and the changes observed at 30 minutes and 120 minutes post-administration presented.

7.6. Post-marketing experience

Rixubis has not been marketed in any country to date.

7.7. Other safety issues

No other safety issues were noted.

7.8. Evaluator's overall conclusions on clinical safety

1. The safety of the pilot material and the commercial preparation were not assessed separately.
2. The number of patients assessed for safety was 91. The median number of Exposure Days (EDs), 83 and the median number of infusions per patient in the program, 85, are small compared to those that would be received in a life-time of treatment, and very small in the paediatric group. It should be remembered therefore that any AEs detected in these studies would be those occurring in the short term. Longer term monitoring is recommended.
3. One hundred and sixty one (161) AEs occurred in 52.7% of patients, of which 155 were non-serious, and 117 of mild severity. Four non-serious AEs in three patients were related to Rixubis – dysgeusia (two events in one patient); pain in an extremity; and the development of rFurin antibodies.
4. Sixty-five (65) temporally-associated AEs (beginning during or within 24 hours of infusion regardless of causality) that occurred in 29 subjects (0.88%) included diarrhoea, pyrexia, gastroenteritis, nasopharyngitis, pharyngitis, procedural pain, abnormal immunological tests, and headache.
5. No inhibitors to FIX, no treatment-related binding antibodies to FIX, and no antibodies to CHO proteins were detected in treated subjects. One subject developed a positive assay for rFurin (confirmed titre 1:80), considered to be not of clinical significance.
6. No thrombotic events or severe allergic reactions were reported in any subject in the integrated analysis.
7. There were no deaths. Eight SAEs were reported in all studies, of which six were relevant to the studies. Two SAEs (car accident, and suicide) were appropriately excluded. The six SAEs were considered not related to Rixubis treatment, and were a bleeding duodenal ulcer (severe); intestinal obstruction (severe); cervical vertebral fracture (severe); traumatic haematoma (severe); convulsion (moderate); and conversion to HepBcAb positive (mild).
8. A majority of patients had past infections with Hepatitis B or C or both and a large number had chronic hepatitis with one or both viruses. One clinically significant event of an abnormal alanine aminotransaminase occurred in a patient with chronic hepatitis B and C.
9. The product has not been marketed in any country so no PMR was available.

Conclusion: The clinical evaluator agreed with the conclusion of the ISS that 'Taken together, the safety assessments utilised in this integrated analysis demonstrate safety and tolerability in subjects with severe or moderately severe haemophilia B', with the addition that safety data from longer term treatment with Rixubis should be provided when available.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

1. The first benefit of Rixubis is that it is effective treatment in reducing the frequency of spontaneous and injury-related bleeding when administered as routine prophylaxis in patients 12 years and in treating and preventing bleeding episodes in patients 12 years and older with severe or moderately severe haemophilia B (congenital FIX deficiency).
2. A second benefit is that Rixubis is a recombinant product and so does not have the potential safety risks of viral transmission associated with plasma derived products.

A benefit of Rixubis in the peri-operative management of patients 12 years and older with severe or moderately severe haemophilia B seems likely, but the data provided in the interim analysis of the relevant study require confirmation from the results of the completed study before this benefit can be claimed with confidence.

8.2. First round assessment of risks

The risks of Rixubis in the proposed usage are those associated with FIX products:

- Thrombotic events - patients potentially at risk are those with signs of fibrinolysis, disseminated intravascular coagulation (DIC) or liver disease, and patients postoperatively or who are otherwise at risk of a thrombotic event or DIC.
- FIX Inhibitor Formation – FIX containing products have been associated with the development of activity-neutralising antibodies (inhibitors) in 1.5 to 3.0% of PTP with severe haemophilia B. As a consequence of FIX inhibitor development, minor and major bleeding cannot always be prevented or treated effectively, potentially resulting in increased morbidity and diminished quality of life.
- Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported for all FIX products.

A correlation has been reported between the occurrence of a FIX inhibitor and allergic reactions. Fifty-one (58%) of the 88 FIX inhibitors reported to the international haemophilia B database in 2005 were associated with an allergic manifestation. There seems to be no difference in the frequency of allergic reactions or inhibitor development in individuals receiving rFIX compared with those receiving plasma derived FIX. A relationship may exist between the presence of major deletion mutations in a patient's FIX gene and an increased risk of inhibitor formation and of acute hypersensitivity reactions. Patients known to have major deletion mutations of the FIX gene should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to FIX products.

