A Phase 3 clinical study to determine the pharmacokinetics, safety and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in subjects diagnosed with von Willebrand disease

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Primary objective:• Assess the pharmacokinetics (PK) of rVWF:rFVIII and rVWF, and to assess the safety and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding events in subjects with severe hereditary VWDSecundary objectives:• Compare the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON38008

Source
ToetsingOnline

Brief title
Baxter 071001

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Blood and lymphatic system disorders congenital

Synonym
Coagulation disorder, Hereditary deficiency of Von Willebrand Factor in blood

Research involving
Human

Sponsors and support

Primary sponsor: Baxter
Source(s) of monetary or material Support: Farmaceutisch indrustie

Intervention

Keyword: Bleeding episodes, Pharmacokinetics (PK), Recombinant von Willebrand Factor, von Willebrand Disease

Outcome measures

Primary outcome

Number of subjects with a treatment success for treated bleeding episodes

Secondary outcome

Efficacy

• Number of treated bleeding episodes with an efficacy rating of 'excellent' or

'good'

• Number of infusions and rVWF:rFVIII and/or rVWF units per bleeding episode

Safety

• Development of inhibitory and total binding anti-VWF antibodies

• Development of inhibitory antibodies to FVIII

• Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse

immunoglobulin G (IgG) and rFurin

• Occurrence of thrombotic events

• Other IP related AEs, such as clinically significant changes in routine

laboratory parameters (hematology and clinical chemistry) and vital signs

Pharmacokinetics

• Area under the plasma concentration/time curve from time 0 to infinity (AUC0-*/Dose); area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose); mean residence time (MRT); clearance (CL); incremental recovery (IR), elimination phase half-life (T1/2); volume of distribution at steady state (Vss) of VWF Ristocetin cofactor (VWF:RCo), VWF antigen (VWF:Ag), VWF collagen-binding (VWF:CB), and FVIII.

• In vivo recovery (IVR) of VWF:RCo, VWF:Ag and VWF:CB.

• Comparison of intra-subject PK of VWF:RCo, VWF:CB and VWF:Ag at baseline and after 6 months in a subset of at least 20 subjects with severe VWD (minimum 6 subjects with type 3 VWD)

Exploratory Endpoints

• Subjective hemostatic efficacy rating

Two instruments to measure Health-related Quality of Life (HRQoL) will be employed as exploratory endpoints:

• Generic: Physical Component Score (PCS) and Mental Component Score (MCS) of the Short Form-36 (SF-36)

• Disease-specific: total score of the unvalidated VWD Impact Questionnaire

Study description

Background summary

The aim of the studie is assessing the pharmacokinetics (PK) of rVWF:rFVIII and rVWF, and to assess the safety and efficacy of rVWF:rFVIII and rVWF in the treatment and prevention of bleeding events in subjects with severe hereditary VWD.

The benefit for the individual subject is anticipated to be significant during the Phase 3 clinical study. The subject may benefit from a product combination 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 which are especially problematic. Baxter*s rVWF product consistently contains low ultra-large molecular weight (ULMW) VWF multimers, which are subsequently cleaved by the patient*s endogenous ADAMTS13. This may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes. By using a recombinant product, the risk of contamination with viruses or variant Creutzfeldt-Jakob Disease associated with the use of products of human or animal origin has been eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

Study objective

Primary objective:
• Assess the pharmacokinetics (PK) of rVWF:rFVIII and rVWF, and to assess the safety and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding events in subjects with severe hereditary VWD

Secundary objectives:
• Compare the PK parameters of rVWF alone or in combination with rFVIII in subjects with type 3 VWD
• