1. NIS INFORMATION

Title	Non-interventional study (NIS) of long term observation of haemophilia A treatment with Haemoctin®
Version identifier of the final study report	Final Version 1.0
Date of last version of the final study report	13-Apr-2017
Study Number	Biotest NIS-013
ENCEPP register number	8063
Active substance	Coagulation factor VIII ATC code B02BD02
Medicinal product	Haemoctin®
Marketing authorisation holder(s)	Biotest Pharma GmbH Landsteinerstr. 5, 63303 Dreieich, Germany
Research question and objectives	The aim of the NIS was to collect data on safety, tolerability, and effectiveness of Haemoctin® during long-term treatment in the context of the usual clinical therapy of patients. The following research questions were investigated: • What is the influence of a long-term or even decades long continuous treatment with Haemoctin® on the health status of patients? • Is it possible to reduce efficiently the bleeding risk over several years? • What is the risk of development of inhibitors under treatment with Haemoctin® for several years in previously untreated patients (PUPs) and previously treated patients (PTPs)?
Country(-ies) of study	Germany and Hungary
Authors	[redacted] Metronomia Clinical Research GmbH Paul-Gerhardt-Allee 42, 81245 München, Germany
	[redacted], Corporate Drug Safety Biotest AG [redacted], Corporate Medical Affairs Biotest AG

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3. ABSTRACT

Title	Non-interventional study (NIS) of long term observation of haemophilia A treatment with Haemoctin®
Keywords	Non-interventional study (NIS), long term documentation, haemophilia A, factor VIII deficiency, Haemoctin®
Rationale and Background	This long term observation was initiated to collect data on the long term safety and effectiveness while using Haemoctin® in the prophylactic or on-demand setting to provide an enhanced database for the long term use of Haemoctin®.
Research question and objectives	The following research questions were investigated: • What is the influence of a long-term or even decades long continuous treatment with Haemoctin® on the health status of patients? • Is it possible to reduce efficiently the bleeding risk over several years? • What is the risk of development of inhibitors under treatment with Haemoctin® for several years in previously untreated patients (PUPs) and previously treated patients (PTPs)?
Study design	Prospective, multicentre, bi-national, non-interventional, single arm, long term safety and effectiveness study
Setting	25 German and 8 Hungarian haemophilia centres
Subjects and Study Size	Enrolled patients: 164 Treatment period documentation: May 1998 until December 2015. Full analysis set: 163 patients (for 1 patient no records of Haemoctin® administration were available in the CRF)
Variables and data sources	Demographic data, assessments of effectiveness, ease of use, tolerability by physician and patient, selected biochemistry and haematology parameters including factor VIII inhibitors, adverse events and serological virus testing were captured in paper CRFs. In addition, dosing regimen of Haemoctin® and reasons for application were captured in diaries.
Results	**Study population** 164 patients enrolled and 163 analysed, 52 patients in 8 Hungarian and 111 patients in 25 German centres. 143 patients were PTPs and 20 patients were PUPs. A subgroup of 133 patients had severe haemophilia. All patients were male. Most PUPs (mean age 5.2 (SD 14.2) years) were under 6 years of age (85.0%) when they had their first treatment (i.e. Haemoctin® treatment), whereas the majority of PTPs (mean age 28.8 (SD 17.1) years) were between 18 and 64 years old (67.8%).

	Treatment Long term documentation of treatment was performed over 1201 patient years with a mean documentation time of 7.46 years per patient. The proportion of patients receiving treatment for prophylaxis increased from 41.1% (data from 90 patients) in 2003 to 65.7% (data from 67 patients) in 2015. Most of the PUPs received their treatment as prophylactic treatment throughout the NIS. The median Haemoctin® exposure dose (HED) was 28.8 IU/kg BW. The HED did not depend on the reason for treatment (i.e. bleeding, follow-on treatment, prophylaxis), and did not show relevant differences between the total population and patients with severe haemophilia. **Effectiveness** Overall, patients had a mean annual bleeding rate of 13.3 (SD: 16.6, median 6.1). The annual bleeding rate was considerably lower for patients who were treated prophylactically with Haemoctin® compared to those patients treated on demand (type of treatment = prophylaxis: median: 3.2; type of treatment = on demand: median: 24.5). The annual bleeding rate decreased over time, from a median annual bleeding rate of 20.7 from 1998 to 2002 to 5.2 from 2008 to 2012 and finally to a median of 2.6 bleedings per year from 2013 to 2015. Investigators assessed the therapeutic effect of treatment as 'as expected' with nearly all (99.29%) treatments, which was very similar in the indications of bleeding, prophylaxis and surgery and slightly lower for follow-on treatments. Also, the global assessment of ease of use was assessed as "very good" by both the investigators (mean (SD) 1.44 (0.54)) and the patients (mean (SD) score 1.48 (0.52)) which was independent from the reason for treatment and severity of haemophilia. **Safety / Tolerability** During the course of the study, AEs were reported in a total of 99 patients (60.7%) by the time of the cut-off of this study. The most frequent and clinically relevant events were gastrointestinal haemorrhage (13 events in 11 patients, all not related), and anti-factor VIII antibody positive (10 events in 9 patients). Further, tooth extraction (13 events in 11 patients), and fall (9 events in 8 patients) were frequently reported events. The incidence of FVIII inhibitor formation in all PUPs within this NIS was 15% (3/20), and 5% (1/20) of high-titre inhibitors. In only 1 PUP (1/20 PUPs), clinically relevant inhibitors developed during the period of the NIS. The incidence of related FVIII inhibitor formation in all PTPs in this NIS was 2.8% (4/143), and 1.4% (2/143) of high-titre inhibitors. None of the developed FVIII inhibitors in PTPs, related to Haemoctin®, were clinically relevant. Two cases (1 PUP

	and 1 PTP) of FVIII inhibitor formation were assessed as clinically relevant. The PTP had been included into the study with pre-existing high-titre FVIII inhibitors, caused by another FVIII product, to perform an immune tolerance induction (ITI) with Haemoctin®. In both cases, ITI was successfully performed with Haemoctin®. 43 serious bleeding episodes (considered bleedings of high relevance) were identified in 29 patients (26 PTPs and 3 PUPs). One case only was assessed by the respective investigator and the marketing authorisation holder (MAH) to be related to the Haemoctin® treatment. None of the serious bleeding events was associated with a clinically relevant formation of FVIII inhibitors. Overall, Haemoctin® was well tolerated.
Discussion	A broad proportion of patients with haemophilia A recorded a very good effectiveness assessment with a low rate of bleeding events during the long-term documentation of treatment with Haemoctin® under everyday clinical practice conditions. The risk of bleeding decreased over the documentation years and a low incidence of inhibitor formation was observed over the long lasting documentation time of 1202 patient years. The annual bleeding rate was considerably lower for patients who were treated prophylactically with Haemoctin® compared to those patients treated on-demand. The regimen for Haemoctin® changed from on-demand treatment to prophylactic treatment over time. There were data recording limitations especially at the beginning of the study, mostly due to the old NIS monitoring system 17 years ago. Therefore, underreporting of AEs related to bleedings (e.g. pain or causes for (traumatic) bleedings, elective procedures and underlying haemophilia and related co-morbidities (e.g. arthropathy) cannot be ruled out. However, the documentation and reporting of clinically relevant, e.g. FVIII inhibitor formation or thromboembolic events (TEEs), are assumed to be reported completely. In addition, the regulatory requirements were changed during the study time. New regulations were becoming active for e.g. the EU good pharmacovigilance praxis (GVP) regulations. Overall, long-term and continuous treatment with Haemoctin® was well tolerated. The risk of bleeding decreased over the documentation years and a low incidence of inhibitor formation in PTPs and PUPs was observed over the long lasting documentation time of 1202 patient years. No new and formerly unknown information with regard to the safety and tolerability of Haemoctin® was reported during the study period confirming the positive benefit–risk profile of Haemoctin® in the indication treatment and prophylaxis of bleeding in patients with haemophilia A. The benefit-risk profile of Haemoctin® remains clearly favourable.
Marketing Authorization Holder	Biotest Pharma GmbH Landsteinerstr. 5 63303 Dreieich, Germany

4. LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
Ag	Antigen
AP	Alkaline phosphatase
ATC	Anatomical Therapeutic Chemical classification system
BU	Bethesda unit
BW	Body weight
CD4	Subpopulation of T-lymphocytes
CD8	Subpopulation of T-lymphocytes
CRF	Case report form
ED	Exposure days
F VIII	Factor VIII
GVP	Good pharmacovigilance practices
HAV	Hepatitis A virus
HBc	Hepatitis B virus core-antigen
HBs	Hepatitis B virus surface-antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Haemoctin® exposure dose
HIV	Human immunodeficiency virus
ICSR	Individual case safety report
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ITI	Immune tolerance induction
IU, I.U.	International unit
LDH	Lactate-Dehydrogenase
MAH	Marketing authorisation holder
MSDB	Master Safety Database

NIS	Non-interventional study
PMS	Post-marketing surveillance
Ph.Eur.	European Pharmacopoeia
PTP	Previously Treated Patients
PUP	Previously Untreated Patients
PV	Pharmacovigilance
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SD	Standard deviation
SGOT	Aspartate aminotransferase
SGPT	Alanine aminotransferase
TEAE	Treatment emergent adverse event
TEE	Thromboembolic event
TNBP	Tri-n-butyl-phosphate
γ-GT	Gamma glutamyl transferase

5. STUDY SITES

See Appendix 1.5 of this report for study sites in Germany and Hungary.

6. OTHER RESPONSIBLE PARTIES

Not applicable.

7. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	-	01-May-1998	
End of data collection	31-Dec-2018	30-Jun-2016	A new NIS in the same indication was started by the MAH with electronic CRFs instead of paper.
Registration in the EU ENCEPP register	-	27-Dec-2014	
Interim report	-	11-Apr-2002	
Interim report	-	12-Jan-2006	
Interim report	-	19-Oct-2010	
Final study report	30-Jun-2019	13-Apr-2017	

8. RATIONALE AND BACKGROUND

Haemophilia A is a congenital deficiency of coagulation factor VIII and needs to be treated for the whole life with factor VIII preparations. Older patients normally apply a factor VIII product when a bleeding occurs whereas paediatric and adolescent patients are treated prophylactically. This prophylactic treatment is mostly continued when these patient grow older. A prophylactic treatment consists of two to three weekly applications of the factor VIII preparation.

This long term observation was initiated to collect real life data on the long term clinical practice and daily routine treatment of patients with haemophilia A, including safety and effectiveness while using Haemoctin® in the prophylactic or on-demand setting to provide an enhanced database for the long term use of Haemoctin®.

Haemoctin® is produced from human plasma which complies with the respective Ph.Eur. monograph. During manufacture, the cryoprecipitate is separated from a representative

plasma pool and purified. Haemoctin® is presented as a powder and solvent for solution for injection in two strengths and three pack sizes: Haemoctin® 250 or 500 contains approximately 50 IU/ml human coagulation factor VIII when reconstituted with 5 or 10 ml sterilised water for injections. Haemoctin® 1000 contains approximately 100 IU/ml human coagulation factor VIII when reconstituted with 10 ml water for injections. The specific activity is approximately 100 IU per milligram of total protein. Haemoctin® does not need any additive proteins. The stabilization of the factor VIII molecule is obtained by the physiological carrier protein (von Willebrand factor).

The manufacturing process of Haemoctin® developed by Biotest Pharma GmbH, Dreieich, Germany, includes two virus eliminating / removal steps using solvent / detergent (Polysorbate 80/TNBP) combined with a monitored heat treatment at 100°C. These two steps guarantee a safe factor VIII preparation in particular with regard to HIV, hepatitis A, B and C virus.

Haemoctin® is a human plasma-derived coagulation factor VIII concentrate (ATC code: B02BD02) for substitution therapy in patients with haemophilia A (congenital factor VIII deficiency). Haemoctin® is a next generation product of the previous factor VIII concentrate Factor VIII Biotest 250, 500 and 1000 which was registered by the German Health Authority in 1991.

The initial marketing authorisations were granted to Biotest Pharma GmbH in November 1991 in Germany as "Factor VIII Biotest 250, 500, 1000" and "Antihämophiles Globulin Biotest 250, 500, 1000". In April 1993 the names of these medicinal products were changed to "Haemoctin SDH 250, 500, 1000" and "AHG Biotest SDH 250, 500, 1000”.

The marketing authorisations for the latter product were transferred to Intersero GmbH on 11-Jun-1996 along with changing the product's name to "Faktor VIII SDH Intersero 250, 500, 1000”. The marketing authorisation held by Biotest in Germany was used for a mutual recognition procedure in 2007. Further countries were included in a repeat-use procedure in 2009.

Haemoctin® is available in two strengths (50 and 100 IU/ml) and three package sizes with clotting factor VIII activities of 250 I.U., 500 I.U. and 1000 I.U., respectively. Further ingredients are glycine, sodium-, calcium-, chloride- and citrate-ions and sterilised water for injections.

After reconstitution in 5 ml (Haemoctin® 250) or 10 ml (Haemoctin® 500, 1000) of sterilised water for injections, respectively, the preparation is injected intravenously.

Haemoctin® is approved for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

Data on successfully performed immune tolerance induction (ITI) have been collected in patients with haemophilia A who have developed inhibitors to factor VIII.

9. RESEARCH QUESTION AND OBJECTIVES

The aim of the NIS was to collect data on safety, tolerability, and effectiveness of Haemoctin® during long-term treatment in the context of the usual clinical therapy of patients.

The following research questions were investigated:

- What is the influence of a long-term or even decades long continuous treatment with Haemoctin® on the health status of patients?
- Is it possible to reduce efficiently the bleeding risk over several years?
- What is the risk of development of inhibitors under treatment with Haemoctin® for several years in previously untreated patients (PUPs) and previously treated patients (PTPs)?

10. AMENDMENTS AND UPDATES

This NIS was conducted over a very long observation period in three study phases. First documentation started with PMS I in August 1993 and ended in May 2001. PMS I is not part of this study report. Documentation with a revised version of the study started with PMS II in May 1998. The study was updated in July 2010 with PMS III. This NIS report contains the data from PMS II and PMS III from May 1998 till end of December 2015. Data documentation for PMS III was completed at 31 June 2016.

Number	Date	Section of study	Reason
1	01-May-1998	PMS II	Study parameters to be documented were updated. Study was restarted with PMS II.
2	01-Jul-2010	PMS III	Inclusion of patient information informed consent and ethic approval of the NIS. Update of the data collected.

11. RESEARCH METHODS

11.1 Study Design

The NIS was designed as an open-label prospective multicentre post-marketing surveillance / non-interventional study according to §67 German Drug Law and was conducted in Germany and Hungary.

With the last update of the NIS, prior to enrolment of new patients or prior to further documentation of already included patients, formal information about the NIS was provided and written informed consent was obtained by the treating physician. The collection of data was performed in the context of routine treatment of patients with congenital haemophilia A. Parameters outside the clinical routine were not collected.

The observation period per patient was planned to be at least 12 months. It was intended to continue the observation for several years. Visit schedules were according to centre specific routine. After the initial visit, investigators were asked to document at least two further examinations per year if possible. In addition, a yearly final visit was to be documented, which was performed within a normal routine visit of a patient.

11.2 Setting

One non-interventional study (NIS; Post-marketing surveillance, PMS) with Haemoctin® was sponsored by the marketing authorisation holder (MAH) Biotest. The study was a multicentre post-marketing surveillance study according to §67 German Drug Law conducted in Germany and Hungary and observed patients with severe haemophilia A. Data were collected over a very long observation period. Data included in this report are from May 1998 until December 2015. In the majority of applications factor VIII products were administered at home, but also applications at the doctor's office and in the clinic were documented.

11.3 Subjects

The NIS was performed in patients with diagnostically confirmed haemophilia A.

Patients known to exhibit a higher incidence of intolerability reactions after administration of plasma products, especially clotting concentrates were not to be enrolled in the NIS.

Concurrent diseases were enquired before enrolment in the NIS.

Previously treated patients (PTPs) and previously untreated patients (PUPs) were enrolled in the NIS. PUPs are defined as those patients who have never been treated with clotting factor products (except previous exposure to blood components). In our NIS the PUPs had not received treatment for their haemophilia with factor VIII products before inclusion into the NIS.

During the observation period the patients were treated with the medicinal product i.e. Haemoctin® in case of prophylaxis and treatment on-demand. The reason for treatment was documented as prophylaxis, bleeding or follow-on treatment.

11.4 Variables

All outcomes, exposures, potential confounders and effect modifiers, including operational definitions and diagnostic criteria, if applicable were documented. If the study addresses medicinal product(s), information relevant to the interpretation of the results

should be provided on the product, e.g. route and mode of administration, dose or duration of exposure.

As it is required in non-interventional settings, within this NIS, the applied routine treatment conditions of FVIII in medical practice were observed. Therefore, the method and frequency of FVIII inhibitor testing were not predefined in the observation plans. FVIII inhibitor testing was performed periodically. According to the NIS plan, patients were expected to show up for performing routine screenings at least via one annual visit at the haemophilia treatment centres. Three to four routine visits per year were performed by most of the patients.

In case of bleeding events due suspicion of lack of efficacy e.g. due FVIII inhibitor formation, this had to be reported immediately to the drug safety department of the MAH. In the case report forms (CRFs) the result of the FVIII inhibitor tests was documented in BU/ml (Bethesda Unit per millilitre). Within the NIS Haemoctin a FVIII inhibitor test was positive when the value was over the normal range (≥ 0.7 BU). A few centres defined the FVIII inhibitor positive according to local definitions (limited by sensitivity of the test used to ≥ 1.0 BU/ml).

Positive FVIII inhibitor tests were not repeated to confirm the positive result. The first positive FVIII inhibitor test was reported as adverse event. For all included patients in the NIS, at least clinically relevant events including lack of efficacy, during normal clinical practice of patients were detected within this NIS.

The following anamnestic data were assessed at admission (visit 1):

- Demographic data: age, sex, ethnicity.
- Body measurements: body height, body weight.
- History of haemophilia including the date of the initial diagnosis, factor VIII baseline activity, previous treatment of haemophilia. Details of previous therapy were to be documented if applicable
- Family history including the questions whether father or mother was currently suffering from immunodeficiencies and whether they had been suffering from infections after previous transfusion.
- Hepatitis A and Hepatitis B vaccination, if ‘yes’ titre should have been documented.
- Consumption habits concerning alcohol, tobacco, and recreational drugs.
- Concomitant diseases and concomitant medication.
- Status of possible inhibitors against factor VIII (Bethesda test).
- Laboratory assessments with respect to selected clinical chemistry and haematology parameters (haemoglobin, haematocrit, platelets, glucose, bilirubin, AP, SGPT, SGOT, γ-GT, LDH, CD4- and CD8-positive lymphocytes) were collected. Values had to be classified whether they were deviating from normal range or not. Comments were to be provided on deviations from normal range.

- Serological assessments were to be documented with respect to anti-HBs, HBs-Ag, anti-HBc, anti-HCV, anti-HAV (IgG, IgM) and anti-HIV-1/2. Positive results on anti-HIV had to be confirmed by Western Blot Analysis.

At each haemophilia monitoring visit the following assessments were documented:

- Date and batch numbers of medicinal product administered.
- The quantity of administered medicinal product was recorded as dose.
- The reason for administration (prophylaxis or bleeding or follow-on treatment).
- The site, severity and treatment of bleeding if applicable
- Type of treatment as 'self-treatment' or 'by doctor'
- Assessment whether the expected therapeutic effect had been reached was indicated as ‘yes’ or ‘no’.
- At each haemophilia monitoring visit patients had to assess their overall condition.

The investigator judged whether an adverse event (AE) had occurred and questioned the patient about possible AEs. AEs were recorded according to:

- diagnosis or signs/symptoms
- date of occurrence
- course: once or occasional
- intensity: mild, moderate, severe, not applicable
- outcome: completely recovered, improved, unchanged, deteriorate, died, unknown
- end or duration of event
- causality classified in a binary system related and not related
- measures:
    - on study medication: unchanged, dose reduction, temporarily interrupted, permanently discontinued
    - on concurrent medication: continued, changed, discontinued, other drug treatment, non-drug treatment
- seriousness: yes, no

In case of serious adverse events (SAE) an additional form had to be filled in concerning:

- demographic data
- body weight
- interval between application of the medicinal product and onset of symptoms
- dosage, frequency, route of application, start and end of treatment

- nature of the SAE event: death, life-threatening, hospitalization, prolongation of hospitalization, persistent or significant disability / incapacity, results in a congenital anomaly / birth defect, other medically important condition
- death, life-threatening, hospitalization, prolongation of hospitalization, incapacity for employment, consequence of overdose, tumour, congenital malformation, abnormal laboratory values
- assumed cause: study product, lack of efficacy, discontinuation of study product, concomitant medication, concomitant sickness, other
- description of the event, relevant data from patient's history
- if applicable: cause of death and whether an autopsy was performed.

Bleedings: There was no need for documentation of bleedings as AE or SAE since prevention of bleeding was an effectiveness criterion of the study. Bleedings were to be reported only in the patient's diary, with the exception that lack of efficacy or an association with an inhibitor formation was assumed. Despite this regulation for documentation of bleedings in the observation plan, most serious bleedings were reported as an SAE. All these bleedings were analysed with respect to FVIII inhibitor formation and are presented in Section 12.6.6 and more detailed in Appendix 2.1, Section 2.

The following laboratory variables were assessed:

- Blood Chemistry
  - Bilirubin
  - AP
  - SGPT
  - SGOT
  - γ-GT
  - LDH
- Haematology
  - Haematocrit
  - Platelets
  - Factor VIII inhibitory antibodies
  - CD4-positive lymphocytes
  - CD8-positive lymphocytes

Values had to be classified whether they were deviating from normal range or not. Comments were to be provided on deviations from normal range.

- Serological Parameters

- Anti-HBs
- HBs-Ag
- Anti-HBc
- Anti-HCV
- Anti-HAV: IgG, IgM
- Anti-HIV-1/2; Positive results on anti-HIV had to be confirmed by Western Blot Analysis

The yearly final assessment was performed documenting the following items:

- NIS End: The date of the end of the NIS was documented, and in cases of a premature discontinuation of the NIS also the reason of premature discontinuation. This was not done, however, for the newer versions of the CRF.
- Global Assessments on Effectiveness: Both the investigator and the patient did global assessments on effectiveness of the study product following a rating of ‘very good’, ‘good’, ‘moderate’, ‘poor’, or ‘none’.
- Global Assessments on Tolerability: Both the investigator and the patient did global assessments on tolerability of the study product following a rating of ‘very good’, ‘good’, ‘moderate’, or ‘poor’.
- Global Assessments on Ease of Use: Global assessments on ease of use of the study product were done by both the investigator and the patient following a rating of ‘very good’, ’good’, ’satisfactory’, ’adequate’, or ’poor’.

11.5 Data Sources and Measurement

Data were entered by a single person from the paper CRFs and diaries into the NIS database at Metronomia Clinical Research GmbH. Several versions of CRFs were used throughout the study and the database was adapted accordingly for each version of the CRF.

11.6 Bias

Data was presented as captured in CRFs. No source data validation as typically performed for interventional trials was performed. Only data obtained in clinical routine and not defined by protocol were documented. For this reason, some data on different parameters are missing. A plausibility check for the data was done only at study end (see also Section 11.8).

11.7 Study Size

It was planned to continue the NIS until a maximal number of patients of 300 patients would be reached or until December 2018. Until December 2015 a total of 164 patients had been enrolled. No formal sample size of power calculation was performed for this NIS.

11.8 Data Transformation

The age was calculated based on the actual date of birth, if available. If only the month and year of birth was provided, the 15th of the month was assumed for calculation. The age at time of enrolment, at first visit and at onset of an adverse event was calculated based on the data that were provided for the date of enrolment, the date of first treatment and the onset date of the AE, respectively.

