A prospective, phase 3, open label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von willebrand disease

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The primary objective of this study is to prospectively evaluate the annualized bleeding rate (ABR) for spontaneous bleeding episodes while on prophylactic treatment with rVWF (vonicog alfa) and to compare it to the subject's historical ABR for...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Blood and lymphatic system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON47063

Source
ToetsingOnline

Brief title
071301 - rVWF in prophylaxis

Condition

- Blood and lymphatic system disorders congenital

Synonym
Inherited severe bleeding disorder, Von Willebrand's

Research involving
Human

Sponsors and support

Primary sponsor: Baxalta Innovations GmbH

Source(s) of monetary or material Support: Pharmaceutical Company

Intervention

Keyword: PROPHYLAXIS, rVWF, von Willebrand factor

Outcome measures

Primary outcome

Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa).

Secondary outcome

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa).

ABR present reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment.

ABR preservation success for pdVWF switch subjects defined as achieving an ABR for spontaneous bleeding episodes during rVWF (vonicog alfa) prophylaxis that is no greater than the subject's own historical ABR during prophylactic treatment with pdVWF.

Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episoces during the 12-month prophylactic treatment with rVWF (vonicog alfa).

Total number of infusions and the average number of infusions per week during

prophylactic treatment with rVWF (vonicog alfa).

Total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment.

Spontaneous ABR by location of bleeding (Gastrointestinal [GI], epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.) while on prophylactic treatment with rVWF (vonicog alfa).

Safety

Adverse events (AEs): incidence, severity, causality

Thromboembolic events

Hypersensitivity reactions

Development of neutralizing antibodies to VWF and FVIII

Development of total binding antibodies to VWF and FVIII

Development of binding antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin.

Clinically seignificant changes in vital signs and clinical laboratory parameters relative to baseline.

Pharmacokinetics (PK) and Pharmacodynamics (PD)

PK parameters after a washout for on-demand subjects: incremental recovery (IR), terminal half-time (T/2), mean residence time (MRT), area under the concentration versus time curve from 0 to infitity (AUC0-infinity), area under

the concentration versus time curve from 0 to the last measurable concentration (AUC0-tlast), maximum concentration (Cmax), minimum time to reach the maximum concentration (Tmax), volume of distribution at steady state (Vss), and clearance (CL) based on VWF:RCo, Von Willebrand Factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB).

PD parameters after a washout for on-demand subjects: Cmax, Tmax, and AUC0-tlast as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).

PK parameters at steady state for on-demand and switch subjects: areas under the concentation versus time curve from 0 to end of the partial dosing interval (AUC0-tau;ss), maximum concentration during the partial dosing interval (Cmax;ss), minimum time to reacht the maximum concentration (Tmin;ss), ad minimum concentration during the partial dosing interval (Cmin;ss) based on VWF:RCo, VWF:Ag, and VWF:CB. PK parameters at steady state will be assessed shortly after reachting stady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.

PD parameters at steady state for on-demand and switch subjects: AUC0-tau;ss, Cmax;ss, Tmax;ss, and Cmin;ss as measured in FVIII activity by the 1-stage clotting assay (FVIII:C). PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the

study for on-demand as well as for switch subjects all based on the longer

interval of the irregular dosing intervals employes.

Time course of FVIII clotting activity (FVIII:C) levels.

Study description

Background summary

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human
recombinant von Willebrand Factor (rVWF), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the
subsequent downstream process. 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). rVWF is intended for the treatment of
von Willebrand disease (VWD).

Study objective

The primary objective of this study is to prospectively evaluate the annualized bleeding rate (ABR) for spontaneous bleeding episodes while on prophylactic treatment with rVWF (vonicog alfa) and to compare it to the subject's historical ABR for spontaneous bleeding episodes during ondemand treatment.

Efficacy of the treatment of perioperative bleeding management, if surgery is required.

Study design

This is a phase 3, prospective, open-label, non-randomized, international multicenter study evaluating efficacy, safety, including immunogenicity and thrombogenicity, and HRQoL of prophylactic treatment regimen with rVWF for

subjects with severe VWD.

Intervention

Subjects transitioning from on-demand treatment will be infused twice weekly with BAX 111 (rVWF) at doses of 50 ± 10 IU/kg rVWF:RCo. The dose may be adjusted within this range based on the PK data, subject*s history of bleeding episodes, and the results from clinical and laboratory assessments.
During treatment any bleeding episodes requiring substitution therapy with VWF concentrate to control bleeding will be treated with rVWF with or without ADVATE.
The dose will be according to the bleeding severity and it will be adjusted to the clinical
response

Study burden and risks

The benefits mentioned in protocol section 6.6 outweigh the following potential risks of rVWF:
• allergic-type hypersensitivity reactions as with any intravenous protein product
• the occurrence of thromboembolic events
• the development of neutralizing antibodies to VWF
Refer to the IB for further details on benefits and risks of the IP.

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

Subjects who meet ALL of the following criteria are eligible for this study:
1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
a. Type 1 (VWF:RCo <20 IU/dL) or,
b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
c. Type 3 (VWF:Ag <=3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient groep, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatment of pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient groep, subject has >=3 documented spontaneous bleeds (ont including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceeding enrollment.
Up to 24 months of retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is >=18 years old at the time of screening and has a body mass index >=15 but <40 kg/m2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
9. Subject is 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. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] 1.4).
2. The subject is currently receiving prophylaxis treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylaxis treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer >=0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or >=0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count 200/mm3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by 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).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level >=2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The 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.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) 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.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has 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.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order

22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.
Delay criteria
1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-01-2018
Enrollment:	1
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Advate
Generic name:	rFVIII
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Recombinant von Willebrand Factor
Generic name:	HUMAN VON WILLEBRAND FACTOR

Ethics review

Approved WMO Date:	08-12-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	08-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2020
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	EUCTR2016-001478-14-NL
CCMO	NL59762.078.16