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Sponsor: Bioverativ, a Sanofi company **Drug substance(s):** rFVIIIFc (Recombinant Coagulation Factor VIII Fc Fusion Protein)	**Study Identifiers:** NCT02234323, 2013-005512-10 **Study code:** 997HA306 / EFC16225
Title of the study: An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia A	
Study center(s): Forty-four sites in 13 countries (Australia, Brazil, Canada, France, Germany, Ireland, Italy, New Zealand, Poland, Spain, Sweden, United Kingdom (UK), and US)	
Study period: Date first subjects enrolled: 12/Jan/2015 Date last subjects completed: 23/Sep/2019	
Phase of development: Phase III	

Objectives:

Primary:

- To evaluate the safety of rFVIIIFc in previously untreated subjects with severe hemophilia A

Secondary:

- To evaluate the efficacy of rFVIIIFc in the prevention and treatment of bleeding episodes in previously untreated patients (PUPs)
- To evaluate rFVIIIFc consumption for the prevention and treatment of bleeding episodes in PUPs
- To describe experience with the use of rFVIIIFc for Immune tolerance induction (ITI) in subjects with inhibitors

Exploratory:

- To evaluate the effect of rFVIIIFc on patient-reported outcomes and health resource utilization
- To assess the efficacy of rFVIIIFc for perioperative management

Methodology:

This was an open-label, single-arm, multicenter study evaluating the safety and efficacy of rFVIIIFc in pediatric PUPs with severe hemophilia A when used according to local standard of care.

ITI with rFVIIIFc was allowed during the study for those subjects who, after exposure to rFVIIIFc study drug, developed a positive high-titer inhibitor (≥5.00 Bethesda unit [BU]/mL) or a positive low-titer inhibitor (≥0.60 and <5.00 BU/mL) with bleeding episodes that could not be adequately treated with rFVIIIFc or requiring bypassing agents to treat bleeding.

The study period consisted of screening, treatment, and follow-up. The duration of individual subject study participation was approximately 6 months to 3 years, including screening and follow-up. For subjects who did not develop an inhibitor, the treatment period was no less than 50 exposure days (EDs) to the study treatment.

For the purposes of this study, 1 ED was defined as a 24 hour period in which a subject received 1 or more doses of rFVIIIFc, with the time of the first injection of rFVIIIFc defined as the start of the ED.

Enrolled subjects reported to the study site for 2 types of required visits during the treatment period:

- Scheduled Interim Visits: every 12 (±2) weeks by calendar date. Subjects who developed high-titer inhibitors switched to a schedule of ITI Visits, and, if they subsequently met ITI complete success criteria within 33 months, received a tapering regimen and participated in Post ITI Success visit,
- ED Milestone Visits: at 5 (±1) EDs, 10 to 15 EDs, 20 to 25 EDs, and 50 to 55 EDs. In addition, ED Milestone Visits at 75 to 80 EDs and 100 to 105 EDs were also completed prior to Amendment 5.

Scheduled visits included safety and efficacy assessments, and rFVIIIFc activity measurements to assess trough and recovery (at 10 [±5] minutes after the end of the injection). In addition, the site contacted subjects' parents/caregivers monthly by telephone to review adverse events (AEs), treatment compliance, and use of concomitant medications and therapies.

For subjects that underwent surgery, postoperative clinic visits could be more frequent. For subjects that underwent major surgery, a visit was required 1 to 2 weeks after surgery, and a further visit occurred when the Investigator determined that the subject could return to the regular pre-surgery regimen if this did not happen at the post-surgery visit. Major surgery was defined as any surgical procedure in which a major body cavity was penetrated and exposed or for which a substantial impairment of physical or physiological function was produced (eg, laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation).

Following confirmation of eligibility and enrollment, the Investigator had the option to treat a subject episodically (on-demand) prior to initiating a prophylaxis regimen. The duration of episodic treatment was at the Investigator's discretion, in accordance with local standard of care. However, it was expected that the prophylactic regimen would be initiated prior to or immediately following a third episode of hemarthrosis (joint bleed).

