Study Protocol

Protocol Title:	A Post-Authorization Study to Assess the Safety and Efficacy of Fanhdi® (Double-inactivated Human Anti-hemophilic Factor) in Subjects with Von Willebrand Disease
Product:	Fanhdi (Double-inactivated Human Anti-hemophilic Factor [VWF/FVIII])
Study Number/Protocol Version Number/Date:	IG1403/Version 3.0/14 May 2018 includes IG1403/Version 2.0/07 Feb 2018 and Version 1.0/02 Nov 2017
Study Identification Code	INS-FAN-2017-01
Study Phase	4
Sponsor's Name and Address:	Instituto Grifols, S.A. Can Guasc, 2 08150 Parets del Vallès, Barcelona Spain
Sponsor's Telephone Number:	Kimberly Steinman, MD +01 919-316-2245

The undersigned confirm that they agree to conduct the study under the conditions described in this protocol:

Kim Steinman	18-May-2018
Sponsor Signature Kimberly Steinman, MD	**Date**

Summary of Changes for Amendment 2

Protocol Version	Date of Approval
3.0 Amendment 2 + Integrated Protocol	14 May 2018
2.0 Amendment 1 + Integrated Protocol	07 Feb 2018
1.0 Original	02 Nov 2017

Amendment 2

The protocol for IG1403 (Version 2.0, dated 07 Feb 2018) has been amended and reissued as Protocol Amendment 2, Version 3.0, dated 14 May 2018 . See Appendix 1 for a summary of changes for Amendment 2.

INVESTIGATOR SIGNATURE PAGE

The undersigned confirms that he/she agrees to conduct the study under the conditions described in this protocol and comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP) and all applicable regulatory requirements:

INVESTIGATOR NAME (Please Print)	LOCATION
INVESTIGATOR SIGNATURE	DATE

Title of the Investigator:

Address of the Site:

Telephone Number:

PROTOCOL SYNOPSIS

Title of Study: A Post-Authorization Study to Assess the Safety and Efficacy of Fanhdi® (Double-inactivated Human Anti-hemophilic Factor) in Subjects with Von Willebrand Disease

Study Number: IG1403

Study Identification Code: INS-FAN-2017-01

Phase: 4

Study Objectives:

Safety Objective

- To evaluate the safety (immunogenicity and thrombogenicity) associated with long term use of Fanhdi

Primary Efficacy Objective

- To evaluate the overall clinical efficacy of Fanhdi in bleeding episodes

Overall Study Design and Description:

This is a Phase 4, observational, multi-center, prospective, post-authorization cohort study examining the safety (immunogenicity and thrombogenicity) and overall clinical efficacy of long term use of Fanhdi in routine clinical practice in approximately 15 subjects with von Willebrand disease (VWD). In this clinical study, subjects will be treated with Fanhdi according to the investigator's standard of care to achieve hemostasis. Enrolled subjects will be treated with Fanhdi as their sole source of von Willebrand factor/coagulation factor FVIII (VWF/FVIII) concentrate for prophylaxis and treatment of all bleeding episodes and surgical or invasive procedures for an observational period of 12 months.

Data will be collected from the information generated during routine examinations and treatments as performed by the investigator per standard of care during an observation period of 12 months, starting with the first Fanhdi infusion. There will be no intervention with the prescribing habits or practices of the investigator's standard of care; however the investigator is expected to treat the subject within the approved labeling for dose and frequency of Fanhdi. Data collection for all subjects will include inhibitor development (immunogenicity), thrombogenicity, adverse events (AEs), bleeding episodes (spontaneous or traumatic bleeding), surgery or invasive procedure, duration and severity, assessment and achievement of hemostasis, and Fanhdi consumption.

Number of Subjects Planned:

Approximately 15 subjects are planned to be enrolled in this clinical study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

A subject who will be treated with Fanhdi must meet all the following inclusion criteria to be eligible for participation in this study:

1. Male or female subjects ≥18 years of age diagnosed with hereditary VWD of any type and severity who require replacement therapy with VWF/FVIII concentrates when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.
2. Subjects with a history of receiving prior treatment with VWF concentrates due to bleeding episodes and/or surgery or invasive procedures (on demand or prophylaxis).
3. Subjects who are expected to experience bleeding episodes and/or surgeries or invasive procedures (including elective surgeries) requiring replacement therapy in the future or with active bleeding at the time of inclusion.
4. Subjects who are willing and able to provide written informed consent or have an authorized representative able to provide written informed consent on behalf of the subject in accordance with local law and institutional policy.

Exclusion Criteria

Subjects with data meeting any of the following exclusion criteria are NOT eligible for participation in this study:

1. Subjects diagnosed with acquired VWD.
2. Subjects with a congenital or acquired platelet function disorder or other concomitant processes that may interfere with coagulation.
3. Subjects who are positive for anti-VWF or anti-FVIII antibodies (≥0.5 Bethesda units) or has been positive in the history of their disease.
4. Subjects with a known intolerance to any substance contained in Fanhdi.
5. Subjects with a history of anaphylactic reactions to blood or blood components.
6. Subjects who are participating in another clinical study involving an investigational treatment or have participated in one in the past 4 weeks.
7. Subjects who, in the opinion of the investigator, the subject may have compliance problems with the protocol.

Study Treatment, Dose, and Mode of Administration:

Fanhdi (Double-inactivated Human Anti-hemophilic Factor [VWF/FVIII]) will be administered intravenously; doses of 40 to 80 IU/kg VWF (VWF:RCo) and 20 to 40 IU/kg FVIII:C are recommended.

Duration of Treatment:

Subjects will be treated according to the investigator's standard of care and followed for a 12 month observation period.

Key Study Variables:

Safety Variables:

- Adverse events including serious AEs and suspected adverse drug reactions (ADRs)
- Clinical laboratory values including inhibitor (immunogenicity) and functional activity testing
- Thrombogenicity assessment
- Vital signs
- Physical examination

Efficacy Variables:

- Bleeding duration
- Bleeding severity
- Investigator's qualitative assessment of hemostasis utilizing a 4-point rating scale (evaluated as "excellent," "good," "poor," or "no response" in response to therapy with Fanhdi received by the subject in a hospital or another location under the investigator's direct supervision).
- Amount of Fanhdi (IU/kg) used per subject and per year
- Amount of Fanhdi (IU/kg) used per infusion
- Use of other hemoderivatives per bleeding episode
- Overall clinical efficacy

Study Assessments and Procedures:

In this clinical study, subjects will receive the most suitable dose of Fanhdi, according to the investigator's discretion, to achieve satisfactory hemostasis. There will be no intervention with the prescribing habits or practices of the investigator's standard medical care; however the investigator is expected to treat the subject within the approved labeling for dose and frequency of Fanhdi.

Subjects will be followed for 12 months after the first infusion of Fanhdi, in which information gathered from any episode (spontaneous or traumatic bleeding), surgery or invasive procedure, and the response to treatment and consumption of Fanhdi will be collected.

An assessment of the overall clinical efficacy of Fanhdi throughout the study will be performed and collected by the investigator utilizing a 4-point rating scale (evaluated as "excellent," "good," "poor," or "no response" in response to therapy with Fanhdi received by the subject in a hospital or another location under the investigator's direct supervision).

Statistical Methods:

Study Population

The Safety population will include all subjects enrolled in the clinical study and will be used for all safety and efficacy analyses.

Safety Analysis

The safety analyses will be addressed by listing and tabulation of AEs (includes suspected ADRs), clinical laboratory tests including inhibitor (immunogenicity) and functional activity testing, thrombogenicity, vital signs, and physical examinations. Data will be described using descriptive analyses.

