NON-INTERVENTIONAL (NI) STUDY REPORT

[redacted]

Title	**Pharmacovigilance evaluation of BeneFIX® in Germany and Austria**
Protocol number	B1821011 (3090A1-4406)
Version identifier of the final study report	Final 1.0
Date of last version of the final study report	24 October 2017
EU Post Authorization Study (PAS) register number	N/A; internal PASS only
Active substance	PF-05208755; Nonacog alfa
Medicinal product	BeneFIX®
Product reference	EU/1/97/047/004, EU/1/97/047/005, EU/1/97/047/006, EU/1/97/047/009, EU/1/97/047/007, EU/1/97/047/008
Procedure number	EMEA/H/C/000139
Marketing Authorisation Holder (MAH)	Pfizer Limited
[redacted]	[redacted]
Research question and objectives	Safety and effectiveness of treatment with BeneFIX® under conditions of routine therapy was investigated. Overall, the benefit-risk profile after marketing authorization of reformulated BeneFIX® under usual care conditions was examined.
Countries of study	Germany and Austria
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Marketing Authorisation Holder

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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annual bleed rate
AE	Adverse event
BfArM	Federal Institute for Drugs and Medical Products (German *Bundesinstitut für Arzneimittel und Medizinprodukte*)
BU	Bethesda unit
CRA	Clinical research associate
CRF	Case report form
EC	European community
ED	Exposure day
EU	European union
FIX	Factor IX
FIX:C	Factor IX activity
GPP	Guidelines for Good Pharmacoepidemiology Practices
HIV	Human immunodeficiency virus
IEC	Independent ethics committee
INN	International non-propriety name
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IU	International unit
IV	Intravenous
LETE	Less than expected therapeutic effect
Max	Maximum

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number (of patients)
NI	Non-interventional
NIS	Non-interventional study
NSTEMI	Non-ST segment elevation myocardial infarction
PAS	Post-authorization study
PASS	Post-authorization safety study
PEI	Paul-Ehrlich Institute
PhRMA	Pharmaceutical Research and Manufacturers of America
PSOC	Primary system organ class
PT	Preferred term
PTP	Previously treated patients
PTT	Prothrombin time
PUP	Previously untreated patients
PV	Pharmacovigilance
rFIX	Recombinant factor FIX
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
ULN	Upper limit of normal
VFA	Association of research-based pharmaceutical companies (German *Verband forschender Arzneimittelhersteller)*

3. INVESTIGATORS

[redacted]

Principal Investigator(s) of the Protocol.

Name, degree(s)	Title	Affiliation
[redacted]	[redacted]	Pfizer

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
CSG Clinische Studien GmbH Berlin, Germany Successor (since 01 June 2012): Winicker Norimed GmbH, Nuremberg, Germany	CRO, responsible for: - Study Management* and Monitoring* - Data Management* and Statistical Analysis - Medical Writing

* Positions flagged with an asterisk were performed by both CROs. Unflagged positions were performed by Winicker Norimed only.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of Independent Ethics Committee (IEC) approval of protocol Original protocol Amendment 1		Germany: 13 Aug 2007 12 Nov 2012 Austria: 05 Oct 2010	
Start of data collection		26 Jun 2007	
End of data collection		31 Oct 2016	
Final report of study results		24 Oct 2017	

6. RATIONALE AND BACKGROUND

BeneFIX® (nonacog alfa) is indicated for treatment and prophylaxis of bleeds in patients with hemophilia B (congenital factor IX [FIX] deficiency).

BeneFIX® contains recombinant coagulation FIX (INN = nonacog alfa). Nonacog alfa is a purified protein that has 415 amino acids in a single chain. It has a primary amino acid sequence that is comparable to the Ala148 allelic form of plasma-derived FIX, and some post-translational modifications of the recombinant molecule are different from those of the plasma-derived molecule. Recombinant coagulation FIX is a glycoprotein that is secreted by genetically engineered mammalian cells (ovary cells of the Chinese hamster).

More detailed information on BeneFIX® is provided in the summary of product characteristics (SmPC).

Randomized controlled trials have demonstrated the efficacy and safety of BeneFIX® for prophylactic treatment, on demand treatment and surgery. Randomized controlled trials are powerful tools in assessing efficacy and safety, but have limitations in terms of transferability to routine clinical practice.

An observational study of unselected patients in everyday conditions was regarded appropriate for the evaluation of the effectiveness and safety of BeneFIX® under clinical routine conditions. Furthermore, due to the limited number of patients in Hemophilia B, observation of long-term outcomes focusing on safety aspects is essential.

A recent open-label, non-interventional, prospective postmarketing study in 59 children/ adolescents and adult hemophilia B patients conducted in France confirmed the safety of the product in a usual care setting [1]. Patients used BeneFIX® either for prophylactic or on-demand treatment and were followed up for a median duration of 3.9 years. One subject, a previously untreated patient (PUP), developed FIX inhibitors during follow-up. No allergic reaction, no blood cell agglutination, no lack of efficacy or recovery, and no thrombotic events were reported.

Pharmacovigilance activities like this non-interventional trial are required by EU Regulation No. 726/2004 and Directive 2001/83/EC. One means is the pharmacovigilance evaluation described herein, which is carried out at the initiative of the approval holder (Pfizer Pharma GmbH) according to the recommendations issued by the German Association of Research-Based Pharmaceutical Companies (German *Verband forschender Arzneimittelhersteller e.V.* – VFA).

This non-interventional study was designated per CT34 as a Post-Authorization Safety Study (PASS; following referenced as “Study”) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of the investigation was the generation of information regarding the safety and effectiveness of treatment with BeneFIX® under conditions of routine therapy, i.e., outside

randomized, controlled trials. Overall, the investigation examined the benefit-risk profile after marketing authorization of reformulated BeneFIX® under usual care conditions.

The primary objective of the study was to collect data regarding safety of treatment with recombinant FIX (rFIX = BeneFIX®) after launch of reformulated BeneFIX® in October 2007. The secondary objective was to collect data on effectiveness of treatment with reformulated BeneFIX®.

8. AMENDMENTS AND UPDATES

The original protocol dated 09 Aug 2007 and was approved by an IEC on 13 Aug 2007. There was 1 amendment to the protocol (see Table 1).

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
Amendment 1	22 Oct 2012	Substantial		Table of contents adapted to new Pfizer template "LETE" with further specification was included in section 9.4 Serious Adverse Events Minor editorial and administrative changes	An internal quality assurance measure revealed that the wording of the previous observation plan did not fully cover the data documentation that in some cases had been prepared retrospec-tively. Furthermore, the section in the observation plan relating to the reporting of adverse events has been adapted in-line with the current Pfizer specifications

9. RESEARCH METHODS

The following subsections present a summary of the research methods applied in this study. Further information, e.g., definition and reporting requirements for AEs are provided in Amendment 1 ([redacted]).

9.1. Study design

This was a prospective, non-interventional trial with an open-label, multicenter design. BeneFIX® had to be prescribed according to local law (German Drug Act -AMG § 67(6) and §48 Austrian Pharmaceuticals Act, respectively)[1].

It was a documentary study in context with the use of the approved preparation of BeneFIX®, wherein neither the integrity of the patient was violated nor the routine therapy affected. In the scope of the treatment, laboratory analyses were conducted regularly. Thus, §§ 40 and 41 AMG (German Drug Law "*Arzneimittelgesetz*") were not applicable in this context. BeneFIX® was refunded by health insurance providers.

The dosage and duration of the substitution therapy depended on the severity of the FIX deficiency, the location and extent of bleed, and the patient's clinical condition. The quantities of FIX to be administered and the frequency of administration always had to be adjusted to the clinical effectiveness in the individual case. FIX products rarely required to be administered more than once daily.

One International Unit (IU) of FIX activity was equivalent to that quantity of FIX in one mL of normal human plasma. Estimation of the required dose of BeneFIX® were based on the finding that one unit of FIX activity per kg body weight was expected to increase the circulating level of FIX, an average of 0.8 IU/dL (range from 0.4 to 1.4 IU/dL) in adult patients.

Pharmacokinetics was to be assessed regularly in each patient and posology was to be adjusted accordingly.

The required dosage was determined using the following formula:

Number of FIX units required (IU)	=	body weight (in kg)	X	desired FIX increase (%) or (IU/dL)	X	reciprocal of observed recovery

For a recovery of 0.8 IU/dL (average increase of FIX), then:

Number of FIX units required (IU)	=	body weight (in kg)	X	desired FIX increase (%) or (IU/dL)	X	1.3 IU/kg

Patients were monitored for the development of FIX inhibitors. If the expected FIX activity plasma levels were not attained, or if a bleed was not controlled with an appropriate dose, inhibitor testing had to be performed to determine if a FIX inhibitor was present.

[1] Centers in Austria received a supplementary sheet referring to applicable laws in Austria, which they had to sign prior to their participation in this study.

BeneFIX® could be administered for long-term prophylaxis for the prevention of bleeds in patients with severe hemophilia B. In a clinical study for routine secondary prophylaxis the average dose for previously treated patients (PTP) had been 40 IU/kg (range 13 to 78 IU/kg) at intervals of 3 to 4 days. In younger patients, shorter dosage intervals or higher doses could be necessary.

BeneFIX® was administered by IV infusion after reconstitution of the powder for solution for injection with 0.234% sodium chloride solution. The reconstituted solution should be used immediately, not later than 3 hours after preparation.

9.2. Setting

Patients were planned to participate in this study as long as they were treated with BeneFIX®, until they withdrew their informed consent, or until the study was closed. Among the patient data that were recorded, background data on the disease, birth date, certain information on origin, the prior medical history, treatments, data on physical height and weight, as well as data that had been collected or were collected in the context of regular checkup exams that were required for this study.

The study was intended to include as many patients as possible. Approximately 80-100 patients at about 40 centers were planned to participate.

9.3. Patients

Written informed consent from the patient or his legal representative was mandatory for participation in this pharmacovigilance investigation.

Patients with hemophilia B receiving or starting treatment with reformulated BeneFIX® were included in the study. Any severity of the disease (severe, moderately severe etc.) and mode of treatment (prophylaxis or on-demand) were included in the analysis.

Patients who received a treatment for hemophilia B with another product than BeneFIX® were excluded.