Bleeding episodes were not recorded as such in the CRF. Data on bleedings was retrieved using the administration data, i.e. the date of administration, the reason for administration and the bleeding site. The reason was documented either as 'prophylaxis', 'bleeding',' follow-on treatment', or 'surgery'. In order to define a bleeding episode, all administrations with reason equal to 'bleeding' that were apart at most 3 days were formed into a single bleeding episode. In a second step it was ensured that the bleeding site did not change within such an episode. If more than one bleeding site was documented, the episode was separated accordingly. Patients with less than 180 days observation period were excluded from the analysis of bleeding episodes.

It should be noted that about 10% of all administrations were recorded without providing a reason. These administrations did not contribute to the definition of bleeding episodes.

The following table gives details on the handling of overall as well as specific data problems. All procedures were applied within the database after the data had been entered.

Problem/Query	Handling/Resolution
Visits or treatments documented twice (due to the structure of CRF) with identical values	One data record was deleted
Visits or treatments documented twice (due to the structure of CRF) with different values	The worst-case approach was applied for safety parameters. In other cases (e.g. weight) the more plausible value was chosen (checking data before and after this critical visit)
'deviation from normal range' = 'No', but inhibitor level = '< 1.0 BU	Inhibitor level was set to '< 0.7BU'.
Inhibitor level< 0.5 BU and 'deviation from normal range' = 'Yes'	'deviation from normal range' was set to 'No'
Application data was provided with a cumulative dose over a certain time period and not on a daily basis	The time period was first separated into smaller periods based on calendar months and the cumulative dose was divided accordingly. In a second step, the dose of each month was allocated to single days using a schedule that was in accordance with the other documented schedules of the patient.
CRF data related to a visit was inconsistent with respect to virology test data from the laboratory	Virology test data from the laboratory was given preference.

11.9 Statistical Methods

11.9.1 Statistical Methods

Descriptive statistical methods were applied. For continuous data, the basic statistics sample size, mean, and standard deviation, minimum, median, and maximum was given. Categorical data were provided in frequency tables showing sample size and absolute and relative frequency.

11.9.2 Main Statistical Methods

Patients with known administration of at least one dose of Haemoctin® were included in the analysis.

All analyses were stratified by whether patients were already treated for haemophilia A with other products or not (PTP vs. PUP). In addition, the subgroup of patients with severe haemophilia A were analysed separately. Severe haemophilia A was defined as a residual factor VIII activity of ≤ 1%. Further, analyses were stratified by country (Germany vs. Hungary). Patients were not distinguished according to the intention-to-treat or per-protocol approaches known for randomized clinical trials.

11.9.3 Effectiveness

Effectiveness was analysed by means of the occurrence of spontaneous bleeding episodes, by evaluating the expected therapeutic effect and the global assessment of effectiveness by the investigator and the patient.

Patients with inhibitor formation at start of or during the study were not included in the summaries of effectiveness (see Section 12.6.5 for case presentation). The identification of inhibitor formation and effectiveness assessments to be excluded from summaries was done via medical review, using the actual data.

The following variables were summarized with respect to occurrence of spontaneous bleeding. Bleeding days were determined on the basis of the reason of administration.

- Total number of bleeding days
- Number of bleeding days per year
- Number of bleeding days per year when treating on demand
- Number of bleeding days per year when using factor VIII as prophylaxis
- Number of bleeding days per month
- Number of bleeding days per month when treating on demand
- Number of bleeding days per month when using factor VIII as prophylaxis

In addition, the number of bleeding episodes per year was calculated overall and for 3-year periods. Patients with less than 180 days observation period were excluded from the analysis of bleeding episodes.

The analysis whether the expected therapeutic effect was confirmed or not, was summarized by reason for treatment (bleeding, follow-on treatment, prophylaxis) and overall.

For the global assessment of effectiveness, the possible ratings were ‘very good’ (=1), ‘good’ (=2), ‘moderate’ (=3), ‘poor’ (=4), or ‘none’ (=5). For the global assessments of ease of use, the possible ratings were very good’ (=1), ‘good’ (=2), ‘satisfactory’ (=3), ‘adequate’ (=4), or ‘poor’ (=5). For the global assessment of tolerability, the possible ratings were ‘very good’ (=1), ‘good’ (=2), ‘moderate’ (=3), or ‘poor’ (=4). The overall satisfaction with regards to haemophilia treatment was assessed by the patient only on a 1-5 scale.

The global assessments of investigator and patients were analysed as continuous variable. For each patient a mean over the whole NIS of all ratings was first calculated, which then was summarized.

Furthermore, the mean ratings of effectiveness were grouped by using the following categories:

- < 1.5 = very good
- ≥ 1.5 - < 2.5 = good
- ≥ 2.5 - < 3.5 = moderate
- ≥ 3.5 - < 4.5 = poor
- ≥ 4.5 = none

The mean ratings of ease of use for each patient were grouped by using the following categories:

- < 1.5 = very good
- ≥ 1.5 - < 2.5 = good
- ≥ 2.5 - < 3.5 = satisfactory
- ≥ 3.5 - < 4.5 = adequate
- ≥ 4.5 = poor

11.9.4 Safety

Virology was summarized by using the last results at the end of the study for each patient, whenever available. HAV, HBV and HCV results were presented by showing the number of patients with no results, number of patients with positive and negative results and the number of patients with vaccinations.

Further, the results at the end of the study were cross-tabulated with results at the start of the study. All possible serum conversions were discussed in the report, taking into account all virology results and vaccinations.

The FVIII antibody development under Haemoctin® therapy is presented in detail, analysing bleeding episodes and clinical outcome associated with inhibitor development. Further, the frequency of testing for factor VIII inhibitors was summarized.

The number of measurements of any laboratory result from clinical chemistry and haematology outside the normal range was summarized relative to the total number of measurements for each parameter.

Adverse events (AEs), which were reported during the NIS, were summarized as treatment emergent adverse events (TEAEs).

The number of TEAEs was displayed by age classes.

The number of patients with TEAEs and the number of TEAEs were further summarized by MedDRA preferred term, by seriousness (yes; no), and by relationship (related; not related; relationship missing).

Further, all AEs of each patient were listed with all available details including the age at study start and at onset of the AE.

11.9.5 Missing Values

Data was analysed as available. No replacement or imputation of missing data was performed with the exception of those variables and conditions indicated in the table below.

Problem/Query	Handling/Resolution
Missing treatment data	If body weight was necessary for calculating the missing values, the nearest (in terms of the date) body weight was taken for calculation
Missing baseline data for serological parameters	For Hepatitis A or B a missing value was set to positive, if a previous vaccination was recorded. In case the first documented value was negative it was assumed, that this was also true for prior visits. If the first documented value was positive, and the viral status of the patient in a previous study visit was also documented as positive, the baseline value was evaluated as positive.
Missing reason for a treatment	Reason for treatment was replaced by medical judgement based on available data. If no data at all was provided prophylaxis was assumed.
Missing previous Hepatitis A or B – vaccination	If the corresponding laboratory measurements were negative the previously vaccination was set to ‘no’.
Missing previous therapy	If details were given previously treated was set to 'yes'.

11.9.6 Sensitivity Analyses

A subgroup analysis of patients with severe haemophilia A was performed in order to assess possible differences between an analysis based on all patients enrolled in the NIS and an analysis based on patients who had severe haemophilia A, defined as a residual factor VIII activity of ≤ 1%.

11.10 Quality Control

After data had been entered into the database, important data were checked using programmed listings with appropriate error messages.

All data except of biochemical parameters were checked. Special emphasis was laid on:

- Determination of factor VIII inhibitors
- Administration of other factor VIII concentrates
- Adverse events
- Documentation of treatment with Haemoctin®.

A reconciliation of all AEs documented in the NIS and the AEs documented in the pharmacovigilance Master Safety Database (MSDB) of Biotest took place prior to the lock of the database. By this procedure it was ensured that all AEs displayed and discussed in this report are also part of the pharmacovigilance MSDB.

However, it needs to be made clear that as common practice in a NIS, CRFs were not monitored at site, no source data verification took place, and no queries for incomplete or inconsistent data were raised (with exception of missing data in AE reports, relevant for the medical assessment, based on the medical judgement of the safety assessor).

12. RESULTS

Statistical tables can be found in Appendix 1.1 (all patients by pre-treatment (PTP/PUP)), Appendix 1.2 (patients with severe haemophilia by pre-treatment (PTP/PUP)), Appendix 1.3 (all patients by country), and Appendix 1.4 (patients with severe haemophilia by country).

12.1 Participants

Overall, 164 patients were enrolled in this NIS during the study phases of PMS II and PMS III. Data collected from treatments with Haemoctin® from May 1998 until December 2015 was included in this analysis. For one of these patients, no records of Haemoctin® administration were available in the CRF, therefore this patient was excluded from all analyses, and 163 patients were included in the analysis in total.

Of the 163 patients analysed, 52 patients were treated in 8 Hungarian centres and 111 patients in 25 German centres. Of the 163 patients, 143 patients were PTPs and 20 patients were PUPs. More detail can be found in Table 1.

30 patients had a residual factor VIII activity of >1% and should not have been enrolled into the NIS according to the original entry criteria for the NIS (refer to Post-text Table 1.12). In detail, these were patients 29, 43, 44, 45, 48, 56, 78, 86, 88, 93, 94, 98, 102, 103, 114, 124, 146, 151, 152, 153, 161, 164, 9951, and 9952 (>1% to ≤10%), patients 60, 97, 116, and 127 (>10% to ≤ 20%), and patients 128 and 131 (>20%).

Patients with severe haemophilia (residual factor VIII activity ≤ 1) were analysed as a subgroup, comprising 133 patients. These were 50 patients in Hungary and 83 patients in Germany; 118 patients with severe haemophilia were PTPs and 15 patients were PUPs.

Medical review of all available data stipulated to exclude all dosing and effectiveness data of patients 69 and 166; and that dosing and effectiveness data from 23-Aug-2010 until 11-Dec-2010 of patient 119 from summary tables related to dosing and effectiveness since this data was related to ITI treatment.

Table 1 Enrolled patients per country and center

	PTP (N=143)		PUP (N=20)		Total (N=163)	
	n	%	n	%	n	%
Germany						
Total	91	63.6	20	100.0	111	68.1
Center 001	10	7.0	0	0.0	10	6.1
Center 002	6	4.2	10	50.0	16	9.8
Center 003	1	0.7	0	0.0	1	0.6
Center 004	9	6.3	0	0.0	9	5.5
Center 005	1	0.7	0	0.0	1	0.6
Center 006	6	4.2	4	20.0	10	6.1
Center 008	1	0.7	1	5.0	2	1.2
Center 009	3	2.1	0	0.0	3	1.8
Center 010	2	1.4	0	0.0	2	1.2
Center 011	18	12.6	0	0.0	18	11.0
Center 012	2	1.4	0	0.0	2	1.2
Center 013	3	2.1	0	0.0	3	1.8
Center 014	4	2.8	0	0.0	4	2.5
Center 015	3	2.1	0	0.0	3	1.8
Center 016	0	0.0	1	5.0	1	0.6
Center 017	2	1.4	0	0.0	2	1.2
Center 018	3	2.1	0	0.0	3	1.8
Center 019	1	0.7	0	0.0	1	0.6
Center 020	1	0.7	0	0.0	1	0.6
Center 021	1	0.7	3	15.0	4	2.5
Center 022	1	0.7	0	0.0	1	0.6
Center 023	1	0.7	0	0.0	1	0.6
Center 024	7	4.9	0	0.0	7	4.3
Center 025	2	1.4	0	0.0	2	1.2
Center 026	3	2.1	1	5.0	4	2.5
Hungary						
Total	52	36.4	0	0.0	52	31.9
Center 027	4	2.8	0	0.0	4	2.5
Center 028	3	2.1	0	0.0	3	1.8
Center 029	13	9.1	0	0.0	13	8.0
Center 030	19	13.3	0	0.0	19	11.7
Center 031	4	2.8	0	0.0	4	2.5
Center 032	1	0.7	0	0.0	1	0.6
Center 033	1	0.7	0	0.0	1	0.6
Center 034	7	4.9	0	0.0	7	4.3

Source: Appendix 1.1 Table 1.13
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

12.2 Descriptive Data

12.2.1 Demographics

Long-time data on the treatment of patients with Haemoctin® could be obtained in this NIS. Patient treatment data were obtained from Mai 1998 till end of December 2015. On average, patients were documented for a time period of 7.46 years (S.D.: 5.29 years, range: 0.03 months to 16.5 years) (Appendix 1.1, Table 3.1).

Most patients were PTPs (143 of 163 patients (87.7%)) and 20 patients (12.3%) were PUPs (Appendix 1.1, Table 1.1). All patients included in the NIS were male, as it is expected according to the sex related prevalence of haemophilia A (two patients with missing information).

At the time of inclusion into the NIS, patients had a mean age of 25.6 years (SD 18.5) ranging from 0 to 80 years. PTPs had a mean age of 28.5 years (SD 17.1) ranging from 0 to 80 years, PUPs had a mean age of 4.8 years (SD 14.3, median 1.0 years) ranging from 0 to 65 years (Table 2). The median age at first treatment for the PUPs was 1.5 years, ranging from 0.0 to 65.0 years. PUPs with severe haemophilia had a median age at first treatment of 1.0 years, ranging from 30.0 to 7.0 years.

Patients enrolled in the German centres had at the time of inclusion a mean age of 23.5 years (SD 19.4), ranging from 0 to 74 years, and those in the Hungarian centres 30.1 years (SD 15.6), ranging from 7 to 80 years. The mean age of patients with severe haemophilia was 20.2 years (SD 17.0) in the German centres and 28.9 years (SD 14.2) in the Hungarian centres (Table 2).

28 patients were younger than 6 years of age (11 PTPs and 17 PUPs), 14 patients between 6 and 11 years (12 PTPs and 2 PUPs), 20 patients between 12 and 17 years (all PTPs), 97 patients between 18 and 64 years (all PTPs), 3 patients between 65 and 74 years (2 PTPs and one PUP), and one PTP was older than 74 years (Table 3).

Of the patients with severe haemophilia (n=133) 23 patients were below 6 years of age (10 PTPs and 13 PUPs), 13 patients between 6 and 11 years (11 PTPs and 2 PUPs), 18 patients between 12 and 17 years (all PTPs), and 79 patients between 18 and 64 years (all PTPs) at the time of inclusion into the NIS (Table 4).

All 28 patients who were younger than 6 years of age were treated in the German centres, of the 14 patients between 6 and 11 years 10 were from Germany and 4 from Hungary. 20 patients were between 12 and 17 years (12 from Germany, 8 from Hungary), 97 patients were between 18 and 64 years (58 from Germany, 39 from Hungary), 3 patients were between 65 and 74 years (all from Germany), and 1 patient was older than 74 years (Hungarian centre) (Table 5).

The age distribution of the patients with severe haemophilia by country was similar to the overall population (Table 6).

Table 2 Age at inclusion and age at first treatment, all patients and patients with severe haemophilia

		n	mean	SD	Min	median	Max
Age at inclusion [years]							
All (N=163)		163	25.6	18.5	0.0	22.0	80.0
Previous Treatment	**PTP (N=143)**	143	28.5	17.1	0.0	27.0	80.0
	PUP (N=20)	20	4.8	14.3	0.0	1.0	65.0
Country	**Germany (N=111)**	111	23.5	19.4	0.0	20.0	74.0
	Hungary (N=52)	52	30.1	15.6	7.0	27.5	80.0
All severe haemophilia (N=133)		133	23.5	16.5	0.0	22.0	63.0
Previous Treatment	**PTP (N=118)**	118	26.3	15.4	0.0	23.0	63.0
	PUP (N=15)	15	1.4	2.3	0.0	0.0	7.0
Country	**Germany (N=83)**	83	20.2	17.0	0.0	17.0	59.0
	Hungary (N=50)	50	28.9	14.2	7.0	27.0	63.0
Age at first treatment [years]							
All (N=163)		161	25.9	18.5	0.0	22.0	80.0
Previous Treatment	**PTP (N=143)**	141	28.8	17.1	0.0	27.0	80.0
	PUP (N=20)*	20	5.2	14.2	0.0	1.5	65.0
Country	**Germany (N=111)**	109	23.9	19.4	0.0	21.0	74.0
	Hungary (N=52)	52	30.1	15.6	7.0	27.5	80.0
All severe haemophilia (N=133)		131	23.8	16.4	0.0	22.0	63.0
Previous Treatment	**PTP (N=118)**	116	26.6	15.2	0.0	24.0	63.0
	PUP (N=15)*	15	1.8	2.1	0.0	1.0	7.0
Country	**Germany (N=83)**	81	20.6	16.9	0.0	18.0	59.0
	Hungary (N=50)	50	28.9	14.1	7.0	27.0	63.0

Source: Appendices 1.1, 1.2, 1.3, 1.4 Table 1.3
PTP = Previously Treated Patients, PUP = Previously Untreated Patients
* median age at first treatment of the PUPs in weeks was 106.5 (ranging from 32 to 3422 weeks)
** median age at first treatment of the PUPs in weeks was 73 (ranging from 32 to 376 weeks)

Table 3 Distribution of patients according to age at inclusion and previous treatment at inclusion, all patients

	PTP (N=143)		PUP (N=20)		Total (N=163)	
[years]	**n**	**%**	**n**	**%**	**n**	**%**
under 6	11	7.7	17	85.0	28	17.2
6 - 11	12	8.4	2	10.0	14	8.6
12 - 17	20	14.0	0	0	20	12.3
18 - 64	97	67.8	0	0	97	59.5
65 - 74	2	1.4	1	5.0	3	1.8
above 74	1	0.7	0	0	1	0.6

Source: Appendix 1.1, Table 1.4
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 4 Distribution of patients according to age at inclusion and previous treatment, patients with severe haemophilia

	PTP (N=118)		PUP (N=15)		Total (N=133)	
[years]	**n**	**%**	**n**	**%**	**n**	**%**
under 6	10	8.5	13	86.7	23	17.3
6 - 11	11	9.3	2	13.3	13	9.8
12 - 17	18	15.3	0	0	18	13.5
18 - 64	79	66.9	0	0	79	59.4

Source: Appendix 1.2, Table 1.4
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 5 Distribution of patients according to age at inclusion and country, all patients

	Germany (N=111)		Hungary (N=52)		Total (N=163)	
[years]	**n**	**%**	**n**	**%**	**n**	**%**
under 6	28	25.2	0	0	28	17.2
6 - 11	10	9.0	4	7.7	14	8.6
12 - 17	12	10.8	8	15.4	20	12.3
18 - 64	58	52.3	39	75.0	97	59.5
65 – 74	3	2.7	0	0	3	1.8
above 74	0	0	1	1.9	1	0.6

Source: Appendix 1.3, Table 1.4

Table 6 Distribution of patients according to age at inclusion and country, patients with severe haemophilia

	Germany (N=83)		Hungary (N=50)		Total (N=133)	
[years]	**n**	**%**	**n**	**%**	**n**	**%**
under 6	23	27.7	0	0	23	17.3
6 - 11	9	10.8	4	8.0	13	9.8
12 - 17	10	12.0	8	16.0	18	13.5
18 - 64	41	49.4	38	76.0	79	59.4

Source: Appendix 1.4, Table 1.4

Distribution of the age of patients at the time point of first treatment of haemophilia A with Haemoctin® within this NIS is shown in Table 7 for all patients by pre-treatment (PTP/PUP), in Table 8 for patients with severe haemophilia and in Table 9 for all patients by country.

More than half of the patients were at least 18 years at the time of first treatment (97 patients (59.5%) between 18 and 64 years, 3 patients (1.8%) between 65 and 74 years and one patient (0.6%) > 74 years). Most of the patients who were PUPs were under 6 years of age (85.0%) when they had their first treatment (which was the study treatment), whereas the majority of PTPs were between 18 and 64 years old (67.8%) when they received their first treatment (i.e. study treatment; see Table 7). Results were similar in the subgroup of patients with severe haemophilia (see Table 8).

Table 7 Distribution of age at first treatment by pre-treatment (PTP/PUP), all patients

	PTP (N=143)		PUP (N=20)		Total (N=163)	
[years]	**n**	**%**	**n**	**%**	**n**	**%**
not available	2	1.4	0	0	2	1.2
under 6	10	7.0	17	85.0	27	16.6
6 - 11	11	7.7	2	10.0	13	8.0
12 - 17	20	14.0	0	0	20	12.3
18 - 64	97	67.8	0	0	97	59.5
65 - 74	2	1.4	1	5.0	3	1.8
above 74	1	0.7	0	0	1	0.6

Source: Appendix 1.1, Table 1.5
PTP = Previously Treated Patients, PUP = Previously Untreated Patients,

Table 8 Distribution of age at first treatment by pre-treatment (PTP/PUP), patients with severe haemophilia

	PTP (N=118)		PUP (N=15)		Total (N=133)	
[years]	**n**	**%**	**n**	**%**	**n**	**%**
not available	2	1.7	0	0	2	1.5
under 6	9	7.6	13	86.7	22	16.5
6 - 11	10	8.5	2	13.3	12	9.0
12 - 17	18	15.3	0	0	18	13.5
18 - 64	79	66.9	0	0	79	59.4

Source: Appendix 1.2, Table 1.5
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

The distribution of age when patients received their first treatment was widely spread in the German centres, whereas all patients in the Hungarian centres (except 4 patients who were between 6 and 11 years) were adolescents or adults (Table 9). Results were similar in the subgroup of patients with severe haemophilia (refer to Appendix 1.4, Table 1.5).

Table 9 Distribution of age at first treatment by country, all patients

	Germany (N=111)		Hungary (N=52)		Total (N=163)	
[years]	**n**	**%**	**n**	**%**	**n**	**%**
not available	2	1.8	0	0	2	1.2
under 6	27	24.3	0	0	27	16.6
6 - 11	9	8.1	4	7.7	13	8.0
12 - 17	12	10.8	8	15.4	20	12.3
18 - 64	58	52.3	39	75.0	97	59.5
65 – 74	3	2.7	0	0	3	1.8
above 74	0	0	1	1.9	1	0.6

Source: Appendix 1.3, Table 1.5

Except for four patients (all in German centres) all patients with information about ethnicity were Caucasian (n=107). Two of the non-Caucasian patients were black, one was Asian and one was Lebanese (Appendix 1.3, Table 1.2). For 52 patients, no information with respect to race was documented; 41 of these patients were PTPs and 11 PUPs (Appendix 1.1, Table 1.2), 45 in the German and 7 in the Hungarian centres (Appendix 1.3, Table 1.2).

Age at first diagnosis is summarized in Table 10. The mean age of patients when first diagnosed with haemophilia was 3.50 years (SD 9.97), which was lower in the subgroup of patients with severe haemophilia (1.30 years (SD 3.83)).

This young mean age at first diagnosis is reflected by the frequency distribution of age at first diagnosis, with most patients (74.4%) being under the age of 6 when first diagnosed with haemophilia (Table 11), which was also similar in both countries (refer to Appendix 1.3, Table 1.11.1). This proportion was even higher (81.2%) in the subgroup of patients with severe haemophilia A (Table 12).

