A Phase 1, Prospective, Open Label, Two Period, Fixed Sequence, Dose-Escalation Study of the PK and Safety of BAX 826 (PSA-rFVIII) in Previously Treated Patients with Severe (FVIII <1%) Hemophilia A: Protocol number: 291501

Published: 04-01-2016
Last updated: 20-04-2024

1. To assess tolerability and safety of BAX 826 after a single infusion in previously PTPs with severe hemophilia A.2. To determine the pharmacokinetic (PK) parameters of BAX 826 compared to ADVATE.3. To evaluate the impact of anti- PSA antibodies...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Platelet disorders
Study type	Interventional

Summary

ID

NL-OMON43447

Source
ToetsingOnline

Brief title
BAX 826 Dose Escalation Safety Study

Condition

- Platelet disorders

Synonym
Hemophilia A; bleeder's disease

Research involving

Human

Sponsors and support

Primary sponsor: Baxter
Source(s) of monetary or material Support: Industry - Baxalta

Intervention

Keyword: Dose-Escalation, Hemophilia A, Phase 1, Severe

Outcome measures

Primary outcome

Primary Analysis

Adverse Events

Adverse events occurring up to 6 weeks±4 days (Visit 4) after infusion with BAX

826 and ADVATE

(the number of AEs [including the number of product related serious and

non-serious AEs] and the

number/proportion of subjects) will be summarized by treatment.

Safety and Tolerability

Vital signs and clinical laboratory assessments will be summarized

descriptively by treatment and cohort at

each scheduled assessment and for the corresponding change from baseline. Shift

tables will also be

presented for clinical laboratory assessments by treatment and cohort at each

scheduled assessment.

Immunogenicity

The number and proportion of subjects will be summarized by treatment for

developing the following:

inhibitory antibodies to FVIII (Nijmegen assay), binding antibodies to BAX 826 (IgG and IgM), total binding antibodies to FVIII (IgG and IgM), anti-PSA antibodies (IgG and IgM), anti-CHO antibodies and anti-HAMA antibodies.

Secondary outcome

Pharmacokinetic

Pharmacokinetic parameters will be calculated using non-compartmental methods and summarized descriptively by treatment: AUC0-*, t1/2, *z, MRT, CL, IR, Vss, Cmax, tmax, AUC0-last and truncated AUCs ([AUC0-72h] and [AUC0-168h] for BAX 826 only).

The ratios of t1/2, MRT and CL between the 2 treatment periods will be computed for each subject and summarized descriptively by cohort.

Log*transformed PK parameters AUC0-*, AUC0-72h, Cmax, t1/2, MRT and CL will be analyzed by cohort for treatment comparison using a linear mixed-effects model with treatment as a fixed effect and subject as a random effect.

Plots of individual and geometric mean and median PK parameters AUC0-*, AUC0-last and Cmax versus dose (both linear and log scale) will be presented, as appropriate. The dose

proportionality of the PK parameters

AUC0-*, AUC0-last and Cmax for BAX 826, over the administered dose range, will

be explored using the

power model.

Exploratory Analysis

Data from the thrombin generation assay will be evaluated to determine the

impact of BAX 826

administration on global hemostasis. The assessments will be summarized

descriptively by treatment at

each scheduled assessment.

The correlation between pre-infusion VWF antigen and BAX 826 t1/2 will be

assessed using appropriate

scatter plots and correlation coefficients. The ratio of pre-infusion VWF

antigen concentrations between the

2 treatment periods will be computed for each subject and descriptive

statistics will be prepared for the

ratios by cohort.

Interim Safety Reviews

There is no planned interim analysis other than a safety and PK data review by

the SRC.

Study description

Background summary

This study is a phase 1 prospective, open label, first-in-man, 2 period, fixed sequence, dose-escalation study in PTPs (male subjects) with severe hemophilia A (FVIII levels <1%) to evaluate the safety and PK parameters of a single dose of BAX 826 compared to a single dose of ADVATE.
The target population is 30 evaluable adult male PTPs with severe hemophilia A (FVIII <1%). To achieve this number of evaluable subjects, it is anticipated that approximately 40 subjects will be enrolled. All eligible, enrolled subjects will receive investigational product unless they discontinue from the study prematurely. Evaluable subjects are subjects who have received at least 1 BAX 826 infusion and who are evaluable for PK for the BAX 826 infusion. Subjects are to remain on their standard treatment (during the screening and follow up period after the PK assessment) and should undergo a minimum 4-day (96-hour) washout period prior to the first ADVATE infusion. Similarly, subjects should revert back to their standard treatment if they have a bleeding episode and then undergo a minimum 4-day (96-hour) washout period before repeating the appropriate study regimen.

Study objective

1. To assess tolerability and safety of BAX 826 after a single infusion in previously PTPs with severe
hemophilia A.
2. To determine the pharmacokinetic (PK) parameters of BAX 826 compared to ADVATE.
3. To evaluate the impact of anti- PSA antibodies on PK parameters.

Study design

Phase 1. Open-label study.

