NIS observation plan

Title	Non-interventional study of long term treatment with Haemoctin SDH
Observation plan version identifier	Version 2.0
Date of last version of the observation plan	18.02.2021
Study Number	Biotest NIS-016
ENCEPP register number	13728
Active substance	Coagulation factor VIII ATC-Code: B02BD02
Medicinal product	Haemoctin SDH
Marketing authorization holder(s)	Biotest AG Landsteinerstr. 5 63303 Dreieich, Germany
Research question and objectives	Documentation of the long term effectiveness of Haemoctin SDH in the prevention of bleedings. Determination of quality of life
Country(-ies) of study	Germany, Hungary, Austria
Author	Prof. Dr. Artur Bauhofer Corporate Medical Affairs, Biotest AG

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
BU	Bethesda Unit
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
eCRF	electronic case record form
FVIII	factor VIII
HEAD-US	hemophilia early arthropathy detection with ultrasound
IEC/IRB	independent ethics committee / institutional review board
ISF	Investigator Site File
NIS	non-interventional study
PTP	previously treated patient
QoL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SPC	summary of product characteristics
WFH	World Federation of Hemophilia
WHO-DDE	World Health Organization - Drug Dictionary Enhanced

3 RESPONSIBLE PARTIES

Sponsor	**Biotest AG** Corporate Medical Affairs Landsteinerstr. 5, 63303 Dreieich, Germany
Scientific Contact	Prof. Dr. Artur Bauhofer Head of Corporate Medical Affairs +49 6103 801 730 artur.bauhofer@biotest.com
CRO	**AMS** Advanced Medical Services GmbH Am Exerzierplatz 2; 68167 Mannheim, Germany
Contact	Alexandra Stricker +49 (0) 621 - 700 95 100 alexandra.stricker@ams-europe.com
Electronic diary	smart medication ™ Rösch & Associates Information Engeniering Max-Plank Straße 20 63303 Dreieich, Germany +49 69 60501211 aroesch@raie.de
Coordinating physician	Dr. Dr. Christoph Königs Dept. for Pediatrics and Adolescent Medicine, Thrombosis and Hemostasis Goethe University Hospital, Frankfurt Theodor-Stern-Kai 7 60596 Frankfurt am Main, Germany +49 69 6301 83030 christoph.koenigs@kgu.de

4 ABSTRACT

Title	**Non-interventional study of long term treatment with Haemoctin SDH**
Rationale and background	Haemoctin SDH is a factor VIII (FVIII) preparation derived from human plasma purified by chromatography. Haemoctin SDH is approved for prevention and treatment of innate and acquired factor VIII deficiencies. Also, patients with a FVIII inhibitor can be treated with Haemoctin SDH. Details are given in the SPC of Haemoctin SDH. The stabilization of the FVIII molecule is carried out by the natural carrier protein von Willebrand factor. There is no need for the addition of auxiliary stabilizers such as sucrose or human serum albumin. Hemophilia A is an inherited, chronic bleeding disorder and patients have to be treated lifelong with FVIII concentrates. Most children and adolescents are treated prophylactically in industrialized countries. Prophylaxis has the goal to avoid bleedings, in order to guarantee the patient a high quality of life (QoL). Patients who have started in childhood with the prophylaxis, this treatment is extended in adulthood. Prophylactic treatment consists of regular FVIII applications, usually three times a week. With this study long-term data will be generated. Unique longterm data obtained form some patients in a previous study with Haemoctin SDH over up to 22 year can be extended with this study. This NIS allows adopting the documentation to the current guidance for observational studies and adjusted focus of the objectives.
Research question and objectives	With this NIS long-term data for the effectiveness in bleeding prevention and on QoL will be generated. The following questions will be examined: • What are the factors influencing the risk of bleeding over the time of treatment? • What are the factors influencing the risk to develop FVIII inhibitors during treatment with Haemoctin SDH? • Can these inhibitors be further characterized? • What impact has a longstanding regular treatment with Haemoctin SDH on QoL?
Study design	Non-interventional, prospective and retrospective, single arm study
Inclusion Criteria	• Treatment in accordance with the SPC of Haemoctin SDH • Children of all ages and adult patients with FVIII deficiency (previously treated and previously untreated patients) • Written informed consent to allow data collection and data transfer to third party
Exclusion Criteria	• Contraindications as provided in the SPC

