Title	Haemonine NIS - Post marketing study for Long-term treatment of Haemophililia B patients
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Medicinal product	Haemonine
Product reference	Registration Number: PEI.H.03626.03.1
Marketing authorisation holder(s)	Biotest AG, Dreieich, Germany
Research question and objectives	Collecting data to enhance knowledge on the safety profile of Haemonine in long-term treatment of haemophilia B patients
Country(-ies) of study	Germany
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Abbreviations

ADR	**Adverse drug reaction**
AE	**Adverse event**
Anti-HBc	**Antibody to hepatitis B core antigen**
Anti-HBs	**Antibody to hepatitis B surface antigen**
AP	**Alkaline phosphatase**
AST	**Aspartate aminotransferase**
ALT	**Alanine aminotransferase**
CRF	**Case report form**
ELISA	**Enzyme-linked immunosorbent assay**
Gamma-GT	**Gamma glutamyl transferase**
HbsAG	**Surface antigen of the hepatitis B virus**
HBV	**Hepatitis B virus**
HCV	**Hepatitis C virus**
HIV	**Human immunodeficiency virus**
IgG	**Immunoglobulin G**
IgM	**Immunoglobulin M**
IU	**International unit**
LDH	**Lactate dehydrogenase**
MAH	**Marketing authorisation holder**
MedDRA	**Medical dictionary for regulatory affairs**
NAT	**Nucleic acid amplification testing**
PMS	**Post-marketing study**
TNBP	**Tri-n-butyl phosphate**
RIA	**Radioimmunoassay**
SAP	**Statistical analysis plan**
SGPT	**Serum glutamic pyruvic transaminase**
SGOT	**Serum glutamic oxaloacetic transaminase**
SPC	**Summary of product characteristics**

1 Introduction

1.1 Background

Haemonine is a highly purified, freeze-dried, double virus-inactivated human coagulation factor IX concentrate which is prepared from human plasma for fractionation (Ph.Eur monograph no. 0853). Haemonine contains approximately 100 IU/ml human coagulation factor IX when reconstituted with either 5 ml (500 IU packaging size) or 10 ml (1000 IU packaging size) water for injections. The potency (IU) is determined using the European Pharmacopoeia one stage clotting test. The specific activity of Haemonine is ≥ 70 IU/mg protein.

Haemonine is indicated for the prophylaxis and treatment of bleeding in patients with haemophilia B (congenital factor IX deficiency).

1.2 Objectives

With Haemonine Biotest succeeded in producing a factor IX concentrate with a high purity level. Two virus inactivating / virus removing processes cover different pathogens by using different active principles: Solvent / detergent treatment with a mixture of TNBP and Polysorbate 80 captures the lipid membrane enclosed viruses, the nanofiltration with 70 kDa filters captures the non-enclosed viruses. Besides these two processes, the antimicrobial safety concept for the manufacture of Haemonine includes the comprehensive testing of single donations and plasma pools (including NAT for HBV, HCV and HIV-1).

The post marketing study (PMS) aimed to enhance knowledge on the safety profile of the preparation in the long-term treatment of haemophilia B patients. Based on the developmental data, there was no particular safety concern for Haemonine. However, thrombogenicity as well as immunogenicity are critical for all factor IX products. Therefore, particular attention was paid to adverse events related to thrombogenicity and immunogenicity. It was expected that the existing safety profile would be confirmed by the collection of data derived from this study.

With regard to the fact that haemophilia B is a congenital disease, this study also aimed to collect data in the paediatric population during routine administration of Haemonine for prophylaxis and on demand.

2 Sample and methods

2.1 Study design

This post-marketing study was open, multi-centered and non-interventional and was planned to be conducted in Austria, Italy, Greece and Germany. Further countries could be included after granting of marketing authorisation. It was expected to involve approximately 10 centers initially with a recruiting rate of 2 patients per country per year, thereof 30 % children. The study started in May 2009.

Final evaluation was planned with 50 patients treated. Since this recruitment target could not be achieved, it was decided to terminate the study as per March 31, 2019.

Within this study, the medicinal product was prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of a patient to a particular therapeutic strategy was the discretion of the physician and within the current practice and the prescription of the medicine. The decision to treat the patient with Haemonine was clearly separated from the decision to include the patient in the study.

The collecting of the research parameters was carried out within the framework of routine treatment of patients with congenital haemophilia B. Additional parameters outside clinical routine were not included.

2.2 Sample

2.2.1 Centers

At the time of this analysis, 6 centers (all from Germany) with totally 8 patients had participated in this PMS. The largest center covered 2 of the patients.

2.2.2 Patients

The PMS was intended for patients with diagnostically confirmed haemophilia B. The factor IX residual activity should be less than 2 %, the patient's inhibitor titer less than 0.6 Bethesda units. Exceptions to these criteria should be motivated.

The concept was well suited to collect efficacy and safety data on Haemonine administration in all age groups. However, the access to pediatric patients is restricted. The patients should be treated in accordance to the actual SPC. The following cases should not be included in the PMS:

- Patients for whom the substitution with factor IX concentrates is contra-indicated.

- Patients where it is known that intolerance reactions have frequently occurred after receiving plasma preparations, especially coagulation concentrates.
- Patients with concurrent infections with fever and shivering.
- Patients of less than 6 years of age.

2.3 Study medication

The human plasma derived coagulation factor IX Haemonine used complied with all the manufacturer's specifications. It was acquired through normal distribution channels in the commercial packaging.

The treatment was carried out in accordance with the guidelines of the relative treatment center. If possible, only the factor IX concentrate Haemonine to be tested was used during the observation period, since with intermittent changes in preparations the data correlation could become unclear. The dosage, the administration frequency and the duration of the substitution therapy depended on the severity of the factor IX deficiency, on the location and extent of the bleeding and on the patient's clinical condition. The following formula could be used for calculating the required factor IX quantities:

- One unit Factor IX (IU) per kilogram body weight raises the factor IX plasma level by 1.2 % of normal activity.
- Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x 0.80

2.4 Concomitant treatment

Patients should not receive any therapies with other blood or plasma derivatives during the observation period. Any other concomitant treatment had to be documented in the Case Report Form (CRF).

2.5 Study procedure

2.5.1 Duration

The observation period for patients should be covering a minimum of 50 exposure days. The examination intervals were in accordance with the requirements of the respective treatment centers. Apart from the initial examination, a minimum of at least one further examination per year should be documented. One case report form (CRF) allowed the documentation of up to 12 follow-up examinations. There should be a final examination at the end of the observation period. Additional CRFs could be used to document the Haemonine treatment for longer time periods.

2.5.2 Study schedule

The following parameters were documented:

At the beginning of the study:

- Demographic data: gender, age, ethnic origin
- Body measurements: body height, body weight
- History of hemophilia including the date of the initial diagnosis, factor IX baseline activity, previous treatment of hemophilia with either the investigational product or with other factor IX preparations
- 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
- Consumption habits concerning alcohol, tobacco, and drugs
- Concomitant diseases and concomitant medication.

At each follow-up examination (within the framework of routine therapeutic care):

- Factor IX antibodies (Bethesda test)
- Hepatitis-B virus marker (HBsAg, Anti-HBs and Anti-HBc using commercial tests such as ELISA or RIA)
- Hepatitis-C virus marker (Anti-HCV by means of ELISA)
- Hepatitis-A virus marker (IgG, IgM)
- HIV-1-/HIV-2 virus marker (Anti-HIV by means of ELISA; Western Blot where anti-HIV findings are positive)
- Liver disease marker (Transaminases AST, ALT and Gamma-GT by means of colorimetry at 37°C; bilirubin, AP and LDH)
- Haematocrit
- Thrombocyte counts
- CD4 and CD8.

Parameters for efficacy

At each haemophilia monitoring visit the following assessments were to be documented on patient's diary forms:

- Treatment period and batch numbers of investigational product administered.
- The administration was due to prophylaxis or treatment on-demand.
- The quantity of administered investigational product in IU
- Expected therapeutic effect reached has to be indicated as YES or NO.

Parameters of safety

At each visit, enquiry was made on:

- Occurence and nature of adverse events
- AEs related to thrombogenicity
- AEs related to immunogenicity
    - Factor IX inhibitors
    - Allergic/anaphylactic reactions
- Decrease of efficacy
- Overall tolerability.

At each collection of blood samples, laboratory assessments including serological monitoring was performed.

2.6 Data management and statistical analysis

2.6.1 Basis of analysis

The statistical analysis was based on the following documents:

- Observational plan
- Statistical analysis plan (SAP) of April 18, 2019
- 28 completed case reports forms (CRF)
- All documented adverse events.

2.6.2 Data management

On arrival, all case report forms were checked for completion and face validity. Then they were registered in a study specific database.

During data entry, an immediate data checking has been carried out in the background, using predefined ranges for most of the parameters. Additionally, programmed data checks and cross-checks were applied before analysing the data.

After data entry, the documents were sorted numerically in ascending order and stored in file folders.

2.6.3 Data cleaning and transformation

In addition to the data checks performed during data entry into the study database, further checks were carried out during the statistical analysis.

Findings were re-checked against the original CRFs. In case of a data entry error, this error was corrected using a validated correction procedure.

Some documentation implausibilites were corrected according to following rules:

- Unanswered yes/no questions with trailing data were coded with ‘yes’.
- Negative time intervals on consecutive dates were coded as ‘unknown / missing’ (due to implausibility).

Concomitant illnesses and adverse events were coded according MedDRA Version 22.0 and documented as ‘Preferred Terms’ (PT) and ‘System Organ Classes’ (SOC).

In order to make laboratory data comparable, they have been transformed to standard units across centers.

After data entry and data cleaning, the clean database was locked and transferred for statistical analysis.

2.6.4 Definition of data sets for analysis

No specific data sets were planned for the statistical analysis. All patients treated at least once with Haemonine were included in the statistical analysis.

The exposure and efficacy analyses was performed for all patients and separately for patients with a mild haemophilia and a known Factor IX residual activity at study entry (>1%) and with severe haemophilia (residual activity at study entry ≤1%).

2.6.5 Statistical analysis

Quantitative parameters are described by mean, standard deviation, median, 25th percentile, 75th percentiles, minimum, maximum and the number of valid observations. Categorical data are displayed in frequency tables showing sample size and absolute and relative frequency.

Casewise data listings show raw data not being summarized as entered in the CRF as well as important derived variables. This applies especially to data with n=1 or answers to categorical variables in the category "other".

The assessments of efficacy and tolerability of Haemonine at the final evaluation are shown as bar graphs.

Missing data were not imputed.

The statistical analysis was performed with the software ‘IBM SPSS Statistics’ Version 23 on personal computers with ‘Windows 10’ operating system.

3 Results[1]

3.1 Description of the study sample

3.1.1 Data overview

Some centers used more than one CRF in order to document the treatment course of a patient longer than one year. Originally, 28 CRFs documented the treatment course of eight patients. Therefore, "new" patient numbers had to be assigned on the basis of the (different) original CRF number(s) (see table 1). Altogether 31 patient-years were documented in the study.

Tab. 1 Reassigned documentation file numbers

documentation-file / original patient no.	new patient no.
11 + 31	1001
09 + 28 + 32 + 42 + 75 + 74 + 61 + 62	1002
03 + 17 + 25 + 14 + 56 + 59 + 58	1003
10 + 29 + 15 + 12 + 40 + 52 + 78	1004
21	1005
18	1006
13	1007
20	1008
patients	8

Totally 8 patients treated with Haemonine were included in the statistical analysis (see table 3). Four patients suffered from mild haemophilia (FIX residual activity > 1%). The remaining four patients suffered from severe haemophilia (FIX residual activity ≤ 1%). See table 2.

Tab. 2 Stratification of the patients according to the severity of the disease
(based on inital FIX residual activity)

	n	%
severe haemophilia (FIX residual activity <=1%)	4	50,0%
mild haemophilia (FIX residual activity >1%)	4	50,0%
patients	8	100,0%

[1] The description of results is based on the Statistical Summary Tables volume. Tables named „T-...“ refer to the Statistical Summary Tables volume.

Tab. 3 Haemonine NIS - Patient flow diagram

Enrollment and Allocation
↓
8 patients enrolled
8 patients treated and documented
↓
Follow-Up
↓
5 patients with 50 exposure days
1 premature study termination due to death
5 patients with adverse events
↓
Analysis
↓
analysed for efficacy: 8 patients
excluded from efficacy analysis: 0 patients
analysed for safety: 8 patients
excluded from safety analysis: 0 patients

3.1.2 Demographics

All patients enrolled were male and Caucasians. The age of the patients ranged from 7 to 80 years (median: 24.5 years, interquartile range: 13.5 – 52.0 years). Patients with severe haemophilia were younger (median: 21.5 years) compared to patients with mild haemophilia (median: 40.5 years). Three patients were children (<18 years) at start of the treatment. The patient's weight ranged from 27 to 96 kg (median: 75.2, interquartile range: 62.3 – 80.5 kg). The patient's height ranged from 125 to 190 cm high (median: 173.5 cm, interquartile range: 172,5 – 179.0 cm). See tables T-4 to T-8 for all demographic patient data.

3.1.3 Anamnestic data

Haemophilia B history

All patients enrolled into the study were suffering from haemophilia B. The median duration of the disease amounted to 15 years (interquartile range: 9 to 36 years). Patients with severe haemophilia were suffering longer (median: 20 years) from the disease compared to patients with mild haemophilia (median: 14 years). See table 4.

Tab. 4 Duration of Haemophilia B before study enrolment (years)

	severe haemophilia	mild haemophilia	total
mean	23	21	22
standard deviation	17	21	18
minimum	6	5	5
25% percentile	10	8	9
median	20	14	15
75% percentile	36	34	36
maximum	46	53	53
patients	N=4	N=4	N=8

The median initial factor IX residual activity (FIX) amounted to 2% (interquartile range: 1% to 5%). Patients enrolled into the study should have a residual factor IX activity of less than 2% (see table 5). Some patients did not fulfill this criterion. Therefore, the analysis was stratified for patients with severe and mild haemophilia.

Tab. 5 FIX residual activity before study enrolment (%)

	severe haemophilia	mild haemophilia	total
mean	1,0	7,0	4,0
standard deviation	,1	5,4	4,8
minimum	,9	3,0	,9
25% percentile	,9	4,0	1,0
median	1,0	5,0	2,0
75% percentile	1,0	10,0	5,0
maximum	1,0	15,0	15,0
patients	N=4	N=4	N=8

Patient no. 1005 was documented with 15% FIX residual activity

Haemophilia of 7 out of 8 patients was pre-treated (see table T-24 of the statistical summary tables volume). Table 6 shows the type of this pre-treatment (different factor IX preparations).

Tab. 6 Type of the pre-treatment of Haemophilia B
Base: Only patients with pre-treatment of Haemophilia B

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
Faktor IX SDN	5	125,0%	0	,0%	5	71,4%
Immunine	3	75,0%	2	66,7%	5	71,4%
Bene FIX	0	,0%	2	66,7%	2	28,6%
Haemonine	2	50,0%	0	,0%	2	28,6%
PPSB	1	25,0%	0	,0%	1	14,3%
FFP	0	,0%	1	33,3%	1	14,3%
unknown	1	25,0%	0	,0%	1	14,3%
patients	4	100,0%	3	100,0%	7	100,0%

Multiple responses are possible. The sum of percentages may exceed 100%.

At the time of inclusion in this study, the most frequent treatment regime was prophylactic (62.5%). See table 7.

Tab. 7 Treatment regime of the patients at the time of inclusion in the PMS

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
treatment on demand	0	,0%	2	50,0%	2	25,0%
prophylactic treatment	3	75,0%	2	50,0%	5	62,5%
treatment on demand and prophylactic treatment	1	25,0%	0	,0%	1	12,5%
patients	4	100,0%	4	100,0%	8	100,0%

A listing of the prophylactic treatment details is provided by table T-27 of the statistical summary tables volume.

None of the patients was diagnosed having an allergic reaction or showing reduced efficacy of factor IX substitution therapy any time during the haemophilia treatment.

Tab. 8 Inibitor or allergic reaction or reduced efficacy of factor IX substitution therapy before documentation start

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
no	4	100,0%	4	100,0%	8	100,0%
yes	0	,0%	0	,0%	0	,0%
patients	4	100,0%	4	100,0%	8	100,0%

Family history

At the initial examination, the family history was documented. None of the patient's parents suffered at that time point from an ***immunodeficiency***. However, the mother of one patient was described as a conductor (asymptomatic carrier of a gene defect). For the parents of another patient, no details were given. See tables 9 and 10.

Tab. 9 Immunodeficiency of the parents

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
unknown	0	,0%	1	25,0%	1	12,5%
no	4	100,0%	1	25,0%	5	62,5%
yes	0	,0%	2	50,0%	2	25,0%
patients	4	100,0%	4	100,0%	8	100,0%

Tab. 10 Listing of comments on parents with an immunodeficiency
Base: Only patients whose parents are suffering from an immunodeficiency

patient no.	subgroup	details
1001	mild haemophilia	mother conductor
1007	mild haemophilia	unknown

Assessment of factor IX tolerance obtained that none of the patient's parents fell ***ill after factor IX transfusion.*** (see table T-11 of the statistical summary).

Hepatitis vaccination

About half of the patients were immunised against Hepatitis A (50%) and against Hepatitis B (62.5%). More frequent patients suffering from severe haemophilia. See tables 11 and 12.

Tab. 11 Patients immunised against Hepatitis A

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
no	1	25,0%	3	75,0%	4	50,0%
yes	3	75,0%	1	25,0%	4	50,0%
patients	4	100,0%	4	100,0%	8	100,0%

Tab. 12 Patients immunised against Hepatitis B

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
no	1	25,0%	2	50,0%	3	37,5%
yes	3	75,0%	2	50,0%	5	62,5%
patients	4	100,0%	4	100,0%	8	100,0%

Consumption of alcohol, tobacco or drugs

Most of the patients neither drank alcohol (62.5%) nor were smokers (75%). None of the patients consumed drugs (see tables 13 to 15).

Tab. 13 Consumption of alcohol

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
does not drink alcohol	4	100,0%	1	25,0%	5	62,5%
drinks very little alcohol (once a week)	0	,0%	2	50,0%	2	25,0%
drinks alcohol daily	0	,0%	1	25,0%	1	12,5%
patients	4	100,0%	4	100,0%	8	100,0%

Tab. 14 Consumption of tobacco

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
smokes up to 20 cigarettes per day	1	25,0%	1	25,0%	2	25,0%
non-smoker	3	75,0%	3	75,0%	6	75,0%
patients	4	100,0%	4	100,0%	8	100,0%

Tab. 15 Consumption of drugs

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
no	4	100,0%	4	100,0%	8	100,0%
yes	0	,0%	0	,0%	0	,0%
patients	4	100,0%	4	100,0%	8	100,0%

Concomitant illnesses and corresponding medication

Three out of eight patients (37.5%) suffered from concomitant diseases at the beginning of the PMS (see table 16).

Tab. 16 Concomitant illnesses at study entry

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
no	3	75,0%	2	50,0%	5	62,5%
yes	1	25,0%	2	50,0%	3	37,5%
patients	4	100,0%	4	100,0%	8	100,0%

In total 12 diseases were documented for three patients (see table 17). Most commonly were infections and infestations, metabolism and nutrition disorders and vascular disorders (25% each).

Tab. 17 Type of concomitant illnesses at study entry (MedDRA Preferred Term)
Base: Only patients with documented concomitant illnesses

	n	%
Hypertension	3	25,0%
Chronic hepatitis C	1	8,3%
Diabetes mellitus	1	8,3%
Hepatitis C	1	8,3%
HIV infection	1	8,3%
Hypertriglyceridaemia	1	8,3%
Hyperuricaemia	1	8,3%
Nephrectomy	1	8,3%
Prostate cancer	1	8,3%
Renal failure	1	8,3%
Concomitant illnesses	12	100,0%

In detail (according to MedDRA Preferred Terms) these diseases were at study entry: hypertension, hepatitis C, diabetes mellitus, HIV infection, hypertriglyceridaemia and hyperuricaemia, nephrectomy, prostate cancer and renal failure. See also table T-18 in the statistical summary tables volume.

Two out of eight patients (25%) got a prior or concomitant medication (see table 18).

Tab. 18 Prior or concomitant medication at study entry

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
no	3	75,0%	3	75,0%	6	75,0%
yes	1	25,0%	1	25,0%	2	25,0%
patients	4	100,0%	4	100,0%	8	100,0%

The concomitant drugs were: zidovudin, lamivudin, ritonavir, gemfibrozil, allopurinol, enalapril and insulin. A full listing of the prior or concomitant medication is given in the table T-21 of the statistical summary tables volume.

3.2 Data during study course

3.2.1 Periods and number of follow-up examinations

The total observation and treatment period within this study was highly variable. The median treatment and observation time was two years (765 days). Interquartile range: 536 to 2557 days. It was much longer in patients with severe haemophilia (median: 2557 days) compared to patients with mild haemophilia (median: 714 days). See table 19.

Tab. 19 Treatment and observation period (days)
Time interval between initial examination and final evaluation

	severe haemophilia	mild haemophilia	total
mean	2171	623	1397
standard deviation	1228	227	1163
minimum	400	289	289
25% percentile	1371	481	536
median	2557	714	765
75% percentile	2971	765	2557
maximum	3170	773	3170
patients	N=4	N=4	N=8

During the observation period, all patients had more than one follow-up examination. The frequency of follow-up examinations per patient ranged from 2 up to 63 examinations per patient. Table T-30 of the statistical summary tables volume shows the details.

3.2.2 Clinical chemistry

Due to the high variability in the number of follow-up examinations, it was difficult to document the longitudinal course of laboratory parameters because of a declining "n". However, summaries have been computed for this purpose and they are documented in the statistical summary tables volume. In addition, the deviations from normals are documented there (see tables T-41 to T-68).

In order to be able to detect systematic changes in laboratory parameters, so-called endpoint comparisons were made, comparing the first and last documented value of a patient, irrespective of the time interval between both measurements.

Bilirubin

Bilirubin levels decreased during the course of the PMS from 0.8 to 0.5 mg/dl (median). See table 20. Table T-42 of the statistical summary tables volume shows this parameter over the course of time and table T-43 is providing a listing of patients with deviations from normal. None of the deviations from normal was associated with the study treatment.

Tab. 20 Endpoint comparison for bilirubin (mg/dl)

	severe haemophilia		mild haemophilia		total	
	first value	last value	first value	last value	first value	last value
mean	,8	,6	1,2	,5	,9	,6
standard deviation	,2	,3	,9	,2	,5	,3
minimum	,5	,3	,5	,3	,5	,3
25% percentile	,6	,4	,5	,3	,5	,3
median	,8	,6	1,2	,5	,8	,5
75% percentile	1,0	,8	1,9	,7	1,0	,7
maximum	1,0	,9	1,9	,7	1,9	,9
patients	N=4	N=4	N=2	N=2	N=6	N=6

From patients no. 1005 and 1008 data are missing
'first value' = first documented value during the study
'last value' = last documented value during the study
Normal range: < 1.1 mg/dl

Alkaline phosphatase (AP)

Median AP levels decreased during the course of the PMS from 149 to 86 U/l (median). See table 21. Table T-45 of the statistical summary tables volume shows this parameter over the course of time and table T-46 is providing a listing of patients with deviations from normal. None of the deviations from normal was of clinical relevance or was associated with the study treatment.

Tab. 21 Endpoint comparison for alkaline phosphatase (U/l)

	severe haemophilia		mild haemophilia		total	
	first value	last value	first value	last value	first value	last value
mean	160,7	157,7	150,5	112,1	155,6	134,9
standard deviation	114,0	179,8	69,3	46,4	84,6	120,0
minimum	61,0	45,0	76,0	76,0	61,0	45,0
25% percentile	61,0	45,0	76,0	76,0	76,0	63,0
median	136,0	63,0	162,6	96,0	149,3	86,0
75% percentile	285,0	365,0	213,0	164,4	213,0	164,4
maximum	285,0	365,0	213,0	164,4	285,0	365,0
patients	N=3	N=3	N=3	N=3	N=6	N=6

From patients no. 1004 and 1005 data are missing
'first value' = first documented value during the study
'last value' = last documented value during the study
Normal range: 140 - 129 U/l

Serum glutamic pyruvic transaminase (SGPT)

SGPT levels decreased slightly during the course of the PMS from 30 to 22 U/l (median). See table 22. Table T-48 of the statistical summary tables volume shows this parameter over the course of time and table T-49 is providing a listing of patients with deviations from normal. None of the deviations from normal was of clinical relevance or was associated with the study treatment.

Tab. 22 Endpoint comparison for serum glutamic pyruvic transaminase (U/l)

	severe haemophilia		mild haemophilia		total	
	first value	last value	first value	last value	first value	last value
mean	61,2	30,3	47,3	23,5	55,3	27,4
standard deviation	69,9	15,5	37,2	2,5	54,4	11,6
minimum	23,0	19,0	22,0	22,0	22,0	19,0
25% percentile	24,4	20,6	22,0	22,0	23,0	22,0
median	27,9	24,6	30,0	22,2	30,0	22,2
75% percentile	98,0	40,0	90,0	26,4	90,0	27,0
maximum	166,0	53,0	90,0	26,4	166,0	53,0
patients	N=4	N=4	N=3	N=3	N=7	N=7

From patient no. 1005 data are missing
'first value' = first documented value during the study
'last value' = last documented value during the study
Normal range: < 50 U/l

Serum glutamic oxaloacetic transaminase (SGOT)

The median SGOT levels decreased slightly during the course of the PMS from 30 to 26 U/l (median). See table 23. Table T-51 of the statistical summary tables volume shows this parameter over the course of time and table T-52 is providing a listing of patients with deviations from normal. None of the deviations from normal was of clinical relevance or was associated with the study treatment.

Tab. 23 Endpoint comparison for serum glutamic oxaloacetic transaminase (U/l)

	severe haemophilia		mild haemophilia		total	
	first value	last value	first value	last value	first value	last value
mean	49,0	27,9	65,2	40,0	55,9	33,1
standard deviation	39,4	8,6	68,9	28,9	49,3	18,9
minimum	27,0	18,0	21,0	21,0	21,0	18,0
25% percentile	28,5	21,3	21,0	21,0	27,0	21,0
median	30,5	27,8	30,0	25,8	30,0	25,8
75% percentile	69,5	34,5	144,6	73,2	108,0	38,0
maximum	108,0	38,0	144,6	73,2	144,6	73,2
patients	N=4	N=4	N=3	N=3	N=7	N=7

From patient no. 1005 data are missing
'first value' = first documented value during the study
'last value' = last documented value during the study
Normal range: < 34 U/l

Gamma glutamyl transferase (Gamma-GT)

Gamma-GT levels increased slightly during the course of the PMS from 24 to 31 U/l (median). See table 24. Table T-54 of the statistical summary tables volume shows this parameter over the course of time and table T-55 is providing a listing of patients with deviations from normal. None of the deviations from normal was of clinical relevance or was associated with the study treatment.

Tab. 24 Endpoint comparison for gamma glutamyl transferase (U/l)

	severe haemophilia		mild haemophilia		total	
	first value	last value	first value	last value	first value	last value
mean	390,8	33,7	57,7	29,7	248,1	32,0
standard deviation	742,8	23,0	51,1	5,2	555,4	16,7
minimum	15,0	16,0	22,8	24,0	15,0	16,0
25% percentile	17,1	17,3	22,8	24,0	19,2	18,6
median	21,6	26,3	34,0	31,2	24,0	31,2
75% percentile	764,5	50,0	116,4	34,0	116,4	34,0
maximum	1505,0	66,0	116,4	34,0	1505,0	66,0
patients	N=4	N=4	N=3	N=3	N=7	N=7

From patient no. 1005 data are missing
'first value' = first documented value during the study
'last value' = last documented value during the study
Normal range: < 66 U/l

Lactate dehydrogenase (LDH)

Median LDH levels increased slightly during the course of the PMS from 211 to 217 U/l. See table 25. Table T-57 of the statistical summary tables volume shows this parameter over the course of time and table T-58 is providing a listing of patients with deviations from normal. None of the deviations from normal was of clinical relevance or was associated with the study treatment.

Tab. 25 Endpoint comparison for lactate dehydrogenase (U/l)

	severe haemophilia		mild haemophilia		total	
	first value	last value	first value	last value	first value	last value
mean	220,6	194,6	222,3	230,5	221,3	210,0
standard deviation	35,2	53,0	27,0	20,2	29,4	43,7
minimum	186,0	133,0	202,8	211,0	186,0	133,0
25% percentile	196,5	153,0	202,8	211,0	202,8	173,0
median	213,6	195,1	211,0	229,2	211,0	217,2
75% percentile	244,6	236,1	253,2	251,4	253,2	251,4
maximum	269,0	255,0	253,2	251,4	269,0	255,0
patients	N=4	N=4	N=3	N=3	N=7	N=7

From patient no. 1005 data are missing
'first value' = first documented value during the study
'last value' = last documented value during the study
Normal range: 135 - 225 U/l

Haematocrit

The median haematocrit remained rather unchanged: 41% at the beginning and 42.0% at the end of the study. See table 26. Table T-60 of the statistical summary tables volume shows this parameter over the course of time and table T-61 is providing a listing of patients with deviations from normal. None of the deviations from normal was of clinical relevance or was associated with the study treatment.

Tab. 26 Endpoint comparison for haematocrit (%)

	severe haemophilia		mild haemophilia		total	
	first value	last value	first value	last value	first value	last value
mean	41,6	41,3	39,4	37,4	40,5	39,4
standard deviation	3,8	3,0	4,5	7,2	4,0	5,5
minimum	36,9	37,1	34,7	28,0	34,7	28,0
25% percentile	39,0	39,5	35,9	31,8	37,0	36,4
median	41,8	42,1	39,0	38,8	41,0	42,0
75% percentile	44,3	43,2	43,0	43,0	43,8	43,2
maximum	46,0	44,0	44,9	44,0	46,0	44,0
patients	N=4	N=4	N=4	N=4	N=8	N=8

From patient no. 1005 data are missing
'first value' = first documented value during the study
'last value' = last documented value during the study
Normal range: 37 - 50 %

Thrombocytes

Median thrombocyte levels increased slightly during the course of the PMS from 178 to 211 *10³ /µl. See table 27. Table T-63 of the statistical summary tables volume shows this parameter over the course of time and table T-64 is providing a listing of patients with deviations from normal. None of the deviations from normal was of clinical relevance or was associated with the study treatment.

Tab. 27 Endpoint comparison for thrombocytes (x1000/µl)

	severe haemophilia		mild haemophilia		total	
	first value	last value	first value	last value	first value	last value
mean	239,0	220,8	128,0	159,5	183,5	190,1
standard deviation	72,5	60,8	75,8	73,3	90,8	70,5
minimum	175,0	147,0	28,0	62,0	28,0	62,0
25% percentile	178,0	183,0	79,0	104,0	136,0	146,5
median	230,0	220,0	136,0	174,5	178,0	211,0
75% percentile	300,0	258,5	177,0	215,0	245,5	224,0
maximum	321,0	296,0	212,0	227,0	321,0	296,0
patients	N=4	N=4	N=4	N=4	N=8	N=8

'first value' = first documented value during the study
'last value' = last documented value during the study
Normal range: 150 - 350 *10³ /µl.

Inhibitors

It was rather difficult to describe this parameter due to many missing data and "zero" measurements. Data were available from seven patients. A listing of these data (see table 28) might be more meaningful compared to summaries (see table T-65 of the statistical summary tables volume).

Tab. 28 Listing of measurements for inhibitors (BU/ml)

patient no.	examination no.	measured value	deviation from norm	comments
1001	4	,39	No	
1003	1	,09	No	
	2	,09	No	
	8	.	No	
	10	.	No	
	12	.	No	
	13	.	No	
	16	,09	No	
	18	,10	No	
	19	,10	No	
1004	6	.	No	
	60	.	Yes	
	62	.	Yes	
	63	.	Yes	
1005	1	,00	No	
	2	,00	No	
	3	,00	No	
	4	,00	No	
1006	2	,00	No	
1007	2	,00	No	
1008	1	,00	No	
	3	,00	No	

Missing values are marked by a '.' dot (numeric) or a ' ' blank (text)

Data from patient no. 1002 were completely missing. In another four patients (no. 1005 to 1008) the inhibitor titer was and remained at zero. One Patient (no. 1001) had an inhibitor titer of 0.39 BU/ml but no follow-up measurements were performed. The inhibitor is below the limit of quantification and no clinical relevance was determined.

CD4-cells

CD4 was measured in two patients only (no. 1002 and 1003). The values were always within the normal range without a significant tendency for a change. See table 29.

CD4-cells

Tab. 29 Listing of measurements for CD4 effector cells (/µl)

patient no.	examination no.	measured value	deviation from norm	comments
1002	15	1.228,00		
	18	941,00	No	
	20	858,00	No	
	21	1.009,00	No	
	23	1.113,00	No	
	25	1.141,00	No	
	26	811,00	No	
	27	1.014,00	No	
	30	1.049,00	No	
	31	1.169,00	No	
1003	2	400,00	No	
	3	569,00	No	
	11	449,00	No	

Missing values are marked by a '.' dot (numeric) or a ' ' blank (text)
Normal range: 300 - 2200 /µl.

CD8-cells

CD8 was measured in two patients only (no. 1002 and 1003). The values were always within the normal range without a significant tendency for a change. See table 30.

Tab. 30 Listing of measurements for CD8 effector cells (/µl)

patient no.	examination no.	measured value	deviation from norm	comments
1002	15	1.023,00		
	18	713,00	No	
	20	589,00	No	
	21	729,00	No	
	23	720,00	No	
	25	766,00	No	
	26	570,00	No	
	27	723,00	No	
	30	705,00	No	
	31	786,00	No	
1003	2	310,00	No	
	3	437,00	No	

Missing values are marked by a '.' dot (numeric) or a ' ' blank (text)
Normal range: 200 - 1750 /µl.

3.2.3 Virology

Anti-HBs

Anti-HBs was measured in all eight patients. Except for one, all patients were already positive at the first measurement. No patient had become positive during the course of the treatment (see also casewise listing in table T-69 of the statistical summary tables volume).

HBs-Ag

HBs-Ag was determined in five out of eight patients. The test result was always negative in these patients (see also casewise listing in table T-70 of the statistical summary tables volume).

Anti-HBc

Anti-HBc was measured in five out of eight patients. The test result was always negative in these patients except for one (see also casewise listing in table T-71 of the statistical summary tables volume).

Anti-HCV

Anti-HCV was measured in all eight patients. One patient (no. 1001) had a continuous positive test result from the study start onwards. Another patient (no. 1003) had one positive test result at examination no. 2, but a negative test result at the three subsequent examinations. The remaining three patients were Anti-HCV negative (see also casewise listing in table T-72 of the statistical summary tables volume).

Anti-HAV

Anti-HAV was measured in six out of eight patients. The test result was negative in four patients. Two patients (no. 1006 and 1008) had a positive test result already at the first measurement (see also casewise listing in table T-73 of the statistical summary tables volume).

Anti-HIV-1/2

Anti-HIV-1/2 was measured in six out of eight patients. The test result was always negative (see also casewise listing in table T-76 of the statistical summary tables volume).

HIV Western Blot

This test should only be done if the antibody test was positive. However, although all patients were Anti-HIV-1/2 negative, this test was done for patient no. 1004. The test results was always negative (see also casewise listing in table T-77 of the statistical summary tables volume).

3.2.4 Body weight

The patient's median body weight increased during the course of the PMS from 75.2 to 81.3 kg (see table 31). Table T-36 of the statistical summary tables volume shows this parameter over the course of time.

Tab. 31 Body weight of the patients at the first and last examination (kg)

	severe haemophilia		mild haemophilia		total	
	first value	last value	first value	last value	first value	last value
mean	58,0	63,3	81,8	85,2	69,9	74,3
standard deviation	23,2	23,1	10,7	4,8	21,0	19,4
minimum	27,0	34,0	70,0	80,0	27,0	34,0
25% percentile	40,8	46,3	75,0	81,3	62,3	65,3
median	62,5	65,3	80,5	85,4	75,2	81,3
75% percentile	75,2	80,3	88,5	89,2	80,5	88,4
maximum	79,9	88,6	96,0	90,2	96,0	90,2
patients	N=4	N=4	N=4	N=4	N=8	N=8

'first value' = first documented value during the study.
'last value' = last documented value during the study.

3.2.5 Body height

The patient's median body height did not change between the endpoints. See tables T-37 and T-38 of the statistical summary tables volume.

3.2.6 Patient's subjective findings

The subjective findings of the patients deteriorated slightly between the endpoints. At the beginning of the study, all patients felt "very good" or "good". At the end of the PMS, a slight switch towards less favourable findings could be observed (see tables 32 and 33): One patient switched from "very good" to "good". Two patients switched from "good" to "moderate". No specific reason for this change was given.

Tab. 32 Endpoint comparison for patient's subjective findings

	severe haemophilia				mild haemophilia			
	first specification		last specification		first specification		last specification	
	n	%	n	%	n	%	n	%
very good	2	50,0%	1	25,0%	2	50,0%	2	50,0%
good	2	50,0%	2	50,0%	2	50,0%	1	25,0%
moderate	0	,0%	1	25,0%	0	,0%	1	25,0%
bad	0	,0%	0	,0%	0	,0%	0	,0%
patients	4	100,0%	4	100,0%	4	100,0%	4	100,0%

'first specification' = first documented finding during the study
'last specification' = last documented finding during the study

Tab. 33 Shift table for patient's subjective findings at the first and last examination

	last examination			total
	very good	good	moderate	
first examination				
very good	3	1	0	4
good	0	2	2	4
moderate	0	0	0	0
patients	3	3	2	8

Table T-79 of the statistical summary tables volume shows this parameter over the course of time.

3.2.7 Follow-up examinations

Adverse events

During the PMS, adverse events occurred in five out of eight patients (see table T-31 of the statistical summary tables volume). These events are described in chapter 3.4 (Adverse events).

Changes in concomitant medication

At the beginning of the study, only one patient (no. 1002) received a concomitant medication. During the PMS two other patients (no. 1001 and 1003) received concurrent (non-haemophilic) medication for different indications. These cases are listed in tables T-82 and T-83 of the statistical summary tables volume.

Changes in the treatment regime

In three out of eight patients the haemophilic treatment regimen was changed during the study: the dosage of Haemonine was increased in these patients. No specific reason for these changes was given. See also tables T-33 and T-34 of the statistical summary tables volume.

3.3 Final evaluation

3.3.1 Patients with fifty completed exposure days

Five out of eight patients had completed 50 exposure days. In two patients this target was not reached. From another patient it was unknown due to missing documentation (see table 34).

Tab. 34 Fifty exposure days completed

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
unknown	1	25,0%	0	,0%	1	12,5%
no	0	,0%	2	50,0%	2	25,0%
yes	3	75,0%	2	50,0%	5	62,5%
patients	4	100,0%	4	100,0%	8	100,0%

From patient no. 1002 data are unknown/missing.

3.3.2 Premature study termination

One out of eight patients (patient no. 1001) terminated the study prematurely because he died due to multi organ failure (not related to the treatment with Haemonine). See also tables T-85 to T-87 of the statistical summary tables volume.

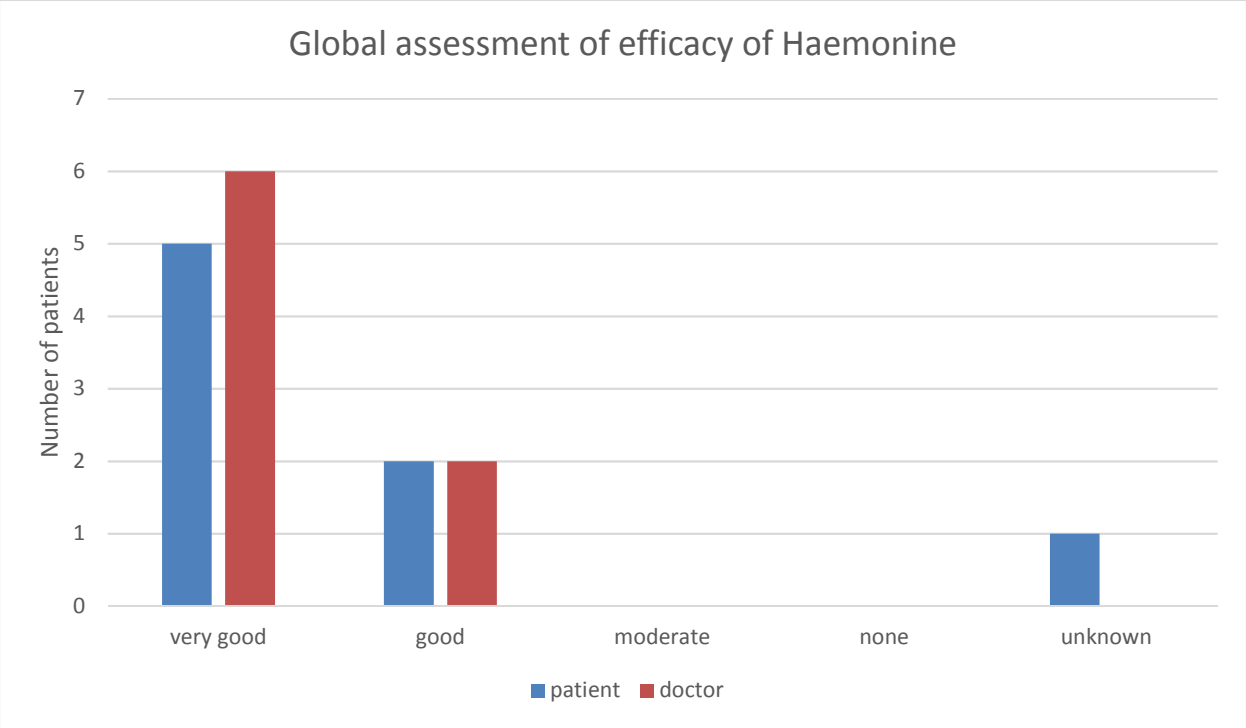
3.3.3 Efficacy of Haemonine

The efficacy of Haemonine was rated to be "very good" or "good" by all patients and doctors. One patient rating was missing (see table 35 and figure 1).

Tab. 35 Evaluation of efficacy of Haemonine

	patient's opinion		doctor's opinion	
	n	%	n	%
very good	5	62,5%	6	75,0%
good	2	25,0%	2	25,0%
moderate	0	,0%	0	,0%
none	0	,0%	0	,0%
unknwon/missing	1	12,5%	0	,0%
patients	8	100,0%	8	100,0%

Further details (stratified evaluation) are shown in tables T-88 and T-89 of the statistical summary tables. The ratings in the subgroups were comparable.



Flg. 1 Patient's and doctor's ratings for the efficacy of Haemonine
This figure is based on table 35.

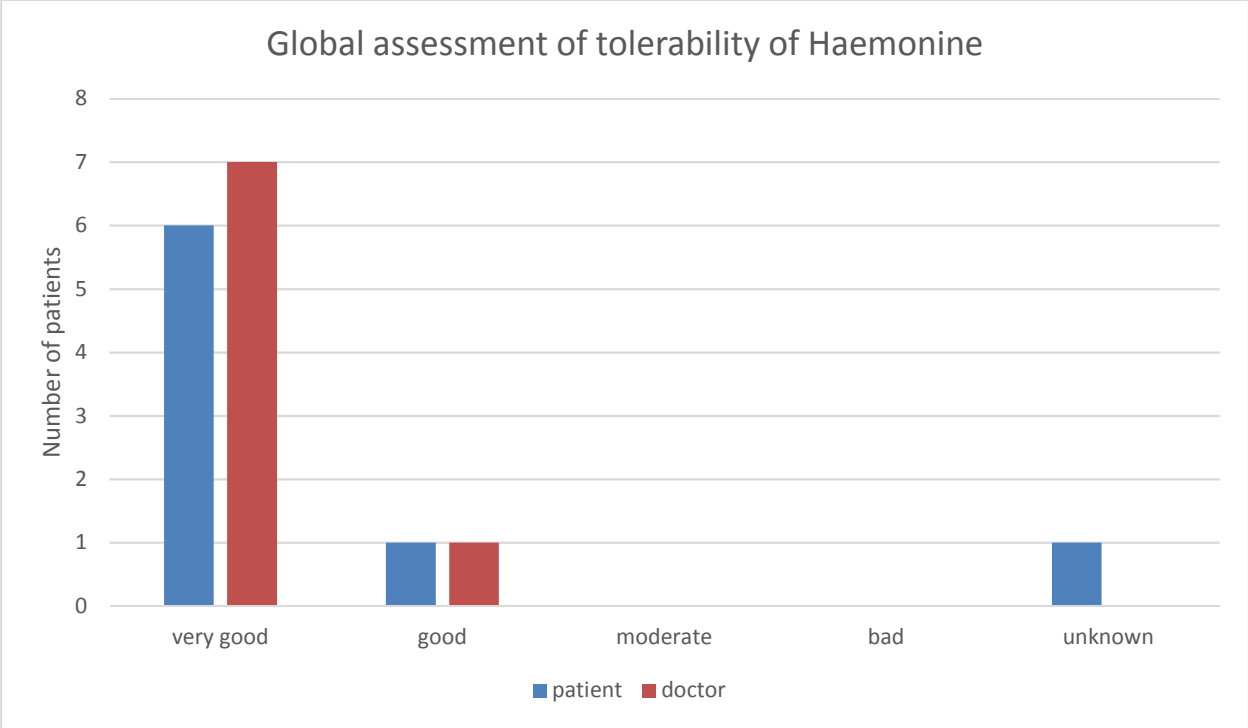
3.3.4 Tolerability of Haemonine

The tolerability of Haemonine was rated to be "very good" or "good" by all patients and doctors. One rating was missing (see table 36 and figure 2).

Tab. 36 Evaluation of the tolerability of Haemonine

	patient's opinion		doctor's opinion	
	n	%	n	%
very good	6	75,0%	7	87,5%
good	1	12,5%	1	12,5%
moderate	0	,0%	0	,0%
bad	0	,0%	0	,0%
unknown/missing	1	12,5%	0	,0%
patients	8	100,0%	8	100,0%

Further details (stratified evaluation) are shown in tables T-90 and T-91 of the statistical summary tables. The ratings in the subgroup of patients with mild haemophilia were slightly better.



Flg. 2 Patient's and doctor's ratings for the tolerability of Haemonine
This figure is based on table 36.

3.3.5 Application of Haemonine (ease of use)

The application of Haemonine (ease of use) was rated slightly better by patients compared to doctors: 5 patients rated the application of Haemonine as "very good" and two patients as "good". In the doctor's opinion, the application of Haemonine was "very good" in 5 patients and "good" in 3 patients (see table 37).

Tab. 37 Evaluation of the application (ease of use) of Haemonine

	patient's opinion		doctor's opinion	
	n	%	n	%
very good	5	62,5%	5	62,5%
good	2	25,0%	3	37,5%
satisfactory	0	,0%	0	,0%
adequate	0	,0%	0	,0%
poor	0	,0%	0	,0%
unknown/missing	1	12,5%	0	,0%
patients	8	100,0%	8	100,0%

3.4 Adverse events

3.4.1 Treatment emergent adverse events

Adverse events were coded using the MedDRA coding dictionary version 22.0.

Treatment emergent adverse events (TEAEs) have been observed in 5 out of 8 patients (see table 38). In total 30 TEAEs were reported in these patients. Some complex events were further subdivided leading to totally 35 single codable symptoms

Tab. 38 Incidence of treatment emergent adverse events (TEAEs)
Base: All patients

	n	%
AEs did not occur	3	37,5%
AEs occurred	5	62,5%
patients	8	100,0%

95% confidence interval for the total incidence: 24.5% to 91.5%.
For 5 patients totally 30 adverse events were documented.
Additionally some complex events were further subdivided leading to totally 35 single codable symptoms.

Based on MedDRA System Organ Class, the most frequent AEs were gastrointestinal disorders (10 events (28.6%)), respiratory, thoracic and mediastinal disorders (7 events (20.0%)), and general disorders and administration site conditions (4 events (11.4%)). See table 39.

Tab. 39 Type of adverse events (MedDRA System Organ Class)
Base: Coded adverse events

	n	%
Gastrointestinal disorders	10	28,6%
Respiratory, thoracic and mediastinal disorders	7	20,0%
General disorders and administration site conditions	4	11,4%
Injury, poisoning and procedural complications	3	8,6%
Surgical and medical procedures	3	8,6%
Vascular disorders	2	5,7%
Blood and lymphatic system disorders	1	2,9%
Hepatobiliary disorders	1	2,9%
Infections and infestations	1	2,9%
Musculoskeletal and connective tissue disorders	1	2,9%
Neoplasms benign, malignant and unspecified (incl cysts and	1	2,9%
Skin and subcutaneous tissue disorders	1	2,9%
coded adverse events	35	100,0%

Table T-96 of the statistical summary tables volume shows the AEs as MedDRA Preferred Terms.

About one third of the AEs were serious (see table 40).

Tab. 40 Seriousness of adverse events
Base: Coded adverse events

	n	%
not serious	23	65,7%
serious	12	34,3%
coded adverse events	35	100,0%

All serious AEs occurred in one patient.

Table 41 shows the type and frequency of the serious adverse events (as MedDRA System Organ Class and Preferred Term).

Tab. 41 Type of serious adverse events (by MedDRA System Organ Class and Preferred Term)
Base: Codes serious adverse events

	n	%
Gastrointestinal disorders		
Diarrhoea	2	16,7%
Duodenal ulcer perforation	1	8,3%
Gastritis erosive	1	8,3%
Gastroenteritis salmonella	1	8,3%
General disorders and administration site conditions		
Mucosal inflammation	1	8,3%
Multiple organ dysfunction syndrome	1	8,3%
Blood and lymphatic system disorders		
Blood loss anaemia	1	8,3%
Hepatobiliary disorders		
Hepatic cirrhosis	1	8,3%
Infections and infestations		
Salmonella sepsis	1	8,3%
Respiratory, thoracic and mediastinal disorders		
Pneumonia	1	8,3%
Skin and subcutaneous tissue disorders		
Erysipelas	1	8,3%
coded adverse events	12	100,0%

According to table 42, no adverse event was reported related to the application of Haemonine.

Tab. 42 Reported causal relationship of adverse events with Haemonine
Base: Coded adverse events

	n	%
not related	35	100,0%
coded adverse events	35	100,0%

Ratings 1-3 (certain, probable, possible) have been transformed to 'related'
Rating 4 (unlikely) has been transformed to 'not related'

A case wise listing of the serious adverse events is provided by table T-102 of the statistical summary tables volume. Table T-100 provides a listing of the non-serious AEs.

One patient (no. 1001), who had totally 14 adverse events died finally due to multi-organ failure. All serious AEs occurred in this patient. Most AEs in other study patients were resolved during the course of the study (cf. table 43).

Tab. 43 Outcome of adverse events
Base: Coded adverse events

	n	%
recovered / resolved	29	82,9%
recovering / resolving	1	2,9%
not recovered	4	11,4%
fatal	1	2,9%
coded adverse events	35	100,0%

Further details and a full listing of all adverse events is provided by tables T-94 to T-111 of the statistical summary tables volume.

3.4.2 Thrombogenicity

No case of thrombogenicity was observed (see tables T-112 to T-115) of the statistical summary tables volume).

3.4.3 Immunogenicity

No case of immunogenicity was observed observed (see tables T-116 to T-118) of the statistical summary tables volume).

3.5 Patient's diary

All eight patients recorded details of their treatment with Haemonine in a patient diary (see table T-119 of the statistical summary tables volume). Per day and application, the following data were documented:

- No. of units (applied)
- Batch no. (tear off label)
- Reason for treatment:
  - Bleeding
  - Follow-Up treatment
  - Prophylaxis
- Area of bleeding
- Therapeutic effect
  - Yes
  - No
- Type of treatment
  - Self-treatment at home
  - Treatment by doctor

In total, 2784 applications of Haemonine have been documented (see table 44).

Tab. 44 Frequency of treatments with Haemonine per patient
Base: All patients

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
1 documented treatment/patient	0	,0%	1	25,0%	1	12,5%
40 documented treatments/patient	0	,0%	1	25,0%	1	12,5%
66 documented treatments/patient	0	,0%	1	25,0%	1	12,5%
170 documented treatments/patient	1	25,0%	0	,0%	1	12,5%
264 documented treatments/patient	0	,0%	1	25,0%	1	12,5%
486 documented treatments/patient	1	25,0%	0	,0%	1	12,5%
744 documented treatments/patient	1	25,0%	0	,0%	1	12,5%
1013 documented treatments/patient	1	25,0%	0	,0%	1	12,5%
patients	4	100,0%	4	100,0%	8	100,0%

Totally 2784 treatments were documented

The median dosage of Haemonine per application was 1.000 units (interquartile range: 1.000 to 2.000 units). Patients with mild haemophilia received a higher median dosage (4.000 IU). Full details about the average dosage of Haemonine applied, also broken by severity of disease and by reason for treatment, is given by table T-127 of the statistical summary tables volume.

The median dosage of Haemonine per kg body weight was 19.1 IU/kg BW (interquartile range: 17.5 to 26.3 IU/kg BW). Patients with mild haemophilia received a higher median dose per kg BW (36.6 IU/kg BW) compared to patients with severe haemophilia (18.6 IU/kg BW). See table 47.

Tab. 45 Dosage of Haemonine per kg body weight (total) and depending on reasons for treatment (IU/kg BW)

subgroup: severe haemophilia	total	reason: bleeding	reason: follow-up	reason: prophylaxis	reason: other
mean	21,1	26,6	29,4	20,7	.
standard deviation	7,5	13,1	16,4	6,6	.
minimum	11,5	11,5	17,0	11,5	.
25% percentile	17,5	17,7	18,3	17,5	.
median	18,6	18,3	23,8	18,5	.
75% percentile	26,3	35,7	29,7	26,3	.
maximum	85,5	53,3	71,3	85,5	.
treatments	N=2405	N=94	N=44	N=2267	N=0

subgroup: mild haemophilia	total	reason: bleeding	reason: follow-up	reason: prophylaxis	reason: other
mean	35,1	43,8	29,9	37,7	20,8
standard deviation	12,4	44,8	11,5	11,6	.
minimum	12,1	12,1	18,3	20,0	20,8
25% percentile	24,1	12,1	19,1	24,1	20,8
median	36,6	43,8	27,5	47,2	20,8
75% percentile	47,2	75,5	41,7	47,2	20,8
maximum	75,5	75,5	56,6	56,6	20,8
treatments	N=331	N=2	N=107	N=221	N=1

all patients	total	reason: bleeding	reason: follow-up	reason: prophylaxis	reason: other
mean	22,8	26,9	29,7	22,2	20,8
standard deviation	9,4	13,9	13,1	8,7	.
minimum	11,5	11,5	17,0	11,5	20,8
25% percentile	17,5	17,6	19,1	17,5	20,8
median	19,1	18,3	23,8	18,7	20,8
75% percentile	26,3	35,7	36,6	26,3	20,8
maximum	85,5	75,5	71,3	85,5	20,8
treatments	N=2736	N=96	N=151	N=2488	N=1

From some patients data are missing for this parameter.

In total 4.630.500 IU of Haemonine were applied (see table 46): 3.307.500 IU in patients with severe haemophilia and 1.323.000 IU in patients with mild haemophilia. The main reason for this ratio is the number of treatments: 2405 treatments in patients with severe haemophilia and 331 treatments in patients with mild haemophilia.

- The mean cumulative dose of haemonine applied in patients with severe haemophilia amouted to 826.875 IU (SD: 438.424 IU).
- The mean cumulative dose of haemonine applied in patients with mild haemophilia amouted to 330.750 IU (SD: 479.330 IU).

Tab. 46 Cumulative dose of Haemonine per patient (IU)

	severe haemophilia	mild haemophilia	total
mean	826875	330750	578813
standard deviation	438424	479330	501170
minimum	170000	1000	1000
25% percentile	594000	67000	139500
median	1034250	139500	594000
75% percentile	1059750	594500	1046750
maximum	1069000	1043000	1069000
patients	N=4	N=4	N=8

For 8 patients totally 4.630.500 IU of Haemonine were used:
3.307.500 IU in patients with severe haemophilia
1.323.000 IU in patients with mild haemophilia

Table 47 provides a listing with the cumulated dose of Haemonine of each patient.

Tab. 47 Listing of patients with their cumulative dose of Haemonine (IU)

patient no.	subgroup	cumulative dose (IU)
1001	mild haemophilia	1043000
1002	severe haemophilia	1050500
1003	severe haemophilia	1018000
1004	severe haemophilia	1069000
1005	mild haemophilia	146000
1006	severe haemophilia	170000
1007	mild haemophilia	133000
1008	mild haemophilia	1000

The therapeutic effect of the application of Haemonine was rated in almost two thirds of the applications. Only in one case (pat. no. 1001) no therapeutic effect was observed at one application. See tables T-131 and T-132 of the statistical summary tables volume.

"Prophylaxis" was the predominant indication (89.4%) for the application of Haemonine in haemophilic B patients. Especially for patients suffering from severe haemophila (93.9%). See table 48.

Tab. 48 Reason for the treatment with Haemonine
Base: Documented treatments with Haemonine

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
bleeding	94	3,9%	2	,5%	96	3,4%
follow-up-treatment	44	1,8%	107	28,8%	151	5,4%
prophylaxis	2267	93,9%	221	59,6%	2488	89,4%
other	0	,0%	1	,3%	1	,0%
unknown/missing	8	,3%	40	10,8%	48	1,7%
treatments	2413	100,0%	371	100,0%	2784	100,0%

Bleedings were treated in 96 cases (mostly with severe haemophilia). The areas of bleeding were quite different (e.g. joints, colon, teeth, etc.). A full listing of all areas of bleeding can be found in table T-124 of the statistical summary tables volume. In some cases (not bleedings), comments were made in the CRF field "area of bleeding". These remarks are listed in table T-126.

Haemonine was predominantely applied as "self-treatment at home" (1750 out of 2784 treatments (62.9%) - especially in cases with severe haemophilia - followed by "treatment by doctor" (263 out of 2784 treatments (9.4%). In patients with mild haemophilia "treatment by doctor" was the predominant type of treatment (70,6%).However in 27.7% of the cases, no data were available for this parameter (see table 49).

Tab. 49 Type of treatment with Haemonine
Base: Treatments

	severe haemophilia		mild haemophilia		total	
	n	%	n	%	n	%
self-treatment at home	1681	69,7%	69	18,6%	1750	62,9%
treatment by doctor	1	,0%	262	70,6%	263	9,4%
unknown/missing	731	30,3%	40	10,8%	771	27,7%
treatments	2413	100,0%	371	100,0%	2784	100,0%

Based on the documentation in the patient diaries 96 bleedings were documented in the 8 study patients. This corresponds to an annual bleeding rate of 0.11% (see table 50).

Tab. 50 Bleeding rates

	severe haemophilia	mild haemophilia	total
bleedings/treatments	94/2413	2/371	96/2784
crude bleeding rate	3,89%	0,54	3,45
patient years	24	7	31
annual bleeding rate (ABR)	0,16	0,08	0,11

4 Summary and biometric evaluation

Based on eight haemophilic patients from six German study centers the final analysis of the non-interventional post-marketing study with Haemonine was conducted.

The patients median age at study inclusion was 24.5 years ranging from 14 to 52 years (including three children <18 years). The patients were suffering from haemophilia B since 15 years (median). Four out of eight patients had an initial residual factor IX activity (FIX) of less or equal 1% (=severe haemophilia). The other four patients residual factor IX activity was >1% (=mild haemophilia). Seven out of eight patients were pre-treated with factor IX preparations, mostly for prophylactic reasons.

Neither inhibitor- or allergic reactions nor reduced efficacy of factor IX substitution had been observed in the patients in the past. The parents of the patients did not suffer from immunodeficiency.

About half of the patients were immunised against Hepatitis A and B. The majority of the patients did not consume alcohol, tobacco or drugs. Comorbidity was present in three out of eight patients.

The median observation and treatment time during this PMS amounted to two years (median: 765 days, range: 289 to 3170 days). Five out of eight patients had completed 50 exposure days. In total 2784 treatments with Haemonine were documented, mostly for prophylactic reasons (89.4%). This corresponds to 31 patient-years of treatment. The median dosage of Haemonine amounted to 19.1 units/kg BW (interquartile range: 17.5 to 26.3 units/kg BW). Patients with mild haemophilia received a higher median dose per kg BW (36.6 IU/kg BW) compared to patients with severe haemophilia (18.6 IU/kg BW). More patients with severe haemophilia received a prophylactic treatment were the dosages are lower compared to the on demand treatment. During the study course altogether, 3.3×10^6 IU were applied in the 4 patients with severe and 1.3×10^6 IU in the 4 patients with mild haemophilia.

Patients' bleedings were well controlled with Haemonine. An annual bleeding rate of 0.11% was determined (0.08% for mild and 0.16% for severe haemophilia).

Apart from one single treatment, a therapeutic effect was always observed. Haemonine was predominantly administered as self-treatment at home. In patients with mild haemophilia predominantly a treatment by doctor.

The efficacy of Haemonine was rated to be "very good" or "good" by all patients and doctors. Equally, the application of Haemonine (ease of use) was rated to be "very good" or "good" by all patients and doctors.

Adverse events (AEs) had been observed in 5 out of 8 patients. In total 35 AEs occurred in these patients. Most frequent AEs were

gastrointestinal disorders (10 events (27%)), respiratory, thoracic and mediastinal disorders (7 events (18.9%)), and general disorders and administration site conditions (4 events (10.8%)). All AEs were reported as "not related" to Haemonine. About one third of the AEs were serious events. All serious AEs occurred in one patient (no. 1001) and one led to death (multi-organ failure). Most AEs in other study patients were resolved during the course of the study. No case of thrombogenicity or immunogenicity was observed. No adverse drug reaction (ADR) was reported throughout the course of the study.

Parameters of clinical chemistry fluctuated without clinical significance during the course of the PMS. Deviations from normal (if any) were never considered as related to Haemonine. In no patient an increase of the inhibitor titer was observed.

Positive initial virological test results were found in
- 7 out of 8 patients for Anti-HBs
- 1 out of 8 patients for Anti-HBc
- 1 out of 8 patients for Anti-HCV
- 2 out of 8 patients for Anti-HAV.

In none of these cases a new virological finding was observed during the PMS.

Test results for HBs-Ag, IgM and Anti-HIV were always negative in all patients.

The subjective findings of the patients deteriorated slightly between the beginning and the end of the PMS. At the beginning of the study, all patients felt "very good" or "good". At the end of the PMS, a slight switch towards less favourable findings could be observed.

The tolerability of Haemonine was rated consistently by patients and doctors. It was rated "very good" or "good" by patients and doctors.

No new unexpected risks by the application of Haemonine became apparent.

The application of Haemonine was shown to be safe and well tolerated and no new and/or unexpected safety finding beyond the established safety profile of Haemonine was detected.

Appendix

List of participating study centers

Germany:

[redacted]