Intervention

The study has 3 distinct cohorts, each of which will consist of 10 evaluable subjects:
- Cohort 1: Eligible subjects will receive an infusion of 25 ±3 IU/kg ADVATE. Following ADVATE infusion, subjects will undergo a minimum 4-day (96-hour) washout period, which includes a 3-day PK evaluation. Following the washout period, subjects will receive a single dose of BAX 826, equivalent to the ADVATE dose they have received, followed by a 7-day PK evaluation.
- Cohort 2: After the data from Cohort 1 have been reviewed and subject to approval by the internal Baxalta Safety Review Committee (SRC), Cohort 2 will receive an infusion of 50 ±5 IU/kg ADVATE. Following the ADVATE infusion, subjects will undergo a minimum 4-day (96-hour) washout period, which includes a 3-day PK evaluation. Following the washout period, subjects will receive a

single dose of BAX 826, equivalent to the ADVATE dose they have received, followed by a 7-day PK evaluation.
- Cohort 3: After the data from Cohort 2 have been reviewed and subject to approval by the SRC, Cohort 3 will receive an infusion of 75 ±5 IU/kg ADVATE. Following the ADVATE infusion, subjects will undergo a minimum 4-day (96-hour) washout period, which includes a 3-day PK evaluation. Following the washout period, subjects will receive a single dose of BAX 826, equivalent to the ADVATE dose they have received, followed by a 7-day PK evaluation.

In Cohort 1, the first human dose of BAX 826 (25 IU/kg) will be administered to the first 3 subjects with a minimum 24-hour staggered interval. The safety of these 3 subjects will be assessed over a minimum of 24 hours' of in-hospital observation. Further subjects in Cohort 1 will only be infused with BAX 826 once it has been confirmed by the SRC that there were no acute post-infusion reactions or safety issues for the first 3 subjects. Subjects should remain at the study site for 12 hours post-infusion, where after they can leave and come back for the following day for the 24-hour PK sampling. Subjects could be screened for the next cohort before the final SRC approval, but the dosing for the next cohort should not start until the SRC has provided approval.

Study burden and risks

An immunological risk assessment revealed that the risk of hemophilia A patients without a history of neutralizing antibodies against FVIII (the patient population of the
phase 1 study) to develop or boost anti-2,8 PSA antibodies after a single dose of
BAX 826 is considered to be low. Moreover, abundant and striking data from in vivo
animal models and clinical trials suggest that anti-2,8 PSA antibodies are non-pathogenic.
Results of the nonclinical safety studies indicated that there are high safety margins compared to an expected maximum clinical dose of 75 IU/kg (8 or 10 times in
monkeys and rats, respectively) and the degree of safety is considered sufficient to
support entry into clinical development in humans.
Factor VIII prophylaxis has been shown to reduce hemarthroses and other bleeding episodes in patients with severe hemophilia A

See section 6.5 of the protocol.

Contacts

Public
Baxter

Industriestrasse 67
Vienna A-1221
AT
Scientific
Baxter

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. Previously treated male subjects aged 18 to 65 years (inclusive) at the time of screening.
2. Prior diagnosis of severe hemophilia A (FVIII level <1%) or as confirmed by the central laboratory at screening.
3. Previously treated with FVIII concentrates for *150 documented EDs.
4. Karnofsky performance score of *60
5. Human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and cluster of differentiation 4 (CD4+) count *200 cells/mm3, as confirmed by the central laboratory at screening
6. Hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing as confirmed by the central laboratory at screening; or HCV+ with chronic stable hepatitis as assessed by the investigator
7. Able to understand and have provided written informed consent including signature on an informed consent form (ICF) approved by an ethics committee (EC)
8. Have provided written authorization for use and disclosure of protected health information
9. Agree to abide by the study schedule and to return for the required assessments

10. Willing and able to comply with the requirements of the protocol

Exclusion criteria

1. Detectable FVIII inhibitor at screening, with a titer *0.6 BU (Nijmegen modification of the Bethesda assay) as determined at the central laboratory
2. Documented history of FVIII inhibitors with a titer *0.4 BU (using the Nijmegen modification of the Bethesda assay or *0.6 with Bethesda assay) at any time prior to screening
3. Known clinical hypersensitivity towards mouse or hamster proteins or to PSA
4. Scheduled elective surgery during study participation
5. Severe chronic hepatic dysfunction (defined as *5 x upper limit of normal [ULN] alanine aminotransferase [ALT] or an international normalized ratio [INR] >1.5).
6. Severe renal impairment (serum creatinine >2.0 mg/dL)
7. Currently receiving, or has recently received (less than 3 months prior to study participation), or is scheduled to receive during the course of the study, other PSA-ylated drugs
8. Have received another investigational drug within 30 days prior to study entry and/or is scheduled to receive additional investigational drug during the course of the study in the context of another investigational drug study
9. Diagnosis of an inherited or acquired hemostatic defect other than hemophilia A
10. Currently receiving, or scheduled to receive during the course of the study, an immune-modulating drug (eg, systemic corticosteroid agent at a dose equivalent to hydrocortisone greater than 10 mg/day, or alpha interferon) other than anti-retroviral chemotherapy
11. Has a clinically significant medical, psychiatric or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect the safety or compliance of the subject during the study
12. Is a family member or employee of the investigator

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-08-2016
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ADVATE
Generic name:	Octocog Alfa (humane stollings factor)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	BAX 826
Generic name:	PSA-rFVIII

Ethics review

Approved WMO Date:	04-01-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-03-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-05-2016

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2015-004079-60-NL
CCMO	NL55816.078.15