None of the above risks, thrombotic events, inhibitor formation, and hypersensitivity reactions, were observed in the studies submitted, nor were any significant product-related adverse events reported.

Note**:** This risk assessment is based on the assumption that the sponsor's answers to questions and requests regarding the large number of major and minor protocol deviations are answered satisfactorily and do no indicate serious breaches of ethics, GCP and guidelines for patient safety (see Clinical Questions).

A remaining risk factor is that the above safety data are derived from relatively short term treatment, compared to a life-time of treatment in such patients. Therefore longer term safety data on the use of Rixubis is necessary.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of Rixubis for routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B, and for the treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital FIX deficiency) is favourable.

The benefit-risk balance of Rixubis for peri-operative management in patients 12 years and older with haemophilia B is unfavourable, but would become favourable if the Surgical Study 251002 were completed and the data supports that of the interim analysis.

9. First round recommendation regarding authorisation

Subject to an acceptable response to the Clinical Questions put to the sponsor the clinical evaluator recommended that Rixubis be approved for:

- Routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B and
- Treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital FIX deficiency)

The clinical evaluator did not recommend approval of Rixubis for peri-operative management of patients 12 years and older with haemophilia B until the Surgical Study 251002 is completed and the results evaluated and confirm those of the interim analysis.

10. Clinical questions

10.1. Protocol deviations

The large numbers and types of major and minor protocol deviations in the pivotal study have resulted in a number of questions and requests to the sponsor and will require an acceptable response before any approval of the requested indications can be made.

10.2. Safety

Does the presence of FIX antigen in a subject's blood interfere with the measurement of FIX activity or on the detection of inhibitor antibodies to FIX?

11. Second round evaluation of clinical data submitted in response to questions

11.1. Protocol deviations

The large numbers and types of major and minor protocol deviations in the pivotal study resulted in a number of questions and requests to the sponsor. The questions and the clinical evaluator's assessment of the sponsor's response follow.

11.1.1. Question 1

11.1.1.1. General

1. Please explain and justify the large number of minor and major protocol deviations that occurred in the pivotal trial.

Sponsor's Response: The sponsor described the Protocol Deviation Plan (PDP) used in the pivotal study and the oversight of the PDs twice a year by an independent Data Management Committee (DMC). Documentation was provided of the DMC's meetings and decision to continue the study without change.

> Comment: The PDP described and defined major and minor deviations in detail but did not include procedures to manage these if the number seemed excessive in number or severity (major). This decision was left presumably to the DMC. This body only met twice a year and was provided at each meeting with the list of PDs to that date. In all cases, no action was taken in relation to the large number of PDs reported, especially in

the early stages of the study. The conclusion then is that the PDP and the DMC failed to raise concerns about the large number of PDs that were occurring.

To explain and justify the large number of PDs, the sponsor made three points:

- Baxter's approach to report PDs at the subject level, not at the site level, leading to a higher number of PDs

  Comment: The point made is not clear to this evaluator. If 10 PDs were reported from one side, was that less worrying than 10 individual subject reports from that site?

- Baxter's approach to list several protocol deviations separately although they relate to the same event: for example, when a site infused a wrong (out of range) dose for PK or IR and used two different lots, two separate PDs were reported, although it affected a single event/infusion only. This has also contributed to the higher number of PDs.

  Comment: The effect of such double reporting on the number of PDs cannot be assessed without knowing the number of such cases. This information was not provided.

- Limited number of subjects per site, thus the experience of the investigator is limited and this contributes to the higher number of reported PDs that would not be otherwise observed, if the investigator could gain experience with many more subjects available.

  Comment: This reason was supported by later data such as the higher occurrence rate of PDs early in the study and by the drop in reported PDs after adequate instructions and training. While explaining the high numbers of PDs, this does not excuse that number and the apparent lack of adequate training and preparation of the investigators before the trial began. The use of ill-prepared facilities for patient treatment, many in foreign countries from the USA, raises substantial ethical issues.

2. Given that the protocol clearly and correctly sets out the schedule and procedures for the trial, and states the method of recording, notifying and reporting protocol deviations, please explain whether the problem was with the investigators or the trial monitoring or both.

