A Phase 2/3, Multi-Center, Open Label Study of Efficacy, Safety, and Pharmacokinetics of PEGylated Recombinant Factor VIII (BAX 855) Administered for Prophylaxis and Treatment of Bleeding in Previously Treated Patients with Severe Hemophilia A

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Primary ObjectiveThe primary objective is to compare the annualized rates of bleeding episodes (ABR)between subjects receiving a prophylactic regimen of BAX 855 with an on-demandtreatment regimen.Secondary ObjectivesThe key secondary objective is to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Blood and lymphatic system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON39872

Source
ToetsingOnline

Brief title
PROLONGATE - PEGylated rFVIII (BAX 855) in Hemophilia A

Condition

- Blood and lymphatic system disorders congenital

Synonym
Severe hemophilia A

Research involving
Human

Sponsors and support

Primary sponsor: Baxter
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: BAX 855, Open label study, Phase 2/3, Severe Hemophilia A

Outcome measures

Primary outcome

The primary outcome measure is the annualized bleed rate (ABR).

Secondary outcome

Efficacy

1. Rate of success of BAX 855 for treatment of bleeding episodes

2. Number of BAX 855 infusions needed for the treatment of bleeding episodes

3. Time intervals between bleeding episodes

4. Weight-adjusted consumption of BAX 855

Safety

1. Occurrence of AEs and SAEs

2. Changes in vital signs and clinical laboratory parameters (hematology,

clinical chemistry, and lipids)

3. Immunogenicity

- Inhibitory antibodies to FVIII

- Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG

- Anti-CHO antibodies

Patient Reported Outcomes

Changes from baseline in the following PROs:

1. Bleed and pain severity as measured using the Haemo-SYM questionnaire

2. Physical HRQoL as assessed using the SF-36 questionnaire

Pharmacokinetics

BAX 855 PK parameters based on FVIII levels following an initial single dose of

BAX 855 and after *50 EDs to BAX 855 (PK subset in Arm A)

1. Primary PK parameters:

- Plasma half-life (T1/2)

- MRT

- Total body clearance (CL)

- Incremental recovery over time (IR)

2. Other PK parameters:

- Area under the concentration versus time curve from 0 to infinity (AUC0-*)

- Apparent volume of distribution at steady state (Vss)

- Maximum plasma concentration Cmax

- Time to maximum concentration in plasma (Tmax)

Exploratory Outcomes Measures

1. Changes in the following PROs:

- Health utility as assessed using the EQ-5D

- Patient satisfaction/preference with treatment as assessed using the

Satisfaction Question Set

- Patient activity level

2. Health resource use

Study description

Background summary

Hemophilia A is an X-linked recessive, congenital bleeding disorder caused by deficient or defective coagulation FVIII. The absence of FVIII leads to 'spontaneous' bleeding episodes (occurring primarily in joints, muscles, and less commonly, in soft tissues) and to excessive bleeding following trauma or injury. Hemophilia A is currently treated with FVIII replacement using either plasma-derived (pdFVIII) or rFVIII concentrates.

The intended indication for BAX 855 is treatment and prevention of bleeding in subjects with hemophilia A. The study design is in compliance with EMA/CHMP/BPWP/144533/2009 recommendations for the study of FVIII in hemophilia A.

The investigational product (IP) in this study is BAX 855, a PEGylated recombinant FVIII (rFVIII), intended for use as a long-acting FVIII replacement therapy in prophylaxis and treatment of bleeding in patients with severe hemophilia A. Current management of severe hemophilia A includes on-demand treatment for bleeding events and prophylaxis to prevent bleeds. Since the half-life of current FVIII products is in the range of 12-14 h, current prophylaxis regimens call for infusion of FVIII every other day, or every 2-3 days when based on each patient*s individual PK profile. PEGylation of FVIII is designed to prolong the half-life of FVIII, with the intent of reducing the frequency of administration while maintaining similar therapeutic benefit as existing FVIII products; improving patient convenience and compliance with therapy; and thereby, improving overall health outcomes.

Study objective

Primary Objective
The primary objective is to compare the annualized rates of bleeding episodes (ABR)

between subjects receiving a prophylactic regimen of BAX 855 with an on-demand treatment regimen.

Secondary Objectives
The key secondary objective is to estimate the rate of success of BAX 855 for treatment
of bleeding episodes.
- To characterize the success of BAX 855 for treatment of bleeding episodes through the number of BAX 855 infusions needed for the treatment of a bleeding episode and through the length of intervals between bleeding episodes
- To compare the total weight-adjusted consumption of BAX 855 for each regimen
- To determine the immunogenicity of BAX 855
- To determine the safety of BAX 855
- To assess Health-Related Quality of Life (HRQoL) over time for subjects receiving BAX 855
- To assess health utility, using the EQ-5D, patient satisfaction, patient activity
levels and health resource use, over time for subjects receiving BAX 855

Study design

This study is a Phase 2/3, multicenter, open label, 2-arm study in a total of approximately 132 adolescent (12 - <18 years) and adult (* 18 to 65 yrs) male PTPs with severe hemophilia A to evaluate efficacy, safety, and PK of BAX 855 and HRQoL in subjects receiving BAX 855. Subjects will be enrolled into 1 of 2 arms: prophylaxis with BAX 855 at a dose of 45 IU/kg twice weekly (Arm A) or ondemand therapy with BAX 855 at a dose of 10-60 IU/kg dose (Arm B). A group of 25 subjects will be included as a PK subgroup of Arm A.

