NON-INTERVENTIONAL (NI) STUDY REPORT

[redacted]

Title	**Pharmacovigilance Evaluation of ReFacto AF® in Germany and Austria**
Protocol number	B1831016 (3082B2-4420)
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Medicinal product	ReFacto AF®
Product reference	EU/1/99/103
Procedure number	EMEA/H/C/000232
Marketing Authorisation Holder (MAH)	Pfizer Limited
[redacted]	[redacted]
Research question and objectives	Evaluation of the benefit-risk profile after marketing authorization of ReFacto AF® in routine clinical practice.
Country(-ies) of study	Germany and Austria
Author	[redacted] Pfizer Pharma GmbH Linkstrasse 10 10785 Berlin

Marketing Authorisation Holder

Marketing Authorisation Holder	Pfizer Limited Ramsgate Road, Sandwich, Kent CT130NJ United Kingdom
MAH contact person	[redacted] Pfizer Pharma GmbH Linkstrasse 10 10785 Berlin

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[redacted]

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
FVIII	Factor VIII
FVIII:C	Factor VIII 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
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
rFVIII	recombinant factor VIII
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 Amendment 2		Germany: 24 Apr 2009 20 Jun 2012 12 Nov 2012 Austria: 05 Oct 2010	
Start of data collection		25 May 2009	
End of data collection		19 Oct 2016	
Final report of study results	19 Sep 2017	09 Oct 2017	

6. RATIONALE AND BACKGROUND

ReFacto AF® is the successor product to ReFacto® and is prepared by a modified process that eliminates any exogenous human- or animal-derived protein in the cell culture process, purification, or final formulation. The purification process uses a series of chromatography steps, one of which is based on affinity chromatography using a synthetic peptide affinity ligand. The process also includes a solvent-detergent viral inactivation step and a virus-retaining nanofiltration step.

ReFacto® and ReFacto AF® contain recombinant coagulation factor VIII (rFVIII; INN = moroctocog alfa). Moroctocog alfa is a purified protein that has 1438 amino acids. It has an amino acid sequence that is comparable to the 90 + 80 kDa form of FVIII (i.e., B-domain deleted) and post-translational modifications that are similar to those of the plasma-derived molecule. Recombinant FVIII is a glycoprotein that is secreted by genetically engineered mammalian cells (ovary cells of the Chinese hamster).

Randomized controlled trials have demonstrated the efficacy and safety of ReFacto AF® 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 clinical practice and daily life. An observational study of unselected patients in everyday conditions is necessary for the evaluation of the effectiveness and safety of ReFacto AF® in clinical routine conditions. Furthermore, due to the limited number of patients in Hemophilia A, observation of long-term outcomes with particular consideration of safety-relevant parameters is essential.

Therefore, regulatory authorities in Europe (e.g., European Medicines Agency) increasingly request pharmaceutical companies to provide sufficient and valid data on post-marketing safety and effectiveness of their products. Pharmacovigilance (PV) activities like this non-interventional study are requested by EU Regulation No. 726/2004 and Directive 2001/83/EC.

Data from an earlier PV evaluation on ReFacto® had already been published in 2007 [1], and the experiences from this study served as the basis for the planning of the ReFacto AF® pharmacovigilance. Comparisons of the collected data – before and after the launch of ReFacto AF® in 2008 – are therefore possible.

This non-interventional study was designated per CT34 as a Post-Authorization Safety Study (PASS; in the 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 ReFacto AF® under routine clinical conditions. Overall, the investigation examined the benefit-risk profile after marketing authorization of ReFacto AF® under routine application.

Primary objective

The primary objective of the study was to collect data on the safety of treatment with ReFacto AF® after its launch under routine clinical conditions in Germany and Austria. Monitoring of inhibitor development on ReFacto AF® (either after switch from the predecessor product ReFacto®, after the switch from another product or in previously untreated patients), as well as other serious adverse events (SAEs) and "less than expected therapeutic effect" (LETE) were the central safety aspects.

Secondary objective

The secondary objective was to collect data on the effectiveness of treatment with ReFacto AF®.

8. AMENDMENTS AND UPDATES

The original protocol, dated 12 January 2009, was agreed by an IEC on 24 April 2009. There were 2 amendments to the protocol.

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	21 May 2012	Administrative	All	Change from Wyeth template to Pfizer template. Change in contact persons.	After the acquisition of Wyeth Pharma GmbH by Pfizer, the structure of the study protocol was adapted to Pfizer standards.
2	22 Oct 2012	Substantial	Section 9	Specification that serious adverse reactions which occurred after the observational period had to be reported to the sponsor. Specification that "LETE" only had to be reported as an SAE, if the criteria for seriousness were met. Specification that clinically significant AEs had to be reported as SAEs. Specification that any exposition (prospective or retrospective) to a Pfizer product had to be reported to Pfizer. Deletion of reporting	Adaption to revised/ updated Pfizer standards.

				obligation for drug exposition during lactation period. Minor editorial and administrative changes.	

9. RESEARCH METHODS

The following subsections present a summary of the research methods applied in this study. Further information (e.g., definition of and reporting requirements for AEs) are provided in Amendment 2 [redacted]

9.1. Study design

This was a prospective, non-interventional study with an open-label, multicenter design conducted at hemophilia treatment centers in Germany and Austria.

The dosage and duration of the substitution therapy depended on the severity of FVIII deficiency, on the location and extent of bleed, and on the patient's clinical condition. Doses administered and frequency of application were titrated to the patient's clinical response.

During self-treatment at home the patient recorded the bleeds and substitution therapy (number of injections, quantity of substituted coagulation factor, etc.). These data were made available to the physician and recorded and analyzed.

Patients on FVIII substitution therapy were monitored for the development of FVIII inhibitors. If the expected FVIII activity plasma levels were not attained, or if a bleed was not controlled with an appropriate dose, an assay had to be performed to determine whether FVIII inhibitors were present.

For long-term prophylaxis of bleeds in patients with severe hemophilia A, the usual doses are 20 to 40 IU of FVIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

ReFacto® and ReFacto AF® are to be administered by intravenous (IV) injection after reconstitution of the lyophilized powder for injection with sodium chloride solution (in a concentration of 9 mg/ml or 0.9%) for IV injection over several minutes. The time of application for this had to be chosen in a way to be comfortable for the patient.

9.2. Setting

Patients were planned to participate in this study as long as they received ReFacto AF®, 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, information on origin, medical history, treatments, data on 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.

Besides the documentation for this study, data collection also included the documentation of data that have been collected prior to the inclusion in the PV evaluation.

In the context of the PV evaluation, the continued treatment was to be documented from as many patients as possible. In the earlier PV evaluation of the predecessor product, ReFacto® (protocol no. 3082A-100690), still ongoing at start of this study, 270 patients had been included at 57 treatment centers of which about 140 were still active. These patients should transition into this study, if they fulfilled the inclusion criteria and gave their consent.

It was the goal to include about 180 patients in the PV evaluation with ReFacto AF®. Of these patients – as mentioned above – 140, who had been treated with the predecessor product ReFacto®, were planned to be included.

The initially planned study duration was 36 months. If the planned patient number of about 180 patients had not been reached until then, or if long-term data were to be collected, the study could be prolonged accordingly beyond the 36 months.

9.3. Patients

Patients (adults and children of all age groups) with hemophilia A of any severity or treatment modality (on-demand, prophylaxis) receiving or starting treatment with ReFacto AF® were included. Patients who previously took part in the PV evaluation with ReFacto® were transitioned to this study, provided they (or their parents/caregivers) gave their informed consent for participation and were not simultaneously participating in another clinical study.

Patients receiving treatment of hemophilia A with a product other than ReFacto AF® during the study were excluded.

