A Phase 3, Multi-Center, Open Label Study of Efficacy and Safety of PEGylated rFVIII (BAX 855) in Previously Treated Patients With Severe Hemophilia A Undergoing Surgical or Other Invasive Procedures

Published: 03-04-2014
Last updated: 20-04-2024

The primary objective is to evaluate the peri-operative hemostatic efficacy of BAX 855 in male PTPs aged 18 - 75 years with severe hemophilia A (FVIII

Ethical review	Approved WMO
Status	Will not start
Health condition type	Blood and lymphatic system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON44734

Source
ToetsingOnline

Brief title
SURGERY - BAX 855 in Hemophilia A Patients Undergoing Surgical Procedures

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, Phase 3 open label, Severe Hemophilia A, Surgical procedures

Outcome measures

Primary outcome

Global Hemostatic Efficacy score, which is composed of 3 individual ratings:

1. Assessment of intra-operative hemostatic efficacy of BAX855 performed by the operating surgeon

2. Assessment of postoperative hemostatic efficacy of BAX855 at postoperative day 1 performed by the operating surgeon

3. Assessment of postoperative hemostatic efficacy of BAX855 at EOS visit performed by the investigator, at discharge or Day 14 , whichever is first.

Secondary outcome

EFFICACY:

* Intra- and post-operative blood loss at the end of surgery, at postoperative Day 1 and until discharge or Day 14 (whichever is first), as applicable, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon

* Volume of blood, red blood cells, platelets, and other blood products transfused

* Occurrence of bleeding episodes and additional need for surgical intervention

* Daily and total weight-adjusted consumption of BAX 855 per subject

SAFETY:

* Incidence of inhibitory antibodies to FVIII

* Development of binding antibodies to FVIII, BAX 855, and PEG

* Development of binding antibodies to CHO proteins

* Occurrence of thrombotic events

* Incidence of severe allergic reactions (e.g. anaphylaxis)

* Other IP-related adverse events (AEs)

* Incidence of clinically significant changes in vital signs and routine

laboratory parameters (hematology, clinical chemistry)

PHARMACOKINETICS

* Presurgical PK (only in subjects undergoing major elective surgery who did

not undergo a PK assessment in previous BAX 855 study)

* Incremental recovery (IR), area under the plasma concentration /time curve

from time 0 to infinity (AUC0-*), area under the plasma concentration versus

time curve from 0 to 96 h (AUC0-96h) terminal half *life (T1/2), mean residence

team (MRT), clearance (CL), volume of

distribution at steady state (Vss) will be calculated.

* Incremental recovery (IR) following the initial bolus infusion prior to

surgery

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) 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.

The study design is in compliance with EMA/CHMP/BPWP/144533/2009 recommendations for the study of FVIII in hemophilia A, 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) and investigates PK properties in 25 subjects of whom at least 6 subjects are adolescents, as well as hemostatic efficacy, safety and immunogenicity in the control and prophylaxis of bleeding episodes in a total of 143 previously treated patients (PTPs) with severe hemophilia A * 12 years of age.
The Phase 3 continuation study 261302 will further evaluate safety, immunogenicity, and hemostatic efficacy of BAX 855, and health-related quality of life over a prolonged period of time.

Study objective

The primary objective is to evaluate the peri-operative hemostatic efficacy of BAX 855 in male PTPs aged 18 - 75 years with severe hemophilia A (FVIII <1%) undergoing major or minor, elective or minor emergency surgical, dental or

other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.

Secondary Objective(s)
* Efficacy
- To determine intra- and post-operative blood loss, volume of blood, red blood cells, platelets, and other blood products transfused, the occurrence of bleeding episodes and additional need for surgical intervention, and daily and total weight-adjusted consumption of BAX 855 per subject

* Safety
- To determine the safety of BAX 855 in subjects undergoing surgery, as assessed by occurrence of AEs and changes in vital signs and clinical laboratory parameters

* Pharmacokinetics
- To determine PK parameters prior to major surgeries,
- To determine IR following the initial bolus infusion prior to surgery

Study design

This is a Phase 3 prospective, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 855 in male PTPs 18 -75 years of age, with severe hemophilia A (FVIII <1%). Subjects will have no history of FVIII inhibitors and will be undergoing, major or minor elective, or minor emergency surgical, dental or other invasive procedures.
Eligible subjects may be actively participating in or have completed participation in another BAX 855 study or may be newly recruited; however newly-recruited subjects will not be enrolled if they require minor emergency and minor elective surgeries.
Elective surgical procedures will prospectively be defined as major or minor by the investigator/surgeon and agreed with the medical director or designee, based on the protocol guidance and definitions and in consideration of each subject*s characteristics. Major emergency surgeries are not in the scope of this study.
Subjects may undergo more than one surgery or 2 parallel surgeries, such as bilateral knee replacement, however in these cases prior approval by the sponsor is required.