Primary objectives	Annual bleeding rate defined as episodes per year in patients with Haemoctin SDH treatment, differentiated by prophylaxis and on demand treatment
Secondary objectives	• AE and subsequent suspected ADR (AE assessed as causally related with Haemoctin treatment) • AE with bleeding = AE of special interest (AESI) with extended bleeding documentation, for e.g. if the duration and severity of the bleeding is within the situation as expected or unexpected • Occurrence and characterization of FVIII inhibitors to Haemoctin SDH • QoL determined with the Euroqol EQ-5D in adults and the EQ-5D-Y in adolescents.
Data sources	Information on Haemoctin SDH treatment, the occurrence of bleedings and potential underlying AE will be obtained from web based patient documentations (smart medication) and/or from paper-based patient diaries. Further information will be obtained from the patient files and during patient visits. Data will be entered and stored in an electronic case record form (eCRF).
Study size	150 patients
Data analysis	All analyses will be performed in an exploratory sense. Data will be analyzed using descriptive statistics. For continuous variables, mean, standard deviation, minimum, maximum, median, 25% and 75% percentiles will be presented. Qualitative and categorical variables will be presented by means of absolute and relative frequencies. A medical evaluation of the findings will be performed. Details of analysis will be described in a statistical analysis plan.
Study duration	Start of documentation March 2016 End of documentation March 2023

5 AMENDMENTS AND UPDATES

Self standing Local Amendment 1.0 for the University Heidelberg

New Version of the study protocol 2.0 including new time lines and an update on protection of human subjects.

6 MILESTONES

Milestone	Planned date
Start of data collection	October-2016
End of data collection	March-2023
Final report of study results	December-2023

7 RATIONALE AND BACKGROUND

This is a non-interventional study (NIS). The observation plan was developed in accordance to the Biotest SOC-CCR-036 for NIS.

7.1 Hemophilia A and the treatment of Hemophilia A

Hemophilia A is an inherited, chronic bleeding disorder and is treated live long with FVIII concentrates. Two treatment regimens are applied, treatment on demand and as prophylaxis. Most children and adolescents are treated prophylactically in industrialized countries. Patients who have started prophylaxis in childhood, this treatment is extended into adulthood. Prophylaxis has the goal to avoid bleedings, in order to prevent bleeds, permanent joint damage and insure a high quality of life (QoL).

Prophylactic treatment consists of regular FVIII applications, usually three times a week.

Development of neutralizing antibodies against FVIII (FVIII inhibitor) is the most significant complication of hemophilia care today. Antibodies inactivate the procoagulant activity of FVIII and inhibit patients' response to replacement therapy. As inhibitors tend to develop early in the course of FVIII treatment, the main challenge consists in avoiding inhibitors in this critical early phase of FVIII exposure as the subsequent risk is much lower [Kruse-Jarres 2013].

Once developed, however, attempts for induction of immune-tolerance induction (ITI) have been successful particularly with plasmatic factor preparations such as Haemoctin SDH [Bidlingmaier *et al.* 2011].

7.2 Haemoctin SDH

Haemoctin SDH is a FVIII preparation derived from human plasma purified by chromatography. Haemoctin SDH is approved for prevention and treatment of congenital and acquired FVIII deficiencies. Details are given in the SPC and German “Fachinformation” of Haemoctin SDH. Clinical efficacy, safety and pharmacokinetic properties of Haemoctin SDH were evaluated in three prospective open-label uncontrolled studies in previously treated patients (PTPs) with severe hemophilia A. In conclusion, Haemoctin SDH has shown to be effective, safe and well tolerated in long-term prophylaxis and treatment on-demand as well as after minor and major surgical procedures [Wolf *et al.* 2004].

Data on successfully performed ITI with Haemoctin SDH have been collected in patients with hemophilia A who have developed inhibitors to factor VIII.

The stabilization of the FVIII molecule is carried out by the natural carrier protein von Willebrand factor. There is no need for the addition of auxiliary stabilizers such as sucrose or human serum albumin. It seems that the FVIII preparations with von Willebrand factor will generate less inhibitors than products without von Willebrand factor [Kallas and Talpsep 2001].

Data obtained form patients in a previous NIS with Haemoctin SDH over 22 year can be in part extended with this new study.

From the previous NIS data from an interim analysis in the year 2010 were published [Nemes *et al.* 2012]. The generation of the final report of the previous NIS is ongoing at the time of the study setup of this study.