Efficacy Analyses

For bleeding episodes, the bleeding duration, severity, achievement of adequate hemostasis, and overall clinical efficacy will be summarized. Also, the number of Fanhdi infusions and the total amount of Fanhdi dosed will be summarized. The proportion of bleeding episodes in which good or excellent clinical efficacy were achieved will also be summarized.

For surgeries or invasive procedures, the surgery type, severity of bleeding episodes, achievement of adequate hemostasis, and overall clinical efficacy will be summarized. Also, the number of Fanhdi infusions and the total amount of Fanhdi dosed will be summarized. The proportion of surgeries or invasive procedures in which good or excellent clinical efficacy were achieved will also be summarized.

For long-term observation, the long-term overall clinical efficacy will be summarized. Also, the number of bleeding episodes and surgeries or invasive procedures will be summarized. The number of infusions, exposure days, and dose per month will be summarized, in addition to the mean quantity of Fanhdi per bleeding episode and/or surgery or invasive procedure.

Determination of Sample Size

Approximately 15 subjects are planned to be enrolled in this clinical study. The sample size is based on clinical considerations and was not formally calculated.

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LIST OF IN-TEXT TABLES

GLOSSARY AND ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARC	absolute reticulocyte count
AST	aspartate aminotransferase
BP	blood pressure
BU	Bethesda units
BUN	blood urea nitrogen
DDAVP	desmopressin
EC	Ethics Committee
eCRF	electronic case report form
Fanhdi	double-inactivated human anti-hemophilic factor (VWF/FVIII)
FVIII	coagulation factor VIII
FVIII:C	FVIII coagulant
GCP	good clinical practice
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
T	temperature
TB	total bilirubin
TEAE	treatment-emergent adverse event
VWD	von Willebrand disease
VWF	von Willebrand factor
VWF:Ag	VWF antigen
VWF:CBA	binding capacity of VWF to collagen
VWF:RCof	ristocetin cofactor activity
WBC	white blood cell

1 INTRODUCTION

1.1 Background

1.1.1 Von Willebrand Disease

Von Willebrand disease (VWD) is the most common hereditary bleeding disorder. It affects both genders and is characterized by qualitative or quantitative abnormalities of von Willebrand factor (VWF), a high molecular weight glycoprotein involved in primary and secondary hemostasis. Von Willebrand factor is synthesized in endothelial cells and megakaryocytes, is stored in platelets, and circulates in plasma as multimers. It functions as a stabilizer and carrier of coagulation factor VIII (FVIII), with which it forms a noncovalently linked complex (1).

The physiological functions and biochemical properties of the FVIII and VWF plasma proteins, which form a macromolecular complex, are described below:

- Factor VIII coagulant (FVIII:C) participates in the activation of the plasma coagulation mechanism. Its activity is considerably reduced in patients with hemophilia A, and patients with hemophilia A require replacement therapy to prevent or resolve bleeding problems.
- Von Willebrand factor supports platelet adhesion to the vascular endothelium and plays an important role in platelet aggregation. Functional alterations of this factor lead to a decrease in FVIII:C activity and an increase in mucocutaneous bleeding (2).

The clinical expression of VWD is variable, manifesting as a bleeding tendency which can be mild, moderate, or severe. The bleeding is characteristically mucocutaneous, although patients with severe VWD tend to suffer from hemarthrosis, as do hemophilia patients, although it tends to be less intense. Epistaxis, menorrhagia, and bleeding following dental extractions are the most frequent symptoms (3,4). Von Willebrand disease is very heterogeneous and is classified depending on the genetic mutation and the degree of the VWF defect. There are 3 main VWD types (1, 2, and 3). Type 1 VWD is found in patients with a partial quantitative deficiency of VWF. Type 2 VWD is due to the qualitative deficiency of VWF and is further divided into 4 variants based on the phenotype (2A, 2B, 2M, and 2N). Type 3 VWF is due to a total deficiency of VWF. The degree of abnormality can be measured by analyzing bleeding time, plasma levels of VWF antigen (VWF:Ag), FVIII:C, ristocetin cofactor (VWF:RCof) activity, and the binding capacity of VWF to collagen (VWF:CBA). In addition, the multimeric distribution of VWF helps to characterize the type and subtype (5,6).

The most common type of VWD is Type 1, accounting for approximately 75% of all VWD cases (7). These patients are characterized by increased bleeding time and low levels of VWF:Ag, with proportional decreases in FVIII:C and VWF:RCof levels. The multimeric distribution of VWF is normal in the majority of cases (8,9).

In Type 2 VWD, the structure of the VWF molecule is abnormal, as high molecular weight multimeric forms are not detected. The majority of subtypes also show considerable reductions in VWF:RCof levels. Subtype 2A is characterized by decreased platelet function, attributable to the absence of high molecular weight VWF multimers. Subtype 2B exhibits an increased affinity of VWF for platelet glycoprotein Ib. Subtype 2M is characterized by a decrease in platelet function not attributable to the absence of high molecular weight VWF multimers. Subtype 2N results in variable bleeding dysfunction and is characterized by a VWF with decreased affinity for FVIII (variable VWF:Ag levels and VWF:RCof activity, with disproportionately low levels of FVIII:C) (10).

Type 3 VWD is the most severe form and it is characterized by undetectable or very low levels of VWF:Ag and FVIII:C and also by poor response to desmopressin (DDAVP) treatment (11). Desmopressin is a vasopressin analog to stimulate the release of endogenous VWF from endothelial cell stores. Desmopressin has been used for over 25 years to treat VWD and its mechanism of action has been reviewed extensively (12-14). Patients with Type 3 VWD have a severe bleeding tendency and in the majority of patients, an increase in VWF is not observed following treatment, or if it does occur, bleeding time is not shortened (15).

A VWD diagnosis is based on the patient's medical history and on laboratory test results. The diagnosis of the disease, especially in Type 1 VWD, may at times be problematic. Low levels of VWF:Ag and VWF:RCof can be difficult to interpret due to the fact that plasma levels of VWF in normal subjects exhibit a high degree of variability. Different factors can contribute to modifications in VWF levels: estrogens, thyroid hormones, diabetes, exercise, pregnancy, age, and ABO blood type. Individuals with blood type O show plasma levels of VWF that are 25% lower than those with other blood groups. In addition, patients with VWD can intermittently have VWF levels in a normal range (8). Therefore, all abnormal or normal results in individuals with high clinical suspicion should be confirmed.

1.1.2 Von Willebrand Disease Treatment

The aim of treatment in VWD is to correct 2 hemostatic defects: abnormal coagulation due to low levels of circulating FVIII and abnormal platelet adhesion, which translates into prolonged bleeding time. There are 3 treatment options for this disease: nonreplacement therapy, replacement therapy, and antifibrinolytic or topical agent administration (12,16,17). Patients may receive any 1 or all 3 treatment options at the same time.

In nonreplacement therapy for VWD, patients are treated with DDAVP. In replacement therapy for VWD, patients are treated with cryoprecipitate or plasma derived concentrates of VWF/FVIII to correct (at least partially) the hemostatic defect and control bleeding in patients. The effectiveness of the treatment of patients with severe VWD with VWF/FVIII concentrates has been demonstrated. Therefore, replacement therapy with FVIII concentrates that contain a large quantity of VWF is indicated in patients who do not respond to treatment with DDAVP or for whom DDAVP is contraindicated (18). Lastly antifibrinolytics or topical agents may also be used to treat VWD in some countries. These agents promote hemostasis and wound healing without substantially altering VWF plasma concentration (17).