Sponsor's response: The sponsor noted the complexity of the treatment, the high number of laboratory assessments and subjects' assessments that contributed to the number of PDs in the early period of the study. As well, the study design was that the patients self-administered the IP at home in the time between the study visits. During this home treatment phase, protocol deviations accumulated, before the site identified the protocol deviations and retrained the subject during the next interval study visit.

Comment: The reasons are acceptable as explanations of the high number of PDs seen.

11.1.2. Question 2

11.1.2.1. Definitions of major and minor deviations:

This question related to two cases of apparent inconsistencies in classifying major and minor deviations.

Sponsor's response: In the first case, significant under-dosing occurred from the required IR dose, so this was a major PD whereas on the second occasion in the same patient the dose was recommended and not required and the administered dose only slightly lower and so classified a minor PD as defined. In the second case two major PDs were reported for the same patient during the one infusion due to under-dosing and to the use of the wrong strength IP, each reported as a major PD.

Comment: The explanation is acceptable.

A related question was to review all deviations in Listing 5 and identify similar contradictions and inconsistencies, for example where the events listed appear to be similar but have been classified differently.

Sponsor's response: Baxter reviewed data and found the following inconsistency:

· Subject under-dosing for prophylactic dosing erroneously classified as major deviation

No other inconsistencies were identified.

11.1.3. Question 3

11.1.3.1. Repeated major deviations:

Ten patients each had two or more major deviations, representing 14% of the total patient population, and 56% of all major deviations. Administration errors (major deviations) occurred repeatedly in some patients. Two patients had one error; eight had two errors each; one had three errors; and two had five errors each, all major deviations. It is disturbing that the same drug administration error occurred in the same patient repeatedly in some of these cases, and at the same study center in different patients (for example Site 06). Please explain how such repeated mistakes occurred and how these are compatible with compliance with GCP.

Sponsor's response (abridged): The sponsor responded that the majority of the repeated major deviations occurred at three sites, namely Site 06, Site 15, and Site 21. A summary of the occurrence of PDs at each of the three sites was then given, with the subsequent action of the site monitor, who acted to correct the problem.

At Site 06, seven major protocol deviations occurred. At Site 15, seven major protocol deviations occurred. At Site 21, five major protocol deviations occurred. Three of them were related to the first three in-clinic infusions. For all other sites with patients with two or one major protocol deviations regarding investigational product administration, the CRAs identified the deviations and re-trained the sites accordingly. As a consequence no further investigational product administration deviations occurred after the Week 5 visits, except for a small number of patients where the protocol deviations occurred at the last study infusion due to sites not following protocol defined procedures and IP dose calculations.

At the three sites listed, the major PDs occurred in most cases prior to the first visit of the site monitor on the 5th week of the trial. The sponsor's response states the 'Clinical Research Associate (CRA) re-trained the site on investigational product administration and from then on no major protocol deviations related to investigational product infusion occurred.'

> Comment: The response explains how multiple major PDs occurred in the same patients at several sites. Appropriate GCP was followed after the problem was identified. However the criticism made above applies here, that prevention by adequate site training should have taken place instead of action post hoc. Prior assessment of the expertise and quality of care provided at these and other sites were initially inadequate and this may be regarded as a breach of GCP.

11.1.4. Question 4

11.1.4.1. Deviations that may have affected patient safety

In the following cases, the protocol deviation listed may have compromised patient safety even though the deviation has been listed in some cases as minor. Please provide for each case below the clinical state of the patient at the time of the deviation; the detailed description of that deviation; and why patient safety was not compromised.

There followed in this question a series of 16 patients, identified by number, with the information as given in the listing of PDs in the report of the pivotal study. The issues involved can be grouped and summarised as follows:

11.1.4.1.1. Under-dosing and safety

In seven cases, the subjects were under-dosed because they were given the prophylactic dose of 40-60IU/kg instead of the IR dose of 70-80IU/kg required by the study design. As the prophylactic dose was still a safe dose, patient safety was not compromised.

In two cases at Site 18, under-dosing occurred because the study drug was not available for prophylactic treatment at that site from 16-25 Jan 2012. The former subject had one bleed during this time and was appropriately treated with Rixubis, but the source of this material was not stated. The second subject did not have any bleeding. This situation potentially compromised safety, as it is unclear how Rixubis could be available to treat bleeds if they occurred and yet not be available to the site, as stated.

