A Phase 3b Continuation study of the Safety and Efficacy of PEGylated Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in Previously Treated Patients with Severe Hemophilia A

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Study Purpose* To continue the evaluation of the safety and efficacy of prophylaxis with BAX 855 for the prevention and treatment of bleeding episodes in PTPs (children and adults from 0 to 75 years of age) with severe hemophilia A.Primary...

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

Summary

ID

NL-OMON45192

Source
ToetsingOnline

Brief title
Continuation study of 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: Baxalta Innovations GmbH
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: BAX 855, Continuation study, Phase 3b, Severe Hemophilia A

Outcome measures

Primary outcome

Safety: Development of inhibitory antibodies to FVIII

Efficacy: Spontaneous ABR

Secondary outcome

Secondary Outcome Measure(s)

Efficacy

1. Total ABR (spontaneous and traumatic bleeding episodes)

2. Overall hemostatic efficacy rating of BAX 855 to treat bleeding episodes

3. Number of BAX 855 infusions to treat bleeding episodes

4. Time intervals between bleeding episodes

5. 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

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

b. Anti-CHO antibodies

Patient Reported Outcomes (PROs)

Changes from baseline in the parent study, if applicable, in the following:

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

2. HRQoL as assessed using the SF-36/PedsQL questionnaire

Exploratory Outcome Measure(s)

1. Patient satisfaction with treatment will be assessed using the Satisfaction

Question Set

2. Patient Activity Level

3. Health resource use data (eg, physician office visits, hospitalizations,

length of stay, days missed from work/school)

Study description

Background summary

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

Study Purpose
* To continue the evaluation of the safety and efficacy of prophylaxis with BAX 855 for the prevention and treatment of bleeding episodes in PTPs (children and adults from 0 to 75 years of age) with severe hemophilia A.

Primary Objective
The co-primary objectives of the study are:
1. To determine the safety of BAX 855 based on the incidence of FVIII inhibitory antibody development
2. To determine the efficacy of BAX 855 based on the annualized bleed rate (ABR) of spontaneous bleeding episodes (episodes not associated with trauma)

Secondary Objective(s)
Efficacy
1. To determine the total ABR (spontaneous and traumatic bleeding episodes)
2. To determine the overall hemostatic efficacy rate of BAX 855 for treatment of breakthrough bleeding episodes
3. To determine the length of intervals between bleeding episodes
4. To characterize the hemostatic efficacy of BAX 855 for treatment of bleeding episodes by the number of BAX 855 infusions for treatment
5. To determine total weight-adjusted consumption of BAX 855 for prophylaxis and for the treatment of bleeding episodes
6. To assess Patient Reported Outcomes (PROs) over time for subjects receiving BAX 855
Safety
1. To determine the safety of BAX 855, as assessed by the occurrence of AEs and changes in vital signs and clinical laboratory parameters
2. To determine the immunogenicity of BAX 855

Exploratory Objective
* To assess patient satisfaction, patient activity levels, and health resource

use over time for subjects receiving BAX 855

Study design

This is a phase 3b, prospective, open label, multi-center study to evaluate the safety and efficacy of BAX 855 for prophylactic use in approximately 200 male children and adult PTPs (0 to 75 years of age) with severe hemophilia A. The study plans to include subjects from other BAX 855 studies and BAX 855-naïve subjects. Subjects will receive BAX 855 for prophylaxis based on their previous treatment regimen and outcome for at least 100 EDs (as accumulated across all BAX 855 studies).
Other BAX 855 studies currently include the phase 2/3 pivotal study (Baxter clinical study 261201), surgery study (Baxter clinical study 261204), and pediatric PTP study (Baxter clinical study 261202).

Intervention

This is a phase 3b continuation study for safety and efficacy of PEGylated recombinant factor VIII (PEG-rFVIII; BAX 855) administred as profylaxis of bleedings in previously treated patients with severe hemophilia A.

The patients can continue after participation in a qualifying study (Prolongate 261201 (closed June 2014), Surgery 261204 and Pediatric study 261202), with the treatment schedule for BAX 855 as described in this study.