Treatment is based on the type and severity of VWD, the severity of the hemostatic challenge, and the nature of the actual or potential bleeding (17). Patients with Type 1 VWD are mainly treated with DDAVP. However, the bleeding time in patients with a low amount of platelet VWF (Subtype 2B) may not be corrected, and a poor response to treatment with DDAVP is observed (8,9). The response of patients with Subtypes 2A, 2M, and 2N to DDAVP treatment is limited, as it promotes the release of an abnormal VWF; thus, bleeding time is generally not shortened. Desmopressin administration may be contraindicated in patients with Subtype 2B due to the possibility of platelet aggregation and thrombocytopenia (19). Patients who have Type 3 VWD rarely experience a clinically relevant increase in VWF:RCo or FVIII levels, and DDAVP is not considered effective treatment in these patients (17).

Fanhdi® is a highly purified, double inactivated anti-hemophilic factor (VWF/FVIII) concentrate prepared from human plasma manufactured by Instituto Grifols, S.A. Administered intravenously, Fanhdi has been commercially available in different countries since December 1994 for the prevention and control of bleeding in patients with hereditary or acquired hemophilia A (20). Since it is a concentrate of highly purified, lyophilized FVIII that contains VWF, the effectiveness of Fanhdi treatment in subjects with VWD was examined and shown to be an effective and safe replacement therapy in subjects with VWD to provide adequate hemostasis in surgical procedures and treatment of bleeding episodes (21,22). Fanhdi has been commercially available for VWD replacement therapy in several countries since June 2009 (21). The VWF concentrates of Fanhdi correct hemostatic abnormalities in subjects with VWD by re-establishing platelet adhesion to the vascular sub-endothelium at the site of vascular damage and by binding to endogenous FVIII to stabilize the protein and avoid rapid degradation (23).

1.2 Rationale

At the request of the Spanish Agency of Medicines and Medical Devices (AEMPS), Instituto Grifols, S.A is conducting a Phase 4, observational, multi-center, prospective, post-authorization cohort study examining the safety (including key safety parameters of inhibitor development [immunogenicity] and thrombogenicity) and clinical efficacy of long term use of Fanhdi in subjects with VWD according to the current guidelines (24). Data on the use of Fanhdi in routine clinical practice in the prophylaxis and/or treatment of subjects with VWD will be collected during an observation period of 12 months.

2 OBJECTIVES

The objective of this Phase 4, observational, multi-center, prospective, post-authorization cohort study is to examine the safety (immunogenicity and thrombogenicity) and overall clinical efficacy of long term use of Fanhdi in subjects with VWD.

2.1 Safety Objective

- To evaluate the safety (immunogenicity and thrombogenicity) associated with long term use of Fanhdi (see Sections 3.5.1.2 and 3.5.1.3)

2.2 Efficacy Objective

- To evaluate the overall clinical efficacy of Fanhdi in bleeding episodes (see Section 3.5.2.1)

3 STUDY DESIGN

3.1 Study Design and Plan

This is a Phase 4, observational, multi-center, prospective, post-authorization cohort study examining the safety (immunogenicity and thrombogenicity) and overall clinical efficacy of long term use of Fanhdi in routine clinical practice in approximately 15 subjects with VWD. In this clinical study, subjects will be treated with Fanhdi according to the investigator's standard of care to achieve hemostasis. Enrolled subjects will be treated with Fanhdi as their sole source of VWF/FVIII concentrate for prophylaxis and treatment of all bleeding episodes and surgical or invasive procedures for an observational period of 12 months.

Data will be collected from the information generated during routine examinations and treatments as performed by the investigator per standard of care during an observation period of 12 months, starting with the first Fanhdi infusion. There will be no intervention with the prescribing habits or practices of the investigator's standard of care, however the investigator is expected to treat the subject within the approved labeling for dose and frequency of Fanhdi as described in Section 3.1.1 (23). Data collection for all subjects will include inhibitor development (immunogenicity), thrombogenicity, adverse events (AEs), bleeding episodes (spontaneous or traumatic bleeding), surgery or invasive procedure, duration and severity, assessment and achievement of hemostasis, and Fanhdi consumption. Data will be transcribed into electronic case report forms (eCRFs) by designated study center personnel.

3.1.1 Approved Fanhdi Dosing in the Treatment of Von Willebrand Disease

To achieve hemostasis in subjects with VWD, 40 to 80 IU/kg VWF (VWF:RCo) and 20 to 40 IU/kg FVIII:C are recommended. An initial dose of 80 IU/kg VWF may be required, especially in subjects with Type 3 VWD where maintenance of adequate levels may require greater doses than in other VWD types. An appropriate dose should be re-administered every 12 to 24 hours. Treatment dose and duration is dependent on the clinical status of the subject, the bleeding type and severity, and VWF:RCo and FVIII:C levels.

Continued treatment with Fanhdi may cause an excessive rise in FVIII:C. After 24 to 48 hours of treatment, the investigator should reduce treatment dose and/or duration.

3.2 Selection of Study Population

3.2.1 Inclusion Criteria

A subject who will be treated with Fanhdi must meet all the following inclusion criteria to be eligible for participation in this study:

1. Male or female subjects ≥18 years of age diagnosed with hereditary VWD of any type and severity who require replacement therapy with VWF/FVIII concentrates when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.
2. Subjects with a history of receiving prior treatment with VWF concentrates due to bleeding episodes and/or surgery or invasive procedures (on demand or prophylaxis).
3. Subjects who are expected to experience bleeding episodes and/or surgeries or invasive procedures (including elective surgeries) requiring replacement therapy in the future or with active bleeding at the time of inclusion.
4. Subjects who are willing and able to provide written informed consent or have an authorized representative able to provide written informed consent on behalf of the subject in accordance with local law and institutional policy.

3.2.2 Exclusion Criteria

Subjects with data meeting any of the following exclusion criteria are NOT eligible for participation in this study:

1. Subjects diagnosed with acquired VWD.
2. Subjects with a congenital or acquired platelet function disorder or other concomitant processes that may interfere with coagulation.
3. Subjects who are positive for anti-VWF or anti-FVIII antibodies (≥0.5 Bethesda units [BU]) or has been positive in the history of their disease.
4. Subjects with a known intolerance to any substance contained in Fanhdi.
5. Subjects with a history of anaphylactic reactions to blood or blood components.
6. Subjects who are participating in another clinical study involving an investigational treatment or have participated in one in the past 4 weeks.
7. Subjects who, in the opinion of the investigator, may have compliance problems with the protocol.

3.2.3 Subject Withdrawal Criteria

Subjects may withdraw or be withdrawn from the study for the following reasons:

1. A severe or serious adverse event (SAE), which, based on medical judgment, prevents completion of participate on in the study (see Section 4.3 for classification of adverse events).
2. Development of VWF/FVIII inhibitors*
   - At a titer ≥0.5 BU or
   - At a titer <0.5 BU that renders Fanhdi treatment ineffective in providing hemostasis.
3. Treatment with other VWF/FVIII concentrates while in the study.
4. Treatment with immunosuppressive drugs.
5. At their own request or at the request of their legally acceptable representative.

6. If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
7. Determination of ineligibility based on eligibility criteria.
8. Termination of the study by a regulatory authority (see Section 5.5).

* If the expected VWF/FVIII plasma activity levels are not attained or if bleeding is not controlled with an appropriate dose, it is recommended that an assay should be performed to determine the development of VWF/FVIII inhibitors as per standard of care. In subjects with high levels of inhibitors, Fanhdi therapy may not be effective and other therapeutic options should be considered (23).

The reason for withdrawal should be recorded in the eCRF and subject's source documents. If a subject withdraws after treatment due to an AE, the study center will attempt to obtain all possible follow-up safety data from that subject.

