A phase 3b, prospective, open-label, uncontrolled, multicenter study on long-term safety and efficacy of rVWF in pediatric and adult subjects with severe von Willebrand disease (VWD)

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To evaluate the efficacy of rVWF (vonicog alfa) prophylaxis based on the annualized bleeding rate (ABR) of spontaneous (not related to trauma) bleeding episodes in adult and pediatric / adolescent subjects (aged 12 to

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

Summary

ID

NL-OMON52575

Source
ToetsingOnline

Brief title
SHP677-304

Condition

- Haematological disorders NEC

Synonym
bleeding disorder, Hemophilia

Research involving
Human

Sponsors and support

Primary sponsor: Baxalta Innovation GmbH - part of Shire
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Bleeding episodes, Extension, Von Willebrands Disease

Outcome measures

Primary outcome

Spontaneous ABR during prophylaxis treatment with rVWF (vonicog alfa) based on

the data collected during the first 12 months on study treatment.

Secondary outcome

Safety:

• AEs/serious adverse events (SAEs): incidence, severity, causality

• Occurrence of thromboembolic events

• Occurrence of hypersensitivity reactions

• Immunogenicity

a. Development of neutralizing antibodies (inhibitors) to VWF and FVIII

b. Development of total binding antibodies to VWF and FVIII

c. Development of binding antibodies to Chinese hamster ovary (CHO) proteins,

mouse immunoglobulin G

(IgG) and rFurin

• Clinically significant changes in vital signs and clinical laboratory

parameters relative to baseline

Efficacy of Prophylaxis:

• Spontaneous ABR under prophylactic treatment with rVWF (vonicog alfa) while

enrolled in the study

• Categorized weekly number of infusions defined as 1, 2 or >= 3 during prophylactic treatment with rVWF (vonicog alfa)

• Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during rVWF (vonicog alfa) prophylaxis

• Time to first bleeding event under each prophylaxis regimen

• Spontaneous ABR by location of bleeding (Gastrointestinal [GI], epistaxis, joint bleeding, menorrhagia, oral, muscle and soft tissue, etc.) while on 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

• Transfusion free maintenance of hemoglobin and ferritin levels over time

Efficacy of the Treatment of Bleeding Episodes:

• Overall hemostatic efficacy rating at the resolution of bleed with respect to the treatment of bleeding episodes for the initial 12 months on study treatment

• Number of infusions of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) utilized to treat bleeding episodes while enrolled in the study

• Weight-adjusted consumption of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) per bleeding episode while enrolled in the study

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

To evaluate the efficacy of rVWF (vonicog alfa) prophylaxis based on the annualized bleeding rate (ABR) of spontaneous (not related to trauma) bleeding episodes in adult and pediatric / adolescent subjects (aged 12 to <18 years) during the first 12 months on study treatment.

Study design

This is a Phase 3b, prospective, open-label, uncontrolled, non-randomized, multicenter study evaluating long-term safety and efficacy of rVWF (vonicog alfa) for prophylaxis and OD treatment of bleeding episodes in pediatric and adult subjects with severe VWD.

Intervention

a. Cohort 1: Adult subjects from Study 071301 who will continue with the same prophylactic treatment regimen from Study 071301, which is expected to be 50 (±10) IU/kg rVWF:RCo twice weekly for the majority of subjects.

b. Cohort 2: Adult subjects from Study 071301 who experienced no clinically significant bleeding episode over the past 6 months and who elected to follow the recommendation by the investigator to start prophylactic treatment in this

study with reduced dosing frequency and/or change of dose per infusion.

(c. Cohort 3: Pediatric subjects aged 12 to <18 years who:
• transition from Study 071102 with at least 3 bleeding episodes (not including menorrhagia) that required treatment with a VWF product and occurred over the past 12 months, and
• are considered eligible for prophylactic treatment per investigator's medical/clinical assessment may receive rVWF (vonicog alfa) for prophylaxis if they elect to go on prophylactic treatment following the recommendation by the investigator.)

The dosage selected may be either:
a) Twice weekly 50 (±10) IU/kg rVWF:RCo, or
b) Once weekly 50 (±10) IU/kg rVWF:RCo
based on the investigator's assessment and recommendation.

(d. Cohort 4: Newly enrolled adult and pediatric subjects (aged 12 to <18 years) who:
• were previously treated with VWF products for bleeding episodes OD, with at least 3 bleeding episodes (BE), excluding menorrhagia, that occurred over the past 12 months, and
• are considered eligible for prophylactic treatment based on the investigator's medical/clinical assessment will receive rVWF (vonicog alfa) at once weekly dose of 50 (±10) IU/kg rVWF:RCo.)

(Cohort 5: will consist of pediatric subjects from Study 071102 who are not considered eligible for prophylactic treatment based on the investigator's medical/clinical assessment or who elect not to follow the recommendation by the investigator to transition to prophylaxis)

Cohort 6: will consist of adult subjects from Study 071301 who want to switch back to OD treatment regimen

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)
Adults (18-64 years)

Inclusion criteria

Subjects who have completed Study 071301 or 071102 (or subjects who have completed the surgery in Study 071102 and want to continue to receive OD treatment) and are willing to immediately transition into this study, must meet the following 2 criteria to be eligible for this study:
1. If female of childbearing potential, has a negative blood/urine pregnancy test at screening and agrees to employ
highly effective birth control measures (including sterilization, implant, intra-uterine device (IUD), correct and consistent use of hormonal contraception, and abstinence) for the duration of the study.
2. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.

New subjects (Cohort 4) who meet the above 2 and ALL the following additional criteria are eligible for this study:
3. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with rVWF concentrate required 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).
Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
4. Subject has been receiving OD therapy with VWF products for at least 12 months, and prophylactic treatment
is recommended by the investigator.
5. Subject has >=3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Subject has available records that reliably evaluate type, frequency, and treatment of bleeding episodes for at least 12 months preceding enrollment; up to 24 months of retrospective data should be collected if available.
7. Subject is >=12 years old at the time of screening and has a body mass index >=15 but <40 kg/m2.

Exclusion criteria

The subject will be excluded from the study if any of the following exclusion criteria are met:
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/international normalized ratio >1.4).
2. The subject has a history or presence of a VWF inhibitor at screening.
3. 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).
4. The subject has a known hypersensitivity to any of the components of the study drugs, such as mouse or hamster proteins.
5. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies, or animal allergies.
6. The subject has a medical history of a thromboembolic event.
7. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm3.
8. 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, but not limited to any of the following:

serum alanine aminotransferase (ALT) greater than 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-Pugh class B or C.
9. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level >=2.5 mg/dL.
10. The subject has a platelet count <100,000/mL at screening. (for subjects with type 2B VWD, platelet count(s) at screening will be evaluated taking into consideration historical trends in platelet counts and the Investigator's medical assessment of the patient's condition).
11. The subject has been treated with an immunomodulatory drug, excluding topical treatment (eg, ointments, nasal sprays), within 30 days prior to signing the informed consent (or assent, if appropriate).
12. The subject is pregnant or lactating at the time of enrollment.
13. The subject has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
14. 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.
15. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
16. For new OD subjects, the subject is scheduled for a surgical intervention.
17. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
18. 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.
19. 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.

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):	08-05-2019
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ADVATE
Generic name:	OCTOCOG ALFA
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Recombinant von Willebrand Factor (rVWF)
Generic name:	VEYVONDI

Ethics review

Approved WMO Date:	28-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-07-2019

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2021
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:	22-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-03-2023
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	EUCTR2018-003453-16-NL
CCMO	NL67609.078.19