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2 SYNOPSIS

Name of Sponsor / Company: Instituto Grifols, S.A.	
Name of Finished Product: Fanhdi®	
Name of Active Ingredient: Double-inactivated Human Anti-hemophilic Factor	
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	
Investigators: There were 5 sites with at least one subject enrolled. Refer to Appendix 16.1.4 for a list of participating investigators.	
Study Center(s): Refer to Appendix 16.1.4 for a list of participating study centers.	
Publication (reference): None.	
Studied Period (years): (date of first enrollment) 20 Feb 2019 (date of last subject completed) 08 Aug 2022	**Phase of Development**: 4

Objectives:

Safety objective

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

Efficacy objective

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

Methodology:

This was 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 received the dose of Fanhdi, according to the investigator's discretion, to achieve satisfactory hemostasis. There was no intervention with the prescribing habits or practices of the investigator's standard medical care; however, the investigator was expected to treat the subject within the approved labeling for dose and frequency of Fanhdi administration.

Enrolled subjects were treated with Fanhdi as their sole source of VWF/FVIII concentrate for prophylaxis and treatment of all bleeding episodes and surgical or invasive procedures. Subjects were followed for 12 months after the first infusion of Fanhdi, during which data was collected to evaluate the response to treatment with Fanhdi for any bleeding episode (spontaneous or traumatic bleeding) and/or surgery or invasive procedure.

Number of subjects (planned and analyzed):

Approximately 15 subjects were planned to be enrolled in this clinical study. Due to the observational and non-interventional nature of the study, some enrolled subjects might not have received Fanhdi after being included in the study. For this reason, the sample size could be increased to ensure enrollment of up to 15 subjects.

A total of 15 subjects were included in the Safety Population, which was used for all safety and efficacy analyses.

Diagnosis and Main Criteria for Inclusion:

The study involved adult subjects with diagnosed hereditary VWD.

Inclusion Criteria:

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 was 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 were 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 were willing and able to provide written informed consent or had an authorized representative able to provide written informed consent on behalf of the subject in accordance with local law and institutional policy.

Exclusion Criteria:

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 were positive for anti-VWF or anti-FVIII antibodies (≥0.5 Bethesda units [BU]) or had 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 were participating in another clinical study involving an investigational treatment or had participated in one in the past 4 weeks.
7. Subjects who, in the opinion of the investigator, could have compliance problems with the protocol.

Investigational Product, Dose and Mode of Administration, Batch Number:

Fanhdi, a double-inactivated Human Anti-hemophilic Factor [VWF/FVIII]) was supplied as a lyophilized powder for solution for intravenous injection containing nominally 250, 500, 1000 or 1500 IU human coagulation factor VIII per vial. Subjects were treated within the approved labeling for dose and frequency of Fanhdi as described in the Summary of Product Characteristics of the product. Doses of 40 to 80 IU/kg VWF (ristocetin cofactor [VWF:RCof]) and 20 to 40 IU/kg FVIII coagulant (FVIII:C) were recommended.

Lot numbers administered in this study: M5NCD00571, M5NCD00901, M5NCD01071, M5NCB01471, M5NCC00161, M5NCC00351, M5NCC00521, M5NCD00131, M5NCD00261, M5NCD00361, M5NCB01474, M5NCE00531, M5MCE00191, M5NCD00221, M5NCD00701, A4NCC01241, M5NCC00501, MSNCD00411

Duration of Treatment: Subjects were treated at the discretion of the investigator and were followed for a 12-month observation period starting with the first Fanhdi infusion.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.

Criteria for Evaluations:

Efficacy:

- 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 at the hospital or another location under the investigator's direct supervision)
- Amount of Fanhdi (IU/kg) used per subject per year
- Amount of Fanhdi (IU/kg) used per infusion
- Use of other hemoderivatives per bleeding episode
- Overall clinical efficacy

Safety:

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

Statistical Methods:

Continuous variables were summarized using descriptive statistics (number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum). For categorical variables, descriptive statistics included counts and percentages per category. No hypothesis testing was done.

Screened subjects were considered as all subjects who signed the informed consent form. Enrolled subjects were those who met all inclusion and exclusion criteria. The Safety Population included all subjects enrolled in the clinical study and received any dose of Fanhdi. The Safety Population was used for all safety and efficacy analyses.
Approximately 15 subjects were planned to be enrolled in this clinical study. The sample size was based on clinical considerations and was not formally calculated. Due to the observational and non-interventional nature of the study, some of enrolled subjects might not have received Fanhdi after being included in the study, for this reason the sample size could be increased to achieve up to 15 patients receiving Fanhdi.

Efficacy Analyses: Efficacy analyses were performed on the Safety population. Listings and tabulations of the data related to bleeding episodes and study drug administration related to bleeding episodes, surgical or invasive procedures, hemostasis and clinical efficacy as determined by the investigator per standard of care utilizing a 4-point rating scale (i.e., excellent, good, poor, and no response), the overall study medication exposure, and the long-term overall clinical efficacy were used for the efficacy analyses. Data were summarized using descriptive analyses.