In the interim analysis [Nemes *et al.* 2012] long-term effectiveness, safety and tolerability were investigated in a total of 109 hemophilia A patients treated for prophylaxis or on-demand, as required. Data collected until June 2010 was included. Most patients (99/109; 90.8%) were previously treated patients (PTPs). The mean observation period was 82.6 months. Overall, patients received 105,131,425 IU Haemoctin SDH during 68,624 administrations. Each patient was given a mean of 635 injections, whereby about half of the administrations were given for treatment of bleeding episodes (46.9%) and the other administrations for prophylactic reasons (53.1%). Patients on prophylaxis had a median of 0.8 bleeding episodes per month. The expected therapeutic effect was reached in 99.3% of treatments. The incidence of clinically relevant inhibitor formation in patients with severe hemophilia (FVIII activity ≤ 1%) was 1.2% for PTPs. One previously untreated patient with severe hemophilia had a clinically relevant transient inhibitor. No treatment related transmissions of hepatitis A, B, C and HIV 1/2 were observed. In conclusion, Haemoctin SDH was effective, safe and well tolerated in long-term prophylaxis and treatment on demand.

With this new long-term study the documentation of some patients can be extended and new patients will be included. The primary focus of the NIS was moved from safety and efficacy to effectiveness and patient reported QoL.

8 RESEARCH QUESTION AND OBJECTIVES

With this NIS longterm data under real life conditions in an international study population will be generated.

8.1 Primary Objective

- Annual bleeding rate defined as episodes per year in patients with Haemoctin SDH treatment, differentiated by prophylaxis and on demand treatment

8.2 Secondary Objectives

- AE and subsequent suspected ADR (AE assessed as causally related with Haemoctin treatment)
- AE with bleeding = AE of special interest (AESI) with extended bleeding documentation, for e.g. if the duration and severity of the bleeding is within the situation as expected or unexpected
- Occurrence and characterization of FVIII inhibitors to Haemoctin SDH
- QoL determined with the Euroqol EQ-5D in adults and the EQ-5D-Y in adolescents

9 RESEARCH METHODS

9.1 Study Design

This is a non-interventional, retrospective and prospective, single-arm, uncontrolled, multi-centre, international, post marketing authorization study.

Haemoctin SDH treatment-related information from patients with hemophilia A will be collected under routine treatment conditions in different countries.

9.2 Setting

Patients will be treated at home and in some exceptional cases in the clinic or a local doctor's practice.

Study duration:

An inclusion period of 7 year is planned. The end of the NIS will be defined as the last documentation performed in March 2023 or if 150 patients have been documented for at least 1 year.

Individual NIS Patient

The individual documentation per patient after start with treatment aims for a documentation of at least 1 year. Treatment related data that has been recorded by the treating physician since inclusion in the NIS will be documented in an eCRF and will be included in the evaluation.

9.2.1 Inclusion Criteria

In particular, only patients meeting all of the following inclusion criteria will be considered for the inclusion into the NIS:

- Treatment in accordance to the SPC with Haemoctin SDH
- Children of all ages and adult patients with FVIII deficiency (previously treated and previously untreated patients)
- Written informed consent to allow data collection and data transfer to third party

9.2.2 Exclusion Criteria

- Contraindications as provided in the SPC

9.3 Variables

- Patient demographics (age, sex, ethnicity, body weight)
- Family history in relation to bleeding disorders, diagnosis (time of determination of hemophilia, date of first bleeding, baseline clotting factor activity, familiarity, mutation type) previous treatment of hemophilia, accompanying diseases
- Treatment (intended regimens: prophylaxis or on demand, total number of exposures per year, mean dose per kg per patient/year, total dose/year, batch number of Haemoctin SDH)
- The annual bleeding rate in patients with Haemoctin SDH prophylaxis or on-demand treatment
- Number and severity of bleedings dependent on the treatment regime (prophylaxis or on demand) with the bleeding score [Poonnoose and van der Net 2015] (See Appendix 2)
- Patient reported QoL will be determined with the Euroqol EQ-5D in adults and the EQ-5D-Y in adolescents [EQ-5D 2014]