Table 10 Age at first diagnosis, all patients and patients with severe haemophilia

Age at First Diagnosis [years]		**n**	**mean**	**SD**	**Min**	**median**	**Max**
Total (N=163)		140	3.50	9.97	0.00	0.00	66.00
Previous Treatment	**PTP (N=143)**	123	3.41	9.17	0.00	0.00	66.00
	PUP(N=20)	17	4.12	14.93	0.00	0.00	62.00
Country	**Germany (N=111)**	90	4.37	11.94	0.00	0.00	66.00
	Hungary (N=52)	50	1.94	4.42	0.00	0.00	27.00
All severe haemophilia (N=133)		114	1.30	3.83	0.00	0.00	27.00
Previous Treatment	**PTP (N=118)**	101	1.43	4.05	0.00	0.00	27.00
	PUP(N=15)	13	0.31	0.63	0.00	0.00	2.00
Country	**Germany (N=83)**	66	0.86	3.24	0.00	0.00	24.00
	Hungary (N=50)	48	1.90	4.49	0.00	0.00	27.00

Source: Appendices 1.1, 1.2, 1.3, 1.4 Table 1.11.1
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 11 Distribution of age at first diagnosis by pre-treatment (PTP/PUP), all patients

Age at First Diagnosis [years]	PTP (N=143)		PUP (N=20)		Total (N=163)	
	n	%	n	%	n	%
not available	20	14.0	3	15.0	23	14.1
under 6	106	74.1	16	80.0	122	74.8
6 - 11	6	4.2	0	0	6	3.7
12 - 17	4	2.8	0	0	4	2.5
18 - 64	6	4.2	1	5.0	7	4.3
65 - 74	1	0.7	0	0	1	0.6

Source: Appendix 1.1 Table 1.11.1
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 12 Distribution of age at first diagnosis by pre-treatment (PTP/PUP), patients with severe haemophilia

Age at First Diagnosis [years]	PTP (N=118)		PUP (N=15)		All (N=133)	
	n	%	n	%	n	%
not available	17	14.4	2	13.3	19	14.3
under 6	95	80.5	13	86.7	108	81.2
6 - 11	3	2.5	0	0	3	2.3
12 - 17	1	0.8	0	0	1	0.8
18 - 64	2	1.7	0	0	2	1.5

Source: Appendix 1.2 Table 1.11.1
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Considering all enrolled patients with available data, the mean time from date of initial diagnosis until inclusion in the study was 22.0 years (SD 16.2, ranging from 0 to 75.3 years) (Table 13).

Considering patients with severe haemophilia only, haemophilia A existed for a mean of 21.6 years (SD 15.2, ranging from 0 to 58.4 years) before inclusion in the NIS.

The mean age at time of diagnosis of PUPs was 1.3 years (SD 2.1, ranging from 0.0 to 6.2 years). Treatment with Haemoctin® in PUPs was started on average 19.5 months (SD 23.3, ranging from 0.0 to 75.6 months) after initial diagnosis (Table 14).

The distribution into decades of pre-existing diagnosis of haemophilia A is given in the Appendix 1.1 to 1.4, Table 1.11.2.

Table 13 Time from date of initial diagnosis until inclusion into the study, all patients and patients with severe haemophilia

Time [years]		n	mean	SD	Min	median	Max
Total (N=163)		147	22.0	16.2	0.0	20.0	75.3
Previous Treatment	**PTP (N=143)**	129	24.9	15.2	0.0	22.2	75.3
	PUP (N=20)	18	1.3	2.1	0.0	0.0	6.2
Country	**Germany (N=111)**	97	19.1	16.7	0.0	17.0	60.3
	Hungary (N=52)	50	27.6	13.7	7.0	26.6	75.3
All severe haemophilia (N=133)		120	21.6	15.2	0.0	20.0	58.4
Previous Treatment	**PTP (N=118)**	106	24.3	14.0	0.0	22.0	58.4
	PUP(N=15)	14	1.2	2.2	0.0	0.0	6.2
Country	**Germany (N=83)**	72	18.4	16.2	0.0	16.0	52.4
	Hungary (N=50)	48	26.4	12.0	7.0	26.4	58.4

Source: Appendices 1.1, 1.2, 1.3, 1.4, Table 1.11.2
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 14 Time from date of initial diagnosis until start of treatment, all patients and patients with severe haemophilia

Time [months]		n	mean	SD	Min	median	Max
Total (N=163)		145	266.9	193.5	0.0	243.4	903.4
Previous Treatment	**PTP (N=143)**	127	302.0	181.0	6.1	270.8	903.4
	PUP (N=20) *	18	19.5	23.3	0.0	10.0	75.6
Country	**Germany (N=111)**	95	233.3	199.8	0.0	204.0	726.3
	Hungary (N=52)	50	330.7	164.8	84.5	319.9	903.4
All severe haemophilia (N=133)		118	262.5	180.5	0.0	240.6	700.8
Previous Treatment	**PTP (N=118)**	104	295.3	166.7	6.1	269.0	700.8
	PUP(N=15) **	14	19.1	25.1	0.0	8.0	75.6
Country	**Germany (N=83)**	70	225.4	193.9	0.0	194.9	628.8
	Hungary (N=50)	48	316.6	144.5	84.5	317.2	700.8

Source: Appendices 1.1, 1.2, Table 1.11.6, Appendices 1.3, 1.4, Table 1.11.5
PTP = Previously Treated Patients, PUP = Previously Untreated Patients
* Median time from initial diagnosis until start of treatment for PUPs was 43.3 weeks (from 0.0 to 328.6 weeks)
** Median time from initial diagnosis until start of treatment for PUPs with severe haemophilia was 34.6 weeks (from 0.0 to 328.6 weeks)

Factor VIII residual activity is shown in Table 15 for all patients by pre-treatment (PTP/PUP). Results are depicted by country in Table 16.

Of all enrolled patients, 80.3% showed a factor residual VIII activity of ≤ 1% of normal at baseline assessment, which falls into the category of severe haemophilia A, depending on the level of factor VIII activity. This proportion was nearly the same among the PTPs (81.8%) and PUPs (70.0%). This group of patients was analysed as a subgroup (see Appendices 1.2 and 1.4).

Distribution of patients with severe and non-severe haemophilia was different between the two countries, with more patients with severe haemophilia in the Hungarian centres and more patients with non-severe haemophilia in Germany (patients with non-severe haemophilia 3.8% in Hungary and 25.2% in Germany).

A by-patient listing of Factor VIII activity assessments at baseline is provided in Appendices 1.1 to 1.4, Table 1.12.

Table 15 Factor VIII residual activity at onset by pre-treatment (PTP/PUP), all patients

	PTP (N=143)		PUP (N=20)		Total (N=163)	
	n	%	n	%	n	%
not available	1	0.7	1*	5.0	2	1.2
< 1 (severe)	88	61.5	12	60.0	100	61.3
1 (severe)	29	20.3	2	10.0	31	19.0
non-severe	25	17.5	5	25.0	30	18.4

Source: Appendix 1.1, Table 1.11.3, * One patient was known to have severe haemophilia and was analysed within the subgroup of patients with severe haemophilia.
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 16 Factor VIII residual activity at onset by country, all patients

	Germany (N=111)		Hungary (N=52)		Total (N=163)	
	n	%	n	%	n	%
not available	2*	1.8	0	0	2	1.2
< 1 (severe)	67	60.4	33	63.5	100	61.3
1 (severe)	14	12.6	17	32.7	31	19.0
non-severe	28	25.2	2	3.8	30	18.4

Source: Appendix 1.3, Table 1.11.3, * One patient was known to have severe haemophilia and was analysed within the subgroup of patients with severe haemophilia.

12.2.2 Family History

Known immune-deficiencies in the family history were recorded for a minority of patients (15.3%), whereas this proportion was higher in the PUPs (30.0%) compared with the PTPs (13.3%) (Table 17). This was similar in the subgroup of patients with severe haemophilia (Table 18). The proportion of patients with known immune-deficiencies in family history was 19.8% in the German centres, whereas it was 5.8% in the Hungarian centres (Table 19), which was similar in the subgroup of patients with severe haemophilia (refer to Appendix 1.4, Table 1.8.1).

None of the patients had records of infections after transfusions in their family history or information was not known or not available (refer to Table 1.8.2 in the respective Appendices).

Table 17 Family history – immune-deficiencies by pre-treatment (PTP/PUP), all patients

	PTP (N=143)		PUP (N=20)		Total (N=163)	
	n	%	n	%	n	%
not available	7	4.9	2	10.0	9	5.5
Yes	19	13.3	6	30.0	25	15.3
No	117	81.8	12	60.0	129	79.1

Source: Appendix 1.1, Table 1.8.1
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 18 Family history – immune-deficiencies by pre-treatment (PTP/PUP), patients with severe haemophilia

	PTP (N=118)		PUP (N=15)		Total (N=133)	
	n	%	n	%	n	%
not available	6	5.1	1	6.7	7	5.3
Yes	15	12.7	4	26.7	19	14.3
No	97	82.2	10	66.7	107	80.5

Source: Appendix 1.2, Table 1.8.1
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 19 Family history – immune-deficiencies by country, all patients

	Germany (N=111)		Hungary (N=52)		Total (N=163)	
	n	%	n	%	n	%
not available	8	7.2	1	1.9	9	5.5
Yes	22	19.8	3	5.8	25	15.3
No	81	73.0	48	92.3	129	79.1

Source: Appendix 1.3, Table 1.8.1

12.2.3 Vaccinations

Overall, 22.7% of patients had received vaccination against Hepatitis A and 39.9% against Hepatitis B (Table 20), which was similar in the subgroup of patients with severe haemophilia (24.1% and 43.6%, Table 21).

The proportion of patients with vaccination against Hepatitis A and B was 30.6% and 43.2% in Germany, respectively, whereas it was 5.8% and 32.7% in Hungary (Table 22), which was similar in the subgroup with severe haemophilia treated in Hungarian centres (6.0% and 34.0%, Appendix 1.4, Table 1.9.1 and 1.9.2).

Table 20 Vaccination against hepatitis A and B by pre-treatment (PTP/PUP), all patients

	PTP (N=143)		PUP (N=20)		Total (N=163)	
	n	%	n	%	n	%
Hepatitis A						
not available	4	2.8	1	5.0	5	3.1
not known	3	2.1	1	5.0	4	2.5
yes	31	21.7	6	30.0	37	22.7
no	105	73.4	12	60.0	117	71.8
Hepatitis B						
not available	3	2.1	1	5.0	4	2.5
not known	1	0.7	0	0	1	0.6
yes	50	35.0	15	75.0	65	39.9
no	89	62.2	4	20.0	93	57.1

Source: Appendix 1.1, Table 1.9.1 and 1.9.2
not available: the CRF did not provide any information; not known: the answer 'not known' was ticked in the CRF.
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 21 Vaccination against hepatitis A and B by pre-treatment (PTP/PUP), patients with severe haemophilia

	PTP (N=118)		PUP (N=15)		Total (N=133)	
	n	%	n	%	n	%
Hepatitis A						
not available	4	3.4	1	6.7	5	3.8
not known	2	1.7	0	0	2	1.5
yes	28	23.7	4	26.7	32	24.1
no	84	71.2	10	66.7	94	70.7
Hepatitis B						
not available	3	2.5	0	0	3	2.3
not known	1	0.8	0	0	1	0.8
yes	45	38.1	13	86.7	58	43.6
no	69	58.5	2	13.3	71	53.4

Source: Appendix 1.2, Table 1.9.1 and 1.9.2
not available: the CRF did not provide any information; not known: the answer 'not known' was ticked in the CRF
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 22 Vaccination against hepatitis A and B by country, all patients

	Germany (N=111)		Hungary (N=52)		Total (N=163)	
	n	%	n	%	n	%
Hepatitis A						
not available	2	1.8	3	5.8	5	3.1
not known	4	3.6	0	0	4	2.5
yes	34	30.6	3	5.8	37	22.7
no	71	64.0	46	88.5	117	71.8
Hepatitis B						
not available	3	2.7	1	1.9	4	2.5
not known	0	0	1	1.9	1	0.6
yes	48	43.2	17	32.7	65	39.9
no	60	54.1	33	63.5	93	57.1

Source: Appendix 1.3, Table 1.9.1 and 1.9.2
not available: the CRF did not provide any information; not known: the answer 'not known' was ticked in the CRF

12.2.4 Other Baseline and Lifestyle Data

Consumption of alcohol, tobacco, and drugs is shown in Table 23 to Table 26 for all patients by pre-treatment (PTP/PUP), by country and for the respective subgroups of patients with severe haemophilia.

More than half of the patients stated not to use alcohol and tobacco. The proportion of patients consuming alcohol was clearly higher in the subgroup of PTPs at the first visit in the study. Of note, most of the PUPs were under 6 years of age (85.0%; see Table 7). In the PTPs (i.e. comprising patients of higher age compared with the PUPs), about one third of patients consumed "little alcohol" (32.2%) and tobacco (<20/day, 28.7%). Almost none of the patients (2 of 163 patients used other drugs) stated to use other drugs at all.

Table 23 Lifestyle data by pre-treatment (PTP/PUP), all patients

	PTP (N=143)		PUP (N=20)		Total (N=163)	
	n	%	n	%	n	%
Consumption of alcohol						
not available	13	9.1	2	10.0	15	9.2
no alcohol	76	53.1	17	85.0	93	57.1
little alcohol	46	32.2	1	5.0	47	28.8
alcohol every day	8	5.6	0	0	8	4.9
Consumption of tobacco						
not available	13	9.1	2	10.0	15	9.2
tobacco < 20/day	41	28.7	9	45.0	50	30.7
tobacco > 19/day	10	7.0	0	0	10	6.1
no smoker	79	55.2	9	45.0	88	54.0
Recreational drugs						
not available	11	7.7	2	10.0	13	8.0
yes	2	1.4	0	0	2	1.2
no drug consumption	130	90.9	18	90.0	148	90.8

Source: Appendix 1.1, Table 1.10
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 24 Lifestyle data by pre-treatment (PTP/PUP), patients with severe haemophilia

	PTP (N=118)		PUP (N=15)		Total (N=133)	
	n	%	n	%	n	%
Consumption of alcohol						
not available	10	8.5	1	6.7	11	8.3
no alcohol	71	60.2	14	93.3	85	63.9
little alcohol	29	24.6	0	0	29	21.8
alcohol every day	8	6.8	0	0	8	6.0
Consumption of tobacco						
not available	10	8.5	1	6.7	11	8.3
tobacco < 20/day	32	27.1	7	46.7	39	29.3
tobacco > 19/day	9	7.6	0	0	9	6.8
no smoker	67	56.8	7	46.7	74	55.6
Recreational drugs						
not available	10	8.5	1	6.7	11	8.3
yes	2	1.7	0	0	2	1.5
no drug consumption	106	89.8	14	93.3	120	90.2

Source: Appendix 1.2, Table 1.10
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 25 Lifestyle data by country, all patients

	Germany (N=111)		Hungary (N=52)		Total (N=163)	
	n	%	n	%	n	%
Consumption of alcohol						
not available	8	7.2	7	13.5	15	9.2
no alcohol	66	59.5	27	51.9	93	57.1
little alcohol	33	29.7	14	26.9	47	28.8
alcohol every day	4	3.6	4	7.7	8	4.9
Consumption of tobacco						
not available	8	7.2	7	13.5	15	9.2
tobacco < 20/day	43	38.7	7	13.5	50	30.7
tobacco > 19/day	7	6.3	3	5.8	10	6.1
no smoker	53	47.7	35	67.3	88	54.0
Recreational drugs						
not available	6	5.4	7	13.5	13	8.0
yes	2	1.8	0	0	2	1.2
no drug consumption	103	92.8	45	86.5	148	90.8

Source: Appendix 1.3, Table 1.10

Table 26 Lifestyle data by country, patients with severe haemophilia

	Germany (N=83)		Hungary (N=50)		Total (N=133)	
	n	%	n	%	n	%
Consumption of alcohol						
not available	4	4.8	7	14.0	11	8.3
no alcohol	59	71.1	26	52.0	85	63.9
little alcohol	16	19.3	13	26.0	29	21.8
alcohol every day	4	4.8	4	8.0	8	6.0
Consumption of tobacco						
not available	4	4.8	7	14.0	11	8.3
tobacco < 20/day	32	38.6	7	14.0	39	29.3
tobacco > 19/day	6	7.2	3	6.0	9	6.8
no smoker	41	49.4	33	66.0	74	55.6
Recreational drugs						
not available	4	4.8	7	14.0	11	8.3
yes	2	2.4	0	0	2	1.5
no drug consumption	77	92.8	43	86.0	120	90.2

Source: Appendix 1.4, Table 1.10

12.3 Outcome Data

According to the current valid Committee for medicinal products for human use guidance document "Guideline of the clinical investigation of human plasma-derived factor VIII and factor IX products" (EMA/CHMP/BPWP/144533/2009 rev. 1) evaluations on effectiveness were based on the *factor VIII consumption* represented as I.U. per kilogram body weight

and month, I.U. per kilogram body weight and year, and I.U. per kilogram body weight and event (prophylaxis, bleeding, follow-on treatment and the combination of bleeding and follow-on treatment).

Medical review of all available data revealed that all dosing and effectiveness data of patient 69 and 166, and that dosing and effectiveness data from 23-Aug-2010 until 11-Dec-2010 of patient 119 were excluded from summary tables on treatment for prophylaxis and on demand since this data was related to ITI.

12.3.1 Documented Patients and Treatments

In this NIS, overall 1202 patient years were documented based all patients, 1080 patient years in the PTPs and 122 patient years in the PUPs; 1024 patient years were documented in patients with severe haemophilia (Table 27).

The mean (± SD) documentation time for all patients was 7.46 ± 5.29 years , for PTPs 7.66 ± 5.32 years and for PUPs 6.08 ± 4.97 years. The mean documentation time of Hungarian patients was considerably longer (11.41 ± 5.13 years) than on German patients (5.58 ± 4.24 years) (Table 27).

On a patient level, the mean (± SD) number of exposure days (EDs) was 683.7 days (± 605.9) for all patients together; 670.4 days (± 599.6) for PTPs and 777.7 days (± 657.4) for PUPs (Appendix 1.3, Table 3.4.1).

Table 27 Documented patient months and years by pre-treatment (PTP/PUP) and country, all patients and patients with severe haemophilia

Documented Patient Months and Years*, All patients	**PTP * (N=141)**	**PUP (N=20)**	**Total (N=161)**
Months	12963	1459	14422
Years	1080	122	1202
Mean ± SD years	7.66 ± 5.32	6.08 ± 4.97	7.46 ± 5.29
Documented Patient Months and Years*, Patients with severe haemophilia	**PTP * (N=116)**	**PUP (N=15)**	**Total (N=131)**
Months	11160	1130	12291
Years	930	94	1024
Mean ± SD years	8.02 ± 5.23	6.28 ± 5.13	7.82 ± 5.22
Documented Patient Months and Years*, All patients	**Germany (N=109)**	**Hungary (N=52)**	**Total (N=161)**
Months	7299	7123	14422
Years	608	594	1202
Mean ± SD years	5.58 ± 4.24	11.41 ± 5.13	7.46 ± 5.29
Documented Patient Months and Years*, Patients with severe haemophilia	**Germany (N=81)**	**Hungary (N=50)**	**Total (N=131)**
Months	5427	6863	12291
Years	452	572	1024
Mean ± SD years	5.58 ± 3.85	11.44 ± 5.16	7.82 ± 5.22

Source: Appendices 1.1, 1.2, 1.3, 1.4, Table 3.1
* All dosing and effectiveness data of patient no. 69 (Germany) and 166 (Germany) were excluded due to acquired

factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

12.3.2 Global Assessment on Effectiveness

At the end of each documentation year, a global assessment on effectiveness was performed by both the investigator and the patient.

For the global assessment of effectiveness, the possible ratings were 'very good' (=1), 'good' (=2), 'moderate' (=3), 'poor' (=4), or 'none' (=5).

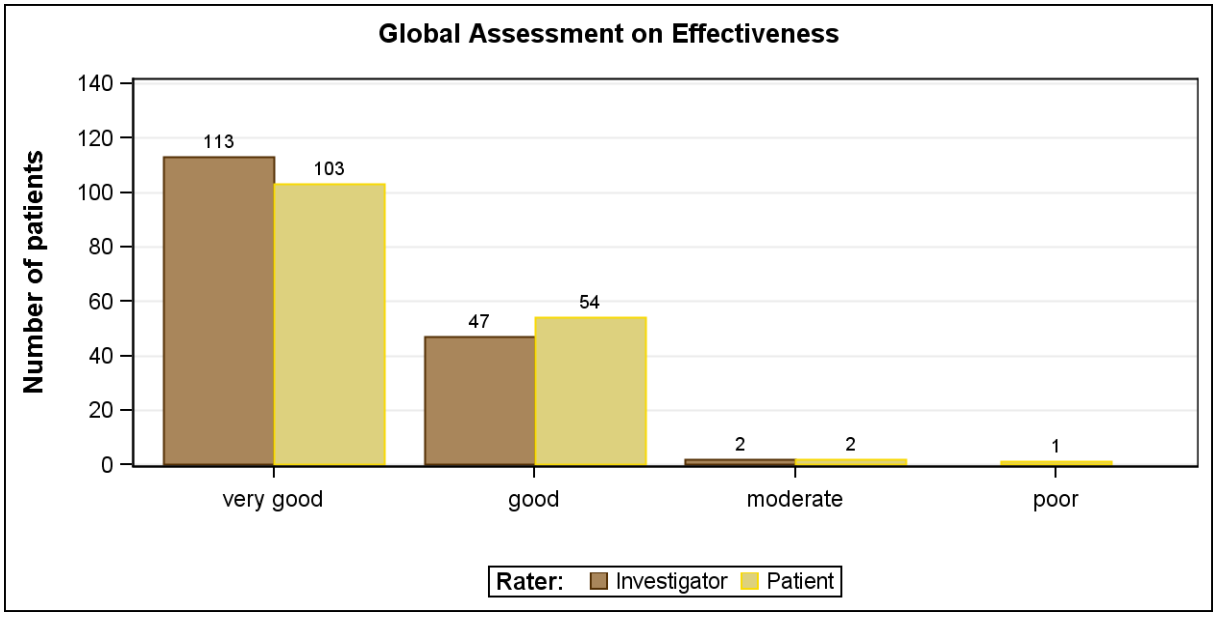
Furthermore, the mean ratings of effectiveness were grouped by using the following categories:

- < 1.5 = very good
- ≥ 1.5 - < 2.5 = good
- ≥ 2.5 - < 3.5 = moderate
- ≥ 3.5 - < 4.5 = poor
- ≥ 4.5 = none

The distribution of ratings is depicted in Figure 1, showing that the majority of both the investigators and patients rated the global effectiveness as very good. Results were similar for patients with severe haemophilia as shown in Figure 2.

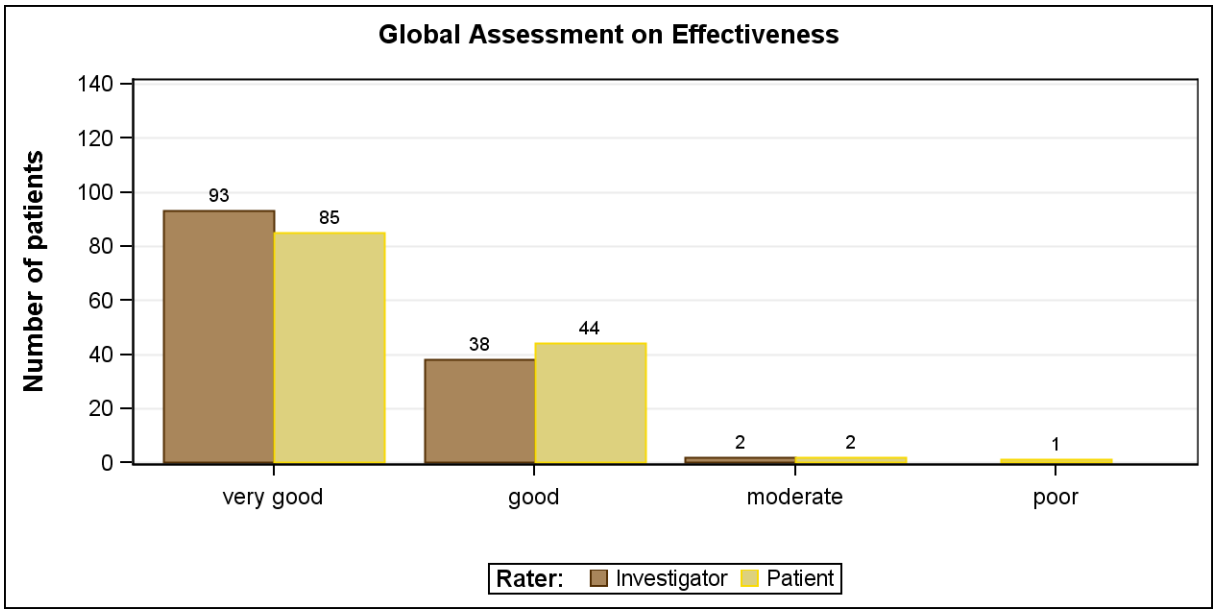
Accordingly, mean effectiveness assessed by investigators was 1.29 (SD 0.40; ranging from 1.00 to 2.50); 1.30 (SD 0.40) for PTPs and 1.27 (SD 0.38) for PUPs. Mean effectiveness assessed by patients was 1.38 (SD 0.45; ranging from 1.00 to 3.50); 1.39 (SD 0.46) for PTPs and 1.29 (SD 0.40) for PUPs. Ratings in the subgroup of patients with severe haemophilia and by country were similar (Table 28 and Table 29).

Figure 1 Global assessment on effectiveness by investigators and patients, all patients



Source: Appendix 1.1, Figure 2.1

Figure 2 Global assessment on effectiveness by investigators and patients, patients with severe haemophilia



Source: Appendix 1.2, Figure 2.1

Table 28 Mean scores of global effectiveness assessment by investigators, all patients and patients with severe haemophilia

Investigator assessment		n	mean	SD	Min	median	Max
Total (N=163)		162	1.29	0.40	1.00	1.05	2.50
Previous Treatment	**PTP (N=143)**	143	1.30	0.40	1.00	1.05	2.50
	PUP (N=20)	19	1.27	0.38	1.00	1.00	2.00
Country	**Germany (N=111)**	110	1.38	0.42	1.00	1.18	2.50
	Hungary (N=52)	52	1.12	0.28	1.00	1.00	2.50
All severe haemophilia (N=133)		133	1.29	0.40	1.00	1.05	2.50
Previous Treatment	**PTP (N=118)**	118	1.30	0.40	1.00	1.05	2.50
	PUP (N=15)	15	1.25	0.39	1.00	1.00	2.00
Country	**Germany (N=83)**	83	1.40	0.42	1.00	1.20	2.50
	Hungary (N=50)	50	1.12	0.29	1.00	1.00	2.50

Source: Appendices 1.1, 1.2, 1.3, 1.4, Table 2.2
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 29 Mean scores of global effectiveness assessment by patients, all patients and patients with severe haemophilia

Patient assessment		n	mean	SD	Min	median	Max
Total (N=163)		160	1.38	0.45	1.00	1.16	3.50
Previous Treatment	**PTP (N=143)**	142	1.39	0.46	1.00	1.16	3.50
	PUP (N=20)	18	1.29	0.40	1.00	1.07	2.00
Country	**Germany (N=111)**	108	1.44	0.45	1.00	1.33	3.00
	Hungary (N=52)	52	1.24	0.44	1.00	1.10	3.50
All severe haemophilia (N=133)		132	1.39	0.46	1.00	1.16	3.50
Previous Treatment	**PTP (N=118)**	118	1.40	0.47	1.00	1.18	3.50
	PUP (N=15)	14	1.29	0.41	1.00	1.07	2.00
Country	**Germany (N=83)**	82	1.47	0.46	1.00	1.38	3.00
	Hungary (N=50)	50	1.25	0.44	1.00	1.10	3.50

Source: Appendices 1.1, 1.2, 1.3, 1.4, Table 2.3
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

12.3.3 Global Assessment on Ease of Use

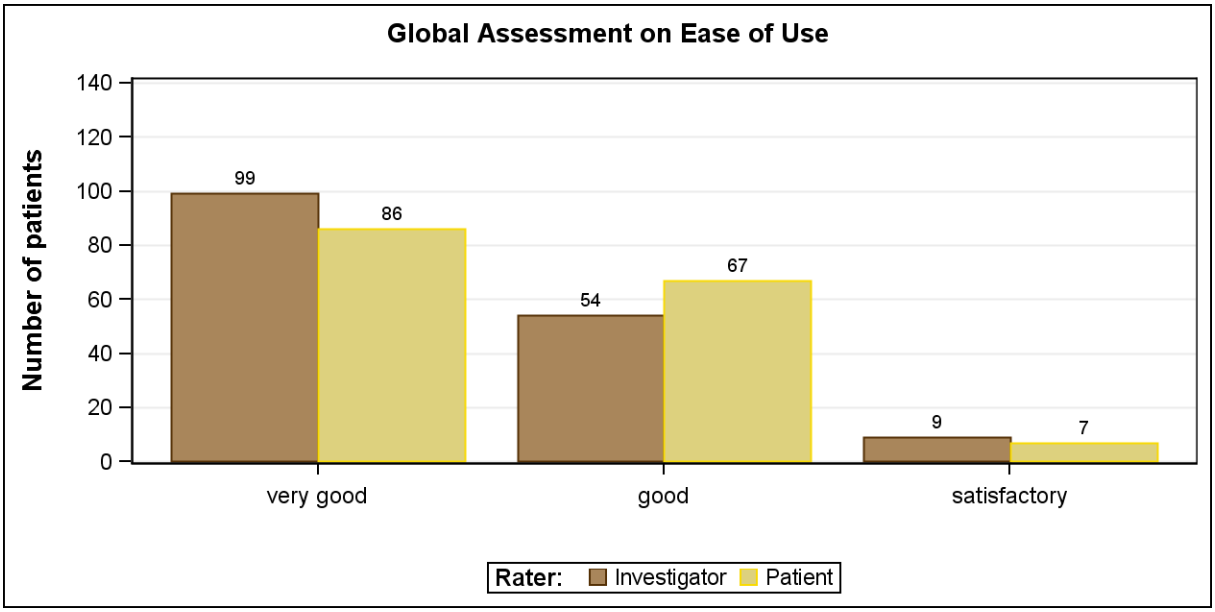
At the end of each documentation year, a global assessment on ease of use of the medicinal product was performed by both the investigator and the patient.

For the global assessments of ease of use, the possible ratings were very good' (=1), 'good' (=2), 'satisfactory' (=3), 'adequate' (=4), or 'poor' (=5). The mean ratings of ease of use for each patient were grouped by using the following categories:

- < 1.5 = very good
- ≥ 1.5 - < 2.5 = good
- ≥ 2.5 - < 3.5 = satisfactory
- ≥ 3.5 - < 4.5 = adequate
- ≥ 4.5 = poor

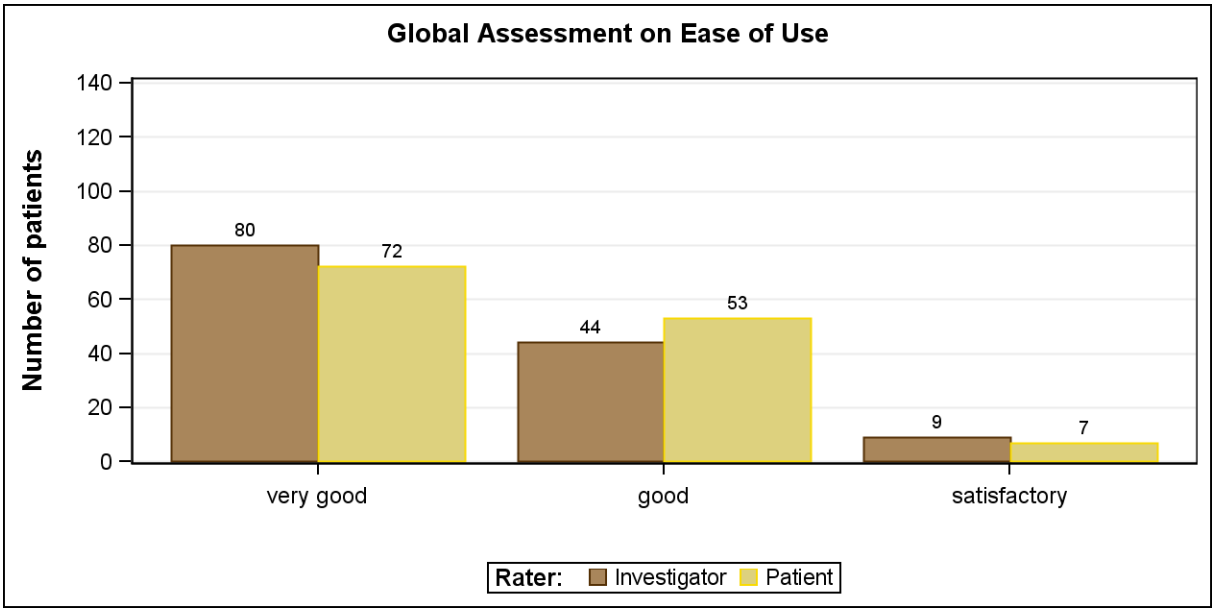
The distribution of ratings is depicted in Figure 3, showing that the majority of both the investigators and patients rated the global ease of use as good to very good. There were no mean ratings of 'adequate' or 'poor'. Results were similar for patients with severe haemophilia (Figure 4).

Figure 3 Global assessment on ease of use by investigators and patients, all patients



Source: Appendix 1.1, Figure 2.4

Figure 4 Global assessment on ease of use by investigators and patients, patients with severe haemophilia



Source: Appendix 1.2, Figure 2.4

Accordingly, mean ease of use assessed by investigators was 1.44 (SD 0.54; ranging from 1.00 to 3.00); 1.43 (SD 0.56) for PTPs and 1.52 (SD 0.43) for PUPs. Mean ease of use assessed by patients was 1.48 (SD 0.52; ranging from 1.00 to 3.00); 1.46 (SD 0.53) for PTPs and 1.66 (SD 0.39) for PUPs. Ratings in the subgroup of patients with severe haemophilia and by country were similar (Table 30 and Table 31).

Table 30 Mean scores of global ease of use assessment by investigators, all patients and patients with severe haemophilia

Investigator assessment		n	mean	SD	Min	median	Max
Total (N=163)		162	1.44	0.54	1.00	1.10	3.00
Previous Treatment	**PTP (N=143)**	143	1.43	0.56	1.00	1.08	3.00
	PUP (N=20)	19	1.52	0.43	1.00	1.56	2.00
Country	**Germany (N=111)**	110	1.64	0.56	1.00	1.63	3.00
	Hungary (N=52)	52	1.02	0.05	1.00	1.00	1.20
All severe haemophilia (N=133)		133	1.47	0.57	1.00	1.11	3.00
Previous Treatment	**PTP (N=118)**	118	1.45	0.58	1.00	1.07	3.00
	PUP (N=15)	15	1.57	0.43	1.00	1.56	2.00
Country	**Germany (N=83)**	83	1.73	0.57	1.00	2.00	3.00
	Hungary (N=50)	50	1.02	0.05	1.00	1.00	1.20

Source: Appendices 1.1, 1.2, 1.3, 1.4, Table 2.5
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 31 Mean scores of global ease of use assessment by patients, all patients and patients with severe haemophilia

Patient assessment		n	mean	SD	Min	median	Max
Total (N=163)		160	1.48	0.52	1.00	1.21	3.00
Previous Treatment	**PTP (N=143)**	142	1.46	0.53	1.00	1.16	3.00
	PUP (N=20)	18	1.66	0.39	1.00	1.78	2.00
Country	**Germany (N=111)**	108	1.69	0.51	1.00	1.82	3.00
	Hungary (N=52)	52	1.05	0.09	1.00	1.00	1.46
All severe haemophilia (N=133)		132	1.49	0.54	1.00	1.20	3.00
Previous Treatment	**PTP (N=118)**	118	1.47	0.55	1.00	1.14	3.00
	PUP (N=15)	14	1.67	0.40	1.00	1.74	2.00
Country	**Germany (N=83)**	82	1.76	0.52	1.00	2.00	3.00
	Hungary (N=50)	50	1.05	0.09	1.00	1.00	1.46

Source: Appendices 1.1, 1.2, 1.3, 1.4, Table 2.6
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

12.3.4 Overall Assessment of Patients‘ Satisfaction

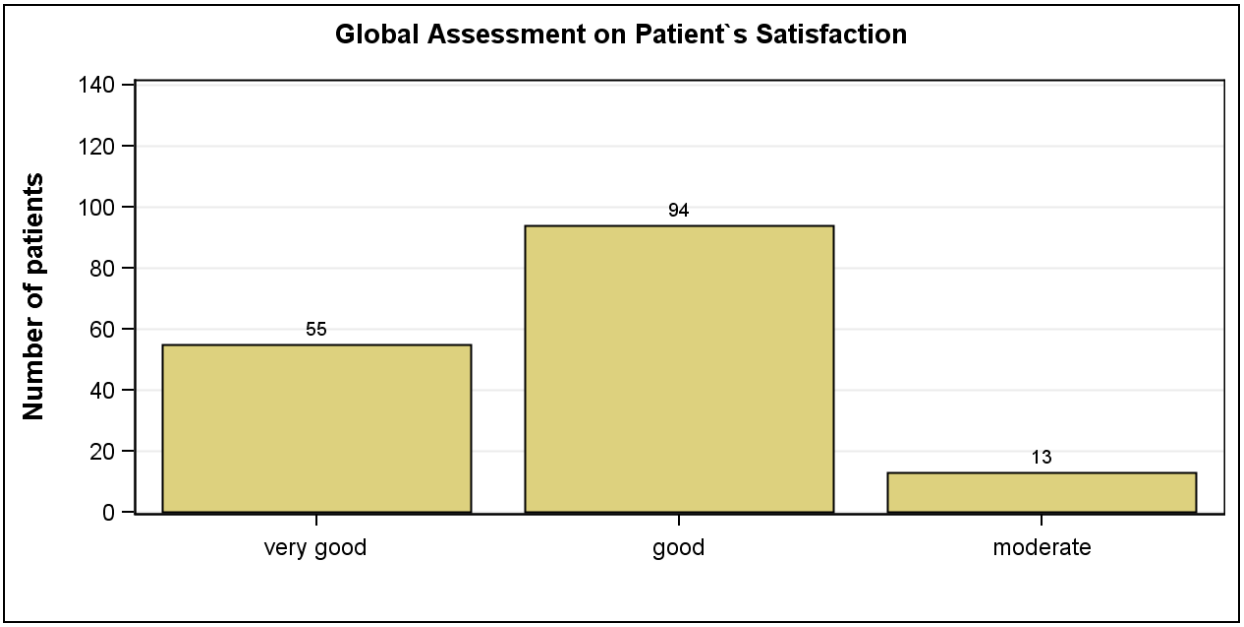
In addition, an overall assessment on patients’ satisfaction with haemophilia treatment was performed by the patient.

Possible ratings were ‘very good’ (=1), ‘good’ (=2), ‘moderate (=3), or ‘poor’ (=4).

Figure 5 shows that all patients rated their satisfaction at least as ‘moderate’ and that nearly all patients had ratings of good (94 patients) or very good (55 patients). Ratings were similar in patients with severe haemophilia (Figure 6)

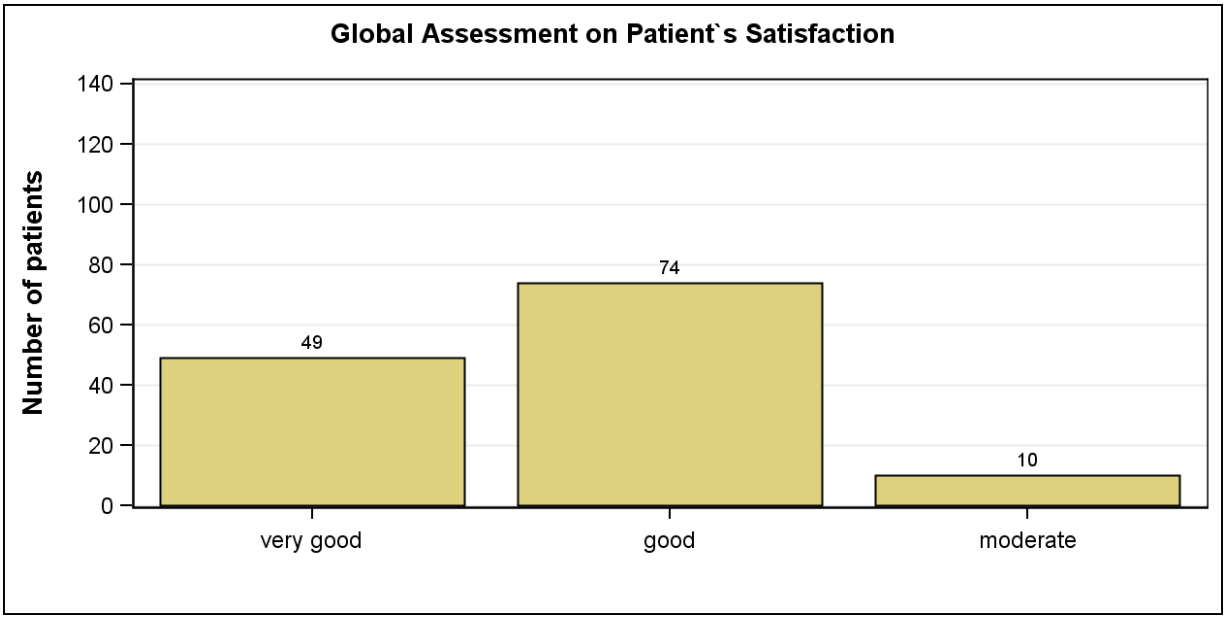
The mean score for the patients’ satisfaction was 1.74 (SD 0.50; ranging from 1.00 to 3.00); 1.78 (SD 0.49) for PTPs and 1.47 (SD 0.48) for PUPs. Ratings in the subgroup of patients with severe haemophilia and by country were similar (Table 32).

Figure 5 Patients' overall assessment of satisfaction, all patients



Source: Appendix 1.1, Figure 6.5

Figure 6 Patients' overall assessment of satisfaction, patients with severe haemophilia



Source: Appendix 1.2, Figure 6.5

Table 32 Mean scores of patients' overall assessment of satisfaction, all patients and patients with severe haemophilia

Assessment		n	mean	SD	Min	median	Max
Total (N=163)		162	1.74	0.50	1.00	1.83	3.00
Previous Treatment	**PTP (N=143)**	143	1.78	0.49	1.00	1.90	3.00
	PUP (N=20)	19	1.47	0.48	1.00	1.28	2.67
Country	**Germany (N=111)**	110	1.84	0.46	1.00	2.00	3.00
	Hungary (N=52)	52	1.54	0.52	1.00	1.39	2.78
All severe haemophilia (N=133)		133	1.72	0.51	1.00	1.80	3.00
Previous Treatment	**PTP (N=118)**	118	1.76	0.50	1.00	1.84	3.00
	PUP (N=15)	15	1.42	0.49	1.00	1.27	2.67
Country	**Germany (N=83)**	83	1.84	0.47	1.00	2.00	3.00
	Hungary (N=50)	50	1.52	0.51	1.00	1.38	2.78

Source: Appendices 1.1, 1.2, 1.3, 1.4, Table 6.4
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

12.4 Main Results

12.4.1 Extent of Exposure

Total units factor VIII concentrate applied (in IU) overall in this study and by reason for treatment are depicted in Table 3.2 in Appendices 1.1 to 1.4.

The median cumulative dose per exposure day (ED) was 1500 IU (28.8 IU/kg BW) in all patients (Table 33 and Table 36) and in patients with severe haemophilia (Table 34 and Table 37), 2000 IU (28.1 IU/kg BW) in the PTP subgroup and 1000 IU (34.4 IU/kg BW)) in PUPs.

The median cumulative dose per treatment in all patients was 4000 IU (66.5 IU/kg BW) when given because of surgery, 2000 IU (29.0 IU/kg BW) when given for current bleeding event, 2000 IU (30.4 IU/kg BW) when given as follow-on treatment, and 1500 IU (28.5 IU/kg BW) when given as prophylaxis. Median cumulative dose was 2000 IU (27.0 IU/kg BW) per treatment in the Hungarian centres and 1000 IU (29.1 IU/kg BW) in German centres (Table 33, Table 36 and Appendix 1.3, Table 3.4.1).

Table 33 Cumulative dose per ED in IU by pre-treatment (PTP/PUP) and country, all patients

Cumulative Dose [IU] per ED*		n	mean	SD	Min	median	Max
All treatments	**Total (N=161)**	110078	1686.9	956.3	100	1500	14000
Previous Treatment	**PTP (N=141)**	94525	1815.7	953.6	100	2000	14000
	PUP (N=20)	15553	904.1	482.1	125	1000	8500
Reason	**Bleeding**	25524	1735.0	782.1	125	2000	10000
	Follow-on-treatment	7147	1853.8	1083.9	100	2000	12000
	Prophylaxis	77288	1651.5	984.1	100	1500	11000
	Surgery	119	4348.7	2267.6	1000	4000	14000
Country	**Germany**	63715	1455.1	948.1	100	1000	14000
	Hungary	46363	2005.6	872.1	100	2000	11250

Source: Appendices 1.1, 1.3, Table 3.3
* All dosing and effectiveness data of patients no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
n = number of EDs, ED = Exposure Day, PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 34 Cumulative dose per ED in IU by pre-treatment (PTP/PUP) and country, patients with severe haemophilia

Cumulative Dose [IU] per ED*		n	mean	SD	Min	median	Max
All treatments	**Total (N=133)**	97485	1649.4	913.5	100	1500	11250
Previous Treatment	**PTP (N=116)**	84293	1767.4	909.2	100	2000	11250
	PUP (N=15)	13192	895.0	475.4	125	1000	8500
Reason	**Bleeding**	24324	1736.2	768.2	125	2000	10000
	Follow-on-treatment	6054	1846.4	997.0	100	2000	11250
	Prophylaxis	66998	1596.0	940.7	200	1500	11000
	Surgery	109	4142.2	1927.0	1000	3000	10000
Country	**Germany**	52949	1382.4	870.8	125	1000	11000
	Hungary	44536	1966.7	860.0	100	2000	11250

Source: Appendices 1.2, 1.4, Table 3.3
* All dosing and effectiveness data of patients no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
n = number of EDs, ED = Exposure Day, PTP = Previously Treated Patients, PUP = Previously Untreated Patients

The cumulative dose per ED in IU and in IU/kg BW, by age class is summarised in Table 35, Table 36 and Table 37. The 0-5 year old patients received a median cumulative dose per ED of 500 IU (35.4 IU/kg BW), the 6-11 year old patients received a median of 1000 IU (29.3 IU/kg BW), and the 12-17 year old patients 1500 IU (26.9 IU/kg BW). Adult patients (18-64 years old) received a median cumulative dose per ED of 2000 IU (28.2 IU/kg BW) and elderly patients (65 years and older) of 2000 IU (39.0 IU/kg BW).

Results were similar in patients with severe haemophilia (Table 3.3, Appendix 1.2 and Table 37).

Table 35 Cumulative dose per ED in IU by age groups, all patients

Cumulative Dose [IU] per ED*		n	mean	SD	Min	median	Max
Age Classes of Interest§							
	0-5	9650	855.6	584.5	120	500	5000
	6-11	18413	956.7	407.5	200	1000	8500
	12-17	14602	1492.9	670.4	250	1500	7000
	0-17	42665	1117.3	614.5	120	1000	8500
	18-64	64210	2032.8	958.5	100	2000	14000
	65-74	2171	2027.5	901.1	1000	2000	8000
	75-84	430	3010.5	348.8	2000	3000	7000
	>=85	602	2991.7	569.2	1680	3000	6000
	>=65	3203	2340.7	913.2	1000	2000	8000

Source: Appendix 1.1, Table 3.3
* All dosing and effectiveness data of patient no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
§ Age at treatment date. The same patient may be displayed in more than one age class.
n = number of EDs, ED = Exposure Day

The extent of exposure for all enrolled patients that could be evaluated for exposure is shown in Table 36.

Results by age groups of interest (0-5, 6-11, and 12-17 years at start of therapy) are provided in Tables 3.4.2, 3.4.3 and 3.4.4 in Appendices 1.1 to 1.4. A by-patient listing of

the clinical effectiveness of factor VIII concentrate is provided in Table 3.5 in Appendices 1.1 to 1.4. A by-patient listing of cumulative dose per age class of interest is provided in Table 3.6 in Appendices 1.1 to 1.4.

Overall, patients had a mean of 683.7 EDs (SD 605.9) in this NIS, with more EDs recorded in Hungary than in Germany (Hungary: 891.6 ± 606.5 EDs, Germany: 584.5 ± 606.5 EDs). On average over all patients and the whole study, the reason for treatment was prophylaxis in 62.4% of EDs and bleeding or follow-on in 36.9% of EDs.

The mean (± SD) number of EDs per month was 8.4 ± 5.3 days in all patients. PUPs tended to have more EDs per month than PTPs (PTPs: 8.0 ± 5.3 days, PUPs: 10.6 ± 4.4 days).

The median Haemoctin® exposure dose (HED) was 28.8 IU/kg BW for all patients, with a trend to higher doses in the PUPs than in the PTPs (PTP: median = 28.1 IU/kg BW, PUP = 34.4 IU/kg BW). The HED in IU/kg BW did not depend on the reason for treatment (Table 36).

Patients with severe haemophilia had a mean of 744.2 EDs (SD 623.7) in this NIS, with more EDs recorded in Hungary than in Germany (Hungary: 890.7 ± 618.5 EDs, Germany: 653.7 ± 613.3 EDs) (Table 37). On average over all patients with severe haemophilia and the whole study, the reason for treatment was prophylaxis in 63.5% of EDs and bleeding or follow-on in 36.4% of EDs.

The mean (± SD) number of EDs per month was 8.8 ± 5.4 days in all patients with severe haemophilia. PUPs tended to have more EDs per month than PTPs (PUPs: 11.7 ± 3.8 days, PTPs: 8.4 ± 5.5 days).

The median HED was 28.5 IU/kg BW for all patients severe haemophilia, with a trend to higher doses in the PUPs than in the PTPs (PTP: median = 28.1 IU/kg BW, PUP = 33.5 IU/kg BW). The HED in IU/kg BW did not depend on the reason for treatment (Table 37).

Patients with severe haemophilia tended to have more EDs but daily HED was similar to the group of all patients.

Table 36 Extent of exposure to Haemoctin®, all patients

Extent of Exposure *	n	mean	SD	Min	median	Max
EDs						
Total	161	683.7	605.9	1	473.0	2528
Germany	109	584.5	582.7	1	389.0	2528
Hungary	52	891.6	606.5	7	973.5	2492
from it Bleeding or Follow-on [%]	161	36.9	37.5	0	19.5	100
from it Prophylaxis [%]	161	62.4	38.3	0	80.2	100
ED/Month						
Total	156	8.4	5.3	0.4	7.9	30.3
PTP	137	8.0	5.3	0.4	7.2	30.3
PUP	19	10.6	4.4	1.6	13.1	16.0
ED/Year						
Total	156	100.3	63.2	4.8	94.2	364.1
PTP	137	96.5	63.8	4.8	86.4	364.1
PUP	19	127.8	52.9	19.6	157.5	191.6
Cumulative exposure/year [IU]						
Total	156	169,013	121,581	49,037	137,222	724,512
PTP	137	177,185	125,363	13,370	150,842	724,512
PUP	19	110,088	66,135	4,903	102,474	281,146
HED in IU/kg BW/month						
Total	154	267.8	277.7	14.4	210.2	2113.1
PTP	135	240.9	238.3	14.4	193.7	2113.1
PUP	19	458.9	434.3	27.8	393.9	1955.1
HED in IU/kg BW/year						
Total	154	3213.6	3331.9	172.6	2522.3	25356.9
PTP	135	2890.8	2859.4	172.6	2324.2	25356.9
PUP	19	5507.4	5211.8	333.5	4726.8	23461.2
HED in IU/kg BW						
Total	159	31.5	14.8	9.8	28.8	122.5
PTP	139	30.3	12.7	9.8	28.1	102.6
PUP	20	39.9	24.1	15.5	34.4	122.5
0-5	26	41.4	24.9	15.5	35.4	122.5
6-12	13	33.1	15.3	13.9	29.3	77.9
12-17	20	27.5	9.0	15.2	26.9	54.0
18-64	96	29.3	10.8	9.8	28.2	59.3
>=65	4	34.6	11.8	17.6	39.0	42.8
HED in IU/kg BW by reason (Total)						
HED in IU/kg BW: prophylaxis	148	31.5	15.1	9.1	28.5	120.4
HED in IU/kg BW: bleeding	143	32.2	14.8	9.7	29.0	83.3
HED in IU/kg BW: follow-on	125	33.0	18.8	10.3	30.4	181.8
HED in IU/kg BW: bleeding or follow-on	148	33.1	17.3	9.8	30.0	160.5
HED in IU/kg BW: surgery	22	68.6	37.8	12.5	66.5	181.8

Source: Appendix 1.1, Tables 3.4.1 – 3.4.6
* All dosing and effectiveness data of patient no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
ED = Exposure Day, HED = Haemoctin® Exposure Dose, PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 37 Extent of exposure to Haemoctin®, patients with severe haemophilia

Extent of Exposure *	n	mean	SD	Min	median	Max
EDs						
Total	131	744.2	623.7	4.0	517.0	2528.0
Germany	81	653.7	613.3	4.0	420.0	2528.0
Hungary	50	890.7	618.5	7.0	973.5	2492.0
from it Bleeding or Follow-on [%]	131	36.4	37.2	0.0	18.0	100.0
from it Prophylaxis [%]	131	63.5	37.3	0.0	82.0	100.0
ED/Month						
Total	129	8.8	5.4	0.4	8.7	30.3
PTP	114	8.4	5.5	0.4	7.9	30.3
PUP	15	11.7	3.8	1.6	13.3	16.0
ED/Year						
Total	129	105.7	65.1	4.8	104.0	364.1
PTP	114	101.2	66.1	4.8	94.7	364.1
PUP	15	140.3	45.5	19.6	159.3	191.6
Cumulative exposure/year [IU]						
Total	129	172,451	119,337	4,903	149,966	724,512
PTP	114	179,830	122,538	13,370	153,715	724,512
PUP	15	116,373	72,084	4,903	104,191	281,146
HED in IU/kg BW/month						
Total	127	283.2	295.3	14.4	218.7	2113.1
PTP	112	251.6	250.5	14.4	206.7	2113.1
PUP	15	519.0	468.5	27.8	403.2	1955.1
HED in IU/kg BW/year						
Total	127	3398.2	3543.3	172.6	2624.5	25356.9
PTP	112	3019.2	3006.3	172.6	2479.8	25356.9
PUP	15	6228.5	5621.9	333.5	4838.1	23461.2
HED in IU/kg						
Total	129	31.2	15.2	9.8	28.5	122.5
PTP	114	30.1	12.7	9.8	28.1	102.6
PUP	15	39.8	27.0	15.5	33.5	122.5
0-5	21	41.7	27.0	15.5	35.3	122.5
6-12	12	33.7	15.9	13.9	29.4	77.9
12-17	18	28.3	9.2	15.2	27.6	54.0
18-64	78	28.7	10.1	9.8	27.8	59.1
>=65	0					
HED in IU/kg by reason (Total)						
HED in IU/kg BW: prophylaxis	124	32.0	15.4	11.6	28.9	120.4
HED in IU/kg BW: bleeding	118	32.1	15.2	9.7	28.6	83.3
HED in IU/kg BW: follow-on	101	33.1	20.0	10.3	29.6	181.8
HED in IU/kg BW: bleeding or follow-on	118	32.9	18.2	9.8	28.8	160.5
HED in IU/kg BW: surgery	18	70.9	40.8	12.5	70.5	181.8

Source: Appendix 1.2, Tables 3.4.1 – 3.4.6
* All dosing and effectiveness data of patient no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
ED = Exposure Day, HED = Haemoctin® Exposure Dose, PTP = Previously Treated Patients, PUP = Previously Untreated Patients

12.4.2 Extent of Exposure Related to the Annual Bleeding Rate

The number of EDs because of bleeding per year was considerably lower for patients who were treated prophylactically with Haemoctin® compared to those patients treated on demand. The median number of EDs per year because of bleeding was 9.8 days in all patients, with a median number of EDs of 4.6 in patients in the prophylaxis setting and a median number of EDs of 30 in patients treated on demand (Table 38).

Overall, patients had a mean annual bleeding rate of 13.3 (SD: 16.6, median 6.1). The annual bleeding rate was considerably lower for patients who were treated prophylactically with Haemoctin® compared to those patients treated on demand (type of treatment = prophylaxis: mean ± SD: 6.3 ± 7.7, median: 3.2; type of treatment = on demand: mean ± SD: 27.4 ± 20.5, median: 24.5) (Table 40).

Patients with severe haemophilia tended to have more bleedings with a mean annual bleeding rate of 15.1 (SD: 17.6, median 9.2). Also in patients with severe haemophilia, the annual bleeding rate was considerably lower for patients who were treated prophylactically with Haemoctin® compared to those patients treated on demand (type of treatment = prophylaxis: mean ± SD: 6.9 ± 8.2, median: 3.3; type of treatment = on demand: mean ± SD: 31.3 ± 19.8, median: 29.7) (Table 41).

The annual bleeding rate decreased over time, from a median annual bleeding rate of 20.7 from 1998 to 2002 to 5.2 from 2008 to 2012 and finally to a median of 2.6 bleedings per year from 2013 to 2015 (Table 40). This should however be seen in the context of the changes in type of treatment, see Section 12.4.4.

Table 38 EDs with reason bleeding, all patients

	n	mean	SD	Min	median	Max
EDs with Reason Bleeding						
Total *	161	158.5	263.7	0.0	44.0	1902.0
PTP	141	172.2	276.8	0.0	55.0	1902.0
PUP	20	62.1	98.8	1.0	17.5	382.0
ED/Month with Reason Bleeding						
Total *	156	1.4	1.6	0.0	0.8	10.2
PTP	137	1.4	1.7	0.0	0.9	10.2
PUP	19	0.8	0.9	0.0	0.4	2.9
ED/Month with Reason Bleeding, Type of Treatment = Prophylaxis						
Total *	104	0.7	0.8	0.0	0.4	3.3
PTP	87	0.7	0.8	0.0	0.4	3.3
PUP	17	0.7	0.8	0.0	0.3	2.3
ED/Month with Reason Bleeding, Type of Treatment = On Demand						
Total *	52	2.7	2.0	0.0	2.5	10.2
PTP	50	2.7	2.0	0.0	2.5	10.2
PUP	2	1.7	1.8	0.4	1.7	2.9
ED/Year with Reason Bleeding						
Total *	156	16.4	19.2	0.0	9.8	121.9
PTP	137	17.3	19.9	0.0	10.7	121.9
PUP	19	9.6	10.8	0.3	4.6	35.0
ED/Year with Reason Bleeding, Type of Treatment = Prophylaxis						
Total *	104	8.6	9.6	0.0	4.6	39.9
PTP	87	8.6	9.7	0.0	4.7	39.9
PUP	17	8.4	9.3	0.3	3.6	27.8
ED/Year with Reason Bleeding, Type of Treatment = On Demand						
Total *	52	32.1	23.6	0.0	30.0	121.9
PTP	50	32.6	23.7	0.0	30.0	121.9
PUP	2	19.8	21.5	4.6	19.8	35.0

Source: Appendix 1.1, Table 3.4.1
* All dosing and effectiveness data of patient no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
ED = Exposure Day, PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 39 EDs with reason bleeding, patients with severe haemophilia

	n	mean	SD	Min	median	Max
EDs with Reason Bleeding						
Total *	131	185.7	283.2	0.0	65.0	1902.0
PTP	116	203.8	295.2	0.0	74.0	1902.0
PUP	15	45.2	70.8	1.0	16.0	252.0
ED/Month with Reason Bleeding						
Total *	129	1.5	1.7	0.0	1.0	10.2
PTP	114	1.7	1.7	0.0	1.2	10.2
PUP	15	0.7	0.8	0.0	0.2	2.3
ED/Month with Reason Bleeding, Type of Treatment = Prophylaxis						
Total *	85	0.8	0.8	0.0	0.4	3.3
PTP	70	0.8	0.9	0.0	0.5	3.3
PUP	15	0.7	0.8	0.0	0.2	2.3
ED/Month with Reason Bleeding, Type of Treatment = On Demand						
Total *	44	3.0	1.9	0.2	3.0	10.2
PTP	44	3.0	1.9	0.2	3.0	10.2
PUP	0					
ED/Year with Reason Bleeding						
Total *	129	18.5	20.2	0.0	11.7	121.9
PTP	114	19.9	20.8	0.0	14.5	121.9
PUP	15	7.9	9.9	0.3	2.7	27.8
ED/Year with Reason Bleeding, Type of Treatment = Prophylaxis						
Total *	85	9.3	10.2	0.0	4.9	39.9
PTP	70	9.5	10.3	0.0	5.5	39.9
PUP	15	7.9	9.9	0.3	2.7	27.8
ED/Year with Reason Bleeding, Type of Treatment = On Demand						
Total *	44	36.4	22.7	2.4	36.3	121.9
PTP	44	36.4	22.7	2.4	36.3	121.9
PUP	0					

Source: Appendix 1.2, Table 3.4.1
* All dosing and effectiveness data of patient no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
ED = Exposure Day, PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 40 Bleeding episodes per year in different time intervals, all patients

	n	mean	SD	Min	median	Max
Total						
During the whole study, all patients	154	13.3	16.6	0.0	6.1	113.3
During the whole study, type of treatment = on demand	51	27.4	20.5	0.0	24.5	113.3
During the whole study, type of treatment = prophylaxis	103	6.3	7.7	0.0	3.2	33.9
1998 – 2002, all patients	90	23.7	23.6	0.0	20.7	118.8
2003 – 2007, all patients	105	18.5	21.5	0.0	9.4	128.2
2008 – 2012, all patients	123	13.2	18.8	0.0	5.2	135.7
2013 – 2015, all patients	70	7.2	10.4	0.0	2.6	46.4
PTP						
During the whole study, all PTP	135	14.3	17.3	0.0	6.9	113.3
During the whole study, type of treatment = on demand	49	28.0	20.5	0.0	25.7	113.3
During the whole study, type of treatment = prophylaxis	86	6.5	8.0	0.0	3.4	33.9
1998 – 2002, all PTP	82	25.6	23.8	0.0	22.2	118.8
2003 – 2007, all PTP	96	19.7	22.0	0.0	11.2	128.2
2008 – 2012, all PTP	106	14.1	19.7	0.0	5.5	135.7
2013 – 2015, all PTP	63	7.4	10.8	0.0	2.5	46.4
PUP						
During the whole study, all PUP	19	5.7	6.9	0.2	2.2	21.5
During the whole study, type of treatment = on demand	2	11.2	14.6	0.9	11.2	21.5
During the whole study, type of treatment = prophylaxis	17	5.1	6.0	0.2	2.2	19.6
1998 – 2002, all PUP	8	4.2	3.8	0.0	3.8	10.7
2003 – 2007, all PUP	9	5.5	6.6	0.0	2.8	17.4
2008 – 2012, all PUP	17	7.8	11.2	0.2	1.0	32.1
2013 – 2015, all PUP	7	5.5	6.0	0.0	3.5	14.2

Source: Appendix 1.1, Tables 3.5.2 and 3.5.3
For each patient in study, the number of bleeding episodes was normalised to 365 days. Patients who were in study for less than 180 days were excluded.

Table 41 Bleeding episodes per year in different time intervals, patients with severe haemophilia

	n	mean	SD	Min	median	Max
Total						
During the whole study, all patients	127	15.1	17.6	0.0	9.2	113.3
During the whole study, type of treatment = on demand	43	31.3	19.8	2.4	29.7	113.3
During the whole study, type of treatment = prophylaxis	84	6.9	8.2	0.0	3.3	33.9
1998 – 2002, all patients	78	26.6	23.9	0.0	22.6	118.8
2003 – 2007, all patients	89	20.3	22.6	0.0	12.7	128.2
2008 – 2012, all patients	102	15.0	19.9	0.0	5.6	135.7
2013 – 2015, all patients	60	8.1	10.9	0.0	3.8	46.4
PTP						
During the whole study, all PTP	112	16.5	18.2	0.0	9.8	113.3
During the whole study, type of treatment = on demand	43	31.3	19.8	2.4	29.7	113.3
During the whole study, type of treatment = prophylaxis	69	7.2	8.6	0.0	3.7	33.9
1998 – 2002, all PTP	72	28.5	23.9	0.0	26.6	118.8
2003 – 2007, all PTP	82	21.7	23.0	0.0	13.9	128.2
2008 – 2012, all PTP	89	16.2	20.7	0.0	6.4	135.7
2013 – 2015, all PTP	54	8.4	11.3	0.0	4.2	46.4
PUP						
During the whole study, all PUP	15	5.1	6.4	0.2	1.5	19.6
During the whole study, type of treatment = on demand	0					
During the whole study, type of treatment = prophylaxis	15	5.1	6.4	0.2	1.5	19.6
1998 – 2002, all PUP	6	3.7	3.0	0.0	3.8	7.1
2003 – 2007, all PUP	7	3.9	5.6	0.0	0.4	14.0
2008 – 2012, all PUP	13	6.9	10.6	0.2	0.9	29.1
2013 – 2015, all PUP	6	5.5	6.5	0.0	2.5	14.2

Source: Appendix 1.2, Tables 3.5.2 and 3.5.3
For each patient in study, the number of bleeding episodes was normalised to 365 days. Patients who were in study for less than 180 days were excluded.

12.4.3 Expected Therapeutic Effect Gained

The expected therapeutic effect obtained was assessed by the investigator at each treatment and documented as ‘yes’ or ‘no’. The number of treatments with a documented effect as expected and the number of treatments in total are shown in Table 42 for all patients and in Table 43 for patients with severe haemophilia.

Of all treatments with a documented effect (n=66,004) during this study, the investigators assessed the effect as ‘yes’ (as expected) with nearly all (99.29%) treatments. Expected effect was very similar in the indications of bleeding, prophylaxis and surgery and slightly lower for follow-on treatments.

In 470 treatments with documented effect (0.71%) the effect was assessed as not expected ('no'), most of them (416 treatments) in patients who received follow-on treatment.

Most of these 470 not expected treatment effects occurred in PTPs (465 of 470), in patients with severe haemophilia (463 treatments, see below and Table 43) and in Hungarian centres (433 of 470 treatments, see Table 44).

Table 42 Expected therapeutic effect by pre-treatment (PTP/PUP), all patients

Expected Effect by Reason for Treatment		PTP (N=143)		PUP (N=20)		Total (N=163)	
		N	%	N	%	N	%
Yes	**Bleeding**	21664	99.89	314	98.43	21978	99.87
	Follow-on-treatment	5474	92.94	194	100.00	5668	93.16
	Prophylaxis	34220	99.93	3556	100.00	37776	99.93
	Surgery	106	100.00	6	100.00	112	100.00
	All	61464	99.25	4070	99.88	65534	99.29
No	**Bleeding**	24	0.11	5	1.57	29	0.13
	Follow-on-treatment	416	7.06	0	0	416	6.84
	Prophylaxis	25	0.07	0	0	25	0.07
	Surgery	0	0	0	0	0	0
	All	465	0.75	5	0.12	470	0.71
Total	**Bleeding**	21688	100.00	319	100.00	22007	100.00
	Follow-on-treatment	5890	100.00	194	100.00	6084	100.00
	Prophylaxis	34245	100.00	3556	100.00	37801	100.00
	Surgery	106	100.00	6	100.00	112	100.00
	All	61929	100.00	4075	100.00	66004	100.00

Source: Appendix 1.1, Table 3.7
All dosing and effectiveness data of patient no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
Yes: expected therapeutic effect was gained; No: expected therapeutic effect was not gained.
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

In patients with severe haemophilia, the investigators assessed the effect as 'yes' (as expected) with nearly all (99.21%) treatments of all treatments with a documented effect (n=58,045) during this study. Expected effect was very similar in the indications of bleeding, prophylaxis and surgery and slightly lower for follow-on treatments.

In 463 treatments with documented effect (0.79%) the effect was assessed as not expected ('no'), most of them (415 treatments) in those patients who were treated for follow-on treatment. Most of the unexpected treatment effects occurred in the PTPs (Table 43).

The assessment of ineffective follow-on treatment derives mainly from patients of only one centre (Debrecen /Hungary). These patients were self-medicating adults (factor VIII substitution), partly with joint impairment. To some extent, the patients did not adhere to the recommendation of the physician (Table 44).

Table 43 Expected therapeutic effect by pre-treatment (PTP/PUP), patients with severe haemophilia

Expected Effect by Reason for Treatment		PTP (N=118)		PUP (N=15)		Total (N=133)	
		N	%	N	%	N	%
yes	Bleeding	21098	99.90	193	97.97	21291	99.88
	Follow-on-treatment	4802	92.05	66	100.00	4868	92.14
	Prophylaxis	28374	99.92	3410	100.00	31784	99.93
	Surgery	100	100.00	2	100.00	102	100.00
	All	54374	99.16	3671	99.89	58045	99.21
no	Bleeding	22	0.10	4	2.03	26	0.12
	Follow-on-treatment	415	7.95	0	0	415	7.86
	Prophylaxis	22	0.08	0	0	22	0.07
	All	459	0.84	4	0.11	463	0.79
Total	Bleeding	21120	100.00	197	100.00	21317	100.00
	Follow-on-treatment	5217	100.00	66	100.00	5283	100.00
	Prophylaxis	28396	100.00	3410	100.00	31806	100.00
	Surgery	100	100.00	2	100.00	102	100.00
	All	54833	100.00	3675	100.00	58508	100.00

Source: Appendix 1.2, Table 3.7
All dosing and effectiveness data of patient no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
Yes: expected therapeutic effect was gained; No: expected therapeutic effect was not gained.
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 44 Expected therapeutic effect by country, all patients

Expected Effect by Reason for Treatment		Germany (N=111)		Hungary (N=52)		Total (N=163)	
		N	%	N	%	N	%
yes	Bleeding	2416	99.46	19562	99.92	21978	99.87
	Follow-on-treatment	1566	99.94	4102	90.81	5668	93.16
	Prophylaxis	20654	99.89	17122	99.99	37776	99.93
	Surgery	17	100.00	95	100.00	112	100.00
	All	24653	99.85	40881	98.95	65534	99.29
no	Bleeding	13	0.54	16	0.08	29	0.13
	Follow-on-treatment	1	0.06	415	9.19	416	6.84
	Prophylaxis	23	0.11	2	0.01	25	0.07
	All	37	0.15	433	1.05	470	0.71
Total	Bleeding	2429	100.00	19578	100.00	22007	100.00
	Follow-on-treatment	1567	100.00	4517	100.00	6084	100.00
	Prophylaxis	20677	100.00	17124	100.00	37801	100.00
	Surgery	17	100.00	95	100.00	112	100.00
	All	24690	100.00	41314	100.00	66004	100.00

Source: Appendix 1.3, Table 3.7
All dosing and effectiveness data of patient no. 69 (Germany) and 166 (Germany) were excluded due to acquired factor inhibitors and data during ITI of patient no. 119 (Germany) were excluded either.
Yes: expected therapeutic effect was gained; No: expected therapeutic effect was not gained.

12.4.4 Type of Treatment Over Time

The change in numbers and percentage of patients being on prophylaxis were displayed from study start in 1998 in 5 year intervals (2003, 2008, 2013) and last year of

documentation in 2015 for all patients and by country, by type of treatment (on demand / prophylaxis) for each of the above mentioned years, as summarized in Table 45.

In 1998, data were available for 8 patients only. During the following years, the proportion of patients receiving treatment for prophylaxis increased from 41.1% (data from 90 patients) in 2003 to 65.7% (data from 67 patients) in 2015, whereas the proportion of patients receiving on-demand treatment decreased from 58.9% to 34.3% during this time period. Most of the previously untreated patient subgroup received their treatment as prophylaxis treatment throughout the NIS.

Results were similar for the patients with severe haemophilia, however, the number of patients was low (Table 3.8, Appendix 1.2).

The type of treatment varied considerably between the two countries (Table 46). In Germany, most patients received a prophylactic treatment during the entire period of time, with increasing ratios from 64.6% in 2003 to 90% in 2015. In Hungary, the ratio between on-demand and prophylaxis treatment changed from year to year.

Table 45 Type of treatment (prophylaxis/on-demand) over time by pre-treatment (PTP/PUP), all patients

	PTP		PUP		All	
Year **Type of treatment**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
1998						
On Demand	1/5	20.0	3/3	100.0	4/8	50.0
Prophylaxis	4/5	80.0	0/3	0.0	4/8	50.0
2003						
On Demand	51/81	63.0	2/9	22.2	53/90	58.9
Prophylaxis	30/81	37.0	7/9	77.8	37/90	41.1
2008						
On Demand	41/80	51.3	1/8	12.5	42/88	47.7
Prophylaxis	39/80	48.8	7/8	87.5	46/88	52.3
2013						
On Demand	24/60	40.0	0/6	0.0	24/66	36.4
Prophylaxis	36/60	60.0	6/6	100.0	42/66	63.6
2015						
On Demand	21/59	35.6	2/8	25.0	23/67	34.3
Prophylaxis	38/59	64.4	6/8	75.0	44/67	65.7

Source: Appendix 1.1, Table 3.8

Table 46 Type of treatment (prophylaxis/on-demand) over time by country

Year Type of treatment	Germany		Hungary		All	
	n/N	%	n/N	%	n/N	%
1998						
On Demand	3/6	50.0	1/2	50.0	4/8	50.0
Prophylaxis	3/6	50.0	1/2	50.0	4/8	50.0
2003						
On Demand	17/48	35.4	36/42	85.7	53/90	58.9
Prophylaxis	31/48	64.6	6/42	14.3	37/90	41.1
2008						
On Demand	17/48	35.4	25/40	62.5	42/88	47.7
Prophylaxis	31/48	64.6	15/40	37.5	46/88	52.3
2013						
On Demand	7/27	25.9	17/39	43.6	24/66	36.4
Prophylaxis	20/27	74.1	22/39	56.4	42/66	63.6
2015						
On Demand	3/30	10.0	20/37	54.1	23/67	34.3
Prophylaxis	27/30	90.0	17/37	45.9	44/67	65.7

Source: Appendix 1.3, Table 3.8

12.5 Other Analyses

Not applicable.

12.6 Adverse Events and Adverse Drug Reactions

Overviews of adverse events, seriousness and relatedness are provided in Appendices 1.1 to 1.4, Tables 7.1.1 to 7.1.3. A by-patient adverse events listing is given in Data Listings 8 in Appendices 1.1 to 1.4. For the description of relationship, all tables are based on the MAH assessment. The by-patient listing contains the assessments of the MAH and the investigator.

Adverse events related to the serological surveillance are not presented in this section. For data related to the serological surveillance please refer to Section 12.6.9.

12.6.1 Summary of Adverse Events

The following Table 47 to Table 50 provide a general summary of the AEs that were reported in this study in the total population and the patients with severe haemophilia, and by pre-treatment (in PTPs and PUPs) and country.

Adverse events were recorded in a total of 99 patients (60.7%) by the time of the cut-off of this analysis. 10 AEs were suspected to be related to study treatment in 7 patients (4.3%). Adverse events were serious in 78 patients (47.9%), of those 6 SAEs were suspected to be related (SADR) to the study treatment according to MAH assessment in 3 patients (1.8%). A summary of the SAEs regardless of relationship is provided in Section 12.6.3 and a detailed description of drug-related SAEs in Section 12.6.4.

Of the 133 patients with severe haemophilia, 81 patients (60.9%) experienced AEs, 7 patients related AEs (5.3%), and 64 patients SAEs (48.1%), which were classified as drug related (according to MAH assessment) in 3 patients (2.3%).

There were data recording limitations especially at the beginning of the study, most part due to the old NIS monitoring system 17 years ago. Therefore, underreporting of AEs related with bleedings (e.g. pain or causes for (traumatic) bleedings, elective procedures and underlying haemophilia and related co-morbidities (e.g. arthropathy) cannot be ruled out. However, the documentation and reporting of clinically relevant, e.g. FVIII inhibitor formation or thromboembolic events (TEE), are assumed to be reported completely.

In addition the regulatory requirements were changed during the study time. New regulations were becoming active e.g. the EU good pharmacovigilance praxis (GVP) regulations.

Concerning the method and frequency of inhibitor-testing, please refer to Section 12.6.7.

Regarding AE incidences overall, there were no considerable differences between the total population (incidence of any AE in 60.7% of patients) and those with severe haemophilia (incidence of any AE in 60.9% of patients).

The overall AE incidence was 61.5% in the PTPs and 55.0% in PUPs. In patients with severe haemophilia, the AE incidence was 61.0% in the PTPs and 60.0% in PUPs. The incidence of related AEs (according to MAH assessment) was lower in the PTPs (4 of 143 patients, 2.8%) than in the PUPs (3 of 20 patients, 15.0%). SAEs occurred in 48.3% (PTPs) and 45.0% (PUPs), respectively.

The overall AE and SAE incidence was slightly higher in Hungarian (63.5% and 53.8%) than in the German patients (59.5% and 45.0%), whereas more AEs were suspected to be related (according to MAH assessment) in Germany (6 of 111 patients, 5.4%) than in Hungary (1 of 52 patients, 1.9%).

Table 47 Adverse events overview by pre-treatment (PTP/PUP), patient-based, all patients

	PTP (N=143)		PUP (N=20)		Total (N=163)	
Adverse event overview	**N**	**%**	**N**	**%**	**N**	**%**
Patients with any adverse event	88	(61.5%)	11	(55.0%)	99	(60.7%)
Patients with any serious adverse event	69	(48.3%)	9	(45.0%)	78	(47.9%)
Patients with any related adverse event	4	(2.8%)	3	(15.0%)	7	(4.3%)
Patients with any serious related adverse event	1	(0.7%)	2	(10.0%)	3	(1.8%)

Source: Appendix 1.1, Table 7.1, Relationship according to MAH assessment
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 48 Adverse events overview by pre-treatment (PTP/PUP), patient-based, patients with severe haemophilia

	PTP (N=118)		PUP (N=15)		Total (N=133)	
Adverse event overview	**N**	**%**	**N**	**%**	**N**	**%**
Patients with any adverse event	72	(61.0%)	9	(60.0%)	81	(60.9%)
Patients with any serious adverse event	57	(48.3%)	7	(46.7%)	64	(48.1%)
Patients with any related adverse event	4	(3.4%)	3	(20.0%)	7	(5.3%)
Patients with any serious related adverse event	1	(0.8%)	2	(13.3%)	3	(2.3%)

Source: Appendix 1.2, Table 7.1, Relationship according to MAH assessment
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 49 Adverse events overview by country, patient-based, all patients

	Germany (N=111)		Hungary (N=52)		Total (N=163)	
Adverse event overview	**N**	**%**	**N**	**%**	**N**	**%**
Patients with any adverse event	66	(59.5%)	33	(63.5%)	99	(60.7%)
Patients with any serious adverse event	50	(45.0%)	28	(53.8%)	78	(47.9%)
Patients with any related adverse event	6	(5.4%)	1	(1.9%)	7	(4.3%)
Patients with any serious related adverse event	2	(1.8%)	1	(1.9%)	3	(1.8%)

Source: Appendix 1.3, Table 7.1, Relationship according to MAH assessment

Table 50 Adverse events overview by country, patient-based, patients with severe haemophilia

	Germany (N=83)		Hungary (N=50)		Total (N=133)	
Adverse event overview	**N**	**%**	**N**	**%**	**N**	**%**
Patients with any adverse event	49	(59.0%)	32	(64.0%)	81	(60.9%)
Patients with any serious adverse event	37	(44.6%)	27	(54.0%)	64	(48.1%)
Patients with any related adverse event	6	(7.2%)	1	(2.0%)	7	(5.3%)
Patients with any serious related adverse event	2	(2.4%)	1	(2.0%)	3	(2.3%)

Source: Appendix 1.4, Table 7.1, Relationship according to MAH assessment

Tables 7.1.1 in Appendices 1.1 to 1.4 present a summary of AEs regardless of relationship coded by MedDRA Preferred Term, which are summarized in Table 51 for AEs occurring in at least 3 patients of the total population only.

The most frequent and clinically relevant events were gastrointestinal haemorrhage (13 events in 11 patients, all not related), and anti-factor VIII antibody positive (10 events in 9 patients). Further, tooth extraction (13 events in 11 patients), and fall (9 events in 8 patients) were also frequently reported events (Table 51 and Appendix 1.1 Table 7.1.3).

These AEs were also most frequently reported in the patients with severe haemophilia with small differences between the two countries. There were 8 patients in the German centres who were anti factor VIII antibody positive but only 1 patient in Hungary with antibody formation (refer to Appendix 1.2 and 1.4, Table 7.1.1).

Table 51 Display of most frequently reported adverse events regardless of relationship (in > 2 patients) by Preferred Term and pre-treatment (PTP/PUP), all patients

Adverse Events by Preferred Term	PTP (N=143)			PUP (N=20)			Total (N=163)		
	Pat. N	Pat. %	AE N	Pat. N	Pat. %	AE N	Pat. N	Pat. %	AE N
Gastrointestinal haemorrhage	11	(7.7%)	13	0	(0.0%)	0	11	(6.7%)	13
Tooth extraction	10	(7.0%)	12	1	(5.0%)	1	11	(6.7%)	13
Anti factor VIII antibody positive	6	(4.2%)	7	3	(15.0%)	3	9	(5.5%)	10
Fall	7	(4.9%)	8	1	(5.0%)	1	8	(4.9%)	9
Contusion	6	(4.2%)	7	1	(5.0%)	1	7	(4.3%)	8
Haematoma	4	(2.8%)	4	1	(5.0%)	1	5	(3.1%)	5
Muscle haemorrhage	5	(3.5%)	7	0	(0.0%)	0	5	(3.1%)	7
Pyrexia	4	(2.8%)	6	1	(5.0%)	1	5	(3.1%)	7
Gastritis	4	(2.8%)	4	0	(0.0%)	0	4	(2.5%)	4
Gastroenteritis	3	(2.1%)	3	1	(5.0%)	1	4	(2.5%)	4
Hypertension	4	(2.8%)	4	0	(0.0%)	0	4	(2.5%)	4
Nasopharyngitis	3	(2.1%)	3	1	(5.0%)	1	4	(2.5%)	4
Traumatic haematoma	4	(2.8%)	5	0	(0.0%)	0	4	(2.5%)	5
Accident	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3
Anaemia	3	(2.1%)	5	0	(0.0%)	0	3	(1.8%)	5
Arthralgia	2	(1.4%)	2	1	(5.0%)	1	3	(1.8%)	3
Bronchitis	2	(1.4%)	4	1	(5.0%)	1	3	(1.8%)	5
Cholecystectomy	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3
Circumcision	2	(1.4%)	2	1	(5.0%)	1	3	(1.8%)	3
Concussion	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3
Haemophilic arthropathy	3	(2.1%)	5	0	(0.0%)	0	3	(1.8%)	5
Head injury	2	(1.4%)	2	1	(5.0%)	4	3	(1.8%)	6
Injury	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3
Knee arthroplasty	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3
Pain in extremity	2	(1.4%)	5	1	(5.0%)	2	3	(1.8%)	7
Road traffic accident	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3

Source: Appendix 1.1, Table 7.1.1
Pat. = patient, PTP = Previously Treated Patients, PUP = Previously Untreated Patients

12.6.2 Adverse events with a suspected causal relationship to study drug

Overall, 10 AEs were suspected to be drug-related in 7 patients as assessed by the MAH (4.3% of all patients) (see Table 47). The adverse drug reactions (ADRs) were reported within 7 individual case safety reports (ICSRs) (case numbers T 156/02, T 46/03, T 48/03, T 243/04, T 206/04, T 231/10, T 40/13). Eight of the AEs were coded as “Anti-factor VIII antibody positive” in 7 patients, 1 AE as “Factor VIII inhibition” in 1 patient, and 1 AE as “Haemorrhagic diathesis” in 1 patient (see Table 53 and below for more details). In ICSR 156/02, the two events “Anti-factor VIII antibody positive“ were assessed as related by the MAH, whereas the other AEs reported within the same ICSR as “Hypotension”, “Anaemia”, “Gastrointestinal haemorrhage”, and “Melaena” were assessed as not related.

MAH and investigator assessment differed in 6 cases concerning 4 patients (19, 80, 101, 117). Five adverse events, reported in 5 of these 6 cases (T 49/06, T 379/16, T 381/16,

T 390/16, T 392/16) which pertain to 3 patients (80; 101; 117), were assessed as not related by MAH, but assessed as unclassifiable, related or no assessment was reported by the investigator. These 5 adverse events are presented in the following table (Table 52). Concerning the 4th patient (patient no. 19; case T 156/02), the MAH assessed the twice reported "Anti-factor VIII antibody positive" as related, and the investigator as not related to Haemoctin® (refer to the case summary in Appendix 2.1, Section 3).

In 2 cases (T 46/03 and T 48/03) which pertain to 2 patients (46 and 47), the MAH assessed the AE as being related whereas the assessment of the investigator was not available.

Table 52 Adverse events with MAH assessment of causality as 'not related' and Investigator assessment of causality other than 'not related'

Case no. Patient no.	Serious (case)	PT name SOC name	Causality (Biotest)	Causality (investigator)	Outcome	Comment
T 49/06 **101**	s	Anti factor VIII antibody positive Investigations	Not related		recovered	Refer to medical evaluation in section 12.6.6 and Appendix 2.1, Section 3
T 379/16 **80**	ns	Arthralgia Musculoskeletal and connective tissue disorders	Not related	Conditional/ unclassified	Unknown	Symptom of underlying haemophilia A; Therapeutic effectiveness and tolerability of Haemoctin was judged to be very good by the reporting physician.
T 381/16 **80**	ns	Pain General disorders and administration site conditions	Not related	Conditional/ unclassified	Unknown	Symptom of underlying haemophilia A; Therapeutic effectiveness and tolerability of Haemoctin was judged to be very good by the reporting physician.
T 390/16 **117**	ns	Joint swelling Musculoskeletal and connective tissue disorders	Not related	Related	recovered	Symptom of underlying haemophilia A; Neither dosage, frequency of Haemoctin® therapy, nor concomitant medication were changed due to the event. Reportedly, no factor VIII inhibitor was diagnosed.
T 392/16 **117**	ns	Haematoma Vascular disorders	Not related	Related	recovered	Neither the dosage, frequency of Haemoctin therapy, nor concomitant medication were changed. Reportedly no factor VIII inhibitor was diagnosed. Therapeutic effectiveness was judged to be very good by the reporting physician.

Source: Appendix 1.1, Listing 8 and pharmacovigilance Master Safety Database
s = serious, ns = not serious

All patients with drug-related AEs belonged to the subgroup of patients with severe haemophilia (refer to Appendix 1.2, Table 7.1.3). Eight of the 10 drug-related AEs were documented in the German study centres (Table 54).

Between 01-May-1998 until 31-Dec-2015, no ADR of thrombosis or thromboembolic event, and no ADR of hypersensitivity reaction have been reported from this NIS.

No case of suspected viral transmission related to Haemoctin® was reported in the non-interventional study. Differences in serological markers at enrolment and at a later time point are explained by vaccination against HAV and HBV. For the 3 patients without documented vaccinations and a difference in serological markers at enrolment and a later timepoint, the positive test results were not confirmed with other tests and no infections or treatments for infection were reported. For details, please refer to Section 12.6.9.

Table 53 Display of drug-related adverse events by Preferred Term and pre-treatment (PTP/PUP), all patients

	PTP (N=143)			PUP (N=20)			Total (N=163)		
Related Adverse Events by Preferred Term	**Pat. N**	**Pat. %**	**AE N**	**Pat. N**	**Pat. %**	**AE N**	**Pat. N**	**Pat. %**	**AE N**
Any related adverse event	4	(2.8%)	5	3	(15.0%)	5	7	(4.3%)	10
Anti factor VIII antibody positive	4	(2.8%)	5	3	(15.0%)	3	7	(4.3%)	8
Factor VIII inhibition	0	(0.0%)	0	1	(5.0%)	1	1	(0.6%)	1
Haemorrhagic diathesis	0	(0.0%)	0	1	(5.0%)	1	1	(0.6%)	1

Source: Appendix 1.1, Table 7.1.1 and Table 7.1.3, Relationship according to MAH assessment
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 54 Display of drug-related adverse events by Preferred Term and country, all patients

	Germany (N=111)			Hungary (N=52)			Total (N=163)		
Related Adverse Events by Preferred Term	**Pat. N**	**Pat. %**	**AE N**	**Pat. N**	**Pat. %**	**AE N**	**Pat. N**	**Pat. %**	**AE N**
Any related adverse event	6	(5.4%)	8	1	(1.9%)	2	7	(4.3%)	10
Anti factor VIII antibody positive	6	(5.4%)	6	1	(1.9%)	2	7	(4.3%)	8
Factor VIII inhibition	1	(0.9%)	1	0	(0.0%)	0	1	(0.6%)	1
Haemorrhagic diathesis	1	(0.9%)	1	0	(0.0%)	0	1	(0.6%)	1

Source: Appendix 1.3, Table 7.1.1 and Table 7.1.3, Relationship according to MAH assessment

12.6.3 Serious Adverse Events

Serious AEs (SAEs) in all patients and by subgroups are provided in Table 7.1.2 of the Appendices 1.1 to 1.4.

In 78 patients 242 SAEs were reported (208 SAEs in 64 patients with severe haemophilia). Most frequently documented serious AEs were gastrointestinal haemorrhage (13 SAEs in 11 patients), anti-factor VIII antibody positive (6 SAEs in 5 patients), contusion (4 SAEs in 4 patients), muscle haemorrhage (5 SAEs in 4 patients), traumatic haematoma (5 SAEs in 4 patients), and fall (4 SAEs in 4 patients). Most frequently reported SAEs occurring in >2 patients within the groups of PTPs or PUPs are also summarized in Table 55.

Overall, SAEs were recorded with comparable frequencies in PTPs and in PUPs (48.3% and 45.0%, respectively). There were no considerable differences with respect to the incidence of SAEs between the two countries (Appendix 1.3, Table 7.1.2).

For a detailed description of bleeding episodes of high relevance and the analysis of association with Factor VIII inhibitor development refer to Section 12.6.6.

Table 55 Display of most frequently reported serious adverse events (in > 2 patients) by Preferred Term and pre-treatment (PTP/PUP), all patients

Adverse Events by Seriousness and PT Preferred Term	PTP (N=143)			PUP (N=20)			Total (N=163)		
	Pat. N	Pat. %	AE N	Pat. N	Pat. %	AE N	Pat. N	Pat. %	AE N
Any serious adverse event (all)	69	(48.3%)	220	9	(45.0%)	22	78	(47.9%)	242
Gastrointestinal haemorrhage	11	(7.7%)	13	0	(0.0%)	0	11	(6.7%)	13
Anti factor VIII antibody positive	3	(2.1%)	4	2	(10.0%)	2	5	(3.1%)	6
Contusion	3	(2.1%)	3	1	(5.0%)	1	4	(2.5%)	4
Fall	3	(2.1%)	3	1	(5.0%)	1	4	(2.5%)	4
Muscle haemorrhage	4	(2.8%)	5	0	(0.0%)	0	4	(2.5%)	5
Traumatic haematoma	4	(2.8%)	5	0	(0.0%)	0	4	(2.5%)	5
Anaemia	3	(2.1%)	5	0	(0.0%)	0	3	(1.8%)	5
Cholecystectomy	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3
Concussion	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3
Haematoma	2	(1.4%)	2	1	(5.0%)	1	3	(1.8%)	3
Knee arthroplasty	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3
Pyrexia	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3
Road traffic accident	3	(2.1%)	3	0	(0.0%)	0	3	(1.8%)	3

Source: Appendix 1.1, Table 7.1.1 and Table 7.1.3
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

12.6.4 Drug-related Serious Adverse Events

Six SAEs were suspected to be drug-related (according to MAH assessment) in 3 patients (1.8% of all patients) and reported in 3 ICSRs. All cases had development of anti factor VIII antibodies as main diagnosis. All these patients were diagnosed with severe haemophilia. Two of the patients were treated in Germany and 1 in Hungary (refer to Appendix 2.1, Table 1 for by-patient AE-Listing).

The 3 ICSRs cases were

- Case no. T 156/02 (Patient No. 19): Twice anti factor VIII antibody positive (both related) with gastrointestinal haemorrhage, hypotension, anaemia, and melaena, which were all not related. The investigator judged the AEs of anti factor VIII antibody positive as not related (refer to evaluation in 12.6.6).
- Case no. T 231/10 (Patient No. 119): Anti factor VIII antibody positive
- Case no T 40/13 (Patient No. 144): Anti factor VIII antibody positive, factor VIII inhibition, and haemorrhagic diathesis, which were all assessed as related (refer to evaluation in 12.6.6).

All patients recovered from these SAEs.

Patient related details can be found in Appendix 2.1., Section 1.

12.6.5 Patients with Positive Inhibitor Results

As it is required in non-interventional settings, within this NIS, the applied routine treatment conditions of FVIII in medical practice were observed. Therefore, the method and frequency of FVIII inhibitor testing was not predefined in the observation plan. FVIII inhibitor testing was performed periodically. According to the NIS plan, patients were expected to show up for performing routine screenings at least via one annual visit at the haemophilia treatment centres. Three to four routine visits per year were performed by most of the patients.

In case of bleeding events due suspicion of lack of efficacy e.g. due FVIII inhibitor formation, this had to be reported immediately to the drug safety department. In the CRFs the result of the FVIII inhibitor tests was documented in BU/ml (Bethesda Unit per millilitre). Within the NIS Haemoctin a FVIII inhibitor test was positive when the value was over the normal range (≥ 0.7 BU). A few centres defined the FVIII inhibitor positive according to local definitions (limited by sensitivity of the test used to ≥ 1.0 BU/ml).

Positive FVIII inhibitor tests were not repeated to confirm the positive result. The first positive FVIII inhibitor test was reported as adverse event. For all included patients in the NIS, at least clinically relevant events including lack of efficacy, during normal clinical practice of patients were detected within this NIS.

Routine inhibitor testing has become a standard and is generally risk-adapted with close monitoring of PUPs during the first 20-50 EDs and less frequent testing of patients on established prophylaxis. The goal of routine inhibitor testing is early detection of inhibitors to be able to start ITI therapy promptly, as the starting titre has been shown to be the most powerful predictor of ITI success (Collins et al. 2013, Auerswald et al. 2008).