In two cases, under-dosing occurred because of lack of subject compliance. In the first case, no bleeding occurred during the period of under-dosing. In the second case, the subject bleed at a rate greater than expected for the prophylaxis group. However the prophylactic dose was only increased towards the end of the study (after 12 bleeding episodes) from initially approximately 49 IU/kg to 67 IU/kg with an average dose over the study of 52.8 IU/kg. In this case the subject's safety was compromised by the failure of adequate supervision and subsequent increase in treatment dosage.

In one case, the subject self-administered study drug every second day for 8 days, contrary to protocol without adverse effects.

11.1.4.1.2. Mistakes in reporting and monitoring

One case of PD was reported in error and some mistakes were made in classification of minor PDs as major. A case of misreporting by a site monitor was more serious and resulted in a delay in reporting that the study drug had been stored at a too high temperature. While potentially compromising safety, no adverse events were reported.

11.1.4.1.3. Mistakes in obtaining informed patient consent

These two mistakes were satisfactorily explained by the sponsor.

> Summary and Comment: The only adverse safety outcome that resulted from the PDs recorded was for one subject who suffered increased frequency of bleeds from inadequate prophylactic dosing associated with a delay in increasing the administered dose for prophylaxis. However a number of other subjects were put a risk of bleeding in such situations as lack of supply of the study drug, and under-dosing due to poor compliance that was not acted upon until late in the study. While the under-dosing because of mistakes in the IR and prophylactic dosing did not constitute a demonstrated safety risk, it does raise questions about adequate pre-trial assessment of the competence and experience of these sites in following a complex clinical trial protocol, and so gives a signal for more care in complying with GCP.

11.1.5. Question 5

11.1.5.1. Deviations that may have affected PK analyses

In two cases, the PD was misreported. In one case, different lot numbers of the study drug were used contrary to protocol, but no safety issue was involved. In a third case, less than the required five day washout period was used, and the data included in the PK analysis. However after this shorter period, the pre-infusion concentration was only 2.3% (presumably of the C_{max} or AUC) so this was acceptable.

11.1.6. Question 6

11.1.6.1. Monitoring of trial sites for compliance

1. The study report of the pivotal trial, states that Baxter performed five site compliance audits out of 29 trial centres participating in the pivotal trial. Please respond to the following questions and requests.

   Only three audit closure certificates (for Sites 18, 45 and 52) were included in the study report. Please provide the certificates from the other two Sites, 01 and 26. Also it is noted that the certificate for Site 45 was not signed by the Lead Auditor but by another person on his behalf. Please explain the role of this person in the audit process.

   Comment: The sponsor supplied copies of the missing certificates and satisfactorily explained the role of the signatory.

2. Please explain why only five sites were audited out of the 29 in the study and why these sites were chosen. It is noted that although Sites 01, 18 and 26 entered most patients –10, 8 and 8 respectively. The total number of patients entered from the five sites was 30, less than half the 72 patients entered in total. These five sites listed only three major protocol deviations compared to 33 major deviations listed by the other 24 sites. Please explain why the sites with the most deviations were not audited.

   Comment: The sponsor's response required an extended evaluation. My conclusion was that Baxter's process followed to select sites to be monitored for compliance failed to identify and monitor the sites with the highest total number of major PDs, and the highest number of PDs per subject. It did select and monitor three of the five sites with the highest number of major and minor PDs in total and per subject. It failed to select and monitor the sites with the highest number of discontinuations before treatment. The fact that a procedure was in place to select sites for monitoring is not acceptable when that procedure does not identify those sites that potentially place subjects at risk. The failure is also of concern with respect to compliance with GCP.

3. Site 52 was audited. This site entered one patient who was reported as having two major and 20 minor protocol deviations. It is noted that doctor conducting the trial had only participated in one clinical trial previously, and although described as specialised in haemophilia as well as HIV/AIDs and Infection Immunity, his/her main publications shown are all in virology. Nevertheless the study report stated that 'No critical observations were cited.'

   Please explain why no criticism was made by the auditor of site 52.

   Comment: Again Baxter justified this situation because certain procedures were followed and definitions used, even though the outcome potentially compromised patient safety, as with site monitoring. In this case only one patient was enrolled and that one patient experienced two major and 20 minor PDs. The clinical evaluator's assessment of the treatment received by this patient was that 'I regard the patient's safety to have been compromised in this case due to a failure of monitoring to increase the prophylactic dose of Rixubis appropriately.'). My further assessment is that in this case Baxter's response that 'observations were cited' was inadequate.