- Occurrence of inhibitors to Haemoctin SDH depended on the treatment regime will be evaluated in patients on prophylaxis and in patients on demand treatment. Only titers ≥ 0.6 BU are considered as of clinically significant [Franchini and Mannucci 2011;Gouw et al. 2013;Verbruggen et al. 1995]
- Immunological characterization of antibodies against FVIII (antibody isotopes, -subclasses and -binding sites) at study start and in case of FVIII inhibitor formation
- In case of FVIII inhibitor formation clinical signs like hematoma formation, the factor VIII trough levels
- The occurrence of adverse events (AEs), seriousness, severity, relation to Haemoctin SDH treatment (related or not related) and outcome of the AE
- Overall assessment by the patient and physician of treatment effectiveness, tolerance and handling of Haemoctin SDH
- Activity of the person and days of illness (e.g. not at work or school) due to hemophilia
- Reasons for stopping the documentation
- Optional, arthropathy progress assessed with ultrasound and quantified with the HEAD-US score (hemophilia early arthropathy detection with ultrasound) [Martinoli et al. 2013] See Appendix 2

9.4 Data Sources

Information on Haemoctin SDH treatment and the occurrence of bleedings will be obtained from patient diaries either web based (smart medication™) [Smart medication 2015] or paper based. Further information will be obtained from the patient files and during patient visits. Patient data will be entered and stored in an electronic case record form (eCRF).

9.5 Study Size

As Hemophilia is a rare disease, a formal sample size calculation is not applicable because the study population is restricted by the number of available patients on Haemoctin SDH treatment.

9.6 Data Management

9.6.1 Data Collection and Handling

Data will be entered into the eCRF at the study site. Data entries will be checked by automatic and manual queries according to the data validation plan. Corrections have to be entered into the eCRF at the study site.

The personnel responsible for data entry performance and controlling and specific data handling procedures will be defined upfront.

Individual information from the patients on their treatment (application of Haemoctin SDH with units, time of application, batch number), the occurrence location of bleedings and association with pain, swelling and restriction of motion will be collected by the use of the app smart medication™ or from paper diaries. The smart medication app will be used

in those study centers where this technique is available and the patients are using it. Paper diaries will be copied and forwarded to the CRO for data entry into the study data base. The choice of electronic or paper based data collection is at the discretion of the patient and investigator.

The final data will be transferred to SAS for subsequent data analyses in accordance with the statistical analysis plan.

Concomitant medication will be coded with the World Health Organization Drug Dictionary Enhanced (WHO-DDE). MedDRA will be used for coding of adverse events, concomitant diseases and medical history.

Questionnaires for quality of life will be handed over to the patients by the clinical staff. After completion of the questionnaires, data have to be entered into the eCRF by the study site personal.

For AE management and reporting, refer to section 11.

9.6.2 Missing Data

All available data will be included in the analyses and will be summarized as far as possible.

Unless otherwise specified there will be no substitution of missing data, i.e. missing data will not be replaced.

9.7 Data Analysis

The statistical planning and evaluation of the NIS will be carried out by a qualified statistician. A medical evaluation of the findings will be performed. Details of data analysis will be described in a statistical analysis plan (SAP) which will be prepared before data base lock.

9.7.1 Analysis Populations

Full Data Set defined as all patients with any data captured within this study.

9.7.2 Criteria for Evaluation

Primary criteria

- Annual bleeding rate during a prophylactic or on demand treatment regimen

Secondary criteria

- Rate of inhibitor formations and characterization of the inhibitors. Only Inhibitors ≥ 0.6 Bethesda Units (BU) will be considered clinically significant and processed as SAE. Inhibitors ≥ 5 BU are defined as high-titre inhibitors.
- Number and severity of bleedings per year assessed with the Orthopedic Advisory Board Committee of the World Federation of Hemophilia (WFH) bleeding score (Annex 2, Bleeding score)
- Quality of life assessed with the Euroqol EQ-5D in adults and the EQ-5D-Y in adolescents during the course of treatment. The questionnaires will be applied at start of documentation, 3 months and 1 year after the start of the study and then

annually. When the patient become adult with 18 year the EQ-5D-Y will be switched to EQ-5-D

Additional criteria

- Dose of Haemoctin SDH applied
- The occurrence of adverse drug reactions (ADRs)
- Overall assessment of health by the patient and physician
- Days of illness (e.g. not at work or school) due to hemophilia
- Optional, arthropathy progress assessed with ultrasound and quantified with the HEAD-US score

9.7.3 Statistical Methods

All analyses will be performed in an exploratory sense. Since there are no confirmatory analyses planned, hypotheses are not formulated. Data will be analyzed using descriptive statistics.

Descriptive statistics

The annual bleeding rate and proportions of patients with an inhibitor formation with will be presented as percentages (total: size of full data set) together with exact (according Pearson-Copper) 1-sided upper 95%-confidence limits.

For continuous variables, mean, standard deviation, minimum, maximum, median, 25% and 75% percentiles will be presented.

Qualitative and categorical variables will be presented by means of absolute and relative frequencies.

Subgroup analysis

A differentiation of the treatment by country in Germany, Austria and Hungary will be made. Further subgroup analyses may be defined in the SAP.

Safety

Frequencies of AEs, SAEs, ADRs and SADRs will be presented in summary tables for the coding levels system organ class (SOC) and preferred term (PT) using the latest MedDRA version. Additionally the number and percentage of injections with at least one ADR to the injection will be determined.

FVIII inhibitors with titers (≥ 0.6 BU) will be analyzed with respect to clinical relevance for the patient (e.g. more bleeding, higher dosages).

<u>Adverse events of special interest (AESI)</u>

Bleeding episodes in general, and of high relevance (all major bleeds, e.g. GI-bleeds, joint bleeds or intracranial hemorrhage, bleeds with unexpected course or severity in context of the underlying situation) and FVIII inhibitor development will be analyzed with respect to assumed treatment regime, treatment compliance and correlation to the FVIII inhibitors formation.

Missing values

There will be no imputation of missing values.

9.8 Quality Control

9.8.1 NIS Initiation Activities

The investigator(s) will be informed about objectives and methods of the NIS by a Clinical Research Associate (CRA) from the CRO. This will occur after a signed contract with the study site, competent authority information and ethic commission approvals have been obtained. No documentation should be done before the site is trained at the initiation visit.

9.8.2 Documentation and Filing

Electronic Case Report Form (eCRF)

All data to be recorded according to this NIS observation plan must be documented in the eCRF. The investigator will be instructed on how to use the eCRF for data entering.

Entries in the eCRF must only be made by the investigator or persons authorized by the investigator. An individual account for each authorized person will be created.

The investigator must verify that all data entries in the eCRF are accurate and correct.

9.8.3 List of Patients (patient identification log)

The investigator will keep a confidential list of names of all patients participating in the NIS, giving reference to the patients' records.

With the help of this list it must be possible to identify the patients and their medical records for the investigator.

9.8.4 Source Data

Source data is all information in original records and certified copies of original records of medical findings, observations, or other activities in a NIS necessary for the reconstruction and evaluation of the NIS. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries in electronic or paper form or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, ultrasound documentations, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments).

9.8.5 Investigator Site File

The CRO will provide an Investigator Site File (ISF) to each site. The ISF will include essential documents as per applicable local requirements.

The investigator will be responsible for the continual update and maintenance of the investigator site file. In case of an audit by the sponsor or an inspection by the Regulatory Authorities these documents will be reviewed. The CRO will help to complete the ISF.

All NIS related documents are to be archived and stored according to legal requirements.

9.8.6 Quality Assurance

The quality of data and adherence to the NIS documentation plan, to legal and ethical requirements according to local laws will be checked by Biotest, the CRO or delegate from the CRO.

A combination of centralized (automatic eCRF and manual checks) and on-site checks will be applied to assure data quality in this NIS.

NIS source data verification is an essential part of the quality assurance process and the investigator must grant direct access to the NIS patients' source data. For this NIS at least one quality assurance visits per site is planned to check the data entered. In addition regular phone contacts are planned to resolve questions regarding data entering in the eCRF.

9.8.7 Audits and Inspections

Audits will be performed according to the corresponding audit program, including the possibility that a member of the sponsor's quality assurance department may arrange to visit the investigator in order to audit the performance of the NIS at the clinical site, as well as all documents originating there. Audits may also be performed by contract auditors. In this case, the sponsor's quality assurance department will agree with the contract auditor regarding the timing and extent of the audit(s). In case of audits at the investigational site, a representative from the CRO will usually accompany the auditor(s).

Inspections by regulatory authority representatives and IECs/IRBs are possible at any time, even after the end of the NIS. The investigator should notify the sponsor immediately of any such inspection. The investigator and institution will permit NIS related quality assurance, audits, reviews by the IEC/IRB and/or regulatory authorities, and will allow direct access to source data and source documents for quality assurance, audits, and inspections.