The baseline source documentation and possibly follow-up documentation(s) could also cover a period prior to the patient's inclusion in the study in order to thereby allow for the optimal recording of the course of treatment with ReFacto®.

9.4. Variables

9.4.1. Demographic variables

The study population was described by:

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

9.4.2. Effectiveness variables

- Bleeds

- Days absent from school or work
- Patient assessment of the drug handling
- Investigator assessment of satisfaction with treatment success

9.4.3. Safety Variables

- All (S)AEs
- (S)AEs with causal relationship
- Inhibitor development using the Nijmegen modification of the Bethesda assay.

Inhibitor development was defined as (1) any measured inhibitor titer >0.6 Bethesda Units (BU) using the Nijmegen modification of the Bethesda assay or (2) an inhibitor titer greater than the upper limit of normal (ULN) of the reporting laboratory. The clinical relevance of inhibitor titers was based on the medical judgement of the investigator.

The definition of FVIII inhibition is the one that was in place at the time of the study.

9.4.4. Other endpoints

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

9.5. Data sources and measurement

In the course of self-treatment at home the patient recorded the bleeds and substitution treatment (number of injections, amount of administered FVIII, etc.) in accordance with §14 German Transfusion Law and §8 iVM §11 Austrian Blood Protection Law. Data recording was either with a paper-based or an electronic diary (e.g., "Haemoassist®"). These data were made available to the physician and recorded and analyzed in the context of the PV evaluation.

The physicians documented patient characteristics as well as diagnosis and treatment-related information during the regular patient visits with special focus on safety aspects (AEs, SAEs, etc.). If possible, each visit was documented. These visits normally took place at intervals of 1-6 months according to clinical routine.

The following parameters were recorded at baseline:

- Date of onset of the treatment with ReFacto AF®*
- Demographic variables (date of birth, height, weight, ethnic group)*
- Hemophilia A history, previous FVIII replacement therapy*
- Disease severity (residual FVIII:C) and genetic mutation type
- Family history
- Immunization and viral infections (human immunodeficiency virus [HIV], hepatitis A/B vaccination, hepatitis A/B/C)
- Inhibitor history*

- History of allergic reactions
- Concomitant diseases
- Orthopedic status
- Medical or non-medical concomitant therapy
- Laboratory values (including previous FVIII:C and recovery, if available)
- Listing of AEs in the previous year (for patients not participating in the earlier ReFacto® PV evaluation)
- Assessment of patient's well-being
- Initial FVIII treatment regimen

Note: Items marked with * were mandatory.

The following parameters were to be recorded at the follow-up visits:

- Date of follow-up evaluation
- Demographic variables (date of birth, weight)
- Treatment regimen
- Laboratory tests (FVIII determination, clinical parameter) – if obtained at routine visits
- FVIII inhibitor testing *
- Assessment of patient 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 FVIII 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 during the study by recording all AEs at each patient visit (see "Follow-up documentation"). The study specifically focused on the inhibitor development during treatment with ReFacto AF® by the explicit recommendation of inhibitor tests at the beginning, after 10-15 and after 50 exposure days (EDs).

Inhibitor positivity (adverse event of special interest) was defined as an inhibitor titer of >0.6 Bethesda Units (BU) either measured using the Nijmegen modification of the Bethesda assay or an inhibitor titer above the upper level of the normal range at the reporting laboratory. There was no central laboratory testing in this study with analysis undertaken through local laboratory testing.

(S)AEs were to be documented and assessed by the physician according to type, onset and end, intensity, seriousness, causality with ReFacto AF®, outcome and any countermeasures.

Effectiveness of ReFacto AF® was to be assessed by the physician at each follow-up visit according to the parameters described above (e.g., number of bleeds, number of injections to stop a bleed, average consumption of FVIII replacement treatment per week) that were recorded in the patient diary. Laboratory values were only documented, if their determination was part of routine visit.

9.6. Bias

Missing or 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. As described in Section 9.2, the continued treatment was to be documented from as many patients as possible in the context of the PV evaluation. Since no statistical hypotheses were 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)

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), were documented in the statistical analysis plan (SAP; [redacted]

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, summary statistics for the last documented visit were 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 analysis was performed by the following cohorts, depending on treatment regimen planned at the baseline visit:

- On demand
- Prophylaxis
- Intermediate prophylaxis

As per version 3 of the SAP (see Section 9.9.5), only discontinuation due to (S)AEs, inhibitor or death were assessed as discontinuation. Patients with discontinuation reasons “lost to follow-up”, “lack of patient compliance” and “other” were treated as completers.

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, no confirmative statistical methods were 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, LETE etc.).

Furthermore parameters characterizing the effectiveness of ReFacto AF® were evaluated descriptively. These included e.g., annual bleed rate on prophylaxis, number of infusions needed to stop a bleed.

Bleed rate adjusted for duration of observation for bleed documentation was analyzed by a negative binomial regression model with the cohorts (on-demand, prophylaxis, intermediate prophylaxis) as factors. P-values were calculated for the difference between the two main cohorts “on-demand” and “prophylaxis”.

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

The incidence of patients with any measured inhibitor titer >0.6 BU was analyzed by the maximum inhibitor titer per patient. This analysis was performed for PTPs, previously untreated patients (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 values, 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 observation 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, dated 18 November 2016:

Version 2, dated 24 November 2016, included the following modifications:

- Analysis of “adverse events of special interest: allergic reactions” was deleted.
- Analysis of “investigator assessment of treatment satisfaction” was added,
- A further analysis regarding “concomitant medication” was added.

Version 3, dated 08 February 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, 8 of the 23 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 study data were recorded on the documentation forms (Case Report Forms = CRFs) or on 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. It fulfilled all applicable legal requirements of Germany and Austria. The patient's self-assessment of the safety and well-being of the patient was documented directly in the CRFs and the patient diary and 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 protect a patient's privacy and confidentiality. Information that could identify a patient was masked on material provided to the sponsor.

The documentation of home treatment and doctor-patient visits could be recorded using two different methods: electronically and/or on paper diaries.

If the patient documented in the conventional manner using paper-based diaries, copies of these diaries were provided for data analyses. If the patient used an electronic documentation system, e.g., "Haemoassist®", data were directly transferred to the study-server of this pharmacovigilance evaluation. The physician commented on the documentations of the patients through his electronic interface, which was considered in the analysis.

The investigator had to determine the preferred method of documentation in advance, if the patient wanted to use both methods. These data were considered source data accordingly.

The investigator also had the possibility to fill out 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.

Centers in Austria received a supplementary sheet referring to applicable laws in Austria (e.g., §48 Austrian Pharmaceuticals Act), which they had to sign prior to their participation in this study.

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 07 July 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 forschender Arzneimittelhersteller*", vfa) were applied.

Furthermore, the study was in accordance with the following recommendations and guidelines: *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 information in the study was based on data collection in routine clinical practice and is reported here as entered by the investigators after routine data clean-up procedures.

Please also 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 101 pediatric and adult patients with hemophilia A were enrolled in this study at 23 hemophilia centers in Austria and Germany (Table 15.1.1).

Of the 101 patients, 22 were on an on-demand treatment, 77 on routine prophylaxis and 2 on an intermediate prophylaxis treatment (Table 15.1.2). Ninety-eight (98) patients completed the study, and 3 patients died. The deaths in these 3 patients (2 on prophylaxis, and 1 on intermediate prophylaxis) were unrelated to the treatment with ReFacto AF® (Listing 15.9.8). None of the patients discontinued the study because of treatment-related AEs or (non-fatal) SAEs, LETE or inhibitor development.

10.2. Descriptive data

10.2.1. Demographic characteristics

The study population consisted of 15 (14.9%) patients ≤6 years of age, 34 (33.7%) aged between 7 and 17 years, and 52 (51.5%) adults ≥18 years old. The majority of patients (95.0%) were Caucasians. Age distribution further showed that an on-demand treatment regimen was followed only by adults and children ≤6 years, whereas the proportions treated on a prophylaxis regimen were more balanced between adults and older children/adolescents.