The study will be conducted globally and will be divided into 5 periods: Screening, Preoperative including PK assessment, Intraoperative, Postoperative, and End of study.

Intervention

This is a phase 3 studie to the efficaty and safety of PEGylated recombinant FVIII (BAX 855) adminsitered to Previously treated patients (PTPs) with severe hemophilia A (FVIII <1%) undergoing elective surgical procedures

The (most) standard treatment for this population is ADVATE (rFVIII). the investigational product BAX 855 has not yet been used during intervention.

Study burden and risks

Patient will be treated with investigational product during surgery, for which he
- normally received his standard FVIII treatment. The patient can enter the follow-up study afterwards (261302)
- or already participate in another BAX 855 study and therefore already receive BAX 855 treatment.
Additional blood samples will be taken to follow the course of the treatment, and see how the body responds to BAX 855.

Contacts

Public
Baxalta Innovations GmbH

Industriestrasse 67
Vienna A-1221
AT
Scientific
Baxalta Innovations GmbH

Industriestrasse 67
Vienna A-1221
AT

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject requires an elective major surgical, dental or other invasive procedure (e.g. biopsy, endoscopy).
2. Subject and/or legal representative has/have provided signed informed consent.
3. Subject is 18 to 75 years of age at the time of enrollment.
4. Subject is male with severe hemophilia A (FVIII level <1%) as confirmed by the central lab at screening.
5. Subject was previously treated with FVIII concentrates with *150 documented exposure days (EDs).
6. Subject is currently receiving prophylaxis or on-demand therapy with FVIII concentrate.
7. Subject has a Karnofsky performance score of *60 at screening.
8. 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.
9. Subject is Hepatitis C virus negative (HCV-) by antibody or PCR testing, as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis as assessed by the investigator. If positive, antibody titer will be confirmed by PCR.
10. Subject is willing and able to comply with the requirements of the study protocol.
11. For subjects transitioning from parent BAX 855 studies, the subjects continue to meet the entry criteria

Exclusion criteria

1. Subject has detectable FVIII inhibitory antibodies (*0.4 BU using the Nijmegen modification of the Bethesda assay) at screening as determined by the central laboratory or at any timepoint prior to screening (*0.4 BU using the Nijmegen modification of the Bethesda assay or *0.6 BU using the Bethesda assay).
2. History of ongoing or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC).
3. Subject has a platelet count <100 x 109/L, as confirmed by central laboratory at screening.
4. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
5. Subject has severe chronic hepatic dysfunction (eg *5 X upper limit of normal alanine aminotransferase (ALT), as confirmed by central laboratory at screening, or a documented INR > 1.5).
6. Subject has a known hypersensitivity towards mouse or hamster proteins, polysorbate 80 or to PEG.
7. Subject is currently using or has recently (< 30 days) used pegylated drugs (other than

BAX855) prior to study participation or is scheduled to use such drugs during trial participation.
8. Subject is currently participating in another clinical drug (other than BAX855) or device study or use of another investigational product or device within 30 days prior to study entry.
9. Subject has a diagnosis of an inherited or acquired hemostatic defect other than hemophilia A.
10. Subject is currently receiving, or scheduled to receive during the course of the study, an immunomodulating drug (e.g., systemic corticosteroid agent at a dose equivalent to hydrocortisone greater than 10 mg/day, or alpha interferon) other than anti-retroviral chemotherapy.
11. Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
12. The subject has an incremental recovery < 1.5 IU/dL:IU/kg as determined in the parent study, if applicable
13. Subjects undergoing minor of major emergency surgery

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	1
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	BAX 855

Ethics review

Approved WMO Date:	03-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2016
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	EUCTR2013-001359-11-NL
ClinicalTrials.gov	NCT#pending
CCMO	NL45421.018.14