9.4. Variables

9.4.1. Demographic variables

The study population was described as follows:

- Demography
- Hemophilia B anamnesis
- Family anamneses
- Baseline viral infection
- Inhibitor anamneses at baseline
- Concomitant diseases at baseline
- History of immune tolerance therapy

9.4.2. Effectiveness variables

- Bleeds
- Days absent in school or job
- Investigator/patient assessment of effectiveness and handling
- Investigator assessment of satisfaction with treatment success

9.4.3. Safety variables

- All (S)AEs
- (S)AEs with causal relationship
- AEs of special interest:
  - Inhibitor development (defined as any measured inhibitor titer >0.6 BU)
  - Allergic reactions to BeneFIX®
  - Less than expected therapeutic effect (LETE). For on-demand treatment, LETE was defined as "no response" after each of 2 successive infusions administered within a 24-hour period for treatment of the same bleed in the absence of confounding factors. For prophylaxis, LETE was defined as failure to prevent spontaneous breakthrough bleeds within 48 hours of a BeneFIX® infusion for routine prophylaxis in the absence of confounding factors (e.g., trauma, injury, incorrect dose).
  - Erythrocyte agglutination in tube system or syringe
  - Thrombus formation
- Investigator/patient assessment of tolerability

9.4.4. Other endpoints

- Hemoglobin
- Thrombocytes
- Changes in concomitant medication
- Discontinuation of study

9.5. Data sources and measurement

In the course of home treatment, the patient documented bleeds and factor substitutions (number of injections, amount of factor injected) in a diary as required by §14 German Transfusion Law and §8 iVM §11 Austrian Blood Protection Law, respectively. These data were made available to the physician, recorded and analyzed in the scope of the pharmacovigilance investigation.

The physicians documented patient characteristics as well as diagnosis and treatment related information during the regular patient visits with special focus on safety aspects (adverse events, serious adverse events etc.). If possible, each visit of the patient with the physician was documented. These visits normally took place at intervals of one to six months during routine treatment.

The following parameters were to be documented at baseline:

- Patient code*
- Date of start of the treatment with BeneFIX®*
- Demographic variables (date of birth, height, weight, ethnical group)
- Medical history, previous therapy
- Disease severity (FIX:C residual activity) and genetic mutation type
- Family history
- Immunization and viral infections (human immunodeficiency virus [HIV] infection, vaccination for hepatitis A/B, hepatitis A/B/C)
- Inhibitor history
- Current inhibitor status – if recorded in the beginning
- History of allergic reactions*
- History of red blood cell agglutination (clustering of erythrocytes in the tubing or syringe)
- Concomitant diseases
- Orthopedic status
- Medical or non-medical concomitant therapy
- Laboratory values (including previous FIX activity and recovery if available)
- Listing of adverse events of the previous year
- Assessment of patient's well-being
- Initial treatment regimen*

Note: Items marked with * were mandatory

The following parameters were to be documented at every follow-up visit (approx. every 1-6 months):

- Patient code*
- Date of follow-up evaluation*
- Demographic variables (date of birth, weight)*
- Treatment regimen*
- Laboratory test (FIX determination, clinical parameter) – if available from routine visits
- FIX recovery
- Test on inhibitors against FIX – if recorded in the course of routine visits*
- Allergic reactions*
- Assessment of patient's substitution diary*
- Intermediate history
- (S)AEs*
- Any change in medical or non-medical concomitant therapy
- Viral infections (HIV, hepatitis A/B/C)
- Assessment of treatment by physician (number of bleeds, number of injections to stop a bleed, average consumption of FIX per week)

- Assessment of effectiveness by physician and patient
- Assessment of tolerability by physician and patient
- Assessment of well-being by physician and patient
- Days missing from work, school etc.

Note: Items marked with * were mandatory

Safety was assessed throughout the course of the study by recording all AEs at each patient visit (see "Follow-up documentation").

(S)AEs were defined according to type, onset and end, intensity, serious yes/no, causal correlation with BeneFIX® therapy, outcome and any potential counter-active measures and were to be documented and evaluated by the physician.

Effectiveness of BeneFIX® was descriptively assessed by physician and patient by different measurement parameters, e.g., number of injections needed to a stop bleed, number of bleeds per year (see follow-up documentation), at each follow-up visit. Laboratory values were only documented if their determination was part of routine visit.

9.6. Bias

Missing and implausible data are always challenges in non-interventional studies. To limit the amount of such data, the participating sites were initially instructed on proper documentation and were asked to also instruct the patients on proper documentation in the patient diaries. Incomplete or implausible entries were queried by the responsible data manager.

9.7. Study Size

Physicians were encouraged to include all eligible patients, consecutively. A statistical sample size calculation was not performed for this study. Neutralizing antibodies to FIX and allergic reactions are the most severe AEs in treatment with coagulation FIX. They occurred with an incidence of 2-3%. Therefore, it is likely to detect cases of inhibitor formation and allergic reactions with the collection of data from 80-100 patients over a longer period of time.

As described in Section 9.2, the continued treatment was to be documented from as many patients as possible in the context of the pharmacovigilance evaluation to reach 80-100 patients at about 40 centers. Since no statistical hypotheses are tested, statistical power was not determined.

9.8. Data transformation

The following variables were derived variables and used for effectiveness analyses:

Variable	Definition
Duration of observation period for bleed documentation (year)	Sum of observations of all diary episodes at post-baseline visits. Duration (year) of diary episodes = (End - Start + 1) / 365.25

Number of documented post-baseline visits	Number of documented post-baseline visits
Total number of bleeds	Number of bleeds over all diary episodes for: bleeds total, joint bleeds, soft tissue bleeds, other bleeds
Bleeds per year	Total number of bleeds / Duration of observation period for bleed documentation (year)
Total average number of substitutions needed to stop a bleed	Weighted mean of average number of substitutions needed to stop a bleed of all diary episodes at post-baseline visits, weighted by total the number of bleeds
Total average consumption of FIX per bleed	Weighted mean of average consumption of FIX of all diary episodes at post-baseline visits, weighted by total the number of bleeds

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP; [redacted] which is dated, filed and maintained by the sponsor.

9.9. Statistical methods

9.9.1. Main summary measures

- All documented data were analyzed descriptively and presented as tables and as graphs, if appropriate.
- Data which were documented repeatedly were analyzed by visit. Furthermore, the last documented visit was displayed, because the number of documented visits varied considerably among patients.

For details refer to the SAP [redacted]

9.9.2. Main statistical methods

The statistical analysis was performed by the treatment scheme (cohorts) planned at the baseline visit:

- On demand
- Prophylaxis
- Intermediate prophylaxis

Only discontinuation due to (serious) adverse events [(S)AE], lack of effectiveness, inhibitor development or death were assessed as discontinuation. Discontinuations due to lost to follow-up, lack of patient compliance and other reason were treated as completer.

For categorical variables, absolute and relative frequencies are provided as well as graphical presentations, if appropriate. For the calculation of relative frequencies, only those patients with available data were included.

For continuous variables, means, standard deviations, medians, minima and maxima are presented.

All data were analyzed descriptively. Since no statistical hypotheses were tested in this non-interventional study, confirmative statistical methods were not performed. Therefore, no level of significance was defined.

The analyses focused on the descriptive assessment of the safety parameters like the incidence of (S)AE (e.g., inhibitor formation, allergic reactions etc.). Furthermore parameters characterizing the effectiveness of BeneFIX® were evaluated descriptively. These included e.g., annual bleed rate, number of infusions needed to stop a bleed.

Bleeds adjusted by duration of observation period for bleed documentation was analyzed by a negative binomial regression model with the cohorts (on-demand/prophylaxis) as factors. For the difference between "on demand" and "prophylaxis" p-values were calculated.

Safety analyses

(S)AEs were analyzed by frequency tables. Incidence rates were calculated on patient basis by MedDRA primary system organ class (PSOC) and preferred tem (PT). MedDRA version 20.0 was used for the coding of (S)AEs.

Additionally, frequency tables were calculated on the following subsets of adverse events:

- AEs with causal relationship
- S(AEs)
- SAEs with causal relationship
- AEs of special interest

The incidence of patients with any measured inhibitor titer >0.6 Bethesda units (BU) was analyzed by the maximum inhibitor titer per patient. This analysis was performed for PTPs, PUPs and all patients.

In addition, the incidence of any measured inhibitor titer > laboratory reference was calculated for PTPs, PUPs and all patients. In case of missing reference, the reference was replaced by 0 (conservative replacement).

For patients with any measured inhibitor titer >0.6 BU or > reference all inhibitor titer values were listed.

Furthermore, the clinical chemistry parameters hemoglobin and thrombocytes were analyzed descriptively.

Details regarding reporting and definition of AEs are provided in the observational plan [redacted]

9.9.3. Missing values

Missing values were not replaced.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

There were 2 updates to the initial statistical analysis plan, Version 1:

Version 2, dated 24 Nov 2016, included editorial changes only.

Version 3, dated 08 Feb 2017, included the following modification:

- Definition of discontinuation: "Only discontinuation due to adverse events, serious adverse events, inhibitor and death will be assessed as discontinuation. Discontinuations due to lost to follow-up, lack of patient compliance and other reason will be treated as completer."

9.10. Quality control

All participating sites were visited at least once by a qualified clinical research associate (CRA) for source data verification and verification of compliance with applicable laws (see also Section 9.11). In addition, 5 of the 19 participating sites underwent an on-site audit. To ensure that there were no unreported SAEs, all centers, which were monitored in 2015 or earlier, and all centers without a 100% patient monitoring in 2016 underwent final monitoring visits, with special focus on SAE reporting.

All information was documented in the documentation forms (Case Report Forms = CRFs) or in an electronic documentation system, such as "Haemoassist®". "Haemoassist®" is an electronic documentation system that improves doctor-patient communication and allowed for a closer monitoring of the patient during his home-treatment. Therefore, it has an impact on the adherence to the planned therapy. It fulfills the legal requirements of Germany and Austria.

The patient assessment of the effectiveness, safety and condition of the patient was documented directly in the CRFs and the patient diary and was considered source data.

All patients received consecutive numbers. Each patient in the study had to be assigned a unique patient number and had to keep that number throughout the study even if he or she transferred to another site. It was strictly prohibited to reassign or reuse a number.