3.3 Study Variables

3.3.1 Safety Variables

- Adverse events including SAEs and suspected adverse drug reactions (ADRs)
- Clinical laboratory values including inhibitor (immunogenicity) and functional activity testing
- Thrombogenicity assessment
- Vital signs
- Physical examination

3.3.2 Efficacy Variables

- Bleeding duration
- Bleeding severity
- Investigator's qualitative assessment of hemostasis utilizing a 4-point rating scale (evaluated as "excellent," "good," "poor," or "no response" in response to therapy with Fanhdi received by the subject in a hospital or another location under the investigator's direct supervision [Table 3-1]).
- Amount of Fanhdi (IU/kg) used per subject and per year
- Amount of Fanhdi (IU/kg) used per infusion
- Use of other hemoderivatives per bleeding episode
- Overall clinical efficacy

3.4 Methods and Timing for Recording Study Parameters

In this clinical study, subjects will receive the most suitable dose of Fanhdi, according to the investigator's discretion, to achieve satisfactory hemostasis. There will be no intervention with the prescribing habits or practices of the investigator's standard medical care; however, the investigator is expected to treat the subject within the approved labeling for dose and frequency of Fanhdi (see Section 3.1.1).

Subjects will be followed for 12 months after the first infusion of Fanhdi, in which information gathered from any episode (spontaneous or traumatic bleeding), surgery or invasive procedure, and the response to treatment and consumption of Fanhdi will be collected.

An assessment of the overall clinical efficacy of Fanhdi throughout the study will be performed and collected by the investigator utilizing a 4-point rating scale (evaluated as "excellent," "good," "poor," or "no response" in response to therapy with Fanhdi received by the subject in a hospital or another location under the investigator's direct supervision). Clinical efficacy assessment ratings are described in Table 3-1 (25).

Table 3-1 Assessment of Clinical Efficacy

Rating	Clinical Efficacy	
Excellent	Hemostasis comparable with that expected for individuals without known bleeding disorders	No increase in FVIII/VWF dosing required
Good	Hemostasis slightly inferior to that expected for individuals without known bleeding disorders	Minor increase in FVIII/VWF dosing required
Poor	Reduced hemostasis is compared with that expected for individuals without known bleeding disorders	Significant increase in FVIII/VWF dosing required; no need for alternative therapy
No Response	Severe bleeding despite FVIII/VWF therapy	Significant increase in FVIII/VWF dosing required and/or need for alternative therapy to control bleeding

3.5 Study Data Collection

The medical records of all subjects meeting the study eligibility requirements will be reviewed. Safety (Section 3.5.1) and efficacy (Section 3.5.2) information will be collected from each subject record (as performed at the discretion of the investigator per standard of care).

3.5.1 Safety Assessments

3.5.1.1 Adverse Events

Adverse events (including suspected ADRs) occurring at any time between signing of the subject's informed consent form (ICF) and the last day of the subject's participation in the clinical study will be recorded in the appropriate eCRF and in the subject's source documents.

Local infusion-site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator, will be collected and documented as AEs.

Adverse events will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff according to the investigator's standard of care.

3.5.1.2 Clinical Laboratory Values Including Inhibitor (Immunogenicity) Testing

Clinical laboratory data will be collected at the discretion of the investigator per standard of care. The presence and titer of FVIII and VWF inhibitors will be determined throughout the observational period as performed at the discretion of the investigator per standard of care. The clinical relevance of the inhibitors (according to the investigator) and the cumulative incidence as a function of the number of exposures to Fanhdi will be collected. Clinical laboratory data will be recorded in the appropriate eCRF and in the subject's source documents.

3.5.1.3 Thrombogenicity Assessment

Monitoring assessments for the clinical signs and symptoms of thromboembolic events will be conducted at the discretion of the investigator per standard of care and collected.

Monitoring for clinical signs and symptoms of thromboembolic events will be performed in subjects who undergo a surgical or invasive procedure according to the investigator's standard of care will be collected. All thromboembolic events will be recorded in the appropriated eCRF and in the subject's source documents as AEs and reported accordingly.

3.5.1.4 Vital Signs

Vital signs will be measured by a medically certified individual or a nurse according to the standard clinical practice.

The following vital signs (assessed at the discretion of the investigator per standard of care) will be collected:

- Temperature (T)
- Heart rate (HR)
- Respiratory rate (RR)
- Blood pressure (BP [systolic and diastolic BP])

Vital signs will be routinely monitored by the study staff according to standard clinical practice. Vital signs will be recorded in the appropriate eCRF and in the subject's source documents. Vital signs abnormalities judged by the investigator as clinically significant will be collected and documented as AEs.

3.5.1.5 Physical Examination

A medically certified individual will conduct a physical examination according to standard clinical practice. Any physical examination abnormalities judged by the investigator as clinically significant will be considered AEs. Physical examination data will be recorded in the appropriate eCRF and in the subject's source documents.

3.5.2 Efficacy Assessments

3.5.2.1 Bleeding Episodes

Information from any bleeding episode occurring during the observation period, including spontaneous or traumatic bleeding will be collected. The response to treatment and extent of exposure to Fanhdi will be recorded in the eCRF and subject's source documents.

A bleeding episode will be categorized according to International Society on Thrombosis and Haemostasis (ISTH) guidelines (26) as follows:

Major bleeds are defined as bleeding:

- with a fall in hemoglobin of ≥2 g/dL, or
- with transfusion of ≥2 units of packed red blood cells or whole blood, or
- that occurs in a critical location, ie, intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or
- that causes death

Clinically relevant non-major bleeds are defined as bleeding:

- that does not meet criteria for major bleeding, and
- that requires any medical or surgical intervention to treat the bleeding

During bleeding episodes, information on the following procedures and assessments (performed at the discretion of the investigator) will be collected:

- The use of any blood derivative (ie, FVIII concentrates, transfusions [plasma, platelets, and red blood cells (RBCs)], cryoprecipitate) or antifibrinolytic agents
- Any complications
- Concomitant medication and AEs
- Clinical evaluation of thrombogenicity

Bleeding severity (mild, moderate, severe) will be based on investigator's assessment. In the instance of a severe bleeding episode, information on any measures of the following (assessed at the discretion of the investigator per standard of care) will be collected:

- Vital signs (T, HR, RR, BP)
- Blood samples for any of the following:
  - Clinical laboratory assessment of renal (creatinine, blood urea nitrogen [BUN]), hepatic (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin [TB]), and/or hematological parameters (including hemoglobin, hematocrit, platelets, RBC count including RBC morphology, white blood cell [WBC] count with differential, and absolute reticulocyte count [ARC])
  - Factor VIII and VWF functional activity

Information on the overall evaluation of the bleeding episode according to the investigator, including the duration and severity of the bleed, clinical correction of hemostasis, and overall clinical efficacy will be collected.

Clinical Efficacy in Bleeding Episodes

To determine the clinical efficacy of Fanhdi for bleeding episodes in subjects with VWD, information will be collected on the nature, location, duration (time to hemostasis of the bleed between the start of the first Fanhdi infusion and the cessation of bleeding) and severity of the bleeding episodes as assessed by the investigator.

In addition, the number of infusions and the total amount of Fanhdi dosed for bleeding episodes and the use of additional blood derivatives (ie, FVIII concentrates, transfusions [plasma, platelets, and RBCs], cryoprecipitate) or antifibrinolytic agents will be collected. Efficacy data will be recorded in the appropriate eCRF and in the subject's source documents.

Information on the clinical correction of hemostasis and overall clinical efficacy of bleeding episodes as assessed by the investigator utilizing a 4-point rating scale ("excellent," "good," "poor," or "no response" [Table 3-1, 25]) will be collected over the course of 12 months of therapy.

