A Phase 3, Prospective, Multicenter, Uncontrolled, Open-Label Clinical Study to Determine the Efficacy, Safety, and Tolerability of rVWF with or without ADVATE in the Treatment and Control of Bleeding Episodes, the Efficacy and Safety of rVWF in Elective and Emergency Surgeries, and the Pharmacokinetics (PK) of rVWF in Children Diagnosed with Severe von Willebrand Disease

Published: 11-01-2018
Last updated: 12-04-2024

Primary objective: The primary objective of the study is to evaluate the hemostatic efficacy and safety of rVWF, with or without ADVATE, in the treatment and control of nonsurgical bleeding events in pediatric subjects (

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

Summary

ID

NL-OMON50545

Source
ToetsingOnline

Brief title
BAX 111 rVWF in Pediatrics

Condition

- Haematological disorders NEC

Synonym
bleeding disorder, Hemophilia

Research involving
Human

Sponsors and support

Primary sponsor: Baxalta Inovation GmbH
Source(s) of monetary or material Support: Baxalta

Intervention

Keyword: Bleeding episodes, Pediatric, Von Willebrands Disease

Outcome measures

Primary outcome

The primary outcome measure is hemostatic efficacy, defined as the number of pediatric subjects with treatment success for rVWF-treated nonsurgical bleeding episodes (using a 4-point scale). Bleeding episode treatment success is defined as a mean efficacy rating score of <2.5.

Timepoint of evaluation:

Timepoint of assessment is within 24 hrs after onset of each bleeding episode an infusion of study drug, recording is made after resolution of each bleeding episode.

Secondary outcome

Efficacy

1. Number of treated nonsurgical bleeding episodes with an efficacy rating of

'excellent' or 'good'.

2. Number of infusions, rVWF units, and ADVATE units (if needed), per bleeding episode.

3. For elective surgery: an overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of rVWF, assessed by the Investigator (hematologist) on a 4-point scale.

Safety

1. Incidence and severity of adverse events (AEs) by system organ class (SOC) and preferred term.

2. Incidence of thrombotic events.

3. Incidence of severe hypersensitivity reactions.

4. Development of neutralizing antibodies to VWF and FVIII.

5. Development of total binding antibodies to VWF.

6. Development of antibodies to CHO proteins, murine IgG, and rFurin.

Pharmacokinetics

1.Area under the plasma concentration/time curve from 0 to 96 hours post-infusion (AUC0-96h), area under the plasma concentration/time curve from time 0 to infinity (AUC0-*), mean residence time (MRT), clearance (CL), incremental recovery (IR), in-vivo recovery (IVR), elimination phase half-life (T1/2), and volume of distribution at steady state (Vss) for VWF:RCo.

2. Area under the plasma concentration/time curve from 0 to 96 hours post-infusion (AUC0-96h) for VWF:Ag and VWF:CB. Point estimates per age cohort

will be presented.

3. Area under the plasma concentration/time curve from 0 to 96 hours post-infusion (AUC0-96h) for FVIII activity. Point estimates per age cohort will be presented.

Timepoint of evaluation:

Hemostatic Efficacy Assessments for surgeries are performed immediately after surgery by operating surgeon and then 24 hours after last perioperative rVWF infusion, Day 7 and Day 14 by the investigator. (See section 11 of protocol for reference)

Study description

Background summary

Von Willebrand factor (VWF) is a large multimeric glycoprotein (with multimers ranging in molecular weight from 500 to >20000 KDa) that is normally found in plasma, alpha-granules of platelets, and intracellular organelles known as Weibel-Palade bodies.
VWF is the carrier molecule for factor VIII (FVIII), an essential cofactor of secondary hemostasis that leads to fibrin clot formation, and facilitates platelet adhesion to subendothelium at sites of vascular injury.

Human VWF produced by recombinant technology provides a new perspective in treatment of von Willebrand disease (VWD). Limitations associated with plasma-derived VWF (pdVWF) concentrates can be overcome by recombinant VWF (rVWF). Baxalta has developed an rVWF, which is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line that expresses the VWF gene.

Recombinant VWF has undergone extensive in vitro and in vivo non-clinical investigation supporting its safe evaluation in humans. The clinical development program consists of 4 completed trials (3 in VWD and 1 in hemophilia) and 1 ongoing trial.

Recombinant VWF was granted licensure in the United States in December 2015

under the brand name VONVENDI for on-demand treatment and control of bleeding episodes in adults diagnosed with VWD, although it is not yet available on the market.

Study objective

Primary objective:
The primary objective of the study is to evaluate the hemostatic efficacy and safety of rVWF, with or without ADVATE, in the treatment and control of nonsurgical bleeding events in pediatric subjects (<18 years of age) diagnosed with severe, hereditary VWD.

Secondary objectives:
Efficacy:
The secondary efficacy objective will be an overall assessment of hemostatic efficacy after the last perioperative rVWF infusion in pediatric subjects undergoing elective or emergency surgery

Safety:
The overall AE profile of rVWF will be assessed by frequency, severity, and seriousness. Additionally, there will be focused review of thrombotic events and severe hypersensitivity events.