The physician had to maintain a patient master log linking the patient number to the patient's name. The physician had to follow all applicable privacy laws in order to ensure a patient's privacy and confidentiality. Information that could identify a person was masked on material provided to the sponsor.

The documentation of home treatment and doctor-patient visits were recorded electronically or on paper.

If the patient documented by the conventional method using paper-based diaries, copies of these diaries were provided for data analyses. If the patient used the electronic documentation system (e.g. "Haemoassist®"), the data that were entered by the patient were directly transferred to the clinical database of the pharmacovigilance evaluation. The physician could comment on the entries documented by the patients through his electronic interface. If a patient used both methods of documentation, the preferred medium into which the entry was made had to be determined by the physician in advance. These data were considered source data accordingly.

The physician also had the possibility to fill in the CRFs on the pharmacovigilance examination electronically via an online application. The data were then imputed directly into the database. If the physician did not document by electronic means, he or she had the CRFs available in paper format.

9.11. Protection of patients

Patient information and consent

Written informed consent [redacted] was obtained prior to the patient entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each patient. Each patient was informed that he could withdraw from the study at any time and for any reason. Each patient was given sufficient time to consider the implications of the study before deciding whether to participate. Patients who chose to participate signed an informed consent document.

For underage patients, the parents or legal guardians gave the consent for study participation. If the child was able to understand the scope of this study, he could jointly sign the consent declaration together with the legal representatives. The assessment of the necessary capability of the child's understanding was in the joint responsibility of the treating physician and the parents.

Independent Ethics Committee (IEC)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by an IEC.

Ethical conduct of the study

In accordance with the requirements of § 67(6) German Pharmaceuticals Act, this pharmacovigilance investigation was registered with the competent authority, the PEI, as well as the *Federal Association of Statutory Health Insurance Physicians, and the Head Association of Health Insurers*. This registration obligation also included the registration of involved investigators and information about the contractually agreed compensation for expenses.

In the implementation of this pharmacovigilance investigation, the requirements of the Joint Recommendations of the Federal Institute for Drugs and Medical Products ("*Bundesinstitut für Arzneimittel und Medizinprodukte*", BfArM) and the Paul-Ehrlich Institute (PEI) regarding the Planning, Implementation and Analysis of Post-Marketing Surveillance Studies in the version dated July 7, 2010 as well as the Recommendations on the Improvement of Quality and Transparency of Non-Interventional Studies of the Association of Research-based Pharmaceuticals Companies ("*Verband forschenden Arzneimittelhersteller*", VFA) were applied.

Furthermore, the study was in accordance with the following recommendations and guidelines: the *Guidelines for Good Pharmacoepidemiology Practices* (GPP) published by the International Society for Pharmacoepidemiology (ISPE), the guidelines of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), as well as the guidelines of the Pharmaceutical Research and Manufacturers of America (PhRMA).

10. RESULTS

Please note that adjusted frequencies are presented in the following sections. This means that percentages are calculated based on non-missing values.

10.1. Participants

A total of 80 pediatric and adult patients with hemophilia B were enrolled in this study at 19 hemophilia centers in Austria and Germany (Table 15.1.1).

Of the 80 patients, 25 were on an on-demand treatment and 55 on prophylaxis (Table 15.1.2). All but one patient who died and one patient who discontinued treatment because of lack of effectiveness, completed the study. The death was unrelated to treatment with BeneFIX® (see also Section 10.6.3).

Another patient was discontinued from treatment because of inhibitor development (see Section 10.6.5.1 for details). His discontinuation, however, was not documented on the respective "Study termination" form of the CRF and is, therefore, not listed in Table 15.1.2. Reversely, the patient who discontinued because of lack of effectiveness was not reported with an adverse event of special interest, i.e., with "LETE" (Table 15.9.5).

10.2. Descriptive data

10.2.1. Demographic characteristics

The study population consisted of 21 (26.3%) patients ≤6 years of age, 27 (33.8%) aged between 7 and 17 years, and 32 (40.0%) adults ≥18 years old. The median age was 16.0 years (range: 0-69 years). The majority of patients (96.3%) were Caucasians.

A summary of the key demographic data is shown in Table 2.

Table 2. Demographic characteristics

Variable	On-demand (N = 25)	Prophylaxis (N = 55)	Total (N = 80)
Age [years]			
n	25	55	80
Mean ± SD	20.2 ± 18.8	16.0 ± 12.2	17.3 ± 14.6
Median	17.0	16.0	16.0
[Min; Max]	[0; 69]	[1; 65]	[0; 69]
Age group			
≤ 6 years	8 (32.0%)	13 (23.6%)	21 (26.3%)
7-17 years	6 (24.0%)	21 (38.2%)	27 (33.8%)
≥ 18 years	11 (44.0%)	21 (38.2%)	32 (40.0%)
Height [cm]			
n	20	48	68
Mean ± SD	155.0 ± 46.4	153.3 ± 32.7	153.8 ± 36.9
Median	175.0	166.0	171.0
[Min; Max]	[59; 205]	[81; 196]	[59; 205]
Weight [kg]			
n	23	55	78
Mean ± SD	49.6 ± 31.1	55.5 ± 32.4	53.7 ± 31.9
Median	65.0	57.0	59.6
[Min; Max]	[3.5; 82.0]	[12.1; 129.0]	[3.5; 129.0]
Race			
Caucasian	24 (96.0%)	53 (96.4%)	77 (96.3%)
Other	2 (4.0%)	2 (3.6%)	3 (3.8%)

Source: Table 15.1.3

10.2.2. History of hemophilia B

Median residual FIX:C was 2.0% in the on-demand group and 1.0% in the prophylaxis group. Accordingly, the proportion of patients with severe hemophilia B (<1% residual FIX:C) were markedly higher in the prophylaxis than in the on-demand group (32.7% vs. 4.0%) (Table 15.1.4.1). The proportion of patients with moderate hemophilia B (residual FIX:C between 1% and 5%) was approximately 65% in both groups, and patients with mild hemophilia B (residual FIX:C >5%) were mostly on an on-demand treatment regimen. In 2 patients treated on-demand, residual FIX:C levels >50% (69% and 83%, respectively) were reported. It must be assumed that these values referred to the FIX:C levels as measured at baseline visit and not to historical FIX:C trough levels.

Overall, 87.5% of the patients were PTPs, and most of them (>80%) had already accumulated more than 100 EDs (Tables 15.1.4.1 and 15.1.4.3). All but 2 of the 10 PUPs received on-demand treatment. Sixty-five percent of the patients had been pretreated with nonacog alfa (Table 15.1.4.2). More than half of the patients (55%) had a family history of hemophilia B, and in 73.1% the mutation type was known (Tables 15.1.4.1 and 15.1.5).

Table 3 summarized the history of hemophilia B and the disease characteristics by treatment group.

Table 3. History of hemophilia B

Variable	On-demand (N = 25)	Prophylaxis (N = 55)	Total (N = 80)
FIX:C – residual [%]			
n	25	55	80
Mean ± SD	12.5 ± 22.1	1.3 ± 3.9	4.8 ± 13.6
Median	2.0	1.0	1.0
[Min; Max]	[0; 83]	[0; 29]	[0; 83]
FIX:C – residual (n; %)			
0%	1 (4.0%)	18 (32.7%)	19 (23.8%)
>0% to <1%	0 (0.0%)	0 (0.0%)	0 (0.0%)
1%	9 (36.0%)	32 (58.2%)	41 (51.3%)
>1%	15 (60.0%)	5 (9.1%)	20 (25.0%)
Disease severity (n; %)			
Severe (<1%)	1 (4.0%)	18 (32.7%)	19 (23.8%)
Moderate (1-5%)	16 (64.0%)	36 (65.5%)	52 (65.0%)
Mild (>5%)	8 (32.0%)	1 (1.8%)	9 (11.3%)
Patient status			
PTP	17 (68.0%)	53 (96.4%)	70 (87.5%)
PUP	8 (32.0%)	2 (3.6%)	10 (12.5%)
Previous exposure days			
n	18	51	69
0 - 20	5 (27.8%)	2 (3.9%)	7 (10.1%)
21 - 50	1 (5.6%)	1 (2.0%)	2 (2.9%)
51 - 100	2 (11.1%)	2 (3.9%)	4 (5.8%)
>100	10 (55.6%)	46 (90.2%)	56 (81.2%)
Family history of hemophilia B			
n	25	55	80
Yes	14 (56.0%)	30 (54.5%)	44 (55.0%)
No	11 (44.0%)	25 (45.5%)	36 (45.0%)
Mutation type known			
n	25	53	78
Yes	13 (52.0%)	44 (83.0%)	57 (73.1%)
No	12 (48.0%)	9 (17.0%)	21 (26.9%)

Abbreviations: FIX:C = FIX activity; PTP = previously treated patient; PUP = previously untreated patient.
Source: Tables 15.1.4.1, 15.1.4.3, 15.1.5

10.2.3. Inhibitor history

None of the patients had a family history of inhibitor development, and only 1 patient (1.3% in the total group) on prophylaxis had his own history of inhibitor development (Tables 15.1.5 and 15.1.7). Further 2 patients were previously tested for the presence of inhibitors. In 1 patient the result was negative, and the other patient showed an inhibitor level of 0.1 BU, which was not rated as inhibitor positivity. Subsequent tests in these 2 patients were negative.

One patient developed inhibitor titers up to 11 BU 13 years ago after his first 20 EDs. After successful immune tolerance therapy with nonacog alfa, his inhibitor titer had returned to ≤0.5 BU (Tables 15.1.7 and 15.1.8). The question regarding previous immunetolerance therapy was answered with “no” for further 4 patients.

A summary of the patients' inhibitor history is presented in Table 4.

