A phase 3 prospective, multicenter study to evaluate efficacy and safety of rVWF with or without ADVATE in elective surgical procedures in subjects with severe von Willebrand disease

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The primary objective of this study is to assess the hemostatic efficacy and safety of rVWF with or without ADVATE in subjects (* 18 years) diagnosed with hereditary severe VWD undergoing major and minor elective surgical procedures.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Platelet disorders
Study type	Interventional

Summary

ID

NL-OMON42081

Source
ToetsingOnline

Brief title
rVWF in subjects with VWD undergoing surgery

Condition

- Platelet disorders

Synonym
extended or excessive bleeding

Research involving
Human

Sponsors and support

Primary sponsor: Baxalta Innovations GmbH
Source(s) of monetary or material Support: Pharmaceutical company

Intervention

Keyword: Phase 3 open label, rVWF, surgical procedures, Von Willebrand disease

Outcome measures

Primary outcome

Overall assessment of hemostatic efficacy assessed by the investigator (hemophilia physician) 24 hours after last perioperative IP infusion or at completion of day 14 visit (whichever occurs earlier) will be summarized by the percentage of subjects in each efficacy category (*excellent*, *good*, *moderate* and *none*).

Point estimates and corresponding two-sided exact confidence intervals (CIs) at the 90% confidence level will be calculated for the rate of subjects with an overall assessment of hemostatic efficacy of *excellent* or *good* 24 hours after last perioperative IP infusion or at completion of day 14 visit, whichever occurs earlier.

The primary efficacy analysis will be based on the FAS. As a supportive analysis, the same calculations will also be carried out on the PPAS.

Secondary outcome

Intraoperative actual versus predicted blood loss as assessed by the operating surgeon at completion of the surgery will be summarized by the percentage of subjects in each efficacy category (*excellent*, *good*, *moderate* and *none*).

Point estimates and corresponding two-sided exact confidence intervals (CIs) at

the 90% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome performed by the operating surgeon based on the intraoperative

actual versus predicted blood loss.

Intraoperative hemostatic efficacy assessed at completion of surgery by the operating surgeon will be summarized by the percentage of subjects in each efficacy category (*excellent*, *good*, *moderate* and *none*).

Point estimates and corresponding two-sided exact confidence intervals (CIs) at the 90% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome performed by the operating surgeon at completion of surgery.

Descriptive statistics (median, quartiles and range) will be used to summarize the actual blood loss expressed as a percentage of the estimated blood loss (EBL),

The summary of average daily and total weight-adjusted doses (average through postoperative day 14) of rVWF with or without ADVATE per subject will be provided using median, quartiles and range.

The secondary efficacy analysis will be performed on the FAS.

Study description

Background summary

Baxter Healthcare Corporation (hereafter referred to as Baxter or sponsor) has developed a human recombinant von Willebrand Factor (rVWF, BAX 111), which is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line that expresses the von Willebrand factor (VWF) gene. To address concerns

regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF are trace quantities of murine immunoglobulin (IgG, from the
immunoaffinity purification), host cell (i.e. CHO) protein, rFurin (used to further process rVWF). This process virtually eliminates any risk of transmission of human blood-borne viruses or other adventitious agents that could, in theory, be introduced by the use of added animal- or human-derived raw materials. rVWF is intended for the treatment of von Willebrand disease (VWD).

Study objective

The primary objective of this study is to assess the hemostatic efficacy and safety of rVWF with or without ADVATE in subjects (* 18 years) diagnosed with hereditary severe VWD undergoing major and minor elective surgical procedures.

Study design

This is a phase 3 prospective, open-label, uncontrolled, nonrandomized, international, multicenter study to evaluate the efficacy
and safety of rVWF with or without ADVATE in adults with severe VWD undergoing major and minor elective surgical procedures.

Intervention

Treatment with rVWF.

Study burden and risks

NA

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects who meet ALL of the following criteria are eligible for this study:
1. Diagnosis of severe VWD as listed and elective surgical procedure planned:
- VWD with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding.
- Type 1 (VWF:RCo < 20 IU/dL) or
- Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2N (Factor VIII coagulation activity [FVIII:C] <10% and historically documented genetics), Type 2M or
- Type 3 (von Willebrand factor antigen [VWF:Ag] * 3 IU/dL)
2. If type 3 VWD (VWF:Ag * 3 IU/dL), subject has a medical history of at least 20 EDs to VWF/FVIII
coagulation factor concentrates (including cryoprecipitate or fresh frozen plasma).
3. If type 1 or type 2 VWD, subject has a medical history of 5 EDs or a past major surgery requiring
VWF/FVIII coagulation factor concentrates (including cryoprecipitate or fresh frozen plasma).
4. At least 18 years of age
5. If female of childbearing potential, subject presents with a negative pregnancy test
6. If applicable, subject agrees to employ adequate birth control measures for the duration of the study
7. Willing and able to comply with the requirements of the protocol.

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 PT/ international normalized ratio [INR] * 1.4)
2. History or presence of a VWF inhibitor at screening
3. History or presence of a factor VIII (FVIII) inhibitor with a titer * 0.4 BU (by Nijmegen-modified
Bethesda assay) or * 0.6 BU (by Bethesda assay)
4. Known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins
5. Medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies
6. Medical history of a thromboembolic event
7. HIV positive with an absolute CD4 count *200/mm3
8. Platelet count < 100,000/mL
9. Diagnosis of significant liver disease, as evidenced by, but not limited to, any of the following: serum alanine aminotransferase (ALT) 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g. presence of otherwise unexplained splenomegaly, history of esophageal varices) or liver cirrhosis classified as Child B or C
10. Diagnosis of renal disease, with a serum creatinine level *2.5 mg/dL
11. Subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g.
ointments, nasal sprays), within 30 days prior to signing the informed consent
12. Subject is pregnant or lactating at the time informed content is obtained.
13. Subject has participated in another clinical study involving an investigational product (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. (Eligible patients participating in the rVWF Prophy study [071301] may be enrolled).
14. Progressive fatal disease and/or life expectancy of less than 3 months
15. Subject is identified by the investigator as being unable or unwilling to cooperate with study
procedures
16. Subject suffers from a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude
17. Subject is in prison or compulsory detention by regulatory and/or juridical order
18. Member of the study team conducting this study or in a dependent relationship with one of the study team members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parents) as well as employees.

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:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ADVATE 500 IU powder and solvent for solution for injection
Generic name:	NA
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Recombinant von Willebrand Factor

Ethics review

Approved WMO Date:	09-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2016
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	EUCTR 2014-003575-3-NL
ClinicalTrials.gov	NCT02283268
CCMO	NL51396.018.14