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

Table 2. Demographic characteristics

Variable	On-demand (N = 22)	Prophylaxis (N = 77)	Intermediate prophylaxis (N = 2)	Total (N = 101)
Age [years]				
n	22	77	2	101
Mean ± SD	34.0 ± 20.2	18.5 ± 12.4	62.0 ± 7.1	22.7 ± 16.6
Median	36.5	15.0	62.0	18.0
[Min; Max]	[1; 72]	[1; 53]	[57; 67]	[1; 72]
Age group				
≤ 6 years	4 (18.2%)	11 (14.3%)	0 (0.0%)	15 (14.9%)
7-17 years	0 (0.0%)	34 (44.2%)	0 (0.0%)	34 (33.7%)
≥ 18 years	18 (81.8%)	32 (41.6%)	2 (100.0%)	52 (51.5%)
Height [cm]				
n	17	52	2	71
Mean ± SD	161.2 ± 37.0	156.0 ± 34.1	164.5 ± 6.4	157.5 ± 34.1
Median	173.0	173.0	164.5	173.0
[Min; Max]	[83; 195]	[80; 192]	[160; 169]	[80; 195]
Weight [kg]				
n	20	76	2	98
Mean ± SD	65.8 ± 30.4	57.4 ± 28.5	58.2 ± 11.5	59.2 ± 28.6
Median	75.0	62.8	58.2	68.3
[Min; Max]	[11.7; 103.0]	[9.0; 132.0]	[50.0; 66.3]	[9.0; 132.0]
Race				
Caucasian	20 (90.9%)	74 (96.1%)	2 (100.0%)	96 (95.0%)
Other	2 (9.1%)	3 (3.9%)	0 (0.0%)	5 (5.0%)

Source: Table 15.1.3

10.2.2. History of hemophilia A

Across all treatment regimens, the median residual FVIII:C was 1.0%. Accordingly, the majority of patients in all groups (88.1% in total) had a residual FVIII:C between 1% and 5%, corresponding to a moderate disease severity (Table 15.1.4.1). Mild hemophilia A (residual FVIII:C of >5%) was present in 6.9% of the patients in total, and severe disease (residual FVIII:C of <1%) was present in 5.0%. Four of the 5 patients with severe hemophilia A received prophylaxis treatment. Overall, 97.0% of the patients were PTPs, and most of them had already accumulated more than 100 EDs (Tables 15.1.4.1 and 15.1.4.3). Most patients (92.1%) had been treated with ReFacto® or ReFacto AF® in the previous 12 months (Table 15.1.4.2). The 3 PUPs[1] participating in this study utilized an on-demand treatment.

Approximately 50% of the patients had a family history of hemophilia A, and in 67% had a known hemophilia inducing genetic mutation (Tables 15.1.4.1 and 15.1.5).

[1] According to the question in the CRF, only patients without prior exposure to FVIII concentrates were counted as PUPs.

Table 3 summarized the history of hemophilia A and the disease characteristics by treatment regimen.

Table 3. History of hemophilia A

Variable	On-demand (N = 22)	Prophylaxis (N = 77)	Intermediate prophylaxis (N = 2)	Total (N = 101)
FVIII:C – residual [%]				
n	22	77	2	101
Mean ± SD	2.1 ± 2.6	2.1 ± 5.5	1.0 ± 0.0	2.1 ± 4.9
Median	1.0	1.0	1.0	1.0
[Min; Max]	[0;9]	[0; 43]	[1; 1]	[0; 43]
FVIII:C – residual				
0%	1 (4.5%)	4 (5.2%)	0 (0.0%)	5 (5.0%)
>0% to <1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1%	15 (68.2%)	64 (83.1%)	2 (100.0%)	81 (80.2%)
>1%	6 (27.3%)	9 (11.7%)	0 (0.0%)	15 (14.9%)
Disease severity				
Severe (<1%)	1 (4.5%)	4 (5.2%)	0 (0.0%)	5 (5.0%)
Moderate (1-5%)	18 (81.8%)	69 (89.6%)	2 (100.0%)	89 (88.1%)
Mild (>5%)	3 (13.6%)	4 (5.2%)	0 (0.0%)	7 (6.9%)
Patient status				
PTP	19 (86.4%)	77 (100.0%)	2 (100.0%)	98 (97.0%)
PUP	3 [a] (13.6%)	0 (0.0%)	0 (0.0%)	3 (3.0%)
Previous exposure days				
0 - 20	4 [a] (18.2%)	0 (0.0%)	0 (0.0%)	4 (4.0%)
21 - 50	1 (4.5%)	1 (1.3%)	0 (0.0%)	2 (2.0%)
51 - 100	0 (0.0%)	3 (3.9%)	0 (0.0%)	3 (3.0%)
>100	17 (77.3%)	73 (94.8%)	2 (100.0%)	92 (91.1%)
Family history of hemophilia A				
n	22	75	2	99
Yes	13 (59.1%)	37 (49.3%)	1 (50.0%)	51 (51.5%)
No	9 (40.9%)	38 (50.7%)	1 (50.0%)	48 (48.5%)
Mutation type known				
n	22	76	2	100
Yes	15 (68.2%)	47 (61.8%)	0 (0.0%)	62 (62.0%)
No	7 (31.8%)	29 (38.2%)	2 (100.0%)	38 (38.0%)

Abbreviations: FVIII:C = FVIII activity; PTP = previously treated patient; PUP = previously untreated patient.
[a] According to the question in the CRF, only patients without prior exposure to FVIII concentrates were counted as PUPs.
Source: Tables 15.1.4.1, 15.1.4.3, 15.1.5

10.2.3. Inhibitor history

Six of the 83 patients (7.2%), where it was recorded, had a family history of inhibitor development, and 9 of 100 patients (9.0% in the total group, all on prophylaxis treatment) had a personal history of inhibitor development (Tables 15.1.5 and 15.1.7). The median time between inhibitor detection and enrolment in this study was 12 years and ranged between 0 and 36 years. This means that at least 1 patient was still inhibitor positive at the time of his

last inhibitor testing before enrolment. This is also in accordance with a maximum inhibitor titer of 7.0 BU as latest measured value. Of the 6 patients with the corresponding documentation, the inhibitor was detected after 27 EDs (median; range: 0 – 60 EDs).

Four of the 9 patients with a history of inhibitors had undergone previous immune tolerance therapy (2 with ReFacto® or ReFacto AF® and 2 with unspecified FVIII products); Table 15.1.8), which was successful in all cases.