9.8.8 Archiving

After evaluation and reporting of the data, all documents relating to the NIS will be transferred to the sponsor and kept in the archives of sponsor for at least 10 years according to national and European law and the clinical site(s) according to applicable local regulatory requirements.

9.9 Limitations of the Research Methods

Limitations of the planned NIS are the typical ones from a NIS. There is no control group and only data obtained in clinical routine can be obtained. It is not possible to guarantee

a documentation of all data defined in this observational plan and to document data in a fixed schedule as done in an interventional clinical study.

9.10 Other Aspects

9.10.1 NIS Administrative Structure

Details for the administrative structure are kept as a separate list filed in the abbreviated NIS Trial Master File.

9.10.2 Insurance

No study specific insurance is required for the NIS.

9.10.3 Study Conduct, Data management and Analysis

The study will be handled by the assigned CRO. Details of the tasks and responsibilities are regulated in the study contract between the sponsor of the study Biotest AG and the CRO.

9.10.4 Written Agreements

A written agreement will be set up between Biotest AG and each investigator setting out any arrangements on delegation and distribution of tasks and obligations and on financial matters.

9.10.5 Confidentiality

The objectives and contents of this NIS as well as its results are to be treated as confidential and may not be made accessible to third parties.

10 PROTECTION OF HUMAN SUBJECTS

This NIS documentation plan and any substantial amendments will be submitted to properly constituted **I**ndependent **E**thics **C**ommittees (IEC) / **I**nstitutional **R**eview **B**oard (IRB) and/or Regulatory Authorities, in agreement with applicable regulatory requirements, for formal approval (if required by law) of the NIS. A copy of these approvals (if applicable) must be submitted to the CRO executing the study before initiation of the NIS and each site needs to keep a copy of these documents.

Patients can decide on a voluntary basis to participate in the NIS. Informed consent provided to participate in the NIS by a patient or the parents can be withdrawn without specification of any reason and without any negative impact on further treatment at the study site. In case of withdrawing the consent in Germany the patient or the parents will be asked if already obtained date can be used for analysis or not. The answer of the patients/parents will define if the data will be used or not used for analysis.

The study is sponsored by Biotest. The NIS is conducted to obtain longterm data on the use of Haemoctin SDH. There is no financial inducement for the participating study sites to take part on this NIS, only the expenses for the time needed for the NIS documentation will be compensated by Biotest.

Pseudonymization will be used to allow only with a list at the study centre to determine patients identity. Only pseudonymized data will be stored and forwarded for analysis. Each patient has to sign an agreement to give his consent to use his medical data after information about the study. This will be part of the patient information and the informed consent form which will be approved by the respective competent EC.

In Germany the NIS is handled as other studies according to § 4 Section 23 AMG. The NIS will be conducted in accordance to the Helsinki Declaration in its actual version from the year 2013. Since hemophilia A is developing early in the youth and factor VIII treatment is the mainstay of current treatment, patients below 18 years of age will be included into the NIS. Informed consent will be obtained by the parents and in case the children become older and more self responsible their opinion on study participation will be respected. This translates into; if the parents or the child is against participation in the NIS no participation is possible. Becoming 18 years of age an informed consent by the patient will be obtained from the patient himself.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE DRUG REACTIONS

Adverse Event (AE)
An AE is any unfavorable or unintended sign, symptom, or disease that appears or worsens in a NIS patient during the period of observation. The AE may be any of the following:

- A new illness
- An exacerbation of a sign or symptom or the underlying condition under treatment or of a concomitant illness,
- Unrelated to participation in the NIS or an effect of the NIS medication or comparator drug,
- A combination of one or more of the above factors.

No causal relationship with the study medication under investigation is implied by the use of the term "AE".

Causality of Adverse Events
Refers to the relationship of the AE to the study drug. Causality will be categorized according to the following criteria:

Not related
AEs for which a reasonable explanation for an alternative cause is considered plausible e.g., no study drug taken, plausible clinical alternative like accidental injury, expected progression of underlying or concomitant disease, pharmacologically incompatible temporal relationship, intercurrent illness.

Related (= suspect ADR)
AEs for which a reasonably possible clinical and/or pharmacological relationship to study drug cannot be excluded e.g., lacking plausible alternatives.

