A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

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To evaluate the perioperative hemostatic efficacy of BAX 802 in male subjects with CHA with inhibitors to human factor VIII (hFVIII) undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Platelet disorders
Study type	Observational non invasive

Summary

ID

NL-OMON47364

Source
ToetsingOnline

Brief title
BAX 802 in Congenital Hemophilia A with Inhibitors

Condition

- Platelet disorders
- Blood and lymphatic system disorders congenital

Synonym
Hemophilia A; bleeding disorder

Research involving
Human

Sponsors and support

Primary sponsor: Baxter
Source(s) of monetary or material Support: Baxalta Innovations GmbH is paying for the costs of this study.

Intervention

Keyword: BAX802, FVIII inhibitor, Hemophilia, Invasive Procedures

Outcome measures

Primary outcome

The primary outcome measure is the proportion of all surgical, dental, or other invasive procedures with a "good"or "excellent"response as measured by GHEA score, which is composed of 3 individual ratings:

- GHEA1: Assessment of intraoperative (Day 0) hemostatic efficacy of BAX 802 performed by the operating surgeon at the end of surgery.
- GHEA2: Assessment of postoperative hemostatic efficacy of BAX 802 at postoperative Day 1 (approximately 24 hours (+ / - 6 hours) post-surgery performed by the operating surgeon. Note: If a patient is discharged <24 hours following surgery, then the GHEA2 hemostatic efficacy assessment will require a return visit the following day.
-GHEA3: Assessment of overall perioperative hemostatic efficacy of BAX 802 at the GHEA3 Visit (discharge or within 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is earlier), performed by

the investigator, and where possible, also by the operating surgeon. Assessment by both is strongly recommended. In cases where there are differing assessments, the Investigator's assessment will be used.

The scores of each of the 3 individual ratings (GHEA1, GHEA2, GHEA3) described above, will be added together to form a GHEA score.

Secondary outcome

Efficacy

1. Intra -and post-operative blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual with similar demographic characteristics as predicted preoperatively by the investigator/surgeon at the following time points:

* Intraoperative, from start until the end of surgery
* Postoperative Day 1, from end of surgery to approximately 24 hours (+ /- 6 hours) after surgery
* Overall perioperative at discharge or 24 to 72 hours after the last perioperative treatment dose of BAX802 (whichever is earlier)

2. Proportion of major surgeries with good or excellent hemostatic score
3. Daily and total weight-adjusted administration of BAX 802 per subject
4. Amount of blood products (e.g whole blood, red blood cells, platelets, and

plasma transfused

Safety

1. Development of, and changes to, the titer of inhibitory and binding

antibodies (IgG and IgM) to PFVIII

2. Development of, and changes to, the titer of inhibitory and binding

antibodies (IgG and IgM) to to hFVIII

3. Development of binding antibodies to BHK proteins

4. Occurrence of thrombo-embolic events

5. Incidence of severe allergic reactions (eg, anaphylaxis)

6. Incidence of other IP-related AEs

7. Incidence of clinically significant changes in vital signs and routine

laboratory parameters (hematology, clinical chemistry)

Study description

Background summary

The investigational product (IP), BAX 802, is a recombinant form of porcine factor VIII (rpFVIII) from which the B domain has been deleted. Deletion of the B domain does not affect the safety or efficacy of this recombinant form of human factor VIII (rhFVIII) in the treatment of hemophilia A. BAX 802 (rpFVIII) is being developed for the perioperative management of hemostasis in subjects with congenital hemophilia A (CHA) with inhibitors to human factor VIII (hFVIII) undergoing surgical or other invasive procedures. This rpFVIII was approved by the United States Food and Drug Administration (FDA) in 2014 for the treatment of bleeding episodes in adults with acquired hemophilia A (AHA; non hemophilia subjects developing spontaneous autoantibody inhibitors to hFVIII) under the trade name OBIZUR®.

Study objective

To evaluate the perioperative hemostatic efficacy of BAX 802 in male subjects with CHA with inhibitors to human factor VIII (hFVIII) undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.