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

Table 4. History of inhibitors to FVIII

Variable	On-demand (N = 22)	Prophylaxis (N = 77)	Intermediate prophylaxis (N = 2)	Total (N = 101)
Family history of inhibitors				
n	17	64	2	83
No	16 (94.1%)	59 (92.2%)	2 (100.0%)	77 (92.8%)
Yes	1 (5.9%)	5 (7.8%)	0 (0.0%)	6 (7.2%)
Patient history of inhibitors				
n	21	77	2	100
Yes	0 (0.0%)	9 (11.7%)	0 (0.0%)	9 (9.0%)
No	18 (85.7%)	68 (88.3%)	2 (100.0%)	88 (88.0%)
Not applicable (PUP)	3 (14.3%)	0 (0.0%)	0 (0.0%)	3 (3.0%)
Time of inhibitor development [years before baseline]				
n	0	9	0	9
Mean ± SD	-	13.4 ± 10.9	-	13.4 ± 10.9
Median	-	12.0	-	12.0
[Min; Max]		[0; 36]		[0; 36]
Exposure days at the time of inhibitor development				
n	0	6	0	6
Mean ± SD	-	27.2 ± 22.4	-	27.2 ± 22.4
Median	-	27.0	-	27.0
[Min; Max]		[0; 60]		[0; 60]
Inhibitor titer at first measurement [BU]				
n	5	18	0	23
Mean ± SD	0.7 ± 0.4	1.9 ± 4.4	-	1.6 ± 3.9
Median	1.0	0.4	-	0.6
[Min; Max]	[0.0; 1.0]	[0.0; 19.0]		[0.0; 19.0]
Inhibitor titer at last measurement [BU]				
n	5	16	0	21
Mean ± SD	0.6 ± 0.4	0.9 ± 1.8	-	0.8 ± 1.6
Median	0.4	0.4	-	0.4
[Min; Max]	[0.0; 1.0]	[0.0; 7.0]		[0.0; 7.0]
Previous immune tolerance therapy?				
n	12	36	1	49
No	12 (100.0%)	32 (88.9%)	1 (100.0%)	45 (91.8%)
Yes	0 (0.0%)	4 (11.1%)	0 (0.0%)	4 (8.2%)
Immune tolerance therapy successful?				
n	0	4	0	4
No	-	0 (0.0)	-	0 (0.0)
Yes	-	4 (100.0)	-	4 (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 22.5% of the patients, followed by HIV-1/2 positivity in 9.0% of the patients with the corresponding recordings (Tables 15.1.6.1 and 15.1.6.2). Chronic hepatitis B and C was reported for 2 and 20 patients, respectively, and 2 patients were reported with acute 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 = 22)	Prophylaxis (N = 77)	Intermediate prophylaxis (N = 2)	Total (N = 101)
HIV-1/2 status (n; %)				
n	20	67	2	89
Negative	17 (85.0%)	63 (94.0%)	1 (50.0%)	81 (91.0%)
Positive	3 (15.0%)	4 (6.0%)	1 (50.0%)	8 (9.0%)
Hepatitis A (n; %)				
n	18	67	1	86
No disease	17 (94.4%)	66 (98.5%)	1 (100.0%)	84 (97.7%)
Acute disease	1 (5.6%)	1 (1.5%)	0 (0.0%)	2 (2.3%)
Chronic disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatitis B (n; %)				
n	16	67	1	84
No disease	16 (100.0%)	65 (97.0%)	1 (100.0%)	82 (97.6%)
Acute disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chronic disease	0 (0.0%)	2 (3.0%)	0 (0.0%)	2 (2.4%)
Hepatitis C (n; %)				
n	19	68	2	89
No disease	12 (63.2%)	57 (83.8%)	0 (0.0%)	69 (77.5%)
Acute disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chronic disease	7 (36.8%)	11 (16.2%)	2 (100.0%)	20 (22.5%)

Source: Tables 15.1.6.1, 15.1.6.2

10.2.4.2. All concomitant diseases at baseline

Concomitant diseases were reported for 35.6% of the total population (Table 15.1.9.1), and chronic diseases were reported for 30.7% (Table 15.1.9.2). Disregarding the 2 patients constituting the “intermediate prophylaxis” group, the percentage of patients with any concomitant diseases was markedly lower in the prophylaxis group than in the on-demand group (29.9% vs. 50.0%). This difference was mainly driven by the higher proportion of on-demand treated patients with musculoskeletal and connective tissue disorders (22.7% vs.

5.2% in the prophylaxis group), such as (hemophilic) arthropathy and osteoarthritis. 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 = 22) n (%)	Prophylaxis (N = 77) n (%)	Intermediate prophylaxis (N = 2) n (%)	Total (N = 101) n (%)
Any concomitant disease	**11 (50.0)**	**23 (29.9)**	**2 (100.0)**	**36 (35.6)**
Cardiac disorders	**1 (4.5)**	**-**	**1 (50.0)**	**2 (2.0)**
Endocrine disorders	**1 (4.5)**	**-**	**-**	**1 (1.0)**
Gastrointestinal disorders	**2 (9.1)**	**4 (5.2)**	**-**	**6 (5.9)**
Chronic gastritis	1 (4.5)	1 (1.3)	-	2 (2.0)
General disorders and administration site disorders	**-**	**2 (2.6)**	**-**	**2 (2.0)**
Hepatobiliary disorders	**2 (9.1)**	**2 (2.6)**	**1 (50.0)**	**5 (5.0)**
Hepatic cirrhosis	1 (4.5)	2 (2.6)	1 (50.0)	4 (4.0)
Immune system disorders	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Infections and infestations	**5 (22.7)**	**11 (14.3)**	**2 (100.0)**	**18 (17.8)**
Chronic hepatitis C	-	1 (1.3)	1 (50.0)	2 (2.0)
HIV infection	2 (9.1)	3 (3.9)	1 (50.0)	6 (5.9)
Hepatitis C	4 (18.2)	8 (10.4)	1 (50.0)	13 (12.9)
Metabolism and nutrition disorders	**1 (4.5)**	**4 (5.2)**	**-**	**5 (5.0)**
Musculoskeletal and connective tissue disorders	**5 (22.7)**	**4 (5.2)**	**2 (100.0)**	**11 (10.9)**
Arthropathy	1 (4.5)	-	1 (50.0)	2 (2.0)
Haemophilic arthropathy	2 (9.1)	1 (1.3)	-	3 (3.0)
Osteoarthritis	2 (9.1)	-	1 (50.0)	3 (3.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Nervous system disorders	**-**	**2 (2.6)**	**1 (50.0)**	**3 (3.0)**
Cerebral haemorrhage	-	1 (1.3)	1 (50.0)	2 (2.0)
Psychiatric disorders	**2 (9.1)**	**2 (2.6)**	**-**	**4 (4.0)**
Depression	1 (4.5)	1 (1.3)	-	2 (2.0)
Renal and urinary disorders	**2 (9.1)**	**-**	**-**	**2 (2.0)**
Nephrolithiasis	2 (9.1)	-	-	2 (2.0)
Respiratory, thoracic and mediastinal disorders	**-**	**2 (2.6)**	**-**	**2 (2.0)**
Skin and subcutaneous tissue disorders	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Surgical and medical procedures	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Vascular disorders	**1 (4.5)**	**2 (2.6)**	**1 (50.0)**	**4 (4.0)**
Hypertension	1 (4.5)	2 (2.6)	1 (50.0)	4 (4.0)

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

Concomitant medications were reported for 27.7% of all patients, with the percentage of patients using concomitant medications being markedly higher in the on-demand group than in the prophylaxis group (50.0% vs. 19.5%; Table 15.8.1). In particular, the proportions of patients using anti-infective for systemic use, antineoplastic and immunomodulating agents, and medication for the musculoskeletal system were markedly higher in the on-demand group than in the group of patients on prophylaxis. Given that patients utilizing an on-demand treatment regimen tend to have more musculoskeletal and connective tissues disorders than those faithfully using a prophylaxis regimen, the finding that more on-demand patients reported concomitant use of medications targeting the musculoskeletal system is not surprising (see Section 10.2.4.2).

Both in the on-demand and in the prophylaxis groups, the highest percentages of patients used anti-infectives for systemic use, in particular antiviral drugs.