For an elaborate overview, please see protocol section 8.

For the Netherlands only the Adults group is applicable.

Intervention

This is a non-randomized, open-label, treatment regimen comparison clinical study.
Subjects will be assigned to prophylaxis (Arm A) or on-demand treatment (Arm B), based upon the type of Factor VIII treatment they received prior to enrollment. Subjects currently receiving prophylaxis will be assigned to the prophylaxis arm (Arm A). Subjects who were previously receiving on-demand therapy will be assigned to the ondemand arm (Arm B). Once the on-demand arm is complete (17 subjects assigned), subjects who had been receiving on-demand treatment prior to study enrollment will be assigned to prophylactic treatment (Arm A).
The 2 treatment arms are as follows:

* Arm A: Prophylaxis with BAX 855 administered twice weekly (ie, every 3-4 days) at a dose of 45 ± 5 IU/kg for *50 EDs (N=115 subjects assigned)
* Arm B: On-demand therapy with BAX 855 at a dose of 10-60 ± 5 IU/kg for an approximate duration of 6 months (N=17 subjects assigned)

Study burden and risks

Preclinical study results suggest that BAX 855 has a comparable safety profile to ADVATE. A safety profile similar to ADVATE is expected for BAX 855 when infused in humans. The most commonly reported adverse drug reactions described for ADVATE in post-marketing clinical studies include: FVIII inhibitors, pyrexia, and headache. Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE and have been manifested by dizziness, paresthesia, rash, flushing, face swelling, urticaria, and pruritus. Additional safety experience for ADVATE is provided in the ADVATE IB.

Since BAX 855 is a PEGylated form of ADVATE, it is possible that additional toxicity related to PEG may be observed. BAX 855 may react with preexisting anti-PEG antibodies, resulting in a clinical hypersensitivity reaction. There is also the potential risk of inducing anti-PEG or anti-BAX 855 antibodies following BAX 855 administration. The PEG component of BAX 855 may become dissociated from the FVIII molecule when incorporated into tissues. This accumulation can lead to formation of macrophage foam cells, which function to actively remove the PEG molecules. In reclinical studies, the presence of these *foamy macrophages* has not been associated with any adverse effects. To date, BAX 855 has been administered as a single dose of 30 IU/kg to 9 subjects and a single dose of 60 IU/kg to 10 subjects with severe hemophilia A in a Phase 1 study (Baxter clinical study 261101).

Based on data from this study, there currently are no anticipated risks of BAX 855, beyond those associated with ADVATE, when administered in human subjects. Additional details related to risks and benefits can be found in the BAX 855 IB.

Based on the comparability of BAX 855 to ADVATE, the preclinical safety profile of BAX 855, and the data from the Phase 1 study, Baxter believes that the risk benefit profile for BAX 855 is acceptable.
Based on the data from Phase 1, BAX 855 appears to be safe and well tolerated after single doseadministration. The mean T1/2 was 1.4 and 1.5-fold higher for BAX 855 compared to ADVATE in Cohorts 1 and 2, demonstrating prolonged circulation of BAX 855 compared to ADVATE. Dosing must be administered twice weekly, at 3 and 4 day intervals.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Subject and/or legal representative has/have voluntarily provided signed informed consent
- Subject is 12 to 65 years old at the time of screening
- Subject is male with severe hemophilia A (FVIII clotting activity < 1%) as confirmed by central laboratory at screening after the appropriate washout period or a documented FVIII clotting activity <1%
- Subject has been previously treated with plasma-derived FVIII concentrates or recombinant FVIII for *150 documented exposure days (EDs)
- Subject is currently receiving prophylaxis or on-demand therapy with FVIII
- Subject has a Karnofsky performance score of * 60 at screening (Table 6)
- Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count > 200 cells/mm3, as confirmed by central laboratory at screening
- Subject is hepatitis C virus negative (HCV-) by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis

- Subject is willing and able to comply with the requirements of the protocol

Exclusion criteria

- Subject has detectable FVIII inhibitory antibodies (* 0.4 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening
- Subject has history of FVIII inhibitory antibodies (* 0.4 BU using the Nijmegen modification of the Bethesda assay or * 0.6 BU using the Bethesda assay) at any time prior to screening
- Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand*s disease).
- Subject has known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80
- Subject has severe chronic hepatic dysfunction [eg, *5 times upper limit of normal alanine aminotransferase (ALT), as confirmed by central laboratory at screening, or a documented INR > 1.5]
- Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
- Subject has current or recent (< 30 days) use of other PEGylated drugs prior to study participation or is scheduled to use such drugs during study participation
- Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
- Subject has a medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance
- Subject is a family member or employee of the investigator

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):	06-12-2013

Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ADVATE
Generic name:	Antihemophilic Factor, Recombinant (rFVIII)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	BAX 855

Ethics review

Approved WMO Date:	17-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-003599-38-NL
ClinicalTrials.gov	NCT01736475
CCMO	NL42730.018.13