In addition to the definition as given, the following special types of ADRs should be recorded:

- Laboratory values that are outside the normal range and if, in the opinion of the investigator, these values represent a clinically relevant change versus pre-treatment values are also defined as AEs.
- If abnormal laboratory values are signs of an AE (e.g. an infection) that has already been recorded, the respective abnormal laboratory value does not constitute a separate AE. Wherever reasonable the reporting investigator will use the clinical term rather than the laboratory term (e.g., anemia versus low hemoglobin value).

Serious Adverse Events (SAEs)

An AE is "Serious" if it:

- results in death,
  - Death is an outcome of an AE and not an AE in itself. All deaths, regardless of cause or relationship must be reported for patients on study.
- is life-threatening,
  - Life-threatening means that the patient was at immediate risk of death at the time the event occurred. Thus, in this context e.g. "cancer" is <u>not</u> life-threatening, but an acute myocardial infarction is.
- requires hospitalization or prolongation of existing hospitalization,
  - Complications that occur during hospitalizations are AEs. However, if a complication prolongs hospitalization or requires new hospitalization, it is an SAE. In-patient hospitalization means the patient has been formally admitted to a hospital for medical reasons, for any length of time, which may or may not be overnight.
  - It does not include presentation and care within an emergency department. If a patient experiences an AE during dosing and remains in hospital until the AE resolves, this is not considered an SAE unless the Investigator considers that the event would have required hospitalization.
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect, or
- is another medically important condition
  - An important medical event that is not immediately life threatening or will result in death or hospitalization, but which may jeopardise the patient or may require medical intervention to prevent one of the seriousness criteria listed above, should be reported as “serious” as well.

Medical and scientific judgment should be exercised in deciding whether a case is serious.

“Occurring at any dose” does not imply that the patient is receiving study drug at the time of the event.

Lack of efficacy is suspected if the expected factor VIII activity plasma levels are not attained or if bleeding is not controlled with a dose of factor VIII that would otherwise be considered appropriate. The reason could be inhibitor formation. The adverse event "Lack of efficacy/ effectiveness" due to FVIII inhibitor formation is a SAE.

Adverse Events of Special Interest (AESI)

In AESI compared to other non-serious AE a broader documentation is desirable. Events identified as AESI are:

AEs resulting in bleeding

Severity of Adverse Events and ADRs (CAVE: Not to be confused with Seriousness)

Refers to the extent to which an AE affects the patient's daily activities. Severity will be categorized according to the following criteria:

AE severity

Mild:	The AE does not interfere with the patient's routine activities.
Moderate:	The AE interferes with the patient's daily routine, but usual routine activities can still be carried out.
Severe:	The AE results in the inability to perform routine activities.

The term "severity" is used to describe the intensity of an event. This is not the same as "serious". Seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

Recording of adverse events (AEs)

In this study all AEs (non-serious and serious) will be recorded in the Sponsor`s Master Safety Database to enable regulatory reporting of suspected ADR. The investigator has to rate the AE to be related or not related to Haemoctin and the investigator has to rate the AE to be serious or non serious. Details are given above in this section.

All **SAEs** have to be forwarded electronically on the AE log of the eCRF **immediately within 24 hours or next working day the latest** to the CDS department of Biotest via e-mail to drugsafety@biotest.com for the MAH assessment and further processing of the individual cases as outlined in the SOPs of Biotest.

All **non-serious AEs** have to be forwarded electronically on the AE log of the eCRF **within 5 working days** to the CDS department of Biotest via e-mail to drugsafety@biotest.com for the MAH assessment and further processing of the individual cases as outlined in the SOPs of Biotest.

For questions regarding AEs, or to provide information that cannot be provided electronically via the eCRF the investigator should contact:

Biotest AG – Department Corporate Drug Safety
Fax: +49 6103 / 801 - 854
E-mail: drugsafety@biotest.com

Product Complaints

Complaints associated with the study drug must be reported to CDS Biotest via e-mail to drugsafety@biotest.com within 24 hours using the "Product Complaint" report form.

In case of corresponding AEs related to suspected quality defects, the AEs have to be entered in the respective eCRF pages (AE page).

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be described in the final report, which will be provided to the competent authorities by the sponsor within the required timelines.

After data analysis on request anonymized data of all NIS patients will be forwarded to the participating study centers.

Each investigator is obligated to keep data pertaining to the NIS secret. He/she must consult with the sponsor before any NIS data are published.

It is planed to prepare a full publication of the data in an international medical journal after preparation of the study report.

