A phase 3 prospective, uncontrolled, multicenter study evaluating pharmacokinetics, efficacy, safety, and immunogenicity of BAX 855 (PEGylated full-length Recombinant FVIII) in previously treated pediatric patients with severe hemophilia A

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7.2 Primary ObjectiveThe primary objective is to assess the incidence of FVIII inhibitory antibodies(>=0.6 Bethesda units [BU] using the Nijmegen modification of the Bethesda assay).7.3 Secondary Objectives1. To evaluate the PK parameters of BAX...

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

Summary

ID

NL-OMON41794

Source
ToetsingOnline

Brief title
BAX 855 Pediatric

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, Pediatric study, Phase 3, Severe Hemophilia A

Outcome measures

Primary outcome

The incidence of FVIII inhibitory antibodies (>=0.6 BU using the Nijmegen modification of the Bethesda assay).

Secondary outcome

Pharmacokinetics

1. Area under the plasma concentration versus time curve from 0 to * hours post-infusion (AUC0-*), AUC0-*/dose, mean residence time, clearance, IR, elimination phase half-life, volume of distribution at steady state following an initial dose of ADVATE followed by BAX 855.

2. IR over time.

Hemostatic Efficacy

1. Annualized bleeding rate (ABR).

2. Consumption of BAX 855: number of infusions and weight-adjusted consumption per month and per year.

3. Number of infusions per bleeding episode, overall hemostatic efficacy rating at resolution of bleed.

4. Weight-adjusted consumption per bleeding episode.

Safety

1. All AEs and SAEs possibly or probably related to BAX 855.

2. Clinical significant changes in vital signs (pulse, respiration, supine

blood pressure, and temperature) and clinical laboratory parameters

(hematology, clinical chemistry, and lipids).

3. Assessment of binding antibodies to FVIII, BAX 855, PEG, and CHO.

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 investigational product (IP), BAX 855, is a novel polyethylene glycol (PEG)-ylated full-length recombinant Factor VIII (rFVIII) molecule. BAX 855 is intended for use as a Factor VIII (FVIII) replacement therapy with extended half-life in prophylaxis and treatment of bleeding events in subjects 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.

The clinical development program for BAX 855 follows the European Medicines

Agency (EMA) guidance outlined in EMA/CHMP/BPWP/144533/2009, and consists of 1 completed, 3 ongoing and 3 planned studies. A Phase 1 study (Baxter Clinical Study 261101) has been completed, and the results showed that BAX 855 was safe and well tolerated.

A Phase 3 pivotal study is ongoing since January 2013 (protocol 261201, METC 2013_102) and investigates PK properties in 25 subjects of whom at least 6 subjects are adolescents, as well as hemostatic efficacy, safety and immunogenicity in approximately 132 subjects (approximately 115 receiving prophylactic treatment and apporximately 17 receiving on-demand treatment) in the control and prophylaxis of bleeding episodes in previously treated patients (PTPs) with severe hemophilia A >= 12 years of age. (note: global EoT has been reported on 02Sep2014).
The Phase 3 Continuation study 261302 (METC 2014_023) will further evaluate safety, immunogenicity, and hemostatic efficacy of BAX 855, and health-related quality of life over a prolonged period of time. This study will include subjects transferring from a BAX 855 study upon completion as well as newly recruited subjects.
A Phase 3 study to evaluate the efficacy and safety of BAX 855 in the perioperative management in subjects undergoing major elective and minor emergency or elective surgical/invasive procedures is currently ongoing (Baxter Clinical Study 261204, METC 2014_109).
More studies are to follow.

Study objective

7.2 Primary Objective
The primary objective is to assess the incidence of FVIII inhibitory antibodies (>=0.6 Bethesda units [BU] using the Nijmegen modification of the Bethesda assay).