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

Table 7. Concomitant medication

WHO-DD ATC Level 1	On-demand (N = 22) n (%)	Prophylaxis (N = 77) n (%)	Intermediate prophylaxis (N = 2) n (%)	Total (N = 101) n (%)
Any concomitant medication	11 (50.0)	15 (19.5)	2 (100.0)	28 (27.7)
Alimentary tract and metabolism	1 (4.5)	6 (7.8)	2 (100.0)	9 (8.9)
Antiinfectives for systemic use	5 (22.7)	7 (9.1)	1 (50.0)	13 (12.9)
Antineoplastic and immuno-modulating agents	3 (13.6)	3 (3.9)	-	6 (5.9)
Cardiovascular system	1 (4.5)	3 (3.9)	1 (50.0)	5 (5.0)
Musculoskeletal system	4 (18.2)	5 (6.5)	-	9 (8.9)
Nervous system	2 (9.1)	3 (3.9)	2 (100.0)	7 (6.9)
Respiratory system	-	1 (1.3)	-	1 (1.0)
Systemic hormonal preparations, excl. sex hormones and insulins	1 (4.5)	-	-	1 (1.0)

Source: Table 15.8.1

During the course of the study, 12.9% of the patients reported the discontinuation of at least 1 concomitant medication, 4.0% a dose reduction of at least 1 drug, 6.9% a dose increase of at least 1 drug, and 28.7% received at least 1 newly prescribed concomitant medication.

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

10.3. Outcome data

For 93 of the 101 enrolled patients, the observation period for bleed documentation was calculable (Table 15.1.11). The mean observation period in this population was 3.6 ± 1.9 years (median: 3.6 years; range: 0.2 – 7.3 years) and similar in the on-demand and prophylaxis groups. The remaining 8 patients either did not have a post-baseline visit or did not complete a diary.

The mean number of post-baseline visits was 9.1 ± 6.8 (median: 8.0; range: 0 – 32; Table 15.1.12). The highest number of visits and documentations were performed in the first 2-3 years (maximum: 213 visits/documentations in 2010) and decreased thereafter up to study closure in 2016 with 39 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/adverse reactions and events of LETE.

10.4.1. Treatment with ReFacto AF®

Most of the patients remained on their current treatment regimen (on-demand, prophylaxis or intermediate prophylaxis) during the observation period (Table 15.2. 1).

The analysis of the planned ReFacto AF® dose was based on the actual treatment regimen the patients applied[2] (Table 15.2.2). At the baseline visit, the mean dose recommended by the treating physicians for patients on on-demand treatment was 23.0 ± 8.0 IU/kg per infusion (median: 22.0 IU/kg), while the mean dose for patient's following a prophylaxis regimen was 26.7 ± 8.4 IU/kg (median 25.8 IU/kg). Overall, the recommended doses remained unchanged up to the patients' last visits, with only minor fluctuations in mean and median doses per infusion.

The median number of recommended weekly prophylaxis infusions was 3 (range: 1 - 4) at baseline and for the most part remained unchanged up to the last documented visit (Table 15.2.5).

10.4.2. FVIII:C and PTT in relation to time of ReFacto AF® administration

FVIII:C

For all 595 FVIII:C measurements in this study, independent of treatment regimen, FVIII:C levels ≥20% were – with 1 exception –present within 72 h post-dose (Table 15.2.3.1). However, the decrease to levels <10% FVIII:C was already observed after 25 h post-dose. Throughout this study, FVIII:C were primarily determined using the one-stage assay (Table 15.2.3.3). Recovery measurements were performed in individual cases only (Table 15.2.3.4).

[2] Note: Switches between treatment regimens (on-demand, prophylaxis) were possible.

Using the FVIII: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 below 2x upper limit of normal[3] (i.e., <76 s) were only observed within 72 h post-dose (Table 15.2.4.1). The lowest median PTT value of 48.7 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 bleeds varied largely among patients (minimum: 0; maximum: 238) both depending on the individual time in the study and the patients' bleeding phenotype (Table 15.3.1). As shown in Table 8, most of the bleeds were joint bleeds.

Table 8. Number of bleeds per patient by type of bleeds

Variable	On-demand (N = 22)	Prophylaxis (N = 77)	Intermediate prophylaxis (N = 2)	Total (N = 101)
Number of all bleeds				
n	17	74	2	93
Median	36.0	12.5	68.5	14.0
[Min; Max]	[0; 238]	[0; 54]	[46; 91]	[0; 238]
Number of joint bleeds				
n	17	74	2	93
Median	28.0	4.0	55.0	5.0
[Min; Max]	[0; 211]	[0; 39]	[43; 67]	[0; 211]
Number of soft tissue bleeds				
n	17	74	2	93
Median	5	2.0	11.0	2.0
[Min; Max]	[0; 156]	[0; 21]	[2; 20]	[0; 156]
Number of other bleeds				
n	17	74	2	93
Median	2.0	2.0	2.5	2.0
[Min; Max]	[0; 44]	[0; 20]	[1; 4]	[0; 44]

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 per patient 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.

As already indicated by the absolute numbers of bleeds, the annual bleed rate (ABR), in particular of joint bleeds, was markedly lower on a prophylaxis than on on-demand regimen

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

(p <0.001; negative binomial model). Although the median ABR of soft tissue bleeds was <2 in both groups, and <1 for other bleeds, they were consistently lower on prophylaxis treatment.

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

Variable	On-demand (N = 22)		Prophylaxis (N = 77)
All bleeds			
n	17		74
Mean ± SD	18.6 ± 19.6		5.1 ± 5.8
Median	8.9		3.3
[Min; Max]	[0.0; 74.7]		[0.0; 31.2]
P-value [a]		<0.001	
Joint bleeds			
n	17		74
Mean ± SD	13.3 ± 16.1		2.5 ± 3.2
Median	6.2		1.1
[Min; Max]	[0.0; 57.7]		[0.0; 17.1]
P-value [a]		<0.001	
Soft tissue bleeds			
n	17		74
Mean ± SD	3.1 ± 5.5		1.2 ± 1.8
Median	1.6		0.5
[Min; Max]	[0.0; 22.6]		[0.0; 11.4]
P-value [a]		<0.001	
Other bleeds			
n	17		74
Mean ± SD	2.3 ± 3.8		1.4 ± 3.0
Median	0.6		0.5
[Min; Max]	[0.0; 13.1]		[0.0; 24.5]
P-value [a]		0.128	

[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. 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 10.

Table 10. Average number of days absent from school/work before study participation

Average number of days/months absent from school or work	On-demand (N = 22) n (%)	Prophylaxis (N = 77) n (%)	Intermediate prophylaxis (N = 2) n (%)	Total (N = 101) n (%)
n	21	74	2	97
Non-working/not school-aged	9 (42.9)	13 (17.6)	2 (100.0)	24 (24.7)
No days absent	5 (23.8)	24 (32.4)	0 (0.0)	29 (29.9)
<6 days absent	7 (33.3)	35 (47.3)	0 (0.0)	42 (43.3)
6-10 days absent	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.0)
>10 days absent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Permanently unable to work/attend school	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.0)

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 the on-demand group, but markedly decreased in the prophylaxis group, as shown in Table 11.

Table 11. 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 = 11) n (%)	Prophylaxis (N = 60) n (%)	Total (N = 71) n (%)
Average number decreased	4 (36.4)	25 (41.7)	29 (40.8)
Average number remained stable	4 (36.4)	29 (48.3)	33 (46.5)
Average number increased	3 (27.3)	6 (10.0)	9 (12.7)
P-value (Wilcoxon sign test)	1.000	< 0.001	0.002

Source: Table 15.4.2

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

10.4.5. Assessment of the treatment with ReFacto AF®

10.4.5.1. Investigator's assessment of the treatment success

Investigators were asked at each visit to assess the success of the patients' hemophilia treatment. With single exceptions, the investigators stated that they were either "very satisfied" or "satisfied" with the treatment success with ReFacto AF® both when used for on-demand and for prophylaxis treatment. These positive assessments persisted throughout the study (Table 15.5.1).

10.4.5.2. Patient's assessment of the handling of ReFacto AF®

Patients were asked at each visit to assess their satisfaction with the handling of ReFacto AF®. With few exceptions, the patients stated that they were either "very satisfied" or "satisfied" with the handling of ReFacto AF®. These positive assessments persisted throughout the study (Table 15.5.2).