Table 4. History of inhibitors to FIX

Variable	On-demand (N = 25)	Prophylaxis (N = 55)	Total (N = 80)
Family history of inhibitors			
n	22	47	69
No	22 (100.0%)	47 (100.0%)	69 (100.0%)
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient history of inhibitors			
n	23	55	78
Yes	0 (0.0%)	1 (1.8%)	1 (1.3%)
No	16 (69.6%)	53 (96.4%)	69 (88.5%)
Not applicable (PUP)	7 (30.4%)	1 (1.8%)	8 (10.3%)
Time of inhibitor development [years before baseline]			
n	0	1	1
Mean ± SD	-	13.0	13.0
Median	-	-	-
[Min; Max]			
Exposure days at the time of inhibitor development			
n	0	1	1
Mean ± SD	-	20.0	20.0
Median	-	-	-
[Min; Max]			
Inhibitor titer at first measurement [BU]			
n	0	3	3
Mean ± SD	-	3.7 ± 6.3	3.7 ± 6.3
Median	-	0.1	0.1
[Min; Max]		[0.0; 11.0]	[0.0; 11.0]
Inhibitor titer at last measurement [BU]			
n	0	3	3
Mean ± SD	-	0.2 ± 0.3	0.2 ± 0.3
Median	-	0.0	0.0
[Min; Max]		[0.0; 0.5]	[0.0; 0.5]
Previous immunetolerance therapy?			
n	5	5	10
No	5 (100.0%)	4 (80.0%)	9 (90.0%)
Yes	0 (0.0%)	1 (20.0%)	1 (10.0%)
Immune tolerance therapy successful?			
n	0	1	1
No	-	0 (0.0%)	0 (0.0%)
Yes	-	1 (100.0%)	1 (100.0%)

Source: Tables 15.1.5, 15.1.7, 15.1.8

10.2.4. Concomitant diseases

10.2.4.1. Viral infections

Infections with HIV-1/2 and hepatitis A/B/C were to be specifically documented.

As shown in Table 5, the most prevalent viral infection in the study population was chronic hepatitis C, which was documented for 13.3% of the patients, followed by HIV-1/2 positivity in 7.6% of the patients with the corresponding recordings (Tables 15.1.6.1 and 15.1.6.2). Chronic hepatitis B was reported for 2 patients in the prophylaxis group, and 1 patient in this group suffered from acute hepatitis B. None of the patients in either groups were reported with hepatitis A.

Test methods for the detection of the different hepatitis types and their results are provided in Tables 15.1.6.3, 15.1.6.4 and 15.1.6.5.

Table 5. Viral infections (HIV-1/2 and hepatitis A/B/C) at baseline

Variable	On-demand (N = 25)	Prophylaxis (N = 55)	Total (N = 80)
HIV-1/2 status (n; %)			
n	15	51	66
Negative	13 (86.7%)	48 (94.1%)	61 (92.4%)
Positive	2 (13.3%)	3 (5.9%)	5 (7.6%)
HIV-1/2: viral load (copies/mL)			
n	2	3	5
Mean ± SD	85.0 ± 63.6	78.3 ± 103.0	81.0 ± 79.6
Median	85.0	40.0	40.0
[Min; Max]	[40; 130]	[0; 195]	[0; 195]
Hepatitis A (n; %)			
n	22	53	76
No disease	22 (100.0%)	53 (100.0%)	75 (100.0%)
Acute disease	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chronic disease	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatitis B (n; %)			
n	23	53	76
No disease	23 (100.0%)	50 (94.3%)	73 (96.1%)
Acute disease	0 (0.0%)	1 (1.9%)	1 (1.3%)
Chronic disease	0 (0.0%)	2 (3.8%)	2 (2.6%)
Hepatitis C (n; %)			
n	22	53	75
No disease	17 (77.3%)	48 (90.6%)	65 (86.7%)
Acute disease	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chronic disease	5 (22.7%)	5 (9.4%)	10 (13.3%)

Source: Tables 15.1.6.1, 15.1.6.2

10.2.4.2. All concomitant diseases at baseline

Any concomitant diseases were reported for 40.0% of the total population, and 27.5% of all patients were reported with chronic diseases (Tables 15.1.9.1 and 15.1.9.2).

Overall, the percentage of patients with concomitant diseases was lower in the prophylaxis group than in the on-demand group (36.4% vs. 48.0%). The most common concomitant diseases in the total population belonged to conditions referring to the MedDRA system organ classes “musculoskeletal and connective tissue disorders” (11.3%), “congenital, familial and genetic disorders” (10.0%) and “nervous system disorders” (8.8%). On a preferred term level, the most common concomitant diseases were “von Willebrand’s disease” (5.0%), “HIV infection” (3.8%), and “hepatitis C” (3.8%).

A summary of all concomitant diseases present at baseline is shown in Table 6.

Table 6. Concomitant diseases by MedDRA system organ class (and preferred term, if present in at least 2 patients of the total group)

MedDRA system organ class Preferred term	On-demand (N = 25) n (%)	Prophylaxis (N = 55) n (%)	Total (N = 80) n (%)
Any concomitant disease	**12 (48.0)**	**20 (36.4)**	**32 (40.0)**
Blood and lymphatic disorders	**-**	**2 (3.6)**	**2 (2.5)**
Cardiac disorders	**1 (4.0)**	**1 (1.8)**	**2 (2.5)**
Congenital, familial and genetic disorders	**3 (12.0)**	**5 (9.1)**	**8 (10.0)**
Von Willebrand's disease	2 (8.0)	2 (3.6)	4 (5.0)
Eye disorders	**-**	**1 (1.8)**	**1 (1.3)**
Gastrointestinal disorders	**1 (4.0)**	**1 (1.8)**	**2 (2.5)**
General disorders and administration site disorders	**-**	**1 (1.8)**	**1 (1.3)**
Hepatobiliary disorders	**-**	**2 (3.6)**	**2 (2.5)**
Immune system disorders	**1 (4.0)**	**1 (1.8)**	**2 (2.5)**
Seasonal allergy	1 (4.0)	1 (1.8)	2 (2.5)
Infections and infestations	**4 (16.0)**	**2 (3.6)**	**6 (7.5)**
HIV infection	2 (8.0)	1 (1.8)	3 (3.8)
Hepatitis C	2 (8.0)	1 (1.8)	3 (3.8)
Injury, poisoning and procedural complications	**1 (4.0)**	**-**	**1 (1.3)**
Investigations	**-**	**1 (1.8)**	**1 (1.3)**
Metabolism and nutrition disorders	**-**	**3 (5.5)**	**3 (3.8)**
Musculoskeletal and connective tissue disorders	**4 (16.0)**	**5 (9.1)**	**9 (11.3)**
Arthropathy	1 (4.0)	1 (1.8)	2 (2.5)
Nervous system disorders	**4 (16.0)**	**3 (5.5)**	**7 (8.8)**
Migraine	2 (8.0)	-	2 (2.5)
Psychiatric disorders	**-**	**1 (1.8)**	**1 (1.3)**
Renal and urinary disorders	**-**	**1 (1.8)**	**1 (1.3)**
Respiratory, thoracic and mediastinal disorders	**-**	**2 (3.6)**	**2 (2.5)**
Skin and subcutaneous tissue disorders	**-**	**2 (3.6)**	**2 (2.5)**
Surgical and medical procedures	**-**	**1 (1.8)**	**1 (1.3)**
Vascular disorders	**-**	**3 (5.5)**	**3 (3.8)**

Source: Table 15.1.9.1

Frequencies of concomitant diseases requiring treatment are displayed in Table 15.1.9.3.

10.2.5. Concomitant medication at baseline

Concomitant medications were reported for 30.0% of all patients, with the percentage of patients using concomitant medications being slightly higher in the on-demand group than in the prophylaxis group (36.0% vs. 27.3%; Table 15.8.1).

Despite some numerical differences between groups regarding the proportions of patients concomitantly taking drugs from specific groups, the numbers were too small to derive any trends.

The percentages of patients taking concomitant medications are displayed by WHO-DD ATC level 1 and treatment schedule in Table 7.

Table 7. Concomitant medication

WHO-DD ATC Level 1	On-demand (N = 25) n (%)	Prophylaxis (N = 55) n (%)	Total (N = 80) n (%)
Any concomitant medication	9 (36.0)	15 (27.3)	24 (30.0)
Alimentary tract and metabolism	-	3 (5.5)	3 (3.8)
Antiinfectives for systemic use	3 (12.0)	2 (3.6)	5 (6.3)
Blood and blood forming organs	1 (4.0)	6 (10.9)	7 (8.8)
Cardiovascular system	1 (4.0)	3 (5.5)	4 (5.0)
Dermatologicals	-	1 (1.8)	1 (1.3)
Genitourinary system and sex hormones	1 (4.0)	1 (1.8)	2 (2.5)
Musculoskeletal system	3 (12.0)	3 (5.5)	6 (7.5)
Nervous system	3 (12.0)	3 (5.5)	6 (7.5)
Respiratory system	-	2 (3.6)	2 (2.5)
Sensory organs	-	1 (1.8)	1 (1.3)
Systemic hormonal preparations, excl. sex hormones and insulins	1 (4.0)	-	1 (1.3)

Source: Table 15.8.1

Further information on concomitant medication, i.e., changes during study participation, discontinued medication, medication with dose changes, and newly prescribed medication is provided in Tables 15.8.2 to 15.8.6.

10.3. Outcome data

For 76 of the 80 enrolled patients, the observation period for bleed documentation was calculable (Table 15.1.11). The mean observation period in this population was 3.9 ± 2.5 years (median: 3.8 years; range: 0.1 – 8.7 years) and shorter in the on-demand than in the prophylaxis group (median: 2.7 vs 4.2 years).

Accordingly, the median number of post-baseline visits was markedly lower in patients treated on-demand than in those treated prophylactically (5.0 vs. 9.0; Table 15.1.12). As to be expected in a long-term observation, the highest number of visits and documentations were performed in the first half of the study period (maximum: 120 visits/documentations in 2010) and decreased thereafter up to study closure in 2016 with 49 visits/documentations (Table 15.1.13).

10.4. Main results

It should be noted that this study was designated as PASS, which primarily focused on the collection of safety data, i.e., on inhibitor development, (S)AEs, (S)AEs assessed as “related” and events of LETE.

10.4.1. Treatment with BeneFIX®

Most of the patients remained on their current treatment schedule (on-demand or prophylaxis) during the observation period (Table 15.2.1). However, 7 of the 25 patients (28.0%) treated on-demand, were switched to prophylaxis up to their last documented visit. Reversely, 3 patients (5.5%) initially on prophylaxis were switched to on-demand treatment and 1 further patient (1.8%) to intermediate prophylaxis.