The dose for prophylaxis could be selected and adjusted based on the subject's response to dosing (ie, available PK data, including FVIII activity levels, level of physical activity, and bleeding pattern), in the range of 25 to 65 IU/kg at 3- to 5-day intervals. However, based on data from the completed clinical studies and knowledge of increased CL of factor concentrates in children <6 years of age, more frequent or higher doses of up to 80 IU/kg may be required. Prophylactic dose titration outside the range of 25 to 80 IU/kg requires discussion with the Sponsor and documentation of rationale.

Surgery was allowed during the study. ITI with rFVIIIFc was allowed during the study for those subjects developing a positive inhibitor after exposure to rFVIIIFc study drug.

Treatments were administered as episodic, prophylaxis, or as ITI, as follows:

- Episodic (optional) regimen: the individual dose of rFVIIIFc to treat bleeding episodes was based on the subject's clinical condition and the type and severity of bleeding event.
- Prophylaxis regimen: it was anticipated that subjects would begin a prophylaxis regimen prior to or immediately following the occurrence of a third hemarthrosis (joint bleed). The dose for prophylaxis could be selected and adjusted based on the subject's response to dosing (ie, available PK data, including FVIII activity levels, level of physical activity, and bleeding pattern), in the range of 25 to 65 IU/kg at 3- to 5-day intervals.
- ITI: the ITI therapy was determined at the discretion of the Investigator for a period of up to 33 months.

Number of subjects:	Planned: 105
	Enrolled: 108
	Treated: 103
Evaluated:	Efficacy: 103
	Safety: 103

Diagnosis and criteria for inclusion:

- Ability of the subject's legally authorized representative (eg, their parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
- Male, age <6 years at the time of informed consent.
- Weight ≥3.5 kg.
- Severe hemophilia A defined as <1 IU/dL (<1%) endogenous FVIII documented in the medical record or as tested during the Screening Period. Enrolled subjects whose central laboratory screening results indicate a baseline FVIII activity level ≥1% of normal are withdrawn.

Study treatments:

Investigational Product: rFVIIIFc

There were 53 lots of study medication.

Duration of treatment: Individual subject study participation was expected to be approximately 6 months to 3 years including screening and follow-up. For each subject, the treatment period is no less than 50 EDs to the study treatment, unless the subject is withdrawn for other reason as inhibitor development or the end of study (EOS) is declared.

Criteria for evaluation:

Safety:

The primary endpoint of the study is the occurrence of inhibitor development.

Efficacy:

The secondary endpoints of the study are as follows:

- The annualized number of bleeding episodes (spontaneous and traumatic) per subject.
- The annualized number of spontaneous joint bleeding episodes per subject.
- Assessments of response to treatment with rFVIIIFc for bleeding episodes, using the 4-point bleeding response scale.
- The total number of EDs per subject per year
- Total annualized rFVIIIFc consumption per subject for the prevention and treatment of bleeding episodes.
- The number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode.
- Response to ITI with rFVIIIFc (complete success, partial success, failure, early withdrawal)
- rFVIIIFc incremental recovery (IR).

Statistical methods:

Planned Analyses

Demographics and Baseline Disease Characteristics:

Subject disposition was summarized for subjects by treatment regimen and overall.

Demographics and baseline characteristics were summarized as continuous variables and as categorical variables, as appropriate, using the Safety Analysis Set.

Exposure:

The total number of EDs on rFVIIIFc for each subject was summarized categorically (<5, 5 to <10, 10 to <20, 20 to <50, 50 to <75, 75 to <100, and ≥100) and with descriptive statistics for the Safety Analysis Set. The total number of injections per subject was summarized overall and by reason for injection (prophylactic regimen, spontaneous bleed, traumatic bleed, follow-up injection, surgical, or other) using descriptive statistics for the Safety Analysis Set.

Duration of rFVIIIFc dosing (weeks) was also summarized using descriptive statistics for the Safety Analysis Set.

Efficacy and Pharmacokinetics:

There were no primary efficacy endpoints for this study.