The patient can only use BAX 855 during study participation, for both prevention and treatment of bleedings. (per protocol Am 4)

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
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

SUBJECTS TRANSITIONING FROM OTHER BAX855 TRIALS:
Subjects transitioning from other BAX 855 studies who meet ALL of the following criteria are eligible for this study:
1. Subject has completed a previous BAX 855 study and is willing to immediately transition into this continuation study.
2. Subject is * 75 years of age at screening of the previous BAX 855study.
3. Subject continues to have a Karnofsky (for subjects aged * 16 years) or Lansky (for subjects aged
< 16 years) performance score of * 60 (see Section 20.5).
4. 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.
5. 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.
6. If female of childbearing potential, subject presents with a negative urine pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
7. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.;BAX 855 NAIVE SUBJECTS:
BAX 855 naïve subjects who are * 12 years of age can only be enrolled in this continuation study after enrollment in the phase 2/3 pivotal study is closed. BAX 855 naïve subjects who are * 12 years of age can only be enrolled in this continuation study after enrollment in the pediatric PTP study is closed.
Enrollment of BAX 55 naïve subjects will only start once the sponsor has notified the study sites accordingly.
BAX 855 naïve subjects who meet ALL of the following criteria are eligible for this study:
1. Subject is *75 years of age at screening.

2. Subject is naïve to BAX 855.
3. Subject has severe hemophilia A (FVIII clotting activity < 1%) as confirmed by central laboratory at screening after at least a 72-hour washout period.
4. Subject aged * 6 years has documented previous treatment with plasma-derived FVIII concentrates or rFVIII for * 150 EDs.
5. Subject aged < 6 years has documented previous treatment with plasma-derived FVIII concentrates or rFVIII for * 50 EDs.
6. Subject is currently receiving prophylaxis or on-demand therapy with FVIII.
7. Subject has a Karnofsky (for subjects aged * 16 years) or Lansky (for subjects aged < 16 years) performance score of * 60 (see Section 20.5).
8. Subject is HIV-; or HIV+ with stable disease and CD4+ count * 200 cells/mm3, as confirmed by central laboratory at screening.
9. Subject is 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.
10. If female of childbearing potential, subject presents with a negative urine pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
11. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.

Exclusion criteria

SUBJECTS TRANSITIONING FROM OTHER BAX855 STUDIES:
Subjects transitioning from other BAX 855 studies who meet ANY of the following criteria are not eligible for this study:
1. Subject had detectable FVIII inhibitory antibodies (* 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.
2. Subject has developed FVIII inhibitory antibodies (* 0.6 BU using the Nijmegen modification of the Bethesda assay as determined at central laboratory in a previous BAX 855 study).
3. Subject has acquired a hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease) in a previous BAX 855 study.
4. Subject has severe chronic hepatic dysfunction (eg, * 5 times upper limit of normal alanine aminotransferase [ALT], as confirmed by central laboratory at screening).
5. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
6. Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry.
7. Subject is scheduled to use other PEGylated drugs during study participation.
8. Subject is planning to take part in any other clinical study during the course of the continuation study, with the exception of any other parallel BAX 855 study.
9. Subject has medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
10. Subject is a family member or employee of the investigator.;BAX 855 NAIVE SUBJECTS:
BAX 855 naïve subjects who meet ANY of the following criteria are not eligible for this study:
1. Subject has detectable FVIII inhibitory antibodies (* 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.

2. Subject has history of FVIII inhibitory antibodies (* 0.6 BU using the Nijmegen modification of the Bethesda assay or the Bethesda assay) at any time prior to screening.
3. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease).
4. Subject has known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80.
5. Subject has severe chronic hepatic dysfunction (eg, * 5 times upper limit of normal ALT, as confirmed by central laboratory at screening).
6. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
7. Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry.
8. Subject has current or recent (< 30 days) use of other PEGylated drugs prior to study participation or scheduled use of such drugs during study participation.
9. Subject has participated in another clinical study involving an IP other than BAX 855 or 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.
10. Subject has medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
11. 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:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-06-2014
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	PEGylated rFVIII

Ethics review

Approved WMO Date:	06-01-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2016

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2018
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	EUCTR2013-002236-24-NL
ClinicalTrials.gov	NCT01945593
CCMO	NL46584.018.13