During the study, the mean number of factor VIII inhibitor measurements per year was 3.9 (SD 11.2; median 2.1, ranging from 0.1 to 91.3) (refer to Appendix 1.1, Table 5.2).

Deviations from normal range with regard to inhibitor results were analysed for

- investigator assessment in the CRF (positive inhibitor results yes/no) and
- laboratory assessments (i.e. ≤ 0.7 BU – no inhibitor, > 0.7 to 5.0 BU – low titre inhibitor, > 5.0 BU – high titre inhibitor) related to the number of measurements.

In contrast to this definition in the single case safety description (Appendix 2.1), inhibitors with 5.0 BU are discussed as high titre inhibitors.

The summary of investigator and laboratory assessments is presented in Table 56 and Table 57. A by-patient listing provided in Appendix 1.1, Table 5.3, shows that there were 15 patients with deviations in inhibitor levels from normal range, and 9 patients with a respective AE recording (PT ‘anti factor VIII antibody positive’ or ‘factor VIII inhibition’) (see Section 12.6.7).

As evaluated by the investigator and documented in the CRFs, in 21 measurements inhibitor values were abnormal during the study (15 measurements in the PTP and 6 in the PUP subgroup), of which 20 results were from patients with severe haemophilia.

According to laboratory assessments, 18 measurements (in 12 patients) showed increased inhibitor levels (>0.7 to 5 BU), 10 measurements (in 4 patients; all with severe haemophilia) showed high titre inhibitors (levels > 5 BU) and in 4 measurements (in 4 patients, all with severe haemophilia) the BU value was unknown but inhibitor level was assessed as 'positive'.

Section 12.6.7 details 9 patients, that reported AEs related to positive inhibitor test results. The other 6 patients with positive test results according to the CRF database are explained in detail in Table 58. None of the results was a deviation from the normal range that should have been reported as AE. Two patients were enrolled with known FVIII inhibitors in order to perform an ITI within the NIS. One patient had a single positive inhibitor results prior to starting treatment with Haemoctin®. For 2 patients, the investigator mistakenly ticked the box for 'deviation from normal range'. For one patient the investigator confirmed that the measured value of 0.8 BU was indeed no deviation from the local normal range of 1.0 BU.

Table 56 Deviations from normal range with respect to inhibitors, all patients

Number (% of Defined Values) of Deviations from Normal Ranges	PTP			PUP			All		
	N$	n	%	N$	n	%	N$	n	%
Inhibitors *	2281	15	0.66	192	6	3.13	2473	21	0.85
Low titre inhibitors > 0.7 BU - 5 BU **	2560	13	0.51	227	5	2.20	2787	18	0.65
High titre inhibitors > 5 BU	2560	9	0.35	227	1	0.44	2787	10	0.36
Inhibitors positive, value unknown	2560	4	0.16	227	0	0.00	2787	4	0.14

Source: Appendix 1.1, Table 5.1
* According to normal range from investigator assessment. ** For one patient, the investigator confirmed that the measured value of 0.8 BU was indeed no deviation from the local normal range of 1.0 BU.
PTP = Previously Treated Patients, PUP = Previously Untreated Patients
$ Total number of measurements

Table 57 Deviations from normal range with respect to inhibitors, all patients with severe haemophilia

Number (% of Defined Values) of Deviations from Normal Ranges	PTP			PUP			All		
	N$	n	%	N$	n	%	N$	n	%
Inhibitors *	2136	14	0.66	163	6	3.68	2299	20	0.87
Low titre inhibitors > 0.7 BU - 5 BU **	2392	12	0.50	189	5	2.65	2581	17	0.66
High titre inhibitors > 5 BU	2392	9	0.38	189	1	0.53	2581	10	0.39
Inhibitors positive, value unknown	2392	4	0.17	189	0	0.00	2581	4	0.15

Source: Appendix 1.2, Table 5.1
* According to normal range from investigator assessment. **For one patient the investigator confirmed that the measured value of 0.8 BU was indeed no deviation from the local normal range of 1.0 BU.
PTP = Previously Treated Patients, PUP = Previously Untreated Patients
$ Total number of measurements

Table 58 Patients with deviations from normal range with respect to inhibitors who did not report an AE related to FVIII inhibitors

Patient No	PTP or PUP	Reported values	MAH comment
20	PTP	one result ticked “yes” w/o value	Nullified case / No case: The reporter stated that "the 'Inhibitors - Deviation from normal range' box was mistakenly crossed"
38	PTP	one result ticked “yes” w/o value	For a single inhibitor measurement „norm deviations" was ticked in the CRF, but no value/ titre was documented. On the same day, the investigator documented that no inhibitor was diagnosed in this patient and that no adverse event occurred. During the next year, the investigator documented again that no inhibitor was diagnosed in this patient and that no adverse event occurred. The treatment regimen was not changed after the first test result. Therefore, most probably the investigator mistakenly ticked the box "norm deviations".
69	PTP	27 BU, 66 BU, 12 BU, 30 BU, 9 BU, 25 BU, 3 BU during the 1st year in NIS, < 0.7 BU and 2< BU during the 2nd year in NIS	Nullified case Inclusion with pre-existing inhibitors to perform ITI with Haemoctin
86	PTP	1.8 BU, once	Inhibitor value (1.8 BU) was measured at initial visit and before the patient was treated with Haemoctin®. Since first application of Haemoctin®, no abnormal inhibitor value was measured.
99	PTP	0.8 BU in 2004	Tick-box "no deviation from normal range" was ticked and the investigator commented that this value was within the normal range (<1.0 BU/mL)
166	PTP	12.3 BU and 23.4 BU during 1st year in NIS; 4.5 BU during 2nd year in NIS	Inclusion with pre-existing inhibitors to perform ITI with Haemoctin

12.6.6 Bleeding Episodes of High Relevance and Analysis of Association with Factor VIII Inhibitor Development

From 01-May-1998 to 31-Dec-2015, 43 serious bleeding episodes (considered bleedings of high relevance) were identified in 29 patients (26 PTPs and 3 PUPs)/ 29 Individual Case Safety Reports (ICSRs) and are presented in Appendix 2.1, Section 2, Table 5 und Table 6.

Seventeen (17) of the 29 patients were under prophylactic treatment and 12 were under on-demand treatment with Haemoctin®.

Most of the 29 patients who suffered from a serious bleeding during the NIS, suffered from severe haemophilia A (18 patients < 1% and 6 patients 1% residual FVIII activity), 3 patients suffered from moderate haemophilia A, and 2 from mild haemophilia A.

Only 1 of the 43 serious bleeding events, in one case (Patient no. 144 (PUP) with severe haemophilia A, T 40/13) was assessed by the respective investigator and by MAH to be related to the Haemoctin® treatment. The bleeding in this patient was most probably caused by trauma, and due to bleeding tendency, the patient received on-demand for 2 days (each day 500 IU) Haemoctin®. The case is presented in detail in Appendix 2.1, Section 2.

For 3 of the 29 patients (Patient 144 (PUP), case T 40/13, and Patient 19 (PTP), case T 156/02 and Patient 76 (PTP), T 866/14) transient FVIII inhibitors and serious bleeding events were reported during their observation in the NIS.

In 2 (T 156/02, T 866/14) of the 3 cases, the FVIII inhibitors could not have caused the bleeding events.

In case T 156/02 (Patient no. 19), the transient FVIII inhibitors first occurred 15 months after start of treatment documentation within the NIS, re-occurred 7.25 years later, disappeared spontaneously (next tests all negative, last test 6 months after re-occurrence, 7 months after re-occurrence a GI-bleeding was reported) and re-occurred after the GI-bleeding events had been recovered.

In case T 866/14 (Patient no. 76), the questionable FVIII formation (FVIII antibody test with reported "borderline" result and repeated test on same day was negative; see Appendix 2.1, Section 3) occurred with at least/approx. 1 year time difference to the serious bleeding events: Patient 76 suffered from 'Gastrointestinal haemorrhage' about 1 year after start of treatment documentation within the NIS and recovered 3 days later. About 1 year later, the FVIII antibody test with reported "borderline" and a negative result was detected. 4.5 years after the GI bleeding, the patient suffered from cerebral haemorrhage, which led to death (case T 128/08). Case T 128/08 is presented in detail in Appendix 2.1, Section 4.

In one (1) further ICSR (Patient no. 101 (PTP), case T 49/06;) the increased frequency of haematoma (non-serious; assessed as unassessable by the reporter and not related by MAH) was reported in relation with the re-occurrence of FVIII antibodies, due to non-compliance of the patient during ITI with Haemoctin®. In this case, the frequency of spontaneous bleedings increased in a close timely relationship with the FVIII inhibitor formation. These haematomas were non-serious and are therefore not included in the table in Appendix 2.1, Section 2.

All cases on FVIII inhibitor formation are presented in Appendix 2.1, Section 3 and were analysed on the occurrence of associated bleeding events.

For all other cases on bleedings, no formation of FVIII inhibitors was reported and no hint on FVIII inhibitor formation was reported.

In general, the rate of serious bleedings is considered low taking into account a total of 1202 patient years. The majority of patients with serious bleedings were under prophylactic treatment with Haemoctin®. A major cause of bleeding included significant trauma, mucosal lesion, or vascular lesion in combination with hypertension and/ or liver diseases.

Cases with fatal outcome are presented in Section 12.6.8 and detailed in Appendix 2.1, Section 4.

12.6.7 Development of Factor VIII Antibodies (Inhibitors) and Analysis of Associated Bleeding Episodes and Clinical Outcome

Within the study period 01-May-1998 to 31-Dec-2015, nine (9) patients developed FVIII antibodies under Haemoctin® therapy and reported these as AEs, thereof 3 PUPs and 6 PTPs.

With exception of 1 patient (PTP), only patients in German centres developed FVIII inhibitors. Eight (8) of these 9 patients were Caucasian, 1 PUP was a black African.

Three (3) ICSRs in PUPs who developed de novo FVIII inhibitors under Haemoctin® therapy from the NIS Haemoctin were retrieved from the Biotest MSDB. In all 3 cases, the PUPs suffered from severe haemophilia A (factor VIII residual activity >1 %).

Concerning the 3 cases in PUPs, in 1 case (patient no. 119; T 231/10) the patient suffered from high-titre (≥ 5 BU/ml) and persistent inhibitors. In the other 2 cases, the PUPs suffered from transient and low-titre inhibitors (< 5 BU/ml).

In PUPs, FVIII inhibitors developed on average after 16 EDs (range 5-27 EDs) and at an average age of 12.3 months (range 10-15 months). The high-titre inhibitors occurred already after ED 5.

The incidence of FVIII inhibitor formation in all PUPs within this NIS was 15% (3/20), and 5% (1/20) of high-titre inhibitors.

Case summaries are presented in Appendix 2.1, Section 3.

Six (6) ICSRs (patient no. 19, case T 156/02 ; patient no. 46, case T 46/03 ; patient no. 47, case T 48/03 ; patient no. 95, case T 243/04; patient no. 101, case T 49/06; patient no. 76, case T 866/14) on PTPs who developed FVIII inhibitors under Haemoctin® within the NIS Haemoctin can be retrieved from the Biotest MSDB. Four (4) of these ICSRs were transient and disappeared without starting an ITI. In the 2 remaining cases an ITI was successfully performed with Haemoctin® (T 243/04, T 49/06).

In 5 of the 6 ICSRs, the patients suffered from severe haemophilia A (residual FVIII activity <1%). In one case (T 46/03; patient no. 46), the patient suffered from moderate haemophilia A (residual FVIII activity 2%; range 1 to ≤ 5% residual FVIII activity).

In 2 (patient no. 101, case T 49/06; patient no. 76, case T 866/14) of the 6 cases in PTPs, the FVIII inhibitor formation was assessed as not related to Haemoctin® by investigator (in 1 case unassessable; patient no. 101; T 49/06) and by MAH. In one (1) case (Patient No. 101, case T 49/06) the patient was included in the NIS with pre-existing FVIII inhibitors to perform an ITI with Haemoctin®. The patient was successfully treated with Haemoctin®, but due to non-compliance (dosage of Haemoctin® was decreased by the parents without consulting the treating physician), the frequency of haematomas increased and FVIII inhibitors re-occurred. This case is presented in detail in Appendix 2.1, Section 3.

In 3 (patient no. 46, case T 46/03; patient no. 47, case T 48/03; patient no. 101, case T 49/06) of the 6 cases in PTPs, high-titre inhibitors developed.

In 2 of these 3 cases (patient no. 46, T 46/03; patient no. 47, T 48/03), maximal titres of 5 BU/ml were reported. The transient and not clinically relevant inhibitors disappeared without changes of treatment.

On average, FVIII inhibitors developed at an age of 28.5 years (range 5-52years) in the 6 PTPs. The high-titre inhibitors occurred on average at 10.3 years (range 5-14 years).

The incidence of FVIII inhibitor formation in all PTPs within this NIS was 2.8% (4/143), and 1.4% (2/143) of high-titre inhibitors.

All ICSRs on FVIII inhibitor formations were analysed on clinical relevance.

The FVIII inhibitor development was assessed as clinically relevant if any of the following applied:

- Persistent and high-titre FVIII inhibitors, which required ITI
- Occurrence of a higher frequency and/or more spontaneous bleeding events

Two (2) cases on FVIII inhibitor formation were assessed as clinically relevant. One (1) case concerned a PUP, Patient no. 119 (T 231/10), and the other case (T 49/06) concerned a PTP, Patient no. 101.

In these 2 cases, ITI was successfully performed with Haemoctin®.

In only 1 PUP (1/20 PUPs), clinically relevant FVIII inhibitors (persistent and high-titre FVIII inhibitors, which required ITI) developed during the NIS, that were assessed as related to Haemoctin® by investigator and MAH.

None of the developed FVIII inhibitors in PTPs, related to Haemoctin®, were clinically relevant.

12.6.8 SAEs with fatal outcome

There were 8 patients who died during the study due to SAEs that were all assessed as not related to the study treatment (according to MAH and according to investigator).

All 8 patients were PTPs. Four of these patients suffered from severe haemophilia A (residual FVIII activity >1%; patients no. 14, 15, 22, 76), 3 patients (no. 2, 18, 57) had 1 % residual FVIII activity, and patient no. 93 suffered from moderate haemophilia A (residual FVIII activity 2%; range 1 to ≤ 5% residual FVIII activity). Seven (7) of the 8 patients, who died during the NIS, were treated in Hungary. The only German patient who died was patient no. 76.

Four (4) of the 8 patients (no. 18, 57, 76, 93) were treated prophylactically with Haemoctin® at the time of death.

Three (3) of the 8 patients died from cerebral haemorrhage, thereof were 2 (patient no.14, 22) treated on-demand and 1 patient (no.76) was treated prophylactically (home treatment) with Haemoctin®.

In all 8 cases alternative explanations and/or sufficient confounding/contributing factors were reported.

Detailed patient narratives and medical assessments are provided in Appendix 2.1, Section 4

- Patient No. 2 (case T 553/14) (39 years old) died from sepsis,
- Patient No. 14 (case T 122/06) (47 years old at the time of death) died from cerebral haemorrhage,
- Patient No. 15 (case T 405/12) (75 years old at the time of death) died from hepatocellular carcinoma and liver disorders
- Patient No. 18 (case T 406/08) (46 years old at the time of death) died from hepatic failure,
- Patient No. 22 (case T 127/06) (24 years old at the time of death) died from haemorrhagic stroke, intracranial haemorrhage and brain oedema,
- Patient No. 57 (case T 132/09) (38 years old at the time of death) died from hepatorenal syndrome,
- Patient No. 76 (case T 128/08) (49 years old at the time of death) died from cerebral haemorrhage,
- Patient No. 93 (case T 396/12) (88 years old at the time of death) died from cardiac/vascular disorders and chronic kidney disease.

12.6.9 Results of the Serological Surveillance

At haemophilia monitoring visits serological determinations concerning anti-HAV (IgG and IgM), HBsAg, anti-HBc, anti-HBs, anti-HCV and anti-HIV 1 and 2 were carried out.

Patients are considered negative for the respective virus type at baseline if they were

- HAV IgM negative and HAV IgE negative
- HBsAg, anti-HBc, and anti-HBs negative
- anti-HCV negative
- anti-HIV negative

Seroconversions are suspected in the following cases:

- HAV: If both anti-HAV IgG and anti-HAV IgM were negative at baseline and at least one turned into constantly positive results during the observation period.
- HBV: If all three HBsAg, anti-HBc, and anti-HBs were negative in the baseline assessments and at least one was changed into constantly positive.
- HCV: If there was a change for anti-HCV during the NIS.
- HIV: If there was a change for anti-HIV during the NIS.

In case of missing results, text or other additional information given by the investigator was used whenever available. In case no additional information was available, a negative result of the following assessment or a vaccination at the next visit was assumed to apply also for the previous time point. Single positive results, followed by negative ones, were considered as false positive and vice versa. Seroconversion was accepted only if a positive result persisted.

An overview of the results of the serological surveillance at the end of the study and when compared to the results at study start are depicted in Table 59 and Table 60.

HAV

At baseline, 24 patients were positive, 86 patients were negative, 24 patients had been vaccinated against HAV prior to study entry and for 29 patients, no HAV test result was available.

32 patients received a vaccination against HAV during the study. Vaccine titres of Anti-HAV IgG were present in these patients after vaccination. For patients No. 25 and No. 100, the positive tests for Anti-HAV IgG were reported as adverse events (MAH case numbers T 285/09 and T 286/09) because their vaccinations were initially not documented. However, information that these patients actually had been vaccinated could be obtained. Both the reporter and the MAH assessed the causality of the events as not related to Haemoctin® application.

For 31 patients (19.0%), that were documented as HAV negative at start of study, the HAV status was not available at end of study and therefore an evaluation of a possible infection could not be done (Table 60).

In the long-term observation of the 163 subjects treated, 2 subjects had a change in the viral status from the beginning of the treatment to the last measurement was observed in the Anti-HAV IgG determined by the Western Blot screening test (Patient No. 3, 141) according to the CRF database.

For Patient 141, it was confirmed that the patient had already been positive with respect to HAV IgG before entering the study, but this had not been entered in the CRF.

For Patient 3, the Anti-HAV IgG and IgM tests were reported throughout as negative in the CRF over the first 10 years of participation in the NIS. After 10 years at the start of PMS III study, the investigator documented laboratory results of the virological status of the patient, revealing that the HAV IgG test was positive. He stated in addition that the "virological findings are not in a causal relationship to former treatment of the patient with Haemoctin SDH". Thereafter, the investigator documented positive Anti-HAV IgG tests for Patient 3 in the CRF for another 3 years. In addition, the investigator always documented, that the patient did not suffer from any intercurrent disease since last visit within the NIS.

HBV

At baseline, 45 patients were positive and 28 were negative, 72 patients had been vaccinated against HBV, and for 18 patients the HBV status was not available.

13 patients were vaccinated against HBV during the study.

For 3 patients that were documented as HBV negative at start of study, the HBV status was not available at end of study and therefore an evaluation of a possible infection could not be done.

Two patients (patients 67 and 141) were HBV negative at baseline and turned into a positive HBV viral status during the study according to the CRF database. Patient 67 had a single positive anti-HBc test about 2.5 years after start of treatment documentation within the NIS but also a negative HbsAg test and negative Anti-HBs antibodies at the same time. Thereafter, no further test results were provided but also no clinical event related to any infection.

For Patient 141, it was confirmed that the patient had already been positive with respect to anti-HBs test before entering the study, but this had not been entered in the CRF. The tests for HbsAG and anti-HBc antibodies were negative according to the documentation outside the CRF and according to CRF database at baseline and stayed negative during the NIS.

For 4 of 18 patients, whose HBV status was not available at the start of the NIS, HBV was reported as positive at the end of study (Table 60).

HCV

At baseline 85 patients were HCV positive and 62 patients were negative. For 16 patients, the HCV status was not available.

For 15 previously negative patients the HCV status was not available at end of study, and therefore, an evaluation of a possible infection could not be done.

For Patient 34, the CRF database contains negative Anti-HCV tests from the beginning of the NIS for about 7 years and positive test results thereafter for another 7.5 years.

The patient did not show any clinical signs of hepatitis and there was no therapy for hepatitis. The negative HCV RNA testing about 9 years after start of Haemoctin® within the NIS is in agreement with the fact that the patient never displayed clinical signs of hepatitis and proves that the patient never suffered from a HCV infection. As the positive or indeterminate results of the Anti-HCV screening tests never were confirmed by immunoblot or NAT testing they are considered "false positive" by the MAH. There is no more the suspicion of a transmission of an infective agent. False positive laboratory results for HCV antibodies were documented for the period before first application of Haemoctin®.

4 patients had no results available at the beginning of the study and were tested HCV positive at the end of the study (Table 60).

HIV

At baseline 2 patients were positive and 137 patients were HIV negative. For 24 patients the HIV status was not assessable.

For 72 previously negative patients, the HIV status was not available at end of study and therefore an evaluation of seroconversion was not possible.

Two Patients (114, 157) had no direct HIV test results documented at the beginning of the study and were tested HIV positive at the end of the study. However, both patients were known to be HIV positive at the beginning of the study (Table 60).

Table 59 Results of the serological surveillance at study end, all patients

Virology Results at End of Study	PTP (N=143)		PUP (N=20)		Total (N=163)	
	n	%	n	%	n	%
HAV						
not available	51	35.7	6	30.0	57	35.0
negative	18	12.6	3	15.0	21	12.9
positive	29	20.3	0	0	29	17.8
vaccination	45	31.5	11	55.0	56	34.4
HBV						
not available	16	11.2	1	5.0	17	10.4
negative	8	5.6	2	10.0	10	6.1
positive	51	35.7	0	0	51	31.3
vaccination	68	47.6	17	85.0	85	52.1
HCV						
not available	23	16.1	6	30.0	29	17.8
negative	34	23.8	14	70.0	48	29.4
positive	86	60.1	0	0	86	52.8
HIV						
not available	85	59.4	9	45.0	94	57.7
negative	54	37.8	11	55.0	65	39.9
positive	4	2.8	0	0	4	2.5

Source: Appendix 1.1, Table 4.1
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 60 Results of the serological surveillance at study end compared with study start, all patients

End of Study	PTP (N=143) _Begin of Study_								PUP (N=20) _Begin of Study_								Total (N=163) _Begin of Study_							
	not available		negative		positive		vacc.		not available		negative		positive		vacc.		not available		negative		positive		vacc.	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HAV																								
negative	0	0.0	18	12.6	0	0.0	0	0.0	0	0.0	3	15.0	0	0.0	0	0.0	0	0.0	21	12.9	0	0.0	0	0.0
positive	4	2.8	2	1.4	23	16.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	2.5	2	1.2	23	14.1	0	0.0
vacc.	0	0.0	25	17.5	0	0.0	20	14.0	0	0.0	7	35.0	0	0.0	4	20.0	0	0.0	32	19.6	0	0.0	24	14.7
not available	22	15.4	28	19.6	1	0.7	0	0.0	3	15.0	3	15.0	0	0.0	0	0.0	25	15.3	31	19.0	1	0.6	0	0.0
HBV																								
negative	0	0.0	7	4.9	1	0.7	0	0.0	0	0.0	2	10.0	0	0.0	0	0.0	0	0.0	9	5.5	1	0.6	0	0.0
positive	4	2.8	2	1.4	45	31.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	2.5	2	1.2	45	27.6	0	0.0
vacc.	0	0.0	8	5.6	0	0.0	60	42.0	0	0.0	5	25.0	0	0.0	12	60.0	0	0.0	13	8.0	0	0.0	72	44.2
not available	13	9.1	3	2.1	0	0.0	0	0.0	1	5.0	0	0.0	0	0.0	0	0.0	14	8.6	3	1.8	0	0.0	0	0.0
HCV																								
negative	0	0.0	32	22.4	2	1.4			0	0.0	14	70.0	0	0.0			0	0.0	46	28.2	2	1.2		
positive	4	2.8	1	0.7	81	56.6			0	0.0	0	0.0	0	0.0			4	2.5	1	0.6	81	49.7		
not available	9	6.3	12	8.4	2	1.4			3	15.0	3	15.0	0	0.0			12	7.4	15	9.2	2	1.2		
HIV																								
negative	0	0.0	54	37.8	0	0.0			0	0.0	11	55.0	0	0.0			0	0.0	65	39.9	0	0.0		
positive	2	1.4	0	0.0	2	1.4			0	0.0	0	0.0	0	0.0			2	1.2	0	0.0	2	1.2		
not available	19	13.3	66	46.2	0	0.0			3	15.0	6	30.0	0	0.0			22	13.5	72	44.2	0	0.0		

Source: Appendix 1.1, Table 4.1
PTP = Previously Treated Patients, PUP = Previously Untreated Patients, vacc. = vaccination

12.6.10 Laboratory Parameters

The laboratory parameter values with deviations from normal ranges are shown in Table 61 for all patients and in Table 62 for patients with severe haemophilia.