The statistical analysis of the planned BeneFIX® dose was based on the actual treatment regimen the patients applied at the respective visit[2] (Table 15.2.2). At the baseline visit, the mean dose recommended by the treating physicians for patients on on-demand treatment was 42.4 ± 16.6 IU/kg per infusion (median: 40.5 IU/kg), which was approximately 50% higher than the dose by the physicians for patients on prophylaxis treatment (34.4 ± 19.3 IU/kg; median 30.0 IU/kg). Overall, the recommended doses decreased slightly up to the patients' last visits, with only minor fluctuations in mean and median doses.

The median number of recommended weekly prophylaxis infusions was 2 (range: 1 to 7) at baseline and remained in general unchanged up to the last documented visit (Table 15.2.5).

10.4.2. FIX:C and PTT in relation to time of BeneFIX® administration

FIX:C

Throughout this study, FIX:C were primarily determined using the one-stage assay (Table 15.2.3.3). Considering all 544 FIX:C measurements in this study, independent of treatment regimen, the data show that FIX:C levels ≥20% were primarily measured within 48 h post-dose (Table 15.2.3.1). This, however, was also the interval for which the majority of measurements were available. Recovery measurements were performed in single cases only (Table 15.2.3.4).

Using the FIX:C levels at the time of the respective visit, percentages of patients falling in the different categories of disease severity are provided in Table 15.2.3.2.

PTT

Median PTT values were consistently below 2x upper limit of normal[3] (i.e., <76 s; Table 15.2.4.1). The lowest median PTT value of 42.7 s was achieved within the first 24 h post-dose.

Summary statistics of PTT values by visit are presented in Table 15.2.4.2.

10.4.3. Occurrence of bleeds

The number of reported bleeds varied largely among patients (minimum: 0; maximum: 110) both depending on the patients' bleeding phenotype and individual time in the study (Table

[2] Note: Switches between treatment regimens (on-demand, prophylaxis) were possible due to the non-interventional character of this study.

[3] Assuming an upper limit of the normal range of approximately 35-38 s.

15.3.1). As shown in Table 8, no specific trend regarding the location of bleeds (joints, soft tissue or other) was detectable in either group.

Table 8. Number of bleeds per patient by type of bleed – absolute numbers

Variable	On-demand (N = 25)	Prophylaxis (N = 55)	Total (N = 80)
Number of all bleeds			
n	22	54	76
Median	3.0	8.5	7.5
[Min; Max]	[0; 70]	[0; 110]	[0.0; 110]
Number of joint bleeds			
n	22	54	76
Median	1.0	2.0	2.0
[Min; Max]	[0; 26]	[0; 80]	[0; 80]
Number of soft tissue bleeds			
n	22	54	76
Median	1.0	2.5	2.0
[Min; Max]	[0; 28]	[0; 17]	[0; 28]
Number of other bleeds			
n	22	54	76
Median	1.0	2.0	2.0
[Min; Max]	[0; 27]	[0; 46]	[0; 46]

Bleeds without start or stop date and patients without post-baseline visits were excluded.
Source: Table 15.3.1

Results of the calculation of the annual bleed rate (ABR) and their comparison between the on-demand and prophylaxis groups are displayed in Table 9. Complete summary statistics are provided in Table 15.3.2.

The ABR, independent of the location, were similar with both treatment regimens. Although the comparison of the ABR for soft tissue bleeds resulted in an inferential p-value of 0.015 in favor of prophylaxis, it should be noted that this comparison was exploratory only and the numbers were too small to allow for a reliable conclusion.

Table 9. Annual bleed rates per patient: On-demand vs. prophylaxis treatment

Variable	On-demand (N = 25)		Prophylaxis (N = 55)
All bleeds			
n	22		54
Mean ± SD	4.7 ± 4.7		4.2 ± 4.3
Median	3.8		2.7
[Min; Max]	[0.0; 18.2]		[0.0; 16.7]
P-value [a]		0.684	
Joint bleeds			
n	22		54
Mean ± SD	1.9 ± 2.4		1.9 ± 2.8
Median	0.6		0.8
[Min; Max]	[0.0; 7.2]		[0.0; 14.6]
P-value [a]		0.859	
Soft tissue bleeds			
n	22		54
Mean ± SD	2.2 ± 2.9		0.9 ± 1.1
Median	0.6		0.6
[Min; Max]	[0.0; 11.3]		[0.0; 3.8]
P-value [a]		0.015	
Other bleeds			
n	22		54
Mean ± SD	0.7 ± 1.3		1.4 ± 2.2
Median	0.2		0.6
[Min; Max]	[0.0; 4.7]		[0.0; 9.5]
P-value [a]		0.103	

[a] Negative binomial model for the comparison on-demand vs. prophylaxis.
Bleeds without start or stop date and patients without post-baseline visits were excluded.
Source: Table 15.3.2

10.4.4. Treatment of bleeds

Table 10 shows that in about 60% of the patients, the bleeds were on average controlled with 1 or 2 FIX infusions and approximately 85% of bleeds with 1-3 infusions (Table 15.3.3). The median total average dose per patient and bleed was 3.14 kIU and ranged from 0.50 to 187.75 kIU (Table 15.3.4). Patients on on-demand treatment tended to require less infusions and had a lower average FIX consumption. In this analysis, however, the type and location of bleeds to be treated, and disease severity was not taken into account.

Table 10. Average number of infusions needed to stop a bleed

	On-demand (N = 25)	Prophylaxis (N = 55)	Total (N = 80)
Total average number [a] [n (%)]			
n	20	49	69
1	8 (40.0)	14 (28.6)	22 (31.9)
2	5 (25.0)	15 (30.6)	20 (29.0)
3	4 (20.0)	13 (26.5)	17 (24.6)
>3	3 (15.0)	7 (14.3)	10 (14.5)
Total average FIX consumption [b] [kIU]			
n	20	49	69
Mean ± SD	7.01 ± 14.33	13.79 ± 30.92	11.82 ± 27.23
Median	2.83	3.17	3.14
[Min; Max]	[0.50; 66.00]	[0.75; 187.75]	[0.50; 187.75]

[a] Mean of average numbers of substitutions from all post-baseline visits, weighted by the total number of bleeds. For calculation ">3" has been replaced by "4".
[b] Mean of average consumptions from all post-baseline visits, weighted by the total number of bleeds.
Source: Tables 15.3.3 and 15.3.4

10.4.5. Days absent from school or work

The distribution of the average days/month absence from school or work before enrolment in this study for the different treatment regimens is displayed in Table 11. The data show that the proportion of working/school-aged patients without any missed days from work/school was markedly higher in the group of patients on prophylaxis.

Table 11. Average number of days absent from school/work before study participation

Average number of days/months absent from school or work	On-demand (N = 25) n (%)	Prophylaxis (N = 55) n (%)	Total (N = 80) n (%)
n	25	53	78
Non-working/not school-aged	9 (36.0)	16 (30.2)	25 (32.1)
No days absent	3 (12.0)	21 (39.6)	24 (30.8)
<6 days absent	11 (44.0)	13 (24.5)	24 (30.8)
6-10 days absent	2 (8.0)	1 (1.9)	3 (3.8)
>10 days absent	0 (0.0)	2 (3.8)	2 (2.6)
Permanently unable to work/attend school	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 15.1.10

Despite some individual changes up to the end of the observation period, the average monthly absence from school/work remained overall unchanged in both groups, as shown in Table 12.

Table 12. Change from baseline in average number of days/months absent from school or work (only patients with pre- and post-baseline documentation

Change from baseline in average number of days/months absent from school or work	On-demand (N = 15) n (%)	Prophylaxis (N = 34) n (%)	Total (N = 49) n (%)
Average number decreased	4 (26.7)	7 (20.6)	11 (22.4)
Average number remained stable	9 (60.0)	20 (58.8)	29 (59.2)
Average number increased	2 (13.3)	7 (20.6)	9 (18.4)
P-value (Wilcoxon sign test)	0.688	1.000	0.824

Source: Table 15.4.2

Shift tables for the absences before and during the study are provided in Table 15.4.1.

10.4.6. Assessment of the treatment with BeneFIX®

Investigators were asked at each visit to assess (a) the effectiveness of the therapy with BeneFIX®, (b) its tolerability, (c) its handling, and (d) the satisfaction with the overall success of the documented treatment regimen.

Based on the last documented assessments (Table 13), the investigators rated the effectiveness, the tolerability and the handling of the drug as “very good” or “good”, and stated that they were “very satisfied” or “satisfied” with the treatment success in more than 95% of the cases.

Table 13. Investigators’ assessments of BeneFIX® (last documented assessments)

Variable	Assessment	On-demand (N = 25) n (%)	Prophylaxis (N = 55) n (%)	Total (N = 80) n (%)
Effectiveness:	n	23	54	77
	Very good	10 (43.5)	24 (44.4)	34 (44.2)
	Good	11 (47.8)	30 (55.6)	41 (53.2)
	Moderate	1 (4.3)	0 (0.0)	1 (1.3)
	Poor	1 (4.3)	0 (0.0)	1 (1.3)
Tolerability:	n	23	54	77
	Very good	16 (69.6)	35 (64.8)	51 (66.2)
	Good	7 (30.4)	18 (33.3)	25 (32.5)
	Moderate	0 (0.0)	1 (1.9)	1 (1.3)
	Poor	0 (0.0)	0 (0.0)	0 (0.0)
Handling of BeneFIX:	n	23	54	77
	Very good	13 (56.5)	34 (63.0)	47 (61.0)
	Good	10 (43.5)	20 (37.0)	30 (39.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)
	Poor	0 (0.0)	0 (0.0)	0 (0.0)
Treatment success:	n	23	54	77
	Very satisfied	12 (52.2)	27 (50.0)	39 (50.6)
	Satisfied	9 (39.1)	27 (50.0)	36 (46.8)
	Dissatisfied	1 (4.3)	0 (0.0)	1 (1.3)
	Very dissatisfied	1 (4.3)	0 (0.0)	1 (1.3)

Source: Tables 15.5.1.1, 15.5.1.2, 15.5.1.3, 15.5.1.4

Also patients were asked at each visit to assess (a) the effectiveness of the therapy with BeneFIX®, (b) its tolerability, and (c) its handling.