3.5.2.2 Surgical or Invasive Procedures

The definitions of surgical procedures (classified into 2 categories [major or minor]) and invasive procedures are provided in Table 3-2 (25). Information from all surgical or invasive procedures occurring during the observation period will be collected and the response to treatment and extent of exposure to Fanhdi will be recorded in the appropriate eCRF and in the subject's source documents.

Table 3-2 Definition of Surgical and Invasive Procedures

Major surgery	Usually involves the use of regional or general anesthesia and penetrates and exposes one of the major body cavities (eg, skull, chest, neck, abdomen) or one of the major joints (eg, shoulder, hip, spine) or stresses vital organs
Minor surgery[a]	Any surgery or procedure not considered major
Invasive procedure[a]	Any procedure that avoids the use of cutting open surgery in favor of closed surgery; such procedures involve the use of instruments with indirect observation of the surgical field through an endoscope or similar device with reduced associated trauma

[a] Data for minor and invasive procedures are combined except for dose and duration of therapy

During a surgery or invasive procedure, information on the following procedures and assessments (performed at the discretion of the investigator per standard of care) will be collected:

- The use of any blood derivative (ie, FVIII concentrates, transfusions [plasma, platelets, and RBCs], cryoprecipitate) or antifibrinolytic agents
- Any complications
- Concomitant medication and AEs during the surgical or invasive procedures
- Clinical evaluation of thrombogenicity

Information on the following measures (assessed at the discretion of the investigator per standard of care) will be collected:

- Vital signs (T, HR, RR, BP)
- Blood samples for any of the following:
  - Clinical laboratory assessment of renal (creatinine, BUN), hepatic (ALT, AST, ALP, and TB), and/or hematological parameters (including hemoglobin, hematocrit, platelets, RBC count including RBC morphology, WBC count with differential, and ARC)
  - Factor VIII and VWF functional activity

During the post-operative period, the administration of Fanhdi will continue per the investigator's standard medical practice.

Clinical Efficacy in Surgery or Invasive Procedure

To determine the clinical efficacy of Fanhdi for surgical or invasive procedures in subjects with VWD, information will be collected on the duration of bleeding (measured from the start of Fanhdi administration through the time to hemostasis) and severity of bleeding (defined in Section 3.5.2.1) as assessed by the investigator.

In addition, the number of infusions, total amount of Fanhdi dosed (at the time of the surgical or invasive intervention and immediately thereafter), and the use of additional blood

derivatives (ie, FVIII concentrates, transfusions [plasma, platelets, and RBCs], cryoprecipitate) or antifibrinolytic agents will be collected. Efficacy data will be recorded in the appropriate eCRF and in the subject's source documents

Clinical correction of hemostasis and overall clinical efficacy in surgery or invasive procedure, as assessed by the investigator utilizing a 4-point rating scale ("excellent," "good," "poor," or "no response" [Table 3-1, 25]) will be collected.

3.5.2.3 Long-term Overall Clinical Efficacy

PROPHYLAXIS AND ON-DEMAND TREATMENT

The long-term clinical efficacy of prophylaxis and/or on-demand treatment with Fanhdi, based on the hemostatic effect, and previous experience, will be determined by the investigator per standard of care utilizing a 4-point rating scale ("excellent," "good," "poor" or "no response" [Table 3-1, 25]) and collected. Efficacy data will be recorded in the appropriate eCRF and in the subject's source documents

FANHDI TREATMENT EXPOSURE

The extent of exposure to Fanhdi will be assessed as a long-term clinical efficacy variable. Information on the amount of Fanhdi (IU/kg) used per subject and per year and the amount of Fanhdi (number of IU/kg) used per infusion will be collected. Efficacy data will be recorded in the appropriate eCRF and in the subject's source documents

3.5.3 Subject Numbering

Within each study center, subjects in the study will receive a consecutive subject number. Subject numbers are generated beginning with the study center number (3 digits, assigned by the sponsor) followed consecutively with a unique number for each subject (4 digits, including leading zeros). For example, if the investigator's center number is 301, subject number will be 3010001, 3010002, 3010003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.

3.5.4 Data Collection Procedures

3.5.4.1 Data Sources

Data for this study will be obtained from medical records based on the information generated in the routine examinations and treatments that the investigator performs according to his or her standard medical practice. Approximately 15 subjects will be included for an observation period of 12 months.

3.5.4.2 Data Collection Procedures

The study data will be recorded and kept current in the eCRF and subject's source documents by the study center personnel directly responsible for the information. Entries made in the eCRF must be verifiable against source documents. The data in the eCRF will be monitored at the study center by Grifols representatives at regular intervals and reviewed for

completeness and compared with the source documents. Examples of acceptable source documents include individual subject medical records, prospective information gathered on source documentation worksheets, laboratory reports, and other diagnoses pertinent to this study which are separate from the eCRF. The listing of types of source documents which will be defined in the source data agreement will be filed in the Trial Master File.

All AEs and SAEs must be recorded in the eCRF and subject's source documents. All SAEs must be recorded on the SAE report form (see Section 4.9.1). The SAE report form must be kept in site records with a copy provided to the designated person as detailed in the study file.

3.5.5 Data Quality

At the completion of the study, all data will be transferred to Grifols according to The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, local laws, regulations, and Grifols requirements. The study file must be kept until such time as the sponsor gives notice that they are to be destroyed.

The investigator must keep the study files. If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the files must be transferred to another person (eg, another investigator). Grifols must be notified in writing of the person responsible for maintaining the file and the notification must be kept in the sponsor study file and the investigator study center file.

4 PROCEDURES FOR ELICITING REPORTS OF AND FOR RECORDING AND REPORTING ADVERSE EVENT AND INTERCURRENT ILLNESSES

4.1 Warnings/Precautions

For complete information on Fanhdi, refer to the Summary of Product Characteristics (23).

4.2 Adverse Event Monitoring

Subjects must be carefully monitored for AEs. This monitoring includes clinical and laboratory tests and physical signs; any abnormalities judged by the investigator as clinically significant will be considered AEs. See Section 4.3 for AE definitions. Adverse events should be assessed in terms of their seriousness, severity, and causal relationship to study treatment.

Adverse events will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff.

All study subjects will be monitored after an AE until it is resolved. This monitoring includes clinical and laboratory tests and vital signs.

Adverse events and SAEs must be documented from signing of the ICF until the subject completes his or her final study visit, whether the subject completes the study or suspends participation early for any reason.

4.3 Adverse Event Definitions

4.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

4.3.2 Suspected Adverse Drug Reactions

All noxious and unintended responses to a medicinal product or study treatment related to any dose should be considered suspected ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product or study treatment and an AE is at least a reasonable possibility.

4.3.3 Thromboembolic Events

Subjects will be monitored for signs and symptoms of arterial and venous thromboembolic events per standard care. According to definitions in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), arterial and venous thromboembolic events include, but are not limited to deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident, acute coronary syndrome, limb thrombosis, sagittal sinus thrombosis, and portal vein or mesenteric artery thrombosis.

All thromboembolic events will be recorded in the eCRF and subject's source documents as an AE and reported accordingly.

4.4 Assessment of Causality of Adverse Event

The investigator is required to provide a causality assessment for each AE reported to the sponsor. The sponsor will consider the investigator's causality assessment and also provide its own assessment.

Causal relationship to the study drug will be established according to medical judgment on whether there is a **reasonable possibility of a causal relationship between the AE and the study drug administration.**

The investigator must determine and classify the AE causality according to the following categories:

Unrelated/Not related: there is not a reasonable possibility of causal relationship between the AE and the study drug.