10.4.6. Clinical chemistry

Clinical chemistry measurements were frequently performed during the study (Table 15.7.1).

Table 12 shows that no relevant changes in mean values for thrombocytes and hemoglobin occurred during the study.

Table 12. Clinical chemistry: change in thrombocyte count and hemoglobin levels

Parameter / Time of measurement	On-demand (N = 22)		Prophylaxis (N = 77)		Intermediate prophylaxis (N = 2)		Total (N = 101)	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
Thrombocytes [G/L]								
Baseline	18	250.7 ± 82.1	74	264.2 ± 73.0	1	87.0	93	259.7 ± 76.3
Last documented value	21	244.7 ± 78.0	77	251.8 ± 75.8	2	72.0 ± 19.8	100	246.7 ± 79.3
Hemoglobin [g/dL]								
Baseline	18	14.8 ± 1.9	71	13.5 ± 2.3	1	11.3	90	13.8 ± 2.2
Last documented value	21	14.9 ± 1.5	77	14.2 ± 1.4	2	11.2 ± 0.1	100	14.3 ± 1.5

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 76 patients (75.2%) 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” (51.5%), “musculoskeletal and connective tissue disorders” (43.6%), and “infections and infestations” (31.7%).

The incidences of AE by system organ classes and for the most common AEs (≥5%) by preferred term are listed in Table 13. The incidences of all AEs are provided in Table 15.9.1.

Exclusively non-serious AEs occurred in 71.3% of the patients (Table 15.9.10). As with all AEs, the incidences were similar in the on-demand treated and the prophylaxis groups. Details of all non-serious AEs are provided in Listing 15.9.11.

Table 13. All adverse events by MedDRA system organ class (and preferred term, if present in at least 5 patients [5%] of the total group)

MedDRA system organ class Preferred term	On-demand (N = 22) n (%)	Prophylaxis (N = 77) n (%)	Intermediate prophylaxis (N = 2) n (%)	Total (N = 101) n (%)
Any adverse event	**15 (68.2)**	**59 (76.6)**	**2 (100.0)**	**76 (75.2)**
Blood and lymphatic system disorders	**1 (4.5)**	**4 (5.2)**	**-**	**5 (5.0)**
Cardiac disorders	**1 (4.5)**	**-**	**-**	**1 (1.0)**
Congenital, familial and genetic disorders	**-**	**2 (2.6)**	**-**	**2 (2.0)**
Ear and labyrinth disorders	**1 (4.5)**	**1 (1.3)**	**-**	**2 (2.0)**
Endocrine disorders	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Eye disorders	**3 (13.6)**	**-**	**-**	**3 (3.0)**
Gastrointestinal disorders	**6 (27.3)**	**11 (14.3)**	**2 (100.0)**	**19 (18.8)**
General disorders and administration site disorders	**2 (9.1)**	**4 (5.2)**	**1 (50.0)**	**7 (6.9)**
Hepatobiliary disorders	**-**	**1 (1.3)**	**1 (50.0)**	**2 (2.0)**
Immune system disorders	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Infections and infestations	**5 (22.7)**	**25 (32.5)**	**2 (100.0)**	**32 (31.7)**
Viral upper respiratory tract infection	1 (4.5)	4 (5.2)	1 (50.0)	6 (5.9)
Injury, poisoning and procedural complications	**12 (54.5)**	**39 (50.6)**	**1 (50.0)**	**52 (51.5)**
Contusion	6 (27.3)	11 (14.3)	-	17 (16.8)
Fall	3 (13.6)	18 (23.4)	-	21 (20.8)
Joint injury	4 (18.2)	14 (18.2)	-	18 (17.8)
Laceration	3 (13.6)	10 (13.0)	-	13 (12.9)
Ligament sprain	1 (4.5)	7 (9.1)	-	8 (7.9)
Limb injury	2 (9.1)	13 (16.9)	-	15 (14.9)
Tongue injury	1 (4.5)	4 (5.2)	-	5 (5.0)
Traumatic haematoma	1 (4.5)	4 (5.2)	-	5 (5.0)
Traumatic haemorrhage	3 (13.6)	16 (20.8)	-	19 (18.8)
Investigations	**2 (9.1)**	**4 (5.2)**	**-**	**6 (5.9)**
Metabolism and nutrition disorders	**-**	**2 (2.6)**	**2 (100.0)**	**4 (4.0)**
Musculoskeletal and connective tissue disorders	**7 (31.8)**	**35 (45.5)**	**2 (100.0)**	**44 (43.6)**
Arthralgia	3 (13.6)	12 (15.6)	-	15 (14.9)
Back pain	2 (9.1)	4 (5.2)	1 (50.0)	7 (6.9)
Haemarthrosis	1 (4.5)	15 (19.5)	-	16 (15.8)
Pain in extremity	4 (18.2)	6 (7.8)	1 (50.0)	11 (10.9)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**-**	**4 (5.2)**	**1 (50.0)**	**5 (5.0)**

(cont.)

Table 13. All adverse events by MedDRA system organ class (and preferred term, if present in at least 5 patients [5%] of the total group) - continued

MedDRA system organ class Preferred term	On-demand (N = 22) n (%)	Prophylaxis (N = 77) n (%)	Intermediate prophylaxis (N = 2) n (%)	Total (N = 101) n (%)
Nervous system disorders	**4 (18.2)**	**4 (5.2)**	**1 (50.0)**	**9 (8.9)**
Product issue	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Psychiatric disorders	**3 (13.6)**	**1 (1.3)**	**-**	**4 (4.0)**
Renal and urinary disorders	**1 (4.5)**	**3 (3.9)**	**1 (50.0)**	**5 (5.0)**
Respiratory, thoracic and mediastinal disorders	**2 (9.1)**	**5 (6.5)**	**1 (50.0)**	**8 (7.9)**
Skin and subcutaneous tissue disorders	**3 (13.6)**	**3 (3.9)**	**2 (100.0)**	**8 (7.9)**
Surgical and medical procedures	**3 (13.6)**	**8 (10.4)**	**1 (50.0)**	**12 (11.9)**
Vascular disorders	**4 (18.2)**	**13 (16.9)**	**1 (50.0)**	**18 (17.8)**
Haematoma	2 (9.1)	5 (6.5)	1 (50.0)	8 (7.9)
Haemorrhage	1 (4.5)	7 (9.1)	-	8 (7.9)

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" added up to 8.9% (9.1% both in the prophylaxis and the on-demand groups, and 0.0% in the intermediate prophylaxis group; Table 15.9.2). All of these AEs are listed by MedDRA system organ class and preferred term in Table 14.

With the exception of an eyelid edema, which occurred in a patient treated on-demand, all other "related" AEs referred to various types of injuries, hemorrhages and hemorrhagic arthropathy, i.e., conditions related to the patients' underlying disease of hemophilia A.

It should be noted that it was not explicitly stated in the CRF that only a causal relationship to ReFacto AF® but not to the underlying hemophilia A was to be assessed.

The AE of eyelid edema occurred approximately 3 weeks after the patient's enrolment in this study. It was of mild intensity and resolved without countermeasures within 1 day and did not recur upon further exposure (Listing 15.9.6).