- The annualized bleeding rate (ABR) was summarized using descriptive and categorical (ie, 0, >0 to 5, >5 to 10, >10 to 15, etc) statistics for the Full Analysis Set.
- ABR was also summarized by type of bleeding (spontaneous, traumatic, unknown), location of bleeding (joint, muscle, internal, skin/mucosa), and by location and type of bleeding for the Full Analysis Set.
- The number of injections, average dose per injection (IU/kg), and total dose (IU/kg) required to resolve a bleeding episode were determined on both a per-bleeding episode and per-subject basis, and summarized for the Full Analysis Set.
- Using the electronic patient diary, each patient's parent/caregiver rated the treatment response to any bleeding episode using a 4-point scale. The assessment of response was summarized for the Full Analysis Set by treatment regimen, and by compliance to treat the bleed and treatment regimen.
- The total number of EDs along with the duration of dosing with rFVIIIFc and total number of injections per subject were summarized for the Safety Analysis Set.
- The total annualized rFVIIIFc consumption per subject for the prevention and treatment of bleeding episodes was summarized for the Full Analysis Set using descriptive statistics.
- IR data was summarized by visit for the Full Analysis Set for exposure in the episodic and prophylactic treatment regimens.

Safety:

Primary Analysis:

The overall incidence of positive inhibitor formation was based on all subjects in the Safety Analysis Set. Any subject who developed an inhibitor following the initial rFVIIIFc administration was included in the numerator. All patients who have received at least 1 dose of rFVIIIFc will be included in the denominator. An exact 95% confidence interval (CI) for the proportion of subjects with a positive inhibitor was calculated using the Clopper-Pearson method for a binomial proportion.

The incidence of positive inhibitor formation was summarized separately for the following types of inhibitors:

- Subjects with high-titer inhibitors.
- Subjects with low-titer inhibitors that met the clinically meaningful criteria.
- Subjects with low-titer inhibitors that did not meet the clinically meaningful criteria.

Other Safety Analyses:

Safety data were summarized by treatment group and overall. The incidence of AEs was summarized. Listings were provided for inhibitor test results, anti- rFVIIIFc antibody results, AEs, clinical laboratory evaluations, vital signs, and abnormal physical examination findings.

Summary:

STUDY SUBJECTS:

110 subjects were screened, of which 108 subjects were enrolled in 13 countries worldwide, of whom 103 received rFVIIIFc. Based on the study data, the following conclusions can be drawn:

- The study population is generally representative of the global population of PUPs with hemophilia A:
  - All subjects were male, in the range of 0.02 years to 4 years of age with the majority <1 year of age (80, 77.7%).
  - Median time since diagnosis of hemophilia was 54.5 days and all 103 subjects who received rFVIIIFc had FVIIIF activity at Screening of <1%.
  - The medical and surgical history was typical for this population.
  - Most subjects (96.1%) had received at least 1 concomitant medication or procedure, which included medications typical for this population such as vaccines, antibiotics, IV fluids, analgesics, and antipyretics etc.
  - Twenty subjects (19.4%%) had a known family history of inhibitors, relatively high compared with published incidences.
- 87 of 108 enrolled subjects completed the study and 21 discontinued study participation prematurely.
- Exposure was representative of how PUPs are treated when they first begin factor replacement therapy, with most subjects starting on episodic treatment and then transitioning to prophylactic treatment.
  - The median total number of injections per subject was 5 and 94 for the episodic and prophylactic, respectively.
  - The median number of EDs for the treatment regimens was 4 and 91 for the episodic and prophylactic, respectively.
  - The subjects with at least 50 EDs was 81 (78.6%).
  - The median average weekly dose for subjects on the prophylactic treatment regimen was 101.4 IU/kg and the median average dose interval was 3.87 days.
  - The overall median annualized consumption of rFVIIIFc was 3971.4 IU/kg and by the 3 treatment regimens was 197.6 IU/kg and 5384.4 IU/kg for the episodic and prophylactic, respectively.