Possibly related: there is evidence to suggest a causal relationship between the study drug and the AE.

Definitely related: there is a reason to conclude that the study drug caused the AE.

Criteria to assess the causal relationship should take into account of the following conditions:

1. A plausible temporal sequence from the study drug administration to the AE onset
2. Whether the event follows a known response pattern to the suspected treatment
3. Whether the AE could be reasonably explained by the subject's clinical state, comorbidities, or concomitant medications
4. The occurrence of improvement on stopping/reducing the treatment (positive dechallenge) and/or reappearance of the event on repeated exposure (positive rechallenge).

For expedited safety reporting purposes, AEs assessed as either "definitively related" or "possible related" will be considered POTENTIALLY RELATED or just RELATED.

4.5 Severity of Adverse Event or Suspected Adverse Drug Reaction

Adverse events and suspected ADRs will be classified depending on their severity according to the following definitions:

Mild: an AE which is well tolerated by the subject, causing minimum degree of malaise and without affecting normal activities.

Moderate: an AE that interferes with the subject's normal activities.

Severe: an AE that prevents the subject from performing their normal activities.

Adverse event and suspected ADR severity gradation must be distinguished from an AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, headache can be mild, moderate or severe but not necessarily serious in all these cases.

The investigator will be responsible for assessing the AE and suspected ADR intensity during the clinical study, taking into account current criteria included in this section.

4.6 Expectedness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR is considered "unexpected" if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information. The expectedness shall be determined by the sponsor according to the reference document (Summary of

Product Characteristics [23]) for any serious suspected ADRs (potentially related SAEs) for expedited safety reporting purposes.

4.7 Seriousness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR is considered "serious" if, in the opinion of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE (life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- In-patient hospitalization or prolongation of existing hospitalization*
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event (important medical event in the definition of "serious" refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject or/and may require medical or surgical or invasive intervention to prevent one of the other outcomes listed above).

*Hospitalization is to be considered only for hospital stays equal to or more than 24 hours. The following hospitalizations should not be reported as SAEs:

- Hospitalization or prolongation of hospitalization as part of a routine procedure followed by the center.
- Hospitalization for a survey visit, annual physicals, or social reasons.
- Elective or pre-planned hospitalizations for a pre-existing condition that had not worsened from Baseline (eg, elective or scheduled surgery or invasive procedure arranged prior to start of the study).
- Admissions not associated with an AE (eg, social hospitalization for purposes of respite care).

This definition permits either the sponsor or the investigator to decide whether an event is "serious". If either the sponsor or the investigator believes that the event is serious, the event must be considered "serious" and evaluated by the sponsor for expedited reporting.

4.8 Adverse Event Documentation

All AEs and SAEs occurring after the subject has **signed the ICF through the final study visit** (ie, last day of the subject's participation in the clinical study, whether the subject completes the study or participation is suspended early for any reason) must be fully recorded

in the subject's eCRF, source documents, and SAE report form (if serious) as well as in the medical record. If no AE has occurred during the study period, this should also be indicated in the eCRF.

It is the responsibility of the investigator to ensure that all AEs (either serious or non-serious) are appropriately recorded in the eCRF and subject's source documents in a timely manner (up to 5 calendar days upon being made aware of AE occurrence).

At each visit, AEs will be elicited by asking the individual a non-leading question such as "Do you feel different in any way since the last visit?" Moreover, AEs will also be collected through directly observed events or spontaneously volunteered by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible.

The following variables must be recorded in the AE eCRF and source documents:

- The verbatim term (a diagnosis is preferred)
- Date/time of onset
- Date/time of resolution
- Severity (mild, moderate, severe)
- Causality (unrelated, possibly related, definitely related)*
- Seriousness (yes, no)
- Action taken (with regard to study treatment)
- Other action (to treat the event)
- Outcome and sequel (follow-up on AE)

*Causality assessment will be made only when the AE occurs after the subject has initiated at least one infusion of the study drug. An AE occurring before subject's exposure to study treatment will be always labeled as "unrelated/not related".

For AEs that occur during infusions, the time of onset of the AE, and the time of AE change materially in intensity (recorded as a separate AE), and/or resolve will be captured in the eCRF.

In addition to the investigator's own description of the AEs, each AE will be encoded according to the Medical Dictionary for Regulatory Activities (MedDRA®).

For example, a laboratory test abnormality considered clinically significant, eg, causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged clinically significant in the context of the subject's medical history by the investigator, should be reported as an AE. Each event must be described in detail along with start and stop dates, severity, relationship to study drug, action taken and outcome. Each event must be adequately supported by documentation as it appears in the subject's medical or case file.

4.9 Reporting of Adverse Events

4.9.1 Reporting of Serious Adverse Events

Any SAE that occurs after **signing the study ICF through the final study visit** (ie, last day of the subject's participation in the clinical study, whether the subject completes the study or participation is suspended early for any reason) must be expeditiously reported. Each SAE must be fully recorded in the subject's eCRF, source documents, and SAE Report Form.

All SAEs will be reported using the designated SAE Report Form. When the investigator becomes aware of a SAE, she/he must submit a completed, signed and dated SAE Report Form (in English) **within 24 hours** to the sponsor by email/fax. The date of this SAE discovery by the site staff should be documented in the source documents (ie, medical records).

Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow-up, and for the outcome, must also be supplied to the sponsor in a timely manner (within 3 days from its identification or within 24 hours for relevant new information) by means of the SAE Report Form. In addition, the sponsor or contract research organization may request additional information and/or reports.

All SAE Report Forms must be reported to:

Grifols Global Pharmacovigilance Email: gds@grifols.com FAX (back-up only): (00)-919-359-7278

When required, and according to local law and regulations, SAEs must be reported to the Ethics Committee (EC) and regulatory authorities. Copies of the investigator's reports must be sent to the sponsor.

4.9.2 Reporting of Non-serious Adverse Events

While investigators are not requested to expeditiously send non-serious AEs to the sponsor with the 24 hour timeframe; they are requested to record them in the eCRF in a timely manner (up to 5 calendar days upon being made aware of AE occurrence). The sponsor will periodically monitor AE records and request additional information from the site if the event meets criteria for a suspected ADR. In the event of a suspected ADR the investigator may be asked to provide additional information to Grifols Global Pharmacovigilance, if necessary. When required, and according to local law and regulations, suspected ADRs must be reported to the EC and regulatory authorities. Copies of the investigator's reports must be sent to the sponsor.

4.9.3 Reporting Pregnancy

While pregnancy itself is not a true "AE," pregnancy occurring in a clinical study must be followed, to collect information regarding the experiences of gestation and pregnancy with study drug exposure. The investigator must report any pregnancy that occurs in a female study subject or partner of a male study subject subsequent to informed consent until 28 days after the last dose of study drug.

A pregnancy not verified before the Baseline Visit but occurring during the course of the study will be not considered an AE, unless a relation to the study drug is suspected. In any case, a *Pregnancy Report Form* must be completed and sent as soon as possible to the sponsor. A copy of the form should be filed at the study site for follow-up until the end of the pregnancy. Any pregnancy must be followed by the investigator until delivery or to the end of pregnancy. Any anomalies, complications, abnormal outcomes, or birth defect observed in the child must be reported as a SAE within 24 hours of the investigator or study personnel's first knowledge.

4.10 Type and Duration of the Follow-Up of Subjects after Adverse Events/Non-Serious Suspected Adverse Drug Reactions

In so far as is possible, all individuals will be monitored until the SAE/ non-serious suspected ADR is resolved. If a SAE/ non-serious suspected ADR is active or in process when the subject completes the study, the course of the event must be monitored until the final result is known or the event has stabilized and no additional changes are expected and the investigator decides that further monitoring is not necessary.