Study design

This study is a Phase 3, uncontrolled, open-label, single-group, multicenter study to determine the safety and efficacy of BAX 802 in at least 10 surgeries in 10 evaluable male subjects with CHA with inhibitors to hFVIII who are undergoing major or minor elective surgical, dental, or other invasive procedures (at least 5 major surgeries in 5 evaluable subjects).

Intervention

BAX 802 will be administered as an intravenous infusion per the dosing schema for major and minor surgeries. Based on the category (minor or major) and type of surgery, the investigator must outline the expected FVIII maintenance plan with target peak and trough levels covering the
surgical, dental or invasive procedure until expected wound healing.
Loading Dose of BAX 802:
* Major Surgery: 80 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII inhibitor titer (BU), administered approximately 1 to 2 hours prior to the surgery
* Minor Surgery: 50 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII inhibitor titer (BU), administered approximately 1 to 2 hours prior to the surgery
Subsequent doses, dosing frequency, and duration of treatment will be based on the clinical judgment and measured FVIII levels achieved, and will require empirically based adjustments until hemostasis is achieved based on the following calculation:
Required dose (U) = [body weight (kg) x desired FVIII rise (U/dL or % of normal)]/1.2 (U/kg per U/dL).

Study burden and risks

OBIZUR® was approved based on the safety and efficacy data from 28 subjects with AHA treated with B-domain deleted rpFVIII glycoprotein in the Phase 2/3 open-label clinical study OBI-1-301. The safety, hemostatic activity, and PK profile of B-domain deleted rpFVIII glycoprotein was also supported by results of an open-label Phase 2 study in patients with CHA with inhibitors (CSR OBI-1-201), and a randomized Phase 1 study comparing B-domain deleted rpFVIII glycoprotein with a plasma-derived pFVIII (CSR OBI-1-101).

Overall, efficacy and safety clinical data for OBIZUR supported a favorable benefit/risk determination for the proposed indication of treatment of bleeding

episodes in adults with AHA. These data support the investigation of efficacy and safety of BAX 802 in subjects with CHA with inhibitors undergoing surgical or other invasive procedures.

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

1. Subject requires a major or minor elective surgical, dental or other invasive procedure.
2. Subject is male * 12 to * 75 years old at the time of screening
3. Subject has provided signed informed consent (and assent for adolescent subjects, as applicable) in accordance with local regulatory requirements
4. Subject has severe (FVIII level < 1%) or moderately severe (FVIII level * 2%) CHA with inhibitors to hfVIII of * 0.6 BU, as tested at screening at the central laboratory

5. Subject is not currently receiving or has received (< 30 days) ITI therapy
6. Subject has a Karnofsky performance score of * 60 at screening
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count * 200 cells/mm3 at screening
8. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease. Positive serologies will be confirmed by PCR testing.
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion criteria

1. The subject requires emergency surgery
2. Severe chronic liver dysfunction or disease (eg, * 5 X upper limit of normal (ULN) alaine aminotransferase (ALT), as confirmed by central laboratory at screening or a documented prothrombin time/international normalized ration (PT/INR) >1.5)
3. Clinically symptomatic renal disease (serum creatinine > 2.0 mg/dl), as confirmed by central laboratory at screening
4. Anti-porcine inhibitor > 10 BU prior to surgery
5. Platelet count < 100,000/*L at screening
6. Subject has another active coagulation disorder other than hemophilia A, as per the medical history
7. Planned use of *-interferon with or without ribavarin for HCV infected patients or planned use of a protease inhibitor for HIV infected patients. Patients currently taking any of these medications for * 30 days are eligible
8. Known hypersensitivity to rpFVIII, or hamster or murine proteins
9. Subject has an ongoing or recent (within 3 months of screening) thrombo-embolic disease, fibrinolysis, or disseminated intravascular coagulation (DIC)
10. Subject has been exposed to an IP 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 is unable to tolerate quantity of blood to be drawn for protocol procedures
12. Subject is a family member or employee of the investigator.

Study design

Design

Study phase:	3
Study type:	Observational non invasive
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-12-2016
Enrollment:	1
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Obizur
Generic name:	Obizur
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-09-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-11-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-04-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-05-2019

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-01-2020
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2015-005521-39-NL
CCMO	NL56865.041.16