Overall, the proportion of measurements with deviations from the normal range was lowest with CD4 (5.17%) and highest with SGPT (25.11%) measurements, with generally more deviations in patients in the PTP subgroup. There were no considerable deviations between the countries (Table 5.1, Appendices 1.3 and 1.4).

Table 61 Laboratory parameter deviations from normal ranges, all patients

Number(% of Defined Values) of Deviations from Normal Ranges	PTP			PUP			All		
	N$	n	%	N$	n	%	N$	n	%
Bilirubin	2563	376	14.67	161	10	6.21	2724	386	14.17
AP	2472	180	7.28	139	4	2.88	2611	184	7.05
SGPT	2668	719	26.95	203	2	0.99	2871	721	25.11
SGOT	2659	492	18.50	209	23	11.00	2868	515	17.96
Gamma-GT	2567	413	16.09	162	1	0.62	2729	414	15.17
LDH	2384	167	7.01	138	12	8.70	2522	179	7.10
Haematocrit	2690	226	8.40	229	37	16.16	2919	263	9.01
Platelets	2679	203	7.58	221	19	8.60	2900	222	7.66
CD4	998	52	5.21	7	0	0.00	1005	52	5.17
CD8	165	12	7.27	7	0	0.00	172	12	6.98

Source: Appendix 1.1, Table 5.1
PTP = Previously Treated Patients, PUP = Previously Untreated Patients
$ Total number of measurements

Table 62 Laboratory parameter deviations from normal ranges, patients with severe haemophilia

Number(% of Defined Values) of Deviations from Normal Ranges	PTP			PUP			All		
	N$	n	%	N$	n	%	N$	n	%
Bilirubin	2403	368	15.31	141	1	0.71	2544	369	14.50
AP	2318	173	7.46	120	2	1.67	2438	175	7.18
SGPT	2486	682	27.43	168	2	1.19	2654	684	25.77
SGOT	2477	465	18.77	172	18	10.47	2649	483	18.23
Gamma-GT	2400	395	16.46	140	0	0.00	2540	395	15.55
LDH	2237	157	7.02	120	10	8.33	2357	167	7.09
Haematocrit	2494	184	7.38	187	26	13.90	2681	210	7.83
Platelets	2482	191	7.70	179	17	9.50	2661	208	7.82
CD4	941	50	5.31	7	0	0.00	948	50	5.27
CD8	147	12	8.16	7	0	0.00	154	12	7.79

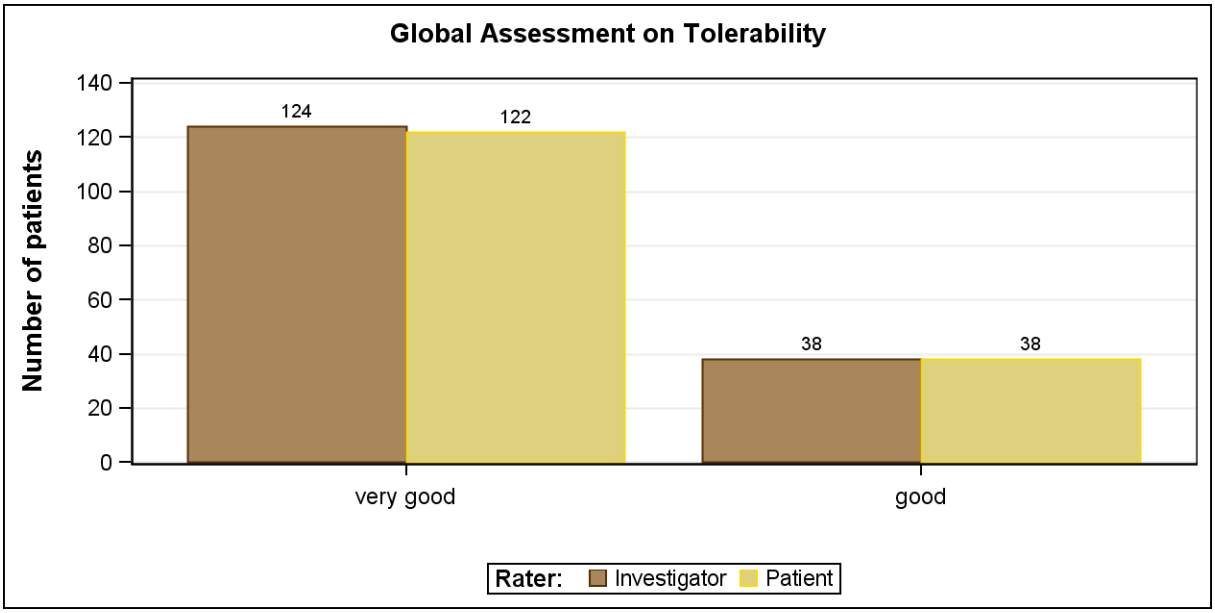
Source: Appendix 1.2, Table 5.1
PTP = Previously Treated Patients, PUP = Previously Untreated Patients
$ Total number of measurements

12.6.11 Global Assessment on Tolerability

At the end of each CRF, a global assessment on tolerability was performed by both the investigator and the patient.

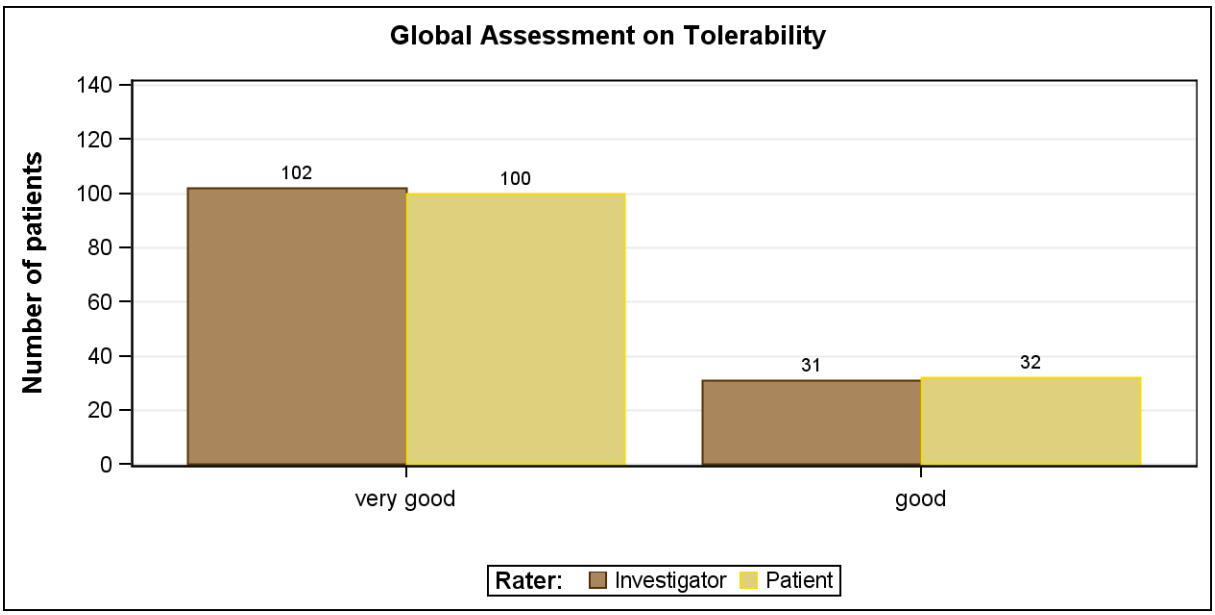
Possible ratings on tolerability were ‘very good’ (=1), ‘good’ (=2), ‘moderate’ (=3), or ‘poor’ (=4).

Figure 7 Global assessment on tolerability by investigators and patients, all patients



Source: Appendix 1.1, Figure 6.1

Figure 8 Global assessment on tolerability by investigators and patients, patients with severe haemophilia



Source: Appendix 1.2, Figure 6.1

The distribution of ratings is depicted in Figure 7, showing that the majority of both the investigators and patients rated the global effectiveness as very good. Results were similar for patients with severe haemophilia (Figure 8). Neither investigators nor any patient assessed the tolerability as moderate or poor.

Accordingly, mean tolerability assessed by investigators was 1.24 (SD 0.37; ranging from 1.00 to 2.00); 1.24 (SD 0.37) for PTPs and 1.29 (SD 0.38) for PUPs. Mean tolerability assessed by patients was 1.26 (SD 0.37; ranging from 1.00 to 2.00); 1.26 (SD 0.37) for PTPs and 1.30 (SD 0.39) for PUPs. Ratings in the subgroup of patients with severe haemophilia and by country were similar (Table 63 and Table 64).

Table 63 Mean scores of global tolerability assessment by investigators, all patients and patients with severe haemophilia by previous treatment and by country

Investigator assessment		n	mean	SD	Min	median	Max
Total (N=163)		162	1.24	0.37	1.00	1.00	2.00
Previous Treatment	**PTP (N=143)**	143	1.24	0.37	1.00	1.00	2.00
	PUP (N=20)	19	1.29	0.38	1.00	1.13	2.00
Country	**Germany (N=111)**	110	1.32	0.39	1.00	1.00	2.00
	Hungary (N=52)	52	1.08	0.24	1.00	1.00	2.00
All severe haemophilia (N=133)		133	1.24	0.36	1.00	1.00	2.00
Previous Treatment	**PTP (N=118)**	118	1.24	0.36	1.00	1.00	2.00
	PUP (N=15)	15	1.28	0.38	1.00	1.13	2.00
Country	**Germany (N=83)**	83	1.34	0.39	1.00	1.15	2.00
	Hungary (N=50)	50	1.08	0.24	1.00	1.00	2.00

Source: Appendices 1.1, 1.2, 1.3, 1.4, Table 6.2
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

Table 64 Mean scores of global tolerability assessment by patients, all patients and patients with severe haemophilia by previous treatment and by country

Patient assessment		n	mean	SD	Min	median	Max
Total (N=163)		160	1.26	0.37	1.00	1.00	2.00
Previous Treatment	**PTP (N=143)**	142	1.26	0.37	1.00	1.00	2.00
	PUP (N=20)	18	1.30	0.39	1.00	1.15	2.00
Country	**Germany (N=111)**	108	1.33	0.41	1.00	1.00	2.00
	Hungary (N=52)	52	1.12	0.23	1.00	1.00	2.00
All severe haemophilia (N=133)		132	1.28	0.37	1.00	1.03	2.00
Previous Treatment	**PTP (N=118)**	118	1.27	0.37	1.00	1.00	2.00
	PUP (N=15)	14	1.30	0.39	1.00	1.15	2.00
Country	**Germany (N=83)**	82	1.37	0.41	1.00	1.20	2.00
	Hungary (N=50)	50	1.12	0.24	1.00	1.00	2.00

Source: Appendices 1.1, 1.2, 1.3, 1.4, Table 6.3
PTP = Previously Treated Patients, PUP = Previously Untreated Patients

13. DISCUSSION

This open-label, prospective, multicentre, long term, observational study (post-marketing study) is reported from May 1998 onwards to present data on the long term safety of Haemoctin® in the prophylactic or on-demand setting to provide an enhanced database for the long term use of Haemoctin® in patients with diagnostically confirmed haemophilia A. Study data were documented till end of December 2015 and, thus, provides data from a very long lasting documentation of Haemoctin® use under routine conditions for over 17 years. On average, patients were documented for a time period of 7.5 years.

Key questions were to evaluate the influence of a long-term continuous treatment with Haemoctin® on general health status, to obtain effectiveness data regarding bleeding event and to assess the risk of FVIII inhibitor development while under long-term prophylaxis or on-demand treatment.

Possible differences between patients who were previously treated with clotting factors (PTPs) and who were previously untreated (PUPs) were determined descriptively. Moreover, patients with severe haemophilia (defined as a residual factor VIII activity of ≤ 1%) were analysed as subgroup, as were the results stratified by country (Hungary and Germany).

13.1 Key Results and Discussion

Study population

- Overall, 164 patients were enrolled and 163 were analysed, 52 patients were treated in 8 Hungarian centres and 111 patients in 25 German centres. Of the 163 patients, 143 patients were PTPs and 20 patients were PUPs. In addition, patients with severe haemophilia were analysed as a subgroup, comprising 133 patients (118 PTPs, 15 PUPs). All patients included in the NIS were male, as it is expected according to the sex related prevalence of haemophilia A. Most of the patients who were PUPs (mean age 5.2 (SD 14.2) years) were under 6 years of age (85.0%) when they had their first treatment (which was the study treatment), whereas the majority of patients included as PTPs (mean age 28.8 (SD 17.1) years) were between 18 and 64 years old (67.8%) when they received their first treatment (i.e. study treatment).

Treatment

- As expected during the course of the study, the proportion of patients receiving treatment for prophylaxis increased from 41.1% (data from 90 patients) in 2003 to 65.7% (data from 67 patients) in 2015, whereas the proportion of patients receiving on-demand treatment decreased from 58.9% to 34.3% during this time period. Most of the PUPs received their treatment as prophylaxis treatment throughout the NIS. In general, today prophylaxis with Factor VIII products is more common than treatment on demand, which is confirmed by the data of this NIS.

- The median cumulative dose per treatment in all patients was 4000 IU (66.5 IU/kg BW) when given because of surgery, 2000 IU (29.0 IU/kg BW) when given for current bleeding event, 2000 IU (30.4 IU/kg BW) when given as follow-on treatment, and 1500 IU (28.5 IU/kg BW) when given as prophylaxis. Median cumulative dose was 2000 IU (27.0 IU/kg BW) per treatment in the Hungarian centres and 1000 IU (29.1 IU/kg BW) in German centres.

Effectiveness

- Overall, patients had a mean annual bleeding rate of 13.3 (SD: 16.6, median 6.1). The annual bleeding rate was considerably lower for patients who were treated prophylactically with Haemoctin® compared to those patients treated on demand (type of treatment = prophylaxis: median: 3.2; type of treatment = on demand: median: 24.5). The annual bleeding rate decreased over time, from a median annual bleeding rate of 20.7 from 1998 to 2002 to 5.2 from 2008 to 2012 and finally to a median of 2.6 bleedings per year from 2013 to 2015.
- Global assessment of effectiveness was evaluated as “very good” both by the investigators (mean (SD) score 1.29 (0.40)) and by the patients (mean (SD) score 1.38 (0.45)). Also, the global assessment of ease of use was assessed as “very good” by both the investigators (mean (SD) 1.44 (0.54)) and the patients (mean (SD) score 1.48 (0.52)). Both effectiveness and ease of use assessments yielded similar ratings among the patients with severe haemophilia as compared with the total population. The mean score for the patients’ satisfaction was 1.74 (SD 0.50), corresponding to a “very good (=1)” to “good (=2)” perceived general satisfaction.
- The investigators assessed the therapeutic effect of treatment as ‘as expected’ with nearly all (99.29%) treatments, which was very similar in the indications of bleeding, prophylaxis and surgery and slightly lower for follow-on treatments.

Reported AEs and general tolerability

- During the course of the study, AEs were reported in a total of 99 patients (60.7%) by the time of the cut-off of this study. Of the 133 patients with severe haemophilia, AEs were reported in 81 patients (60.9%).
- The most frequent and clinically relevant events were gastrointestinal haemorrhage (13 events in 11 patients, all unrelated), and anti-factor VIII antibody positive (10 events in 9 patients). Further, tooth extraction (13 events in 11 patients), and fall (9 events in 8 patients) were also frequently reported events.
- Overall, 10 AEs were suspected to be drug-related in 7 patients as assessed by the MAH (4.3% of all patients). Eight of the AEs were coded as “Anti-factor VIII antibody positive” in 7 patients, 1 AE as “Factor VIII inhibition” in 1 patient, and 1 AE as “Haemorrhagic diathesis” in 1 patient.
- In 78 patients 242 SAEs were reported (208 SAEs in 64 patients with severe haemophilia). Most frequently documented serious AEs were gastrointestinal haemorrhage (13 SAEs in 11 patients), anti-factor VIII antibody positive (6 SAEs in

5 patients), contusion (4 SAEs in 4 patients), muscle haemorrhage (5 SAEs in 4 patients), traumatic haematoma (5 SAEs in 4 patients), and fall (4 SAEs in 4 patients).

- Six SAEs were suspected to be drug-related (according to MAH assessment) in 3 patients and reported in 3 ICSRs. All cases had 'development of anti factor VIII antibodies' as main diagnosis.
- There were 8 patients who died during the study due to AEs that were all assessed as not related to the study treatment (according to MAH and according to investigator).
- Between 01-May-1998 until 31-Dec-2015, no ADR on thrombosis or thromboembolic event, and no ADR on hypersensitivity reaction have been reported from this NIS.
- No cases of suspected viral transmission related to Haemoctin® were reported in the non-interventional study. Differences in serological markers at enrolment and at a later time point are explained by vaccination against HAV and HBV. Single positive results were not confirmed. For the 3 patients without documented vaccinations and a difference in serological markers at enrolment and a later timepoint, the positive test results were not confirmed with other tests and no infections or treatments for infection were reported.
- The incidence of FVIII inhibitor formation in all PUPs within this NIS was 15% (3/20), and 5% (1/20) of high-titre inhibitors.
- The incidence of related FVIII inhibitor formation in all PTPs in this NIS was 2.8% (4/143), and 1.4% (2/143) of high-titre inhibitors. None of the developed FVIII inhibitors in PTPs, related to Haemoctin®, were clinically relevant.
- Two cases (1 PUP and 1 PTP) of FVIII inhibitor formation were assessed as clinically relevant, i.e. as persistent and in conjunction with high-titre FVIII inhibitors, which required ITI. The PTP had been included in the NIS with pre-exsisting high-titre FVIII inhibitors caused by another FVIII product, in order to perform an ITI with Haemoctin®. In both cases, the ITI was successfully performed with Haemoctin®.
- The tolerability of treatment was globally assessed as 'very good' (=1) to 'good' (=2) by both the investigators (mean (SD) score 1.24 (0.37)) and the patients (mean (SD) score 1.26 (0.37)).

Bleeding episodes of high relevance

- Overall, 43 serious bleeding episodes (considered bleedings of high relevance) were identified in 29 patients (26 PTPs and 3 PUPs). One case only was assessed by the respective investigator and the MAH to be related to the Haemoctin® treatment.

- In general, the rate of serious bleedings is considered low taking into account a total of 1202 patient years. The majority of patients with serious bleedings were under prophylactic treatment with Haemoctin®. A major cause of bleeding included significant trauma, mucosal lesion, or vascular lesion in combination with hypertension and/ or liver diseases. None of the serious bleeding events was associated with a clinically relevant formation of FVIII inhibitors.

13.2 Limitations

- There were data recording limitations especially at the beginning of the study, most part due to the old NIS monitoring system 17 years ago. Therefore, underreporting of AEs related with bleedings (e.g. pain or causes for (traumatic) bleedings, elective procedures and underlying haemophilia and related co-morbidities (e.g. arthropathy) cannot be ruled out. However, the documentation and reporting of clinically relevant, e.g. FVIII inhibitor formation or TEEs, are assumed to be reported completely. In addition the regulatory requirements were changed during the study time. New regulations were becoming active for e.g. the EU good pharmacovigilance praxis (GVP) regulations.
- Investigators did not consequently report not related AEs that resulting in bleeding events of patients, e.g. accidents or surgeries. In consequence, the explanations for bleeding events are partly missing since the root cause was not reported.
- 31 of 163 patients with non-severe haemophilia A had a residual factor VIII activity of >1% and should not have been enrolled into the NIS according to the initial inclusion criteria of PMSII, which were changed later.
- Documentation of data was performed using paper CRFs and no electronic CRF, which would have allowed the implementation of automated checks to ensure better consistency of documentation within a single patient. Data from paper CRFs underwent single-data entry without the possibility to raise queries to sites in order to question inconsistencies, with exception of queries on AE reporting. No source data validation was performed as done for clinical studies.

13.3 Interpretation

Overall, the results of treatment with Haemoctin® are in line with the expectation of the MAH and the treating physicians. Both, physicians and patients provided high ratings of overall effectiveness and confirmed the ease of use of Haemoctin® in daily life.

No new and formerly unknown information with regard to the safety of Haemoctin® became apparent in this NIS.

13.4 Generalisability

The long term documentation period of over 17 years (in 1202 patient years) provided data on the long term use of the Haemoctin®. Patients documented in this NIS, which included patients living in Germany and in Hungary, can be regarded as representative

for haemophilia A patients living in the EU, at least for Caucasian patients. Except for four patients (all living now in Germany), all patients with information about ethnicity were Caucasian (n=107). Two of the non-Caucasian patients were black, one was Asian and one was Lebanese.

The cohort of patients who had been pre-treated patients with clotting factor products (PTPs) and the cohort of patient who had not been treated with such products except previous exposure to blood components (PUPs) provided data for this NIS.

14. OTHER INFORMATION

Not applicable.

15. CONCLUSION

A broad proportion of patients with haemophilia A recorded a very good effectiveness assessment with a low rate of bleeding events during the long-term documentation of treatment with Haemoctin® under everyday clinical practice conditions. The treatment effect was evaluated as ‘as expected‘ by the investigators in nearly all treatments of patients. The annual bleeding rate was considerably lower for patients who were treated prophylactically with Haemoctin® compared to those patients treated on-demand and decreased over the years of documentation in the NIS. It could be observed, that the regimen for Haemoctin® changed from on-demand treatment to prophylactic treatment over time.

Overall, long-term and continuous treatment with Haemoctin® was well tolerated. The risk of bleeding decreased over the documentation years and a low incidence of inhibitor formation in PTPs and PUPs was observed over the long lasting documentation time of 1202 patient years. No new and formerly unknown information with regard to the safety and tolerability of Haemoctin® was reported during the study period confirming the positive benefit–risk profile of Haemoctin® in the indication treatment and prophylaxis of bleeding in patients with haemophilia A. The benefit-risk profile of Haemoctin® remains clearly favourable.

16. REFERENCES

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17. APPENDICES

17.1 List of stand-alone documents

Number	Document reference number	Date	Title
1	Appendix 1.1	10-Mar-2017	Appendix 1.1 Tables – by Previous Treatment, all patietns
2	Appendix 1.2	13-Apr-2017	Appendix 1.2 Tables – by Previous Treatment, Severe haemophilia Patients
3	Appendix 1.3	22-Mar-2017	Appendix 1.3 Tables – by Country
4	Appendix 1.4	22-Mar-2017	Appendix 1.4 Tables – by Country, Severe haemophilia Patients
5	Appendix 1.5	22-Mar-2017	List of Centres Participating in the NIS
6	Appendix 2.1	22-Mar-2017	Individual Safety Data and Analysis

17.2 Additional information

Not applicable.