7.3 Secondary Objectives
1. To evaluate the PK parameters of BAX 855 in pediatric PTPs <12 years of age.
2. To monitor IR of BAX 855 over time.
3. To evaluate hemostatic efficacy of BAX 855 in the management of acute bleeding
episodes and for prophylaxis over a period of 6 months.
4. To assess all adverse events (AEs) possibly or probably related to BAX 855.
5. To evaluate immunogenicity (binding antibodies to FVIII, BAX 855, PEG, and CHO) and clinically significant changes in routine laboratory parameters (hematology, clinical chemistry, and lipids) and vital signs.

Exploratory objective(s)
1. To evaluate changes in HRQoL and health resource use.

Study design

This study is a Phase 3, prospective, uncontrolled, multicenter, open label study to investigate PK, hemostatic efficacy, safety, immunogenicity, and HRQoL in a total of 60 pediatric PTPs with severe hemophilia A. All subjects will receive twice weekly prophylactic treatment with 50 ±10 IU/kg of BAX 855 over a period of 6 months or at least 50 EDs, whichever occurs last.
There will be 2 age cohorts of 30 subjects each (25 evaluable), with the following age range: <6 years and >=6 to <12 years.
A subset of 14 subjects (12 evaluable) within each age cohort will participate in the PK portion of the study: prior to the start of the 6-month prophylactic treatment they will undergo a PK analysis with a single dose of 60 ±5 IU/kg ADVATE followed by a single dose of 60 ±5 IU/kg BAX 855. All subjects participating in the PK portion of the study will have one pre-infusion blood draw and 3 post infusion blood draws. The latter will be randomly selected from 3 choices for each blood draw.

Intervention

This is an open label study consisting of 2 age groups. Patients will receive a profylaxis treatment with BAX 855 for about 6 months.

The patient can only use BAX 855 during the study, both for prevention as for on demand treatment of bleads.

The patient can participate in a PK sub study, for which addition blood tests will be done.

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
Children (2-11 years)

Inclusion criteria

1. The subject has severe hemophilia A (FVIII <1%) as determined by the central laboratory or a historical FVIII level <1% as determined at any local laboratory and/or a FVIII gene mutation consistent with severe hemophila A.
2. Subject is <12 years old at the time of screening.
3. Subjects aged >=6 to <12 years of age have been previously treated with plasma-derived and/or rFVIII concentrate(s) for a minimum of 150 EDs (based on the subjects* medical records).
4. Subjects <6 years of age have been previously treated with plasma-derived and/or rFVIII concentrate(s) for at least 50 EDs (based on the subjects* medical records).
5. Subject is human immunodeficiency virus (HIV) negative; or HIV positive with stable disease and CD4+ count of >=200 cells/mm3, as confirmed by central laboratory.
6. The subject and/or legal representative accepts prophylactic treatment over a period of 6 months.
7. The subject and/or the legal representative is willing and able to comply with the requirements of the protocol.

Exclusion criteria

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 a confirmed history of FVIII inhibitory antibodies (>=0.6 BU using the Nijmegen modification of the Bethesda assay or >=0.6 BU using the Bethesda assay) at any time prior to screening.
3. Subject has known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80.
4. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand*s disease).
5. Subject*s platelet count is <100,000/µL.
6. Subject has severe chronic hepatic dysfunction (eg, >=5 times upper limit of normal [ULN] alanine aminotransferase as confirmed by central laboratory at screening, or a documented international normalized ratio >1.5).
7. Subject has severe renal impairment (serum creatinine >1.5 times ULN).
8. Subject is scheduled to receive during the course of the study, an immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone >10 mg/day, or α-interferon) other than anti-retroviral chemotherapy.
9. 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.
10. 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.
11. 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.
12. Subject*s legal representative is a member of the team conducting this study or is in a

dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

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):	06-03-2015
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:	PEGylated rFVIII

Ethics review

Approved WMO

Date:	01-10-2014

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2015
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	EUCTR2014-000742-30-NL
ClinicalTrials.gov	NCT02210091
CCMO	NL50120.018.14