An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant, Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia B.

Published: 01-11-2013
Last updated: 25-04-2024

Primary: The primary objective of the study is to evaluate the long-term safety of rFIXFc in subjects with hemophilia B.Secondary: The secondary objective of this study is to evaluate the efficacy of rFIXFc in the prevention and treatment of…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON40613

Source
ToetsingOnline

Brief title
BYOND (9HB01EXT)

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
Bleeding episodes, Clotting disorder

Research involving
Human

Sponsors and support

Primary sponsor: Biogen
Source(s) of monetary or material Support: Pharmaceutical Company: Biogen

Intervention

Keyword: Extension Study, Hemophilia B, rFIXFc

Outcome measures

Primary outcome

The occurence of inhibitor development.

Secondary outcome

- The annualized number of bleeding episodes (spontaneous and traumatic) per subject

- The annualized number of spontaneous joint bleeding episodes per subject

- The total number of days of exposure per subject per year

- The consumption of rFIXFc as total dose per kg per subject per year

- Physician*s global assessment of the subject's response to his treatment regimen using a 4-point scale

- Subject*s/caregiver*s assessment of response to treatment of bleeding episodes using a 4-point scale

- The incidence of adverse events (AEs) and serious adverse events (SAEs)

Study description

Background summary

Hemophilia B, or Christmas disease, is a deficiency in the clotting Factor IX (FIX)and is a recessively inherited coagulation disorder due to an X-chromosome mutation carried by females and expressed mainly in males, affecting approximately 80,000 people worldwide. A deficiency of FIX in subjects results in bleeding into joints, soft tissue, and muscle that can be associated with trauma or can occur in the absence of trauma (spontaneous bleeding). Depending on the severity of the bleeding it can also pose a life-threatening situation (e.g. intracranial hemorrhage, other internal bleeding) for a subject if not treated appropriately. FIX, a serine protease, and factor VIII, a cofactor for FIX, work in concert to activate Factor X, a central step in the clotting cascade. The coagulation cascade has 2 pathways, the Contact Activation Pathway (Intrinsic Pathway) and the Tissue Factor Pathway (Extrinsic Pathway). The plasma factors are activated in the form of a cascade one after the other until the soluble plasma protein fibrinogen is transformed into a fibrinous clot.

There is no available cure for hemophilia B, so treatment focuses on the replacement of FIX with the intravenous (IV) administration of FIX-containing coagulation products to promote clotting. The goal of treatment with FIX-containing coagulation products is to raise the circulating level of FIX to the lowest effective dose to achieve either resolution of bleeding (on-demand treatment) or prevention of bleeding (prophylaxis treatment) The frequency of administration of FIX products differs among subjects and is usually tailored to the subject*s clinical status, taking into consideration the type of bleeding episode, frequency of bleeding, and goal of treatment for the subject. The dose of FIX required also varies and has been based on observations over the years and guidelines established by organizations such as the National Hemophilia Foundation of the United States and the WFH.
The use of FIX-containing, plasma-derived coagulation products, available for almost 40 years, has led to vast improvements in the care of hemophilia B, subject life expectancy, and quality of life for people with hemophilia. Risks of plasma-derived products include subject infection with serious blood-borne pathogens, including human immunodeficiency virus (HIV) and hepatitis B and C, as well as thrombosis. Recombinant coagulation products with no animal- or human-plasma-derived proteins, developed more recently have a safety advantage in that the risk of disease transmission is minimal.

Identified priorities for hemophilia B therapy include the development of more convenient dosing options and investigation into modified FIX agents with a longer half-life to decrease injection frequency. Current therapy is focused on home therapies, which, taken prophylactically or administered at the onset of a bleeding episode, reduce short-term disability and long-term joint damage and improve subjects* overall quality of life and functional independence.

rFIXFc (BIIB029) is a recombinant coagulation Fc fusion protein, which comprises FIX covalently attached to the Fc domain of human IgG and is in development as a long-acting version of rFIX for the treatment of hemophilia B. rFIXFc has been tested in 14 subjects with severe, previously treated

hemophilia B in a Phase 1/2a study and is currently under investigation in a preceding study in subjects aged 12 years and older. Preclinical and clinical experience to date has shown an extended half-life of FIX activity compared with commercially available recombinant FIX product. This extended half-life may reduce the frequency of IV injections required for prevention of bleeding and treatment for bleeding episodes in hemophilia B subjects. A therapy with these characteristics may also improve treatment compliance and quality of life.

Study objective

Primary:
The primary objective of the study is to evaluate the long-term safety of rFIXFc in subjects with hemophilia B.

Secondary:
The secondary objective of this study is to evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes.

Study design

This is an open-label, multi-center, long-term study of intravenous (IV) administration of rFIXFc in previously treated patients (PTPs) with hemophilia B who have completed the B-LONG study (998HB102), the pediatric study (9HB02PED), or any other study with rFIXFc. This is a global study and will include those countries participating in these studies.

Based on estimated sample sizes from these studies, approximately 100 subjects from the ongoing B-LONG study and approximately 20 subjects from the pediatric study may be eligible to enroll in this extension study. The End of Treatment (EOT) Visit of the previous study may serve as the screening visit of the extension study. Assessments performed at this visit will be used to confirm eligibility for participation in the extension study.

Study visits are scheduled at 6-month (±2 weeks) intervals following completion of Visit 1. Unscheduled visits may occur as deemed necessary by the Investigator. For subjects from the pediatric study (9HB02PED) who undergo surgery and enter the extension study before completing their Last Post-Operative Visit, the Last Post-Operative Visit assessments will be performed when the subjects switch from their post-surgery dosing regimen to a regimen outlined in Section 5.3.2 of the protocol. Inhibitor testing will be performed at the time subjects reach 10-15 and 50-75 EDs, and after 100 EDs, as applicable. The number of exposure days for inhibitor testing is comprised of the number of exposure days from the parent study and this extension study, combined. If the timing for inhibitor testing does not coincide with a scheduled visit, an unscheduled visit may be conducted.

For subjects undergoing surgery, post-operative clinic visits may be more frequent and, for subjects undergoing major surgery, a visit is required 1-2 weeks after surgery (Visit 3) and when subjects return to a regular rFIXFc regimen (Visit 4). Scheduled visits will include safety and efficacy assessments, and FIX activity measurements to assess trough and peak (recovery). In addition, the site will contact study subjects and/or caregivers by telephone on a bimonthly basis to review adverse events, treatment compliance, use of concomitant medications and therapies, and other issues.

Treatment will be self-administered as prophylaxis or as an on-demand regimen. Subjects will be able to switch from one regimen to another at scheduled or unscheduled visits during the study, per Investigator discretion.

To ensure accuracy of trough/peak (recovery) and inhibitor testing, subjects following a prophylaxis regimen should schedule clinic visits 72 hours after the previous dose of rFIXFc, whenever possible.

Subjects are expected to be followed through at least 100 exposure days (EDs) to rFIXFc and may continue in this study for up to 4 years or until rFIXFc is commercially available in the applicable participating country.

Intervention

rFIXFc will be administered over several minutes by slow intravenous (IV) injection. The rate of administration should be determined by the subject*s comfort level. Any missed doses should be taken as soon as possible or per the instructions of the Investigator.
Subjects will follow either a prophylaxis or on-demand regimen based on the subject*s clinical profile and by PK profiles and dosing levels from the prior rFIX Fc study.
Subjects will be allowed to change from prophylaxis to on-demand, and from on-demand to prophylaxis during this study. All treatment regimen changes will be discussed between the Investigator and the subject (and parent/guardian, as applicable).

The prophylaxis regimen may comprise doses of rFIXFc 20 IU/kg to 100 IU/kg once weekly, or a tailored prophylaxis regimen taken at individualized intervals. Individualized doses and dosing intervals can be based on PK profiles and dosing levels from the preceding rFIXFc studies or FIX trough and/or peak (recovery) levels obtained during this extension study.
Prophylaxis treatment options may include weekly prophylaxis, individualized dosing intervals, or personalized prophylaxis.

The individual dose of rFIXFc to treat bleeding episodes will be based on the subject*s clinical condition and the type and severity of the bleeding event.

For subjects who require emergent or elective surgery during the study period,

the dose and regimen of rFIXFc shall be that deemed appropriate for the type of surgery to be performed.
All surgeries must take place in a center that can provide study treatment, trained study personnel, post-operative assessments, and hematological consult by the Investigator or Co-Investigator. If the surgery does not occur in such a setting, the subject will be withdrawn from the study.
In addition, subjects who require major surgery may receive rFIXFc if
1. The surgery occurs within the contracted Institution for the trial and/or a separate agreement has been executed, permitting the use of study drug and Biogen Idec*s rights to data generated in the trial at an alternative Institution deemed appropriate by the Principal Investigator.
2. The Investigator and/or appropriate qualified/licensed delegate is available to
a. Administer all rFIXFc doses required during surgery and during post-operative rehabilitation (if applicable).
b. Provide medical oversight and guidance throughout the duration of the pre-operative and the intra-operative periods.

Surgeries, elective or emergent, will be classified as major or minor, as follows: Major surgery is defined as any surgical procedure (elective or emergent) that usually, but not always, involves general anesthesia and/or respiratory assistance, in which a major body cavity is penetrated and exposed, or a substantial impairment of physical or physiological functions is produced (e.g., laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation). Minor surgery is defined as any surgical procedure (elective or emergent) that does not involve general anesthesia and/or respiratory assistance (e.g., minor dental extractions, incision, and drainage of abscess, joint or other injections, or simple excisions).
Inhibitor testing should be performed 2 to 4 weeks prior to the scheduled surgery, pre-operatively on the day of surgery, 1-2 weeks post-surgery, and at the last post-operative visit (for minor surgery, testing is not performed at the last 2 timepoints). On the day of surgery, subjects will be given a pre-operative loading dose of rFIXFc as a bolus, and, in the case of emergency surgery, as soon as possible prior to the procedure. Pre-dose FIX activity levels will be sampled followed by FIX peak (recovery) samples 30 ±5 minutes post-dosing.

A repeat sample will be taken approximately 6 to 9 hours after this dose, but may alternatively follow the local standard of care for determination of subsequent rFIXFc dosing. During the subject*s hospitalization, FIX activity will be measured daily at the local laboratory, and a plasma aliquot will be prepared for each blood sample drawn so that subsequent analysis at the central laboratory can be performed.
Doses higher than 100 IU/kg may be used in the context of surgery to achieve the required FIX levels to prevent bleeding. However, the maximum number of daily or every-other-day doses will not exceed the predicted accumulated Cmax of approximately 150% of normal (normal ranges are 50% to 150% FIX activity).

All surgical dosing plans will be discussed with and approved by the Sponsor Medical Monitor before surgery.

Study burden and risks

The use of a prophylaxis regimen in young children with hemophilia improves their long-term clinical outcome by preventing joint bleeding in the early years of life and subsequent hemophilic arthropathy. At 6 years of age, children on a prophylaxis regimen had significantly less joint damage than children treated with an on-demand regime.
This trial gives the opportunity for less frequent administration regime.

Side effects that have been reported in previous rFIXFc studies or with other FIX products.

Possible serious side effects
• Allergic reaction (including anaphylaxis).
• Abnormal formation of blood clots.
•Nephrotic syndrome. A disorder of the kidneys has been reported in hemophilia B patients who have had a history of allergic reactions to FIX and who have received large, frequent doses of FIX to stop these allergic reactions and to help them to respond better to it.

Contacts

Public
Biogen

Innovation House, 70 Norden Road 70 Norden Road
Berkenshire SL6 4AY, Maidenhead
GB
Scientific
Biogen

Innovation House, 70 Norden Road 70 Norden Road
Berkenshire SL6 4AY, Maidenhead
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Subjects who have completed the studies 998HB102, 9HB02PED, or future studies with rFIXFc.

Exclusion criteria

Confirmed positive high-titer inhibitor test (>=5.00 BU/mL)
Current enrollment in any other clinical study
Inability to comply with study requirements
Other unspecified reasons that, in the opinion of the Investigator or Biogen Idec, make the subject unsuitable for enrollment.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-01-2014

Enrollment:	1
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Recombinant, Human Coagulation Factor IX Fusion Protein (rFIXFc)

Ethics review

Approved WMO Date:	01-11-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-12-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	25-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-003075-11-NL
ClinicalTrials.gov	NCT01425723
CCMO	NL43947.041.13