The sponsor must be notified if the investigator performs or conducts additional studies (in a manner not required by the protocol) in order to determine the nature and/or causality of the SAE/non-serious suspected ADR.

New relevant information regarding a SAE/non-serious suspected ADR must be recorded in a follow-up report. The updated or corrected information must also be recorded in the revised eCRF and in the subject's source documents.

5 STATISTICAL ANALYSIS

Unless otherwise specified, descriptive statistics will include the number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum values for the continuous/quantitative data or absolute and relative frequency counts and percentages for categorical/qualitative data.

Data handling and evaluation procedures will be described in the Statistical Analysis Plan.

5.1 Population for Statistical Analyses

The Safety population will include all subjects enrolled in the clinical study and will be used for all safety and efficacy analyses.

5.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized. For quantitative variables, mean, SD, median, and minimum, and maximum will be provided. For qualitative variables, the frequency and percentage will be provided.

5.3 Safety Analysis

The safety analyses will be addressed by listing and tabulation of AEs (includes suspected ADRs), clinical laboratory tests including inhibitor (immunogenicity) and functional activity testing, thrombogenicity, vital signs, and physical examinations. Data will be described using descriptive analyses.

5.3.1 Adverse Events

Safety analysis will be primarily focused on a descriptive analysis of suspected ADRs. Safety assessment will be based on the prevalence of suspected ADRs that occurred during the clinical study.

Adverse events will be coded and classified using MedDRA terms (system organ class [SOC] and preferred term [PT]).

Adverse events will be classified as treatment-emergent AEs (TEAEs) or non-treatment-emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start date/time of study treatment after the subject joins the study. A TEAE will be defined as an AE which occurs between the beginning of the first infusion of study treatment after the subject joins the study and the final visit of the clinical study. A non-TEAE will be defined as an AE which occurs prior to the start of study treatment after the subject joins the study. Non-TEAEs and TEAEs will be summarized separately.

All AEs will be summarized by presenting subject incidences and percentages, and they will also be listed by subject and by SOC.

In addition, TEAEs, including suspected ADRs, will be summarized by SOC, PT, causal-relationship, intensity (severity) and seriousness (serious vs non-serious) using descriptive statistics. Each subject will only be counted once at each level of SOC or PT. For the summary by severity or causality, a subject will only be counted once per SOC or PT using the most severe AE or the AE with the strongest causal relationship to study treatment.

Adverse events temporally associated to the infusion of study treatment (ie, infusional AEs, including infusional suspected ADRs), will be summarized by presenting infusion/subject incidences and percentage and ordered by ordinal number of infusions, and listed. Temporally associated AEs occurring during study drug infusion or within 24 hours post the end of study drug infusion, and occurring during or within 72 hours post the end of study drug infusion will be summarized separately.

Subjects with a SAE or who withdraw from the study because of an AE will also be individually listed and summarized.

5.3.2 Clinical Laboratory Values Including Inhibitor (Immunogenicity) and Functional Activity Testing

All clinical laboratory data will be listed for each subject. The investigator will be required to classify out of the normal range laboratory results reported by the laboratory as clinically significant or not according to his/her criteria. Out of the normal range laboratory results judged by the investigator as clinically significant in the context of the subject's medical history will be considered AEs.

The presence and titer of FVIII and VWF inhibitors and functional activity testing results will be listed for each subject.

5.3.3 Thrombogenicity Assessment

Arterial and venous thromboembolic AEs, according to ICD-9-CM definitions, will be separately summarized. Temporally-associated events occurring during or within 72 hours post the end of study drug infusion will be separately presented.

5.3.4 Vital Signs

Vital signs will be listed for each subject. Clinically significant vital sign abnormalities will be reported and analyzed as AEs.

5.3.5 Physical Examinations

Physical examination findings (normal and abnormal) will be listed for each subject. Any clinically significant abnormality developed during the clinical study and not already present at screening will be reported and analyzed as an AE.

5.4 Efficacy Analysis

For bleeding episodes, the bleeding duration, severity, achievement of adequate hemostasis, and overall clinical efficacy will be summarized. Also, the number of Fanhdi infusions and the total amount of Fanhdi dosed will be summarized. The proportion of bleeding episodes in which good or excellent clinical efficacy were achieved will also be summarized.

For surgeries or invasive procedures, the surgery type, severity of bleeding episodes, achievement of adequate hemostasis, and overall clinical efficacy will be summarized. Also, the number of Fanhdi infusions and the total amount of Fanhdi dosed will be summarized. The proportion of surgeries or invasive procedures in which good or excellent clinical efficacy were achieved will also be summarized.

For long-term observation, the long-term overall clinical efficacy will be summarized. Also, the number of bleeding episodes and surgeries or invasive procedures will be summarized. The number of infusions, exposure days, and dose per month will be summarized, in addition to the mean quantity of Fanhdi per bleeding episode and/or surgery or invasive procedure.

5.5 Study Size Determination

Approximately 15 subjects are planned to be enrolled in this clinical study. The sample size is based on clinical considerations and was not formally calculated.

5.6 Limitations of Research Methods

The main limitation of the study is the fact that is an observational, non-interventional study. Therefore, confounding factors such as the selection of the population may be present. The inclusion of subjects will be done arbitrarily by the investigators in the context of clinical practice. The source of data will be available in the investigator's department and the sponsor or its representatives will have access thereto. However, some details in the subjects' medical records may not have been previously collected in the medical history of the subjects. The sponsor will have a special interest in resolving this possible problem of classification (eg, the absence of diagnostic records or a lack of information regarding tolerance of the treatment) and will attempt to verify the data sources insofar as it is possible. Efforts to reduce potential errors will be discussed with the investigators to the extent possible.

5.7 Premature Termination of Study/Closure of Center

The sponsor, EC, and/or regulatory authorities have the right to close this study or a study center, and the investigator/sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The EC must be informed. Should the study center be closed prematurely, all study materials (except documentation that has to remain stored at the study center) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

A study center can be closed for the following reasons:

- Lack of enrollment
- Non-compliance with the requirements of the study protocol
- Non-compliance with ICH GCP

6 PROTECTION OF HUMAN SUBJECTS

The procedures set out in this protocol pertaining to the conduct, evaluation, and documentation of this study is designed to ensure that the sponsor and investigator continue to abide by the ICH GCP guidelines. The study must also be carried out in keeping with applicable local laws and regulations.

Modifications to the study protocol may not be implemented by the sponsor or the investigator without agreement between both parties.

6.1 Ethics Committee

Documented approval from appropriate ECs must be obtained for all participating study centers prior to study start. Upon request, ECs must provide the sponsor with a list of all members involved in the voting and a statement in which it is declared that the EC is organized and operates according to GCP and applicable laws. When necessary, an extension, modification, or renewal of the approval of the EC shall be obtained and sent to the sponsor.

6.2 Subject Information and Informed Consent

Subject information and ICF will be provided to investigator study centers. Prior to the beginning of the study, the investigator must have the EC written approval/favorable opinion of the written ICF and any other written information to be provided to subjects. The written approval of the EC together with the approved subject information/ICF must be filed in the study files and a copy of the documents must also be provided to the sponsor by the investigator study center.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files. A signed copy of the subject ICF will be provided to the subject or subject's authorized representative.

6.3 Confidentiality

All records identifying the subjects must be kept confidential and, to the extent permitted by applicable laws and/or regulations, they may not be made publicly available.