4. Data Management Procedures in the report of the pivotal study, states 'The handling of data by INC Research, including data quality assurance, was to comply with regulatory guidelines (for example, ICH GCP) and the standard operating procedures of the CRO.

   Please describe how INC Research handled the reporting of protocol deviations and relate these procedures to the potential failures in safety and GCP based on the questions asked above.

Comment: Baxter again argues that because the Protocol Deviation Plan was followed, no action needed to be taken about site deficiencies except retraining. This and other cases show that Baxter waits for a protocol deviation to occur then begins retraining after the patient had been put at potential risk. If the site had been better assessed before patient treatment began, the PDs seen in this trial would have been reduced and the patients placed at less risk.

11.1.6.2. Actions of the data monitoring committee with respect to PDs

The report of the pivotal study describes the oversight of the trial data by the independent Data Monitoring Committee (DMC). These sections only describe monitoring related to safety results from the trial based on available data.

Did the DMC review protocol deviations at any time? If so, please provide the details of such reviews on each occasion they were done.

Comment: The submitted documents confirm the oversight described. After every meeting, the DMC gave a 'GO' decision. Presumably this was because the DMC followed set guidelines in its decisions. Again, following company guidelines did not produce the desired outcome for patient safety since the DMC did not express any concern about the frequency of PDs and the quality of the sites in the trial.

11.2. Safety question relating to assay of FIX

This question arose because a number of patients have inactive FIX (FIX antigen) circulation in their blood.

Does the presence of (endogenous) FIX antigen in a subject's blood interfere with the measurement of FIX activity or on the detection of inhibitor antibodies to FIX?

Comment: The first half of the sponsor's response reviewed the ELISA assay for neutralising antibodies. In this assay, endogenous FIX antigen does interfere with the measurement of inhibitors to FIX and cannot be avoided. The presence of inhibitors is assumed when no FIX-specific antibodies are detected in the ELISA assay, as was the case in the pivotal trial. FIX activity is measured by its biological activity. The sponsor claims that FIX antigen does not result in false positive results, shown by the fact that patients with detectable FIX antigen levels had no or very low FIX activities. In addition, the assay is designed to provide all reagents in excess thus FIX antigen does not compete with active FIX. PCE may wish to comment.

11.3. Response from sponsor concerning evaluation of surgical study 251002

The response was to issues identified in the evaluator's conclusions on clinical efficacy for two indications. The issues and responses were as follows:

1. The numbers of patients who had major surgery (n=11) and minor surgery (n=5) were small, given the intention had been to recruit a total of 30 subjects. This report is an interim analysis, but no clear reason is given for not waiting to complete the study.

The response explained that the 30 subjects were chosen to allow participants in the Continuing section of the pivotal trial to have necessary surgery and still receive Rixubis to ensure treatment continuity. The sponsor stated 'Since the data provided in the interim analysis meet the requirements of the EMA guidelines as well as the FDA requirements, the interim report should rather be considered as a final analysis'.

Comment: It was acknowledged that the number of patients (n=5) met the CPMP guidelines, but five patients remain a small number to support a new indication. Meeting

the requirement for numbers does not mean that any resulting outcome is acceptable. As requested, I will consider the trial report as final.

2. The PK properties of Rixubis in seven patients studied differed from those in other patients in the pivotal study and no statistical comparison could be done. This may relate to the failure to obtain adequate FIX levels in patients in the post-operative period although a specified protocol was followed.

The sponsor responded by referring to the marked inter-individual variability in both studies, that is, in the pivotal and the surgery study, that although median and mean values differ for both studies, the ranges (minimum and maximum values) either overlap or are contained within the range of the pivotal study (in case of MRT), and that no comparison was intended. Baxter believed that patients were treated according to their standard of care instead of following the protocol specific treatment guidance. Once in-depth re-training was performed, the postoperative pre-infusion FIX levels were higher.

> Comment: The PK parameters do differ in the surgical patient population, and many of these do not depend on following protocol. The difficulty in following this treatment protocol is noted.

3. The postoperative blood loss at drain removal exceeded the maximum predicted in four of seven subjects who had major surgery.