The data from the last documented patient assessment are presented in Table 14. These data show that the patient satisfaction with the treatment, was at least as high as the one of the investigators.

Table 14. Patients' assessments of BeneFIX® (last documented assessments)

Variable	Assessment	On-demand (N = 25) n (%)	Prophylaxis (N = 55) n (%)	Total (N = 80) n (%)
Effectiveness:	n	22	52	74
	Very good	11 (50.0)	27 (51.9)	38 (51.4)
	Good	10 (45.5)	25 (48.1)	35 (47.3)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)
	Poor	1 (4.5)	0 (0.0)	1 (1.4)
Tolerability:	n	22	52	74
	Very good	16 (72.7)	37 (71.2)	53 (71.6)
	Good	6 (27.3)	14 (26.9)	20 (27.0)
	Moderate	0 (0.0)	1 (1.9)	1 (1.4)
	Poor	0 (0.0)	0 (0.0)	0 (0.0)
Handling of BeneFIX®:	n	22	52	74
	Very good	13 (59.1)	37 (71.2)	50 (67.6)
	Good	8 (36.4)	15 (28.8)	23 (31.1)
	Moderate	1 (4.5)	0 (0.0)	1 (1.4)
	Poor	0 (0.0)	0 (0.0)	0 (0.0)

Source: Tables 15.5.2.1, 15.5.2.2, 15.5.2.3

Investigators' assessments by visit are provided in Tables 15.5.1.1, 15.5.1.2, 15.5.1.3 and 15.5.1.4. The corresponding data for the patients' assessments can be found in Tables 15.5.2.1, 15.5.2.2 and 15.5.2.3.

10.4.7. Thrombocyte count and hemoglobin levels

Measurements of full blood count were frequently performed during the study (Table 15.7.1).

Table 15 shows that no relevant changes in mean values for thrombocytes and hemoglobin occurred during the study.

Table 15. Change in thrombocyte count and hemoglobin levels

Parameter	On-demand		Prophylaxis		Total	
Time of measurement	(N = 25)		(N = 55)		(N = 80)	
	n	mean ± SD	n	mean ± SD	n	mean ± SD
Thrombocytes [G/L]						
Baseline	23	311.9 ± 142.3	54	277.7 ± 65.3	77	287.9 ± 95.3
Last documented value	25	252.0 ± 82.8	55	265.9 ± 78.1	80	261.6 ± 79.3
Hemoglobin [g/dL]						
Baseline	20	14.2 ± 2.0	51	13.5 ± 2.5	71	13.7 ± 2.4
Last documented value	25	14.2 ± 1.6	55	14.0 ± 2.5	80	14.1 ± 2.2

Source: Tables 15.7.2, 15.7.3

10.5. Other analyses

None.

10.6. Adverse events

10.6.1. All adverse event

A total of 68 patients (85.0%) reported at least one AE during the observation period (Table 15.9.1). The largest proportions of patients reported AEs referring to the MedDRA system organ classes “injury, poisoning and procedural complications” (61.3%), “musculoskeletal and connective tissue disorders” (60.0%), and “infections and infestations” (30.0%). In all of these 3 categories, the proportions of patients reporting such events were markedly lower in the on-demand group than in the prophylaxis group.

The incidences of AE for all system organ classes and for the most common AEs (≥5%) by preferred term are listed in Table 16. The incidences of all AEs are provided in Table 15.9.1.

Exclusively non-serious AEs occurred in 85.0% of the patients (Table 15.9.9). As with all AEs, the incidences were lower in the on-demand group than in the prophylaxis group. Details of all non-serious AEs are provided in Listing 15.9.10.

Table 16. All adverse events by MedDRA system organ class (and preferred term, if present in at least 4 patients [5%] of the total group)

MedDRA system organ class Preferred term	On-demand (N = 25) n (%)	Prophylaxis (N = 55) n (%)	Total (N = 80) n (%)
Any adverse event	**19 (76.0)**	**49 (89.1)**	**68 (85.0)**
Blood and lymphatic system disorders	**-**	**4 (7.3)**	**4 (5.0)**
Cardiac disorders	**-**	**3 (5.5)**	**3 (3.8)**
Congenital, familial and genetic disorders	**-**	**2 (3.6)**	**2 (2.5)**
Ear and labyrinth disorders	**1 (4.0)**	**2 (3.6)**	**3 (3.8)**
Endocrine disorders	**-**	**2 (3.6)**	**2 (2.5)**
Eye disorders	**1 (4.0)**	**4 (7.3)**	**5 (6.3)**
Gastrointestinal disorders	**7 (28.0)**	**13 (23.6)**	**20 (25.0)**
Abdominal pain	3 (12.0)	3 (5.5)	6 (7.5)
Diarrhoea	1 (4.0)	5 (9.1)	6 (7.5)
General disorders and administration site disorders	**6 (24.0)**	**12 (21.8)**	**18 (22.5)**
Local swelling	1 (4.0)	4 (7.3)	5 (6.3)
Hepatobiliary disorders	**-**	**1 (1.8)**	**1 (1.3)**
Immune system disorders	**1 (4.0)**	**1 (1.8)**	**2 (2.5)**
Infections and infestations	**3 (12.0)**	**21 (38.2)**	**24 (30.0)**
Viral upper respiratory tract infection	2 (8.0)	8 (14.5)	10 (12.5)
Injury, poisoning and procedural complications	**13 (52.0)**	**36 (65.5)**	**49 (61.3)**
Bone contusion	2 (8.0)	3 (5.5)	5 (6.3)
Concussion	1 (4.0)	3 (5.5)	4 (5.0)
Contusion	4 (16.0)	14 (25.5)	18 (22.5)
Fall	7 (28.0)	23 (41.8)	30 (37.5)
Joint injury	3 (12.0)	5 (9.1)	8 (10.0)
Laceration	3 (12.0)	10 (18.2)	13 (16.3)
Ligament sprain	1 (4.0)	12 (21.8)	13 (16.3)
Limb crushing injury	-	7 (12.7)	7 (8.8)
Limb injury	3 (12.0)	10 (18.2)	13 (16.3)
Skin abrasion	2 (8.0)	7 (12.7)	9 (11.3)
Traumatic haematoma	1 (4.0)	10 (18.2)	11 (13.8)
Traumatic haemorrhage	5 (20.0)	12 (21.8)	17 (21.3)
Investigations	**3 (12.0)**	**6 (10.9)**	**9 (11.3)**
Metabolism and nutrition disorders	**1 (4.0)**	**3 (5.5)**	**4 (5.0)**

(cont.)

Table 16. All adverse events by MedDRA system organ class (and preferred term, if present in at least 4 patients [5%] of the total group) - continued

MedDRA system organ class Preferred term	On-demand (N = 25) n (%)	Prophylaxis (N = 55) n (%)	Total (N = 80) n (%)
Musculoskeletal and connective tissue disorders	**9 (36.0)**	**39 (70.9)**	**48 (60.0)**
Arthralgia	2 (8.0)	18 (32.7)	20 (25.0)
Arthropathy	1 (4.0)	3 (5.5)	4 (5.0)
Back pain	1 (4.0)	3 (5.5)	4 (5.0)
Haemarthrosis	3 (12.0)	14 (25.5)	17 (21.3)
Haemophilic arthropathy	-	7 (12.7)	7 (8.8)
Joint effusion	1 (4.0)	4 (7.3)	5 (6.3)
Joint swelling	1 (4.0)	7 (12.7)	8 (10.0)
Muscle haemorrhage	3 (12.0)	6 (10.9)	9 (11.3)
Muscular discomfort	1 (4.0)	3 (5.5)	4 (5.0)
Musculoskeletal pain	1 (4.0)	4 (7.3)	5 (6.3)
Osteoarthritis	1 (4.0)	3 (5.5)	4 (5.0)
Pain in extremity	1 (4.0)	9 (16.4)	10 (12.5)
Synovitis	1 (4.0)	3 (5.5)	4 (5.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**2 (8.0)**	**4 (7.3)**	**6 (7.5)**
Nervous system disorders	**1 (4.0)**	**9 (16.4)**	**10 (12.5)**
Headache	1 (4.0)	4 (7.3)	5 (6.3)
Pregnancy, puerperium and perinatal conditions	**-**	**1 (1.8)**	**1 (1.3)**
Product issue	**-**	**2 (3.6)**	**2 (2.5)**
Psychiatric disorders	**-**	**2 (3.6)**	**2 (2.5)**
Renal and urinary disorders	**-**	**6 (10.9)**	**6 (7.5)**
Haematuria	-	4 (7.3)	4 (5.0)
Reproductive system and breast disorders	**1 (4.0)**	**2 (3.6)**	**3 (3.8)**
Respiratory, thoracic and mediastinal disorders	**4 (16.0)**	**10 (18.2)**	**14 (17.5)**
Epistaxis	1 (4.0)	7 (12.7)	8 (10.0)
Skin and subcutaneous tissue disorders	**2 (8.0)**	**14 (25.5)**	**16 (20.0)**
Surgical and medical procedures	**3 (12.0)**	**7 (12.7)**	**10 (12.5)**
Vascular disorders	**5 (20.0)**	**17 (30.9)**	**22 (27.5)**
Haematoma	3 (12.0)	12 (21.8)	15 (18.8)
Haemorrhage	1 (4.0)	7 (12.7)	8 (10.0)

Source: Table 15.9.1

10.6.2. All adverse events with causal relationship

The proportion of patients with AEs for which the investigators answered the question regarding causal relationship with “yes” amounted to 12.5% (8.0% in the on-demand group and 14.5% in the prophylaxis group; Table 15.9.2). The incidences of these AEs are listed by MedDRA system organ class and preferred term in Table 17.

Most of these "related" AEs referred to various types of injuries, hemorrhages and joint disorders, i.e., conditions related to the patients' underlying disease of hemophilia B. It should be noted that it was not explicitly stated in the CRF that only a causal relationship to BeneFIX® but not to the underlying hemophilia B was to be assessed.

"Inhibitory antibodies positive", "infusion related reaction" and "swelling face" may (theoretically) constitute true ADRs:

- "Inhibitory antibodies positive": In 1 patient, this was not assessed as clinically relevant. In the other patient, it was assessed as clinically relevant (see Section 10.6.5.1).