Table 14. All adverse events assessed as "related" by the treating physician

MedDRA system organ class Preferred term	On-demand (N = 22) n (%)	Prophylaxis (N = 77) n (%)	Intermediate prophylaxis (N = 2) n (%)	Total (N = 101) n (%)
Any adverse reaction	**2 (9.1)**	**7 (9.1)**	**0 (0.0)**	**9 (8.9)**
Eye disorders	**1 (4.5)**	**-**	**-**	**1 (1.0)**
Eyelid oedema	1 (4.5)	-	-	1 (1.0)
Injury, poisoning and procedural complications	**1 (4.5)**	**4 (5.2)**	**-**	**5 (5.0)**
Contusion	1 (4.5)	-	-	1 (1.0)
Eyelid injury	-	1 (1.3)	-	1 (1.0)
Face injury	-	1 (1.3)	-	1 (1.0)
Joint injury	1 (4.5)	1 (1.3)	-	2 (2.0)
Limb injury	1 (4.5)	3 (3.9)	-	4 (4.0)
Mouth injury	-	1 (1.3)	-	1 (1.0)
Traumatic haemorrhage	1 (4.5)	2 (2.6)	-	3 (3.0)
Musculoskeletal and connective tissue disorders	**-**	**3 (3.9)**	**-**	**3 (3.0)**
Haemophilic arthropathy	-	1 (1.3)	-	1 (1.0)
Muscle haemorrhage	-	1 (1.3)	-	1 (1.0)
Soft tissue haemorrhage	-	1 (1.3)	-	1 (1.0)
Skin and subcutaneous tissue disorders	**1 (4.5)**	**-**	**-**	**1 (1.0)**
Dry skin	1 (4.5)	-	-	1 (1.0)
Vascular disorders	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Haemorrhage	-	1 (1.3)	-	1 (1.0)

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

10.6.3. All serious adverse events

About one third of the patients (31.8% treated on-demand, 32.5% on prophylaxis and both patients with intermediate prophylaxis) experienced SAEs (Table 15.9.3). Most of the SAEs occurred in single patients only.

Table 15 shows that the highest incidences were observed for SAEs referring to the system organ classes "infections and infestations" (8.9%), "musculoskeletal and connective tissue disorders" (8.9%) and "gastrointestinal disorders" (7.9%). Overall, the most frequent SAE on a preferred term level was "appendicitis", which occurred in 3 patients.

Three patients died during this study (a 53-year-old patient died from sepsis and multiple organ failure, a 2-year old child died from pneumonia, and in a 67-year-old patient the cause of death was unknown). None of these deaths were related to the treatment with ReFacto AF®.

By-patient listings of all SAEs and deaths are provided in Listing 15.9.7 and 15.9.8.

Table 15. All serious adverse events by MedDRA system organ class (and preferred term, if present in at least 2 patients [2%] of the total group)

MedDRA system organ class Preferred term	On-demand (N = 22) n (%)	Prophylaxis (N = 77) n (%)	Intermediate prophylaxis (N = 2) n (%)	Total (N = 101) n (%)
Any serious adverse event	**7 (31.8)**	**25 (32.5)**	**2 (100.0)**	**34 (33.7)**
Blood and lymphatic system disorders	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Congenital, familial and genetic disorders	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Eye disorders	**1 (4.5)**	**-**	**-**	**1 (1.0)**
Gastrointestinal disorders	**2 (9.1)**	**5 (6.5)**	**1 (50.0)**	**8 (7.9)**
Inguinal hernia	1 (4.5)	1 (1.3)	-	2 (2.0)
Tongue haemorrhage	1 (4.5)	1 (1.3)	-	2 (2.0)
Vomiting	-	1 (1.3)	1 (50.0)	2 (2.0)
General disorders and administration site disorders	**-**	**1 (1.3)**	**1 (50.0)**	**2 (2.0)**
Hepatobiliary disorders	**-**	**1 (1.3)**	**1 (50.0)**	**2 (2.0)**
Hepatic cirrhosis	-	1 (1.3)	1 (50.0)	2 (2.0)
Infections and infestations	**1 (4.5)**	**8 (10.4)**	**-**	**9 (8.9)**
Appendicitis	-	3 (3.9)	-	3 (3.0)
Injury, poisoning and procedural complications	**1 (4.5)**	**3 (3.9)**	**-**	**4 (4.0)**
Laceration	-	2 (2.6)	-	2 (2.0)
Investigations	**1 (4.5)**	**-**	**-**	**1 (1.0)**
Musculoskeletal and connective tissue disorders	**1 (4.5)**	**6 (7.8)**	**2 (100.0)**	**9 (8.9)**
Haemophilic arthropathy	1 (4.5)	-	1 (50.0)	2 (2.0)
Osteochondrosis	-	2 (2.6)	-	2 (2.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**-**	**3 (3.9)**	**1 (50.0)**	**4 (4.0)**
Nervous system disorders	**-**	**2 (2.6)**	**-**	**2 (2.0)**
Psychiatric disorders	**2 (9.1)**	**-**	**-**	**2 (2.0)**
Renal and urinary disorders	**-**	**3 (3.9)**	**-**	**3 (3.0)**
Haematuria	-	2 (2.6)	-	2 (2.0)
Respiratory, thoracic and mediastinal disorders	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Skin and subcutaneous tissue disorders	**-**	**1 (1.3)**	**-**	**1 (1.0)**
Vascular disorders	**-**	**2 (2.6)**	**1 (50.0)**	**3 (3.0)**
Haemorrhage	-	2 (2.6)	-	2 (2.0)

Source: Table 15.9.3

10.6.4. All serious adverse events with causal relationship

As assessed in the medical judgment of the investigator, none of the SAEs were reported as related to ReFacto AF® (Table 15.9.4).

10.6.5. Adverse events of special interest

Inhibitor development was the adverse event of special interest in this study.

With 2 exceptions (1 each at post-baseline visits 1 and 2), inhibitor testing was exclusively performed either with the Bethesda assay or its Nijmegen modification (Table 15.6.8).

Two different definitions were used for the assessment of "inhibitor positivity"

1. Inhibitor levels >0.6 BU and/or
2. Inhibitor levels exceeding the reference value at the laboratory.

The clinical relevance of an inhibitor titer was based on the medical judgement of the investigator.

In totality, 97 patients underwent inhibitor testing during the course of the study with 7 patients meeting at least one of the above criteria. Three (3) patients (3.1%) met the protocol specified inhibitor titer of >0.6 BU. Two patients (both PTPs on routine prophylaxis) tested positive (>0.6 BU) at baseline (Tables 15.6.1 and 15.6.2; Listing 15.6.6). Specifically, both patients had titers of 1.0 BU, but neither were considered clinically relevant by the investigator (local reference value: 1.0 BU). The third patient with an inhibitor was a 33-year old PTP on an on-demand treatment regimen who had an inhibitor titer of 0.8 BU at post-baseline visit 8. Subsequent inhibitor testing was negative. Notably, the investigator did not rate this positive inhibitor test as clinically relevant or related to study drug, but the finding was reported as an SAE (Listing 15.9.6).

Five (5) patients, including the patient with the inhibitor titer 0.8 BU (see above), had inhibitor titers higher than the reference range at the laboratory where the test was performed [4]. All patients were PTPs (3 on-demand and 2 prophylaxis), and in 2 of them, the inhibitor titers were higher than the reference value already at baseline. With the exception of the patient with the inhibitor titer of 0.8 BU, none of the other 4 patients had an inhibitor titer >0.6 BU. The investigator rated each of the afore-mentioned cases as clinically not relevant.

None of the 3 PUPs developed an inhibitor (Tables 15.6.3 and 15.6.4).

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. One other patient was assessed by the physician as having a clinically relevant inhibitor, despite not testing positive (0.1 BU/mL, reference value: 0.4 BU/mL). The inhibitor titer in this patient was not reported as an (S)AE, as it did not meet the protocol definition for inhibitory positivity (Listing 15.9.6).

During the study, i.e., post-baseline, none of the patients were scheduled for an immune tolerance therapy (Table 15.6.7).

[4] The reference value was set to "0", if it was not reported (conservative approach).