13 REFERENCES

Bidlingmaier C, Kurnik K, Escuriola-Ettingshausen C *et al*. Immune tolerance induction with a factor VIII concentrate containing von Willebrand factor (Haemoctin SDH) in 14 patients with severe haemophilia A. Haemophilia 2011; 17: e837-e840.

EQ-5D. What is the EQ-5D - EQ-5D™ is a standardised instrument for use as a measure of health outcome. 2014.

Franchini M, Mannucci PM. Inhibitors of propagation of coagulation (factors VIII, IX and XI): a review of current therapeutic practice. Br J Clin Pharmacol 2011; 72: 553-562.

Gouw SC, van der Bom JG, Ljung R *et al*. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med 2013; 368: 231-239.

Kallas A, Talpsep T. von Willebrand factor in factor VIII concentrates protects against neutralization by factor VIII antibodies of haemophilia A patients. Haemophilia 2001; 7: 375-380.

Kruse-Jarres R. Inhibitors: our greatest challenge. Can we minimize the incidence? Haemophilia 2013; 19 Suppl 1: 2-7.

Martinoli C, Della Casa AO, Di MG *et al*. Development and definition of a simplified scanning procedure and scoring method for Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US). Thromb Haemost 2013; 109: 1170-1179.

Nemes L, Pollmann H, Becker T. Interim data on long-term efficacy, safety and tolerability of a plasma-derived factor VIII concentrate in 109 patients with severe haemophilia A. Haemophilia 2012; 18: 496-502.

Poonnoose PM, van der Net J. Musculoskeletal Outcome in Hemophilia: Bleeds, Joint Structure and Function, Activity, and Health-Related Fitness. Semin Thromb Hemost 2015.

Smart medication. www.smart medication.de. 2015.

Verbruggen B, Novakova I, Wessels H, Boezeman J, van den Berg M, Mauser-Bunschoten E. The Nijmegen modification of the Bethesda assay for factor VIII:C inhibitors: improved specificity and reliability. Thromb Haemost 1995; 73: 247-251.

Wolf DM, Rokicka-Milewska R, Lopaciuk S *et al*. Clinical efficacy, safety and pharmacokinetic properties of the factor VIII concentrate Haemoctin SDH in previously treated patients with severe haemophilia A. Haemophilia 2004; 10: 438-448.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Version Ref. No.	Date	Title
1	Amendment 2.0	18 Feb 2021	Signature page for observation plan approval
2	3.0	27 Jul 2019	Patient information
3	3.0	27 Jul 2019	Informed consent
4	1.0	23 Mar 2018	Study centre list
5	Mai 2020		German Fachinformation Haemoctin SDH

ANNEX 2. ADITIONAL INFORMATION

1. Bleeding score

Bleeding score	Number of joint bleeds per year
0	None
1	No major bleeds, 1–3 minor bleeds
2	1–2 major, or 4–6 minor bleeds more
3	3 or more major bleeds or 7 or minor bleeds
Guidelines defining minor and major bleeds	
Minor bleeds	**Major bleeds**
Mild pain	Pain
Minimal swelling	Effusion
Minimal restriction of motion	Limitation of motion
Resolves within 24 h of treatment	Failure to respond within 24 h

[Poonnoose and van der Net 2015]

2. HEAD-US score (hemophilia early arthropathy detection with ultrasound)

Disease activity (synovitis)	Scale
Hypertrophic synovia	
0. Absent/Minimal	**0**
1. Mild/Moderate	**1**
2. Severe	**2**
Disease damage (articular surfaces)	
Cartilage	
0. Normal	**0**
1. Echotexture abnormalities, focal partial/full-thickness loss of the articular cartilage involving <25% of the target surface	**1**
2. Partial/full-thickness loss of the articular cartilage involving at least _50% of the target surface	**2**
3. Partial/full-thickness loss of the articular cartilage involving >50% of the target surface	**3**
4. Complete cartilage destruction or absent visualization of the articular cartilage on the target bony surface	**4**
Bone	
0. Normal	**0**
1. Mild irregularities of the subchondral bone with/without initial osteophytes around the joint	**1**
2. Deranged subcondral bone with/without erosions and presence of prominent osteophytes around the joint	**2**
Note: Elbow: anterior aspect of the distal humeral epiphysis, Knee: femoral trochlea; Ankle: anterior aspect of the talar dome	

[Martinoli *et al* 2013]