- "Infusion related reaction": This event was also assessed as serious. For details, see Section 10.6.5.2.

- "Swelling face": This event occurred in connection with a fall. Therefore, it was not reported as an adverse event of special interest.

Table 17. All adverse events assessed as "related" by the treating physician

MedDRA system organ class Preferred term	On-demand (N = 25) n (%)	Prophylaxis (N = 55) n (%)	Total (N = 80) n (%)
Any adverse reaction	**2 (8.0)**	**8 (14.5)**	**10 (12.5)**
Gastrointestinal disorders	**-**	**1 (1.8)**	**1 (1.3)**
Mouth haemorrhage	-	1 (1.8)	1 (1.3)
Tooth loss	-	1 (1.8)	1 (1.3)
Injury, poisoning and procedural complications	**1 (4.0)**	**5 (9.1)**	**6 (7.5)**
Bone contusion	-	1 (1.8)	1 (1.3)
Fall	1 (4.0)	2 (3.6)	3 (3.8)
Infusion related reaction	-	1 (1.8)	1 (1.3)
Ligament sprain	-	1 (1.8)	1 (1.3)
Limb crushing injury	-	1 (1.8)	1 (1.3)
Limb injury	-	1 (1.8)	1 (1.3)
Lip injury	-	1 (1.8)	1 (1.3)
Skin abrasion	1 (4.0)	1 (1.8)	2 (2.5)
Tongue injury	-	1 (1.8)	1 (1.3)
Traumatic haematoma	-	1 (1.8)	1 (1.3)
Traumatic haemorrhage	-	2 (3.6)	2 (2.5)
Investigations	**1 (4.0)**	**1 (1.8)**	**2 (2.5)**
Inhibitor antibodies positive	**1 (4.0)**	**1 (1.8)**	**2 (2.5)**
Musculoskeletal and connective tissue disorders	**-**	**3 (5.5)**	**3 (3.8)**
Arthralgia	-	2 (3.6)	2 (2.5)
Haemarthrosis	-	1 (1.8)	1 (1.3)
Joint swelling	-	1 (1.8)	1 (1.3)
Skin and subcutaneous tissue disorders	**-**	**1 (1.8)**	**1 (1.3)**
Swelling face	-	1 (1.8)	1 (1.3)

Note: It was not explicitly stated in the CRF that only a causal relationship to BeneFIX® but not to the underlying hemophilia B was to be assessed.
Source: Table 15.9.2

10.6.3. All serious adverse events

Nearly half of the patients (46.3% in total, 32.0% treated on-demand, 52.7% on prophylaxis) experienced SAEs (Table 15.9.3). Most of the SAEs occurred in single patients only.

Table 18 shows that the highest incidences were observed for SAEs referring to the system organ classes "musculoskeletal and connective tissue disorders" (18.8%), "injury, poisoning and procedural complications" (16.3%) and "infections and infestations" (13.8%). Overall, the most frequent SAEs on a preferred term level were "appendicitis", "fall" and "muscle haemorrhage", which occurred in 3 patients each.

A by-patient listing of all SAEs is provided in Listing 15.9.7.

Table 18. All serious adverse events by MedDRA system organ class (and preferred term, if present in at least 2 patients [2.5%] of the total group)

MedDRA system organ class Preferred term	On-demand (N = 25) n (%)	Prophylaxis (N = 55) n (%)	Total (N = 80) n (%)
Any serious adverse event	**8 (32.0)**	**29 (52.7)**	**37 (46.3)**
Blood and lymphatic system disorders	**-**	**2 (3.6)**	**2 (2.5)**
Cardiac disorders	**-**	**2 (3.6)**	**2 (2.5)**
Congenital, familial and genetic disorders	**-**	**2 (3.6)**	**2 (2.5)**
Ear and labyrinth disorders	**-**	**1 (1.8)**	**1 (1.3)**
Eye disorders	**-**	**1 (1.8)**	**1 (1.3)**
Gastrointestinal disorders	**2 (8.0)**	**6 (10.9)**	**8 (10.0)**
Abdominal pain	-	2 (3.6)	2 (2.5)
Gastrointestinal haemorrhage	-	2 (3.6)	2 (2.5)
General disorders and administration site disorders	**1 (4.0)**	**4 (7.3)**	**5 (6.3)**
Immune system disorders	**-**	**1 (1.8)**	**1 (1.3)**
Infections and infestations	**1 (4.0)**	**10 (18.2)**	**11 (13.8)**
Appendicitis	-	3 (5.5)	3 (3.8)
Pilonidal cyst	-	2 (3.6)	2 (2.5)
Injury, poisoning and procedural complications	**4 (16.0)**	**9 (16.4)**	**13 (16.3)**
Fall	1 (4.0)	2 (3.6)	3 (3.8)
Investigations	**2 (8.0)**	**2 (3.6)**	**4 (5.0)**
Inhibitor antibodies positive	1 (4.0)	1 (1.8)	2 (2.5)
Metabolism and nutrition disorders	**-**	**1 (1.8)**	**1 (1.3)**
Musculoskeletal and connective tissue disorders	**4 (16.0)**	**11 (20.0)**	**15 (18.8)**
Haemarthrosis	-	2 (3.6)	2 (2.5)
Haemophilic arthropathy	-	2 (3.6)	2 (2.5)
Muscle haemorrhage	1 (4.0)	2 (3.6)	3 (3.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**-**	**2 (3.6)**	**2 (2.5)**
Nervous system disorders	-	3 (5.5)	3 (3.8)
Product issues	**-**	**1 (1.8)**	**1 (1.3)**
Renal and urinary disorders	**-**	**1 (1.8)**	**1 (1.3)**
Respiratory, thoracic and mediastinal disorders	**1 (4.0)**	**2 (3.6)**	**3 (3.8)**
Tonsillar hypertrophy	1 (4.0)	1 (1.8)	2 (2.5)
Skin and subcutaneous tissue disorders	**2 (8.0)**	**2 (3.6)**	**4 (5.0)**
Surgical and medical procedures	**-**	**3 (5.5)**	**3 (3.8)**

Source: Table 15.9.3

One patient with multiple (S)AEs, which were all unrelated to BeneFIX®, finally died from severe pneumonia (Listing 15.9.8).

10.6.4. All serious adverse events with causal relationship

SAEs rated by the investigators as "related" occurred in 3 patients (3.8%; Table 15.9.4). It should be noted that it was not explicitly stated in the CRF that only a causal relationship to BeneFIX® but not to the underlying hemophilia B was to be assessed

These were 1 case of an infusion-related reaction in a patient on prophylaxis, and 2 cases of inhibitor development (in 1 patient on on-demand treatment and 1 patient on prophylaxis).

The case of the patient with a clinically relevant increase in inhibitor titer is described in Section 10.6.5.1. In the second patient, the elevated inhibitor titer was rated as being not clinically relevant. It was transient and normalized within 6 months without specific countermeasures.

10.6.5. Adverse events of special interest

10.6.5.1. Inhibitor development

Most of the inhibitor tests were performed either with the Bethesda assay or its Nijmegen modification (Table 15.6.8). In 3 patients, other methods (e.g., plasmapheresis) were used.

At baseline, 2 patients (both in the prophylaxis group and both were PTPs) were tested positive (>0.6 BU) for inhibitors to FIX (Tables 15.6.1 and 15.6.2).

At the last documented visit, 1 PTP and 1 PUP (both on prophylaxis treatment) showed inhibitor titers >0.6 BU (Tables 15.6.1, 15.6.2 and 15.6.3). Maximum inhibitor titers >0.6 BU at any time during the observation period were measured in 1 PTP on on-demand treatment (5.6%) and in 3 patients on prophylaxis (5.6%; 1 PUP and 2 PTPs; Table 15.6.4).

In 1 patient, the inhibitor titer was rated as clinically relevant:

This was a 9-month-old Caucasian boy (PUP) with severe hemophilia B (FIX:C <1%; large deletion of the FIX gene [exon 1-8]) who started prophylaxis treatment with BeneFIX® at a 3x/week schedule with a dose 33 IU/kg. About 9 weeks after treatment start (after approx. 66 EDs), an inhibitor titer of 1.3 BU was detected during routine testing (first test in this patient). The patient also exhibited an increased tendency for bleeds. The inhibitor development was reported as a serious ADR, and therapy with BeneFIX® was discontinued. The boy was retested 2 weeks later, and his inhibitor titer had continued to increase to 5.0 BU. Further measurements performed at 2-weekly intervals showed decreasing titers (to 4.4 BU, 3.0 BU and finally 1.2 BU). Complete safety information on this case is available in the safety database of the sponsor.

In relation to the individual reference ranges used in the respective laboratories, 1 PTP (0 PUP) treated on-demand and 3 PTPs and 1 PUP on prophylaxis treatment showed inhibitor titers above the reference value for inhibitor positivity (Table 15.6.5).

Listing 15.6.6 displays all patients who presented at least with one inhibitor titer either >0.6 BU or above the reference value including the assessment of clinical relevance.

None of the patients were scheduled for an immune tolerance therapy (Table 15.6.7).

10.6.5.2. Thrombus formation

A 65-year-old man (PTP) with severe hemophilia B received prophylaxis treatment with BeneFIX® for wound healing after removal of pseudo-tumor left thigh (total daily dose: 2 infusions of 2,000 IU). Five days after discharge from hospital, he developed angina pectoris symptoms, cardiac arrhythmia and bradycardia within 10 minutes after a BeneFIX® infusion and was hospitalized again. Cardiac catheterization revealed a right coronary artery stenosis and a non-ST segment elevation myocardial infarction (NSTEMI) in coronary three vessel disease was diagnosed, which was considered an infusion related reaction, but not an allergic reaction. Coronary artery thrombosis was diagnosed with coronary angiography. The event was treated with anticoagulants and a bare-metal stent was placed. The patient recovered within 1 day. Thereafter, the BeneFIX® dosage was reduced to 1,000 IU 3 times per day. No further thromboembolic events were reported in this patient during the study.

The patient had a history of coronary heart disease, which is a known risk factor for thrombosis. He also had a myocardial infarction 3 years before the present event.