The response given to this issue was lengthy. The main arguments related to explanations for the failure of the pre- and post-operative FIX concentrations to equal those required by the trial protocol, and whether this failure contributed to the unexpected blood loss in four patients.

The guidance provided in the study protocol recommended that pre-infusion levels of 30-60% for minor surgery and 80-100% for major surgery be maintained until adequate wound healing followed by 30-60% for the subsequent seven days. The mean pre-infusion FIX levels on the first two postoperative days were approximately 55% and the minimum FIX levels were 34.1 and 27.1%, respectively. On postoperative Day 3, the mean pre-infusion level was slightly higher with 59.33 ± 23.69%, with a range of 28.5-88.2%. Since the mean and in particular the minimum FIX levels are considerably lower than the recommended 80-100%, and also lower than the dose recommended by the World Federation of Haemophilia, Baxter concluded that it seemed the majority of investigators adhered to their standard of care regimen rather than to the guidance recommended in the study protocol.

The sponsor then presented details of the four patients with postoperative blood loss greater than expected, making the following points.

In the first case, the excessive blood loss was small (10ml), the use of a tourniquet made the measurements of blood loss difficult, and the postoperative FIX levels were satisfactory (89.5%).

> Comment: The clinical evaluator accepted that the 'excessive' blood loss in this case is doubtful and of clinical significance.

In two cases the post-operative FIX levels were 34-40%, and 40-56% respectively and the blood loss 30% and 27% greater than predicted.

In the third case, the postoperative FIX level fell on one occasion to 55%.

> Comment: In three cases of seven in the study, treatment with Rixubis did not prevent excessive blood loss. The sponsor agrees that 'the low pre-infusion FIX levels in two surgeries in the early postoperative phase and a drop in FIX activity on postoperative Day 2 to 55% in one surgery may explain the higher actual than predicted maximum blood loss'.

4. The surgery called 'major' included two cases of abdominal surgery, each for herniorraphy. This abdominal surgery does not compare to abdominal surgery such as liver transplantation or splenectomy for risk of blood loss, the latter two having been part of the assessment of a commercial rFIX product (BeneFIX) and reported in the PI for that product. As well, as shown in Table 18 Description of Surgery, Study 251002 FAS 1, one case of dental extraction was classed as major surgery and two other cases as minor.

The sponsor provided definitions and criteria used as a guidance for major and minor surgery based on two sets of guidelines, one from the American College of Surgeons, and the other from the Australian Haemophilia Centre Directors' Organisation. The classification in the trial was consistent with those definitions.

> Comment: While major and minor surgery was correctly defined in the trial, the sponsor agreed "that there is a difference between herniorrhaphy and liver transplantation or splenectomy" (with respect to potential blood loss).

5. All assessments of haemostatic efficacy were by the operating surgeon, so that bias was possible, although again this was according to recommendations of the CPMP Guidelines.

The sponsor responded that the surgeon was responsible for the intra- and postoperative efficacy assessment whereas the principal investigator who was the haemophilia expert was responsible for the haemostatic efficacy assessment on the day of discharge.

> Comment: The principal investigator could hardly be regarded as independent for the purpose of independent assessments.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Rixubis in the proposed usage are unchanged for the first indication. For the second indication, use in surgical patients, the associated recommendation has been changed to read as follows:

> The interim analysis of Surgical Study 251002 is now to be regarded as final at the sponsor's request. Although a benefit of Rixubis in the peri-operative management of patients 12 years and older with severe or moderately severe haemophilia B seems likely, the data provided from seven patients who had major surgery is not sufficiently convincing on its own to justify a new indication.

12.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Rixubis in the proposed usage are unchanged from those previously identified.

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Rixubis, given the proposed usage for routine prophylaxis of bleeding episodes in patients 12 years and older with hemophilia B, and for the treatment and prevention of bleeding episodes in patients 12 years and older with hemophilia B (congenital FIX deficiency) is favourable.

> The benefit-risk balance of Rixubis for peri-operative management in patients 12 years and older with haemophilia B is unfavourable, but may become favourable if further studies provide more convincing evidence of efficacy.

13. Second round recommendation regarding authorisation

The clinical evaluator recommended that Rixubis be approved for:

- Routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B and
- Treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital FIX deficiency)

The clinical evaluator does not recommend approval of Rixubis for peri-operative management of patients 12 years and older with haemophilia B.

14. References

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