Safety Analyses: The safety analyses were addressed by listing and tabulation of AEs (including SAEs and suspected ADRs), clinical laboratory tests including inhibitor (immunogenicity) and functional activity testing, thrombogenicity, vital signs, and physical examinations. Data were summarized using descriptive analyses.

SUMMARY – CONCLUSIONS

SUBJECT DISPOSITION:

From 18 screened subjects, a total of 15 were included in the safety population and 3 were excluded. The reasons for exclusion were failed screening (1 subject) and treatment with Fanhdi not applied (2 subjects).

EFFICACY RESULTS:

This report constitutes the analysis of data from subjects with up to 52 weeks of exposure to Fanhdi in this post-authorization study conducted to assess the safety and efficacy of Fanhdi (Double-inactivated Human Anti-hemophilic Factor) in subjects with VWD. A total of 15 subjects received at least 1 dose of the study medication and were, thus included in the Safety Population which was used for the efficacy and safety analyses. Of the 15 subjects, 9 (60%) subjects were treated with Fanhdi due to bleeding, and 5 (33.3%) subjects were treated with Fanhdi due to surgery or invasive procedure.

- The efficacy was assessed during 46 bleeding episodes reported for 9 (60%) subjects, and 6 surgical/invasive procedures reported for 5 (33.3%) subjects.
- Mean bleeding duration reported for bleeding episodes (excluding surgery or invasive procedures) was 4.81 days on the subject level and 4.66 days on the episode level.
- The majority of bleeding episodes (excluding surgery or invasive procedures) were of moderate severity, i.e., 29 (63.0%) of 46 bleeding episodes, reported for 6 [66.7%] of 9 subjects.

- The mean number of Fanhdi infusions per bleeding episode (excluding surgery or invasive procedures) on the subject level was 2.6, which was comparable to the mean number of 2.3 infusions on the episode level.
- The mean total Fanhdi dose per bleeding episode, on the subject and episode levels, was 75.96 IU/kg and 68.13 IU/kg respectively.
- Of the 6 reported surgical/invasive procedures, 3 (50%) were major and 3 (50%) minor.
- No bleeding episodes related to surgical or invasive procedures were reported.
- The mean number of Fanhdi infusions per surgical/invasive procedure on subject level was 3.5, which was comparable to the mean number of 3.7 infusions on surgical/invasive procedure level.
- The mean total Fanhdi dose per surgical/invasive procedure, on the subject and surgical/invasive procedure levels, was 83.31 IU/kg and 95.30 IU/kg respectively.
- In bleeding episodes (excluding surgery or invasive procedures), adequate hemostasis was achieved in 5 (55.6%) of 9 subjects, in 37 (80.4%) of 46 bleeding episodes.
- Adequate hemostasis during surgical/invasive procedures was achieved in 4 (80.0%) of 5 subjects, in 5 (83.3%) of 6 surgical/invasive procedures.
- During the 12-months follow-up period, hemostasis was evaluated as excellent at 16 (33.3%) and good at 31 (64.6%) of 48 follow-up assessments.
- A total of 476 Fanhdi infusions were administered during the study.
- Duration of exposure to Fanhdi varied from 0.1 to 52.1 weeks, and the mean exposure was 24.35 weeks.
- The mean total Fanhdi dose per year was 1135.08 IU/kg
- Long-term overall clinical efficacy for prophylaxis and/or on-demand treatment with Fanhdi during participation in the study for the Safety population had ratings of excellent for 7 (46.7%) subjects and good for 8 (53.3%) subjects.The results of the study demonstrated efficacy of treatment with Fanhdi for prophylaxis and/or on-demand treatment.

SAFETY RESULTS:

In total, 27 TEAEs were observed. Eight (53.3%) subjects reported at least one TEAE. The most frequently reported TEAEs were originating from the MedDRA SOC Gastrointestinal disorders (14 events reported for 5 [33.3%] subjects). The most frequently observed AEs were upper gastrointestinal hemorrhage (9 events in 2 [13.3%] subjects) and gastrointestinal hemorrhage (2 events in 2 [13.3%] subjects). The incidence of non-serious TEAEs was greater than that of serious TEAEs (7 [46.7%] subjects and 3 (20%) subjects, respectively). Of 27 reported TEAEs, 11 were serious TEAEs, reported for 3 (20.0%) subjects. The majority of SAEs were related to gastrointestinal bleedings.

No suspected ADRs or adverse reactions (ARs), infusion site reactions, or thromboembolic events were reported. No deaths or TEAEs leading to withdrawal from the study were observed. No clinical signs and symptoms were reported that caused immunogenicity assessments to be performed according to standard clinical practice.

No clinically meaningful abnormal vital signs and physical examination findings were reported during the study. However, conclusions were based on limited data as it was not

possible to assess the change from baseline in vital signs because there were no subjects with both baseline and post-baseline information reported.

Fanhdi was well tolerated when used as treatment and prophylaxis according to the standard clinical practice. No safety concerns were raised during the conduct of this observational study.

CONCLUSION:

In conclusion, the results of the study demonstrated efficacy of treatment with Fanhdi for prophylaxis and/or on-demand treatment. Fanhdi was well tolerated when used as treatment and prophylaxis according to the standard clinical practice. No thromboembolic events were reported during the 12 months follow-up, and no safety concerns were raised during the conduct of this observational study.