A listing of all (S)AEs the patient experienced during the study is provided in Listing 15.9.7.

Complete safety information on this case is available in the safety database of the sponsor.

10.6.5.3. Other adverse events of special interest

Based on the assessments in the CRF, no other adverse events of special interest occurred in any of the patients (Table 15.9.5).

11. DISCUSSION

11.1. Key results

A total of 80 mostly Caucasian hemophilia B patients of all age groups (median age: 16.0 years; range: 0-69 years) participated in this study. The majority of patients (65.0%) had moderate hemophilia B with a residual FIX:C between 1% and 5%. Of the 19 patients (24% in the total population) who presented with severe disease, all but 1 were treated on a prophylaxis schedule (33% of the prophylaxis group). Seventy of the 80 patients (87.5%) were PTPs, and most of them had already accumulated >100 EDs. Nearly 70% of the patients (N=55) were on prophylaxis treatment, and most of the patients (65.0% in total) had used nonacog alfa for FIX substitution in the previous 12 months. One patient on prophylaxis (1.3%) had a history of inhibitors to FIX, which occurred approximately 13 years before baseline, when the patient had 20 EDs. The patient had undergone successful immune tolerance therapy.

Concomitant diseases were reported for 40.0% of the total population, and 27.5% of all patients were reported with chronic diseases. The percentage of patients with any concomitant diseases was markedly lower in the prophylaxis group than in the on-demand group

(36.4% vs. 48.0%). The most prevalent chronic viral infection was hepatitis C, present in 13.3% of the total population.

The mean observation period per patients was 3.9 ± 2.5 years (median: 3.8 years; range: 0.1 – 8.7 years) and shorter in the on-demand than in the prophylaxis group (median: 2.7 vs 4.2 years). Most of the patients remained on their current treatment regimen (on-demand, prophylaxis or intermediate prophylaxis) during the observation period. At the baseline visit, the mean BeneFIX® dose recommended by the treating physicians for patients on on-demand treatment was 42.4 ± 16.6 IU/kg (median: 40.5 IU/kg), which was about 25% higher than the recommended dose to be used for prophylaxis treatment (34.4 ± 19.3 IU/kg; median 30.0 IU/kg; 2 infusions per week). Overall, the recommended doses remained unchanged up to the patients' last visits, with only minor fluctuations in mean and median doses.

During the observation period, all patients were asked to record the occurrence of bleeds in a diary. Annualization of these data showed that patients on prophylaxis had a slightly lower annual bleed rate than patients treated on-demand (median: 2.7 vs. 3.8 bleeds/year; p=0.684, negative binomial model). About 60% of all bleeds were controlled with 1 or 2 FIX infusions and approximately 85% with 1-3 infusions. The average FIX consumption per bleed varied largely among patients, and was about 3,000 IU per bleed.

Regarding the influence of the treatment regimen on the extent of absence from school or work, the number of missed days remained stable over time, irrespective of treatment schedule (p=0.824; Wilcoxon sign test).

With few exceptions, investigators and patients were either "very satisfied" or "satisfied" with the effectiveness and tolerability of BeneFIX®, as well as with its handling. These positive assessments persisted throughout the study.

No influence of the treatment with BeneFIX® was seen for thrombocyte count or hemoglobin levels.

Analysis of the incidences of (S)AEs and (S)ADRs did not reveal any new or unexpected safety findings, which would have an impact on the risk-benefit profile of BeneFIX®. A total of 68 patients (85.0%) reported at least one AE during the observation period. The largest proportions of patients reported AEs referring to the MedDRA system organ classes "injury, poisoning and procedural complications" (61.3%), "musculoskeletal and connective tissue disorders" (60.0%), and "infections and infestations" (30.0%). It was found that these AEs were more frequent in patients on prophylaxis treatment.

AEs denoted by the investigators as adverse reactions occurred in 12.5% of the patients. With the exception of 2 cases of inhibitor development and 1 case of NSTEMI, all other "related" AEs referred to conditions related to the patients' underlying disease of hemophilia B.

The incidence of SAEs was 46.3% in total without any relevant differences between the on-demand and the prophylaxis groups. The highest incidences were observed for SAEs referring to the system organ classes "musculoskeletal and connective tissue disorders"

(18.8%), “injury, poisoning and procedural complications” (16.3%) and “infections and infestations” (13.8%). Overall, the most frequent SAEs on a preferred term level were “appendicitis”, “fall” and “muscle haemorrhage”, which occurred in 3 patients each. One patient died during this study. His death, however, was unrelated to his hemophilia treatment.

In 3 patients, the SAEs were assessed as “related”. These were 1 case of an infusion-related reaction in a patient on prophylaxis, and 2 cases of inhibitor development (in 1 patient on on-demand treatment and 1 patient on prophylaxis). In the patient on on-demand treatment, the inhibitor level normalized within 6 months without countermeasures. One PUP developed a clinically relevant inhibitor titer within the first 9 weeks of prophylaxis treatment with BeneFIX® (after approx. 66 EDs). Consequently, treatment with BeneFIX® was discontinued. Although the titers were decreasing over time, he was still inhibitor positive at the end of the study. An immune tolerance therapy was not started. The patient with the infusion-related reaction experienced NSTEMI within 10 minutes after a BeneFIX® infusion. The event resolved on anticoagulant treatment and after a stent placement. The patient continued on BeneFIX® prophylaxis at a reduced dosage.

Overall, none of the patients discontinued the study because of AEs, SAEs other than inhibitor development or LETE.

11.2. Limitations

Inherent limitations of non-interventional, observational studies in general are the risk of selection bias and other potential cofounding factors. A further limitation of all long-term observations is the decreasing number of observations over time when quite a large proportion of patients drop out or get lost to follow-up.

Annualization of bleed data is a common method for the assessment of the effectiveness of treatment in hemophilia B and is – at least to some extent – able to compensate for early drop-outs. However, statistical methods cannot account for unmeasured or untested confounders.

As in all studies, especially in non-interventional studies, an underreporting of AEs/ADRs cannot be excluded. In order to account for this known problem, all participating sites were visited at least once by an experienced clinical research associate for data verification and identification and resolution of potential problems. In addition, 5 of the 19 participating sites underwent an on-site audit. At the end of the study, all study sites without a recent monitoring visit and sites without a 100% patient monitoring underwent final monitoring visits by the responsible clinical research associate to ensure that all adverse event, in particular serious adverse events, were reported.

11.3. Interpretation

This study provides relevant information on a representative sample of patients with hemophilia B, i.e., all age groups, all disease severities, on-demand and prophylactically treated patients. The majority of patients were PTPs (most of them with >100 EDs) and had used nonacog alfa within the previous year; 10 patients were PUPs.

The BeneFIX® doses recommended by the treating physicians were well within the dose range recommended in the current version of the summary of product characteristics for this drug. Mean/median observation period was 3.8 years per patient. During this period, 1 PUP on a 3x/week prophylaxis regimen newly developed a clinically relevant inhibitor. Inhibitor formation, especially during the first weeks of exposure to factor concentrates in PUPs, is a known complication with all substitution therapies in hemophilia patients. The overall incidence of inhibitor formation (1/80 patients or 1.25%) is within the expected range and does not give rise to any major safety concerns. The same applies to the event of STEMI. The patient had several risk factors for thromboembolic events and also a history of myocardial infarction. Myocardial infarction is not listed in the current summary of product characteristics for BeneFIX®. This case would not indicate a reasonable causal association with the treatment.

Most of the non-serious AEs assessed by the investigators as “related” were various types of trauma bleeds and conditions associated with hemophilia. One “related” AE (“swelling face”), which was technically identified as a hypersensitivity reaction, occurred in connection with a “related” fall. Thus, the causality to the treatment with BeneFIX® may actually be excluded. The fact that the incidences of AEs relating to the system organ classes “injury, poisoning and procedural complications”, “musculoskeletal and connective tissue disorders”, and “infections and infestations” were higher in the prophylaxis group may be owing to the high proportion of patients with severe hemophilia in this group. These patients are expected to be at a higher risk of relevant injuries and musculoskeletal disorders.

The absolute ABR – as a measure for the effectiveness of BeneFIX® – was only slightly lower on prophylaxis than on on-demand treatment. Notably, 18 of the 19 patients with severe disease and only 1 of the 9 patients with mild disease were treated on prophylaxis. As the bleeding tendency is closely related to disease severity, this difference may have been more pronounced if both groups had been more balanced with regard to disease severity. A similar picture arose with the average number of injections and average dose required to stop a bleed. Although approximately 60% of the patients in both groups required on average 1-2 injections at an average dose of approximately 3,000 IU/kg, the data showed a mild trend towards fewer injections and lower doses per bleed in patients on on-demand treatment.

Overall, both patients and investigators were (very) satisfied with the use of BeneFIX®, and the data collected in this study had not impact on the known risk-benefit profile of the product.

11.4. Generalizability

The study results are based on a sample of 80 evaluable patients. In contrast to randomized controlled trials, patients were not selected by any study-specific eligibility criteria. Although the sample size of 80 patients may appear small, it must be taken into account that hemophilia B is a rare disease worldwide. Furthermore, considering a mean/median observation period of 3.8 years/patient, more than 300 patient years were documented in this study. Thus, the study population is expected to reflect the "real-life" situation of hemophilia B patients in Austria and Germany.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In summary, the data collected in this study showed that treatment with BeneFIX® is effective and safe and confirmed the known positive benefit-risk profile also under routine clinical conditions.

14. REFERENCES

1. Lambert T, Rothschild C, Volot F, et al. A national French noninterventional study to assess the long-term safety and efficacy of reformulated nonacog alfa. Transfusion 2017:57 (4),1066-1071.

15. LIST OF SOURCE TABLES AND FIGURES

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15.9.2 Adverse events with causal relationship by MedDRA primary system organ class and preferred term

15.9.3 Serious adverse events by MedDRA primary system organ class and preferred term

15.9.4 Serious adverse events with causal relationship by MedDRA primary system organ class and preferred term

15.9.5 Adverse events of special interest

15.9.6 Adverse events listing

15.9.7 Serious adverse events listing

15.9.8 Listing of deaths

15.9.9 Non-serious adverse events by MedDRA primary system organ class and preferred term

15.9.10 Non-serious adverse event listing