Pharmacokinetics:
The PK profile of rVWF will be assessed.

Exploratory Objectives:
1. Health-related Quality of Life (HRQoL) variables
2. Health resource use

Study design

This is a Phase 3, prospective, open-label, uncontrolled, multicenter study to evaluate the efficacy, safety, tolerability, and PK of rVWF, with or without ADVATE, for the treatment and control of nonsurgical bleeding episodes and bleeding associated with elective and emergency surgery in pediatric subjects with severe VWD.

Intervention

Infusion with study drug, if in the elective or emergency surgery groups: surgery

Study burden and risks

The benefit for the individual subject is anticipated to outweigh the potential

risks of rVWF during this Phase 3 clinical study. The subject may benefit from a product that minimizes excessive FVIII administration. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD patients, especially mucosal bleeds with unpredictable efficacy outcomes.
By using a recombinant product, the risk of contamination with blood-borne viruses or variant Creutzfeldt-Jakob Disease associated with the use of products of human or animal origin has been virtually eliminated. As with any IV protein product, allergic-type hypersensitivity reactions may occur, as well as neutralizing antibodies to VWF.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Subjects who meet ALL of the following criteria are eligible for this study:
1. Diagnosis of severe VWD (defined as VWF:RCo <20%):
a. Type 1 (VWF:RCo <20 IU/dL); or
b. Type 2A (VWF:RCo <20 IU/dL), Type 2B (as diagnosed by genotype), Type 2N (FVIII:C
<10% and historically documented genetics), Type 2M; or
c. Type 3 (VWF:Ag *3 IU/dL).
2. Age 0 to <18 years at the time of screening
3. The subject has provided assent (if appropriate) and legally authorized representative(s) has
provided informed consent
4. If female of childbearing potential, subject presents with a negative serum pregnancy test
5. If applicable, subject agrees to employ adequate birth control measures for the duration of the study
6. Subject and/or the legally authorized representative are willing and able to comply with the requirements of the protocol, which should also be confirmed based on a prescreening evaluation held between the Investigator and the Sponsor, to ensure no eminent risk is present that could challenge the subject's compliance with the study requirements.

Additional inclusion criteria for previously treated subjects and subjects undergoing surgery are as follows:
1. Unable to tolerate or are inadequately responsive to deamino-delta-Darginine vasopressin
2. The subject has had a minimum of 1 documented bleed requiring VWF coagulation factor
replacement therapy (ie, treatment with a VWF product) during the previous 12 months prior to enrollment
and overall historically
3 or more exposure days (EDs) to plasma-derived VWF.
Additional inclusion criterion for previously untreated subjects are as follows:
1. The subject has not received prior VWF coagulation factor replacement therapy

Exclusion criteria

Subjects who meet ANY of the following criteria are not eligible for this study:
1. Diagnosis of pseudo-VWD or another hereditary or acquired

coagulation disorder (eg, qualitative
and quantitative platelet disorders or elevated prothrombin
time/international normalized ratio
>1.4)
2. History or presence of a VWF inhibitor at Screening
3. History or presence of a FVIII inhibitor with a titer *0.4 Bethesda
units (BU) (by Nijmegen assay)
or *0.6 BU (by Bethesda assay)
4. Documented history of a VWF:RCo half-life <6 hours
5. Known hypersensitivity to any of the components of the study drug,
such as mouse or hamster
proteins
6. Medical history of immunological disorders, excluding seasonal
allergic rhinitis/ conjunctivitis/
asthma, food allergies, or animal allergies
7. Medical history of a thromboembolic event
8. Human immunodeficiency virus positive, with an absolute CD4 count
*200/mm3
9. In the judgment of the Investigator, the subject has another clinically
significant concomitant
disease (eg, uncontrolled hypertension, cancer) that may pose additional
risks for the subject
10. Diagnosis of significant liver disease, as evidenced by, but not
limited to, any of the following:
serum alanine aminotransferase 5 times the upper limit of normal;
hypoalbuminemia; portal vein
hypertension (eg, presence of otherwise unexplained splenomegaly,
history of esophageal varices)
or liver cirrhosis classified as Child B or C
11. Diagnosis of renal disease, with a serum creatinine level *2.5 mg/dL
12. Immunomodulatory drug treatment other than anti-retroviral
chemotherapy (eg, *-interferon, or
corticosteroid agents at a dose equivalent to hydrocortisone greater than
10 mg/day (excluding
topical treatment [eg, ointments, nasal sprays]), within 30 days prior to
signing the informed
consent (or assent, if appropriate)
13. If female, subject is pregnant or lactating at the time informed
consent (or assent, if appropriate) is
obtained
14. Subject has participated in another clinical study involving an IP,
other than rVWF with or
without ADVATE, 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

15. Subject's legal representative 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):	23-07-2018
Enrollment:	1
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Recombinant von Willebrand Factor 650IU
Generic name:	-

Ethics review

Approved WMO Date:	11-01-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2018

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-08-2021
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	EUCTR2016-001477-33-NL
ClinicalTrials.gov	NCT02932618
CCMO	NL62983.078.17