EFFICACY RESULTS:

This study evaluated the efficacy of rFVIIIFc in the prevention and treatment of bleeding episodes in PUPs with severe hemophilia A as secondary objectives. A summary of the efficacy and conclusions is provided below:

- rFVIIIFc was highly effective as prophylaxis treatment in PUPs with hemophilia A.
  - The median ABR by treatment regimen was 2.24 (range 0 to 39.8) and 1.49 (range 0 to 18.7) for subjects on the episodic and prophylactic, respectively.
- rFVIIIFc was highly effective for the treatment of bleeding episodes in PUPs
  - The median number of injections required for resolution of a bleeding episode was 1 for each of the regimens. The majority of bleeding episodes required ≤2 injections to resolve: 132 (89.2%) and 201 (93.5%) for the episodic and prophylactic, respectively.
  - Combining “excellent” and “effective,” the Investigator global assessment of response was 111 responses (95.7%) for subjects on the episodic regimen, 275 responses (97.2%) for subjects on the prophylactic regimen, and overall 386 responses (96.7%).
  - The median dose per injection was 45.45 and 48.08 for bleeding episodes in the episodic and prophylactic, respectively.
- The IR for the baseline PK profile of subjects on the episodic regimen was similar to that of the prophylactic regimen. IR remained stable throughout the study, with both regimens exhibiting similar IR values for the duration (through Week 120). The IR values observed in the study were consistent with those observed in prior studies of rFVIIIFc in PTPs

SAFETY RESULTS:

Overall, the safety profile of rFIVIIIVcFc in PUPs in Study 997HA306 was assessed in 103 subjects ≤4 years of age, with a median age of 0.58 years and an age range from 0.02 years to 4 years; 77.7% of subjects were <1-year-old at study entry.

The total subject-years followed on the study was 140.44 years (excluding major surgical periods) with a total of 11255 EDs allowing for a robust safety evaluation. rFVIIIFc was generally well tolerated. The primary safety results included the following:

- Primary Endpoint: The extent of exposure was adequate for assessing inhibitor development. Of 90 subjects in the Safety Analysis Set with ≥10 EDs to rFVIIIFc and at least 1 subsequent inhibitor test result or who had an inhibitor, 28 subjects (31.11% [95% CI: 21.77%, 41.74%]) developed an inhibitor to rFVIIIFc during the study.
- Of the 28 subjects who developed inhibitors, 14 developed high-titer inhibitors and 14 developed low-titer inhibitors.
- One death due to the pre-treatment unrelated SAE of intracranial hemorrhage occurred during the study.
- Of the 157 TESAEs reported in 103 subjects,126 were assessed by the Investigator as unrelated to rFVIIIFc and 31 were assessed by the Investigator as related to rFVIIIFc (28 cases of factor VIII inhibition, 1 event of deep vein thrombosis, 1 event of device-related thrombosis, and 1 TESAE of soft tissue hemorrhage). Two subjects had TESAEs resulting in withdrawal of study treatment (2 cases of factor VIII inhibition)
- The type and incidence of TEAEs observed in the study were similar to what is expected for the pediatric hemophilia population. The most common TEAEs observed (incidence ≥10%) were, in descending order of incidence, fall, pyrexia, head injury, nasopharyngitis, upper respiratory tract infection, Factor VIII inhibition, central venous catheterization, ear infection, vomiting, viral infection, diarrhea, cough, viral upper respiratory tract infection, and teething. Six (5.8%) subjects had study treatment discontinued for TEAEs: 2 subjects for FVIII inhibition, 2 subjects for intracranial hemorrhage, 1 subject for intraventricular hemorrhage, and 1 subject for poor venous access. All of these events were considered serious. Although no subject was reported as having withdrawn from the study due to a TEAE, 3 subjects subsequently terminated early from the study for reasons related to the management of a TEAE.
- There were no reports of anaphylaxis and 1 report of hypersensitivity or allergy event associated with rFVIIIFc. One subject developed a papular rash, considered non-serious and related to study treatment by the Investigator. The rash occurred 2 days after the first dose of rFVIIIFc and resolved; the subject later developed a low-titer CM inhibitor.
- There were 2 TESAE related to a thrombotic event: a case of deep vein thrombosis and a case of device related thrombosis, both in subjects with central venous catheters.
- No clinically meaningful patterns or trends were observed in abnormalities of hematology or clinical chemistry.
- No clinically meaningful patterns or trends were observed in vital sign abnormalities.

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