Subject names may not be provided to the sponsor. Only the subject number is to be recorded in the eCRF, and if a subject's name should appear on any document, it must be deleted before a copy of the document may be supplied to the sponsor. Study findings stored on a computer must be stored in accordance with local data protection laws. Subjects must be informed in writing that representatives of the sponsor, the EC, or the regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for an audit or inspection will be handled in strictest confidence and in accordance with local laws if they allow for the patients' information to be identified.

7 STUDY PERSONNEL

Information regarding key personnel involved in the conduct of the study, including the names and contact details of participating study centers, monitors, clinical laboratories, technical departments, and/or institutions, as well as information on members of additional committees, will be kept in the study file of the sponsor and at the participating study centers together with the study reference manual/file.

8 USE OF DATA AND COMMUNICATION OF STUDY RESULTS

Institution and the investigator agree that the first publication shall be made in conjunction with the presentation of a joint, multi-center publication of the study results from all appropriate study centers. If such a multi-center publication is not submitted within 12 months after conclusion of the study at all study centers or after Grifols confirms there will be no joint, multi-center publication, then institution and/or investigator shall have the right, at their discretion, to publish, either in writing or orally, the results of the study performed under the protocol, subject to the conditions outlined below:

- The results of the study will be reported in the publicly accessible registry(ies).
- Institution and/or investigator shall furnish Grifols with a copy of any proposed publication at least 30 days in advance of the date of submission for publication.
- Within said 30 day period, Grifols shall:
  - Review such proposed publication for Confidential Information (other than Study results) and for subject information subject to applicable privacy laws;
  - Review such proposed publication for the unauthorized use of the name, symbols and/or trademarks of Grifols;
  - By written notice to the investigator, identify with specificity the text or graphics in such proposed publication that Grifols contends contains Confidential Information, protected subject information, or the unauthorized use of Grifols' name, symbols and/or trademarks so that the proposed publication may be edited appropriately to remove such text or graphics before publication; and
  - By written request, Grifols may delay proposed publications up to 60 days to allow Grifols to protect its interests in Grifols Inventions described in such publications.

Institution and/or investigator shall give Grifols the option of receiving an acknowledgment for its sponsorship of the study in all such publications or presentation.

9 REFERENCES

1. Dobrkovska A, Krzensk U, Chediak J. Pharmacokinetics, efficacy and safety of Humate-P® in von Willebrand disease. Haemophilia 1998; 4 (suppl 3): 33-39.
2. Scott JP, Montgomery R. Therapy of von Willebrand disease. Sem Thromb Haemost 1993;19: 37-47.
3. UK von Willebrand Working Party. Definition, inheritance, clinical features and diagnosis of von Willebrand disease. Haemophilia 1997;3 (suppl 2): 1-8.
4. Woods A, Meschengieser S, Blanco A, Salviú M, Farías C, Kempfer A, et al. Clinical features and laboratory patterns in a cohort of consecutive Argentinian patients with von Willebrand's disease. Haematologica 2001;86: 420–427.
5. Sadler J, Budde U, Eikenboom J, Favaloro E, Hill F, Holmberg L, et al. Working Party on von Willebrand Disease Classification. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand factor. J Thromb Haemost 2006;4: 2103–2114.
6. Federici AB, Mannucci PM. Diagnosis and management of von Willebrand disease. Haemophilia 1999;5 (suppl 2): 28-37.
7. Castaman G, Federici A, Rodeghiero F, Mannucci P. Von Willebrand's disease in the year 2003: towards the complete identification of gene defects for correct diagnosis and treatment. Haematologica 2003;88: 94–108.
8. Mannucci P, Ruggeri Z, Pareti F, Capitanio A.1-Desamino-8-D-arginine vasopressin: a new pharmacological approach to the management of haemophilia and von Willebrands' diseases. Lancet 1977;1: 869–872.
9. Mannucci P, Canciani M, Rota L, Donovan, B. Response of factor VIII/von Willebrand factor to DDAVP in healthy subjects and patients with haemophilia A and von Willebrand's disease. Br J Haematol 1981;47: 283–293.
10. Favaloro E, Franchini M, Lippi G. Biological therapies for von Willebrand disease. Expert Opin Biol Ther 2012;12(5):551-564.
11. Revel-Vilk S, Schmugge M, Carcao M, Blanchette P, Rand M, Blanchette V.. Desmopressin (DDAVP) responsiveness in children with von Willebrand disease. J Pediatr Hematol Oncol 2003;25: 874–879.
12. Mannucci P. Treatment of von Willebrand's disease. J Intern Med 1997;242 (suppl 740): 129-132.
13. Kaufmann J, Vischer U. Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). J Thromb Haemost 2003;Apr;1(4):682–689.
14. Mannucci P. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. Blood 1997;Oct;90(7):2515–2521.
15. Lak M, Peyvandi F, Mannucci P. Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease. Br J Haematol 2000;111: 1236–1239.
16. Ewestein B. Von Willebrand's disease. Ann Rev Med 1997; 48: 525-542.

17. The National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Full Report. The Diagnosis, Evaluation, and Management of von Willebrand Disease. NIH Publication No. 08-5832. December 2007.
18. Nichols W, Hultin M, James A, Manco-Johnson M, Montgomery R, Ortel T, et al. Von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia 2008;14: 171-232.
19. Holmberg L, Nilsson I, Borge L, Gunnarsson M, Sjörin E. Platelet aggregation induced by 1-desamino-8- D-arginine vasopressin (DDAVP) in type IIB von Willebrand's disease. N Engl J Med 1983;309: 816–821.
20. Fanhdi® [package insert]. Barcelona Spain: Instituto Grifols, S.A. 2015.
21. Bello I, Yuste V, Molina M, Navarro, F. Fanhdi, efficacy and safety in von Willebrand's disease: prospective international study results. Haemophilia 2007;Dec;13 Suppl 5:25-32.
22. Federici A, Baudo F, Caracciolo C, Mancuso G, Mazzucconi M, Musso R, et al. Clinical efficacy of highly purified, doubly virus-inactivated factor VIII/von Willebrand factor concentrate (Fanhdi) in the treatment of von Willebrand disease: a retrospective clinical study. Haemophilia 2002;Nov;8(6):761-767.
23. Fanhdi® [Summary of Product Characteristics]. Barcelona Spain: Instituto Grifols, S.A. 2015.
24. Guideline on the Clinical Investigation of Human Plasma Derived Von Willebrand Factor Products (CPMP/BPWG/220/02).
25. Rivard G, Aledort L, Alphanate Surgical Investigators. Efficacy of factor VIII/von Willebrand factor concentrate Alphanate in preventing excessive bleeding during surgery in subjects with von Willebrand disease. Haemophilia. 2008 Mar;14(2):271-275.
26. Kaatz S, Ahmad D, Spyropoulos A, Schulman S; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015 Nov;13(11):2119-2126.

Appendix 1 **Summary of Changes for Amendment 2**

(Note: Administrative changes including minor administrative corrections and the changes in the protocol synopsis are not included in Protocol Summary of Changes.)

Sections	Change From: (Version 2.0, dated 07 Feb 2018)	Change To: (Version 3.0, dated 14 May 2018)	Rationale:
Synopsis, Section 3.2.1	Inclusion Criteria: A subject who will be treated with Fanhdi must meet all the following inclusion criteria to be eligible for participation in this study: 1. Male or female subjects ≥18 years of age diagnosed with hereditary VWD of any type and severity who require replacement therapy with VWF/FVIII concentrates.	Inclusion Criteria: A subject who will be treated with Fanhdi must meet all the following inclusion criteria to be eligible for participation in this study: 1. Male or female subjects ≥18 years of age diagnosed with hereditary VWD of any type and severity who require replacement therapy with VWF/FVIII concentrates when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.	Per the Ethics Committee request to provide the clarification on the Fanhdi indication.