11. DISCUSSION

11.1. Key results

A total of 101 male, mostly Caucasian hemophilia A patients of all age groups (median age: 18.0 years; range: 1-72 years) participated in this study. The majority of patients (88.1%) had moderate hemophilia A with a residual FVIII:C between 1% and 5%. All but 3 patients were PTPs and had already accumulated >100 EDs. Accordingly, more than 75% of the patients (N=77) were on prophylaxis treatment, and most of the patients (92.1%) had used moroctocog alfa for FVIII substitution in the previous 12 months. An on-demand treatment regimen was only followed by young children and adults (N=22 in total), but not by older children/ adolescents. Two further patients used intermediate prophylaxis.

Nine patients on prophylaxis (11.7%) had a history of inhibitors to FVIII. In 6 of these patients, the inhibitor was detected after 0-60 EDs (for the remaining 3 patients, this information was missing). Four of the patients had already undergone an immune tolerance therapy, which was successful in all cases.

Concomitant diseases were reported for 35.6% of the total population, and 30.7% of all patients were reported with chronic diseases. Disregarding the 2 patients constituting the "intermediate prophylaxis" group, the percentage of patients with any concomitant diseases was markedly lower in the prophylaxis group than in the on-demand group (29.9% vs. 50.0%). This difference was mainly driven by the higher proportion of on-demand treated patients with musculoskeletal and connective tissue disorders (22.7% vs. 5.2% in the prophylaxis group), such as (hemophilic) arthropathy and osteoarthritis. This means that patients treated on-demand had more joint complications than patients on prophylaxis treatment. The most prevalent chronic viral infection was hepatitis C, present in 22.5% of the total population.

The mean observation period per patients was 3.6 ± 1.9 years (median: 3.6 years; range: 0.2 – 7.3 years) and similar in the on-demand and prophylaxis groups. 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 ReFacto AF® dose recommended by the treating physicians for patients on on-demand treatment was 23.0 ± 8.0 IU/kg (median: 22.0 IU/kg), which was slightly lower than the recommended dose for patients on prophylaxis treatment (26.7 ± 8.4 IU/kg; median 25.8 IU/kg; median number of weekly infusions: 3). 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 nearly 3-fold lower annual bleed rate than patients treated on-demand (median: 3.3 vs. 8.9 bleeds/year; $p<0.001$, negative binomial model). In particular the ABR for joint bleeds, which constituted the majority of bleeds, was lower on prophylaxis treatment (median: 1.1 vs. 6.2 bleeds/year; $p<0.001$, negative binomial model). The beneficial effect of prophylaxis was also observed for the ABRs of soft tissue and other bleeds, which were lower in patients utilizing

prophylaxis versus those utilizing on-demand treatment only (0.5 vs. 1.6 bleeds/year and 0.5 vs. 0.6 bleeds/year, respectively).

Regarding the influence of the treatment regimen on the extent of absence from school or work, the number of missed days appeared to decrease over time only in the prophylaxis group ($p<0.001$; Wilcoxon sign test).

With single exceptions, investigators and patients were either "very satisfied" or "satisfied" with the treatment success and the handling of ReFacto AF®, respectively. These positive assessments persisted throughout the study.

In none of the patients (N=3) reporting inhibitor titers above 0.6 BU or patients (N=5) reporting inhibitor titers exceeding the upper reference value of the local laboratory the inhibitor values were assessed by the investigator as being clinically relevant. Additionally, none of these patients were scheduled to undergo immune tolerance therapy.

Analysis of the incidences of (S)AEs and those rated as "related" did not reveal any new or unexpected safety findings. A total of 76 patients (75.2%) 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" (51.5%), "musculoskeletal and connective tissue disorders" (43.6%), and "infections and infestations" (31.7%).

AEs denoted by the investigators as "related" occurred in 8.9% of the patients. With the exception of an eyelid edema, which occurred in a patient treated on-demand, all other "related" AEs referred to various types of injuries, hemorrhages and hemorrhagic arthropathy, i.e., conditions related to the patients' underlying disease of hemophilia A. The treatment-related event of eyelid edema was assessed as mild in severity, occurred approximately 3 weeks after enrolment and resolved without countermeasures on the same day. It did not recur upon further exposure.

The incidence of SAEs was 33.7% 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 "infections and infestations" (8.9%), "musculoskeletal and connective tissue disorders" (8.9%) and "gastrointestinal disorders" (7.9%). Overall, the most frequent SAE on a preferred term level was "appendicitis", which occurred in 3 patients on prophylaxis treatment. Three patients died during this study. None of the SAEs/deaths had a causal relationship to the treatment with ReFacto AF® in the medical judgement of the investigator.

Overall, none of the patients discontinued the study because of treatment-related AEs or SAEs, LETE or inhibitor development.

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 due to decreasing patient participation, e.g. drop outs and lost to follow-up.

Annualization of bleed data is a common method for the assessment of the effectiveness of treatment in hemophilia 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 at least once visited by an experienced clinical research associate for data verification and identification and resolution of potential problems. In addition, 8 of the 23 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 AEs, in particular SAEs, were reported.

11.3. Interpretation

A representative sample of patients with hemophilia A, i.e., all age groups, all disease severities (predominantly moderate or severe), on-demand and prophylactically treated patients, including 3 PUPs, participated in this study. Most of the PTPs (the majority with >100 EDs) had used moroctocog alfa within the previous year.

The ReFacto AF® doses recommended by the treating physicians were within the dose range recommended in the current version of the ReFacto AF® Summary of Product Characteristics (SmPC). Both mean and median observation period was 3.6 years per patient. During this period, only 1 PTP (1%) developed a post-baseline inhibitor titer >0.6 BU (specifically 0.8 BU), and it was assessed as not clinically relevant by the investigator. No change in inhibitor titers was observed in the 2 patients with pre-existing low-titer inhibitors at baseline.

Data on (S)AEs did not suggest any safety issues. Most of the non-serious AEs identified by the investigators as “related” were various types of trauma bleeds and conditions associated with hemophilia. Aside from these, there was one event of eyelid edema assessed as mild and related to treatment with ReFacto AF®. The event was transient and did not recur on re-exposure to ReFacto AF®.

The effectiveness of treatment was confirmed with the comparison of the ABRs between the groups of patients treated on-demand versus prophylaxis. In particular joint bleeds, which are the main reason for long-term joint damages and resulting disability in patients with hemophilia, were effectively prevented on prophylaxis treatment (median ABR: 1.1 joint bleeds/year).

Overall, both patients and investigators were (very) satisfied with the use of ReFacto AF®.

11.4. Generalizability

The study results are based on a sample of 101 patients. In contrast to randomized controlled trials, patients were not selected by any study-specific eligibility criteria. Although the sample size of 101 patients appears small, it must be taken into account that hemophilia A is a rare disease worldwide. Nevertheless, considering a mean observation period of 3.6 years per patient, more than 350 patient years were documented in this study. Thus, the study population is expected to reflect the "real-life" situation of hemophilia A patients in Austria and Germany.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

Overall, the data collected in this study showed that treatment with ReFacto AF® is effective and does not impact the known positive benefit-risk profile also under routine clinical conditions.

14. REFERENCES

1. Pollmann H, Externest D, Ganser A et al. Efficacy, safety and tolerability of recombinant factor VIII (REFACTO) in patients with haemophilia A: interim data from a postmarketing surveillance study in Germany and Austria. Haemophilia 2007; 13(2):131-143

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15.8 CONCOMITANT MEDICATIONS

15.8.1 Concomitant medications at baseline

15.8.2 Changes since last visit

15.8.3 Discontinued medications

15.8.4 Medications with dose reduction

15.8.5 Medications with dose increase

15.8.6 Newly prescribed medications

15.9 ADVERSE EVENTS

15.9.1 Adverse events by MedDRA primary system organ class and preferred term

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 event listing

15.9.7 Serious adverse event listing

15.9.8 Listing of deaths

15.9.9 Adverse events listing for patients who are excluded from any analysis

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

15.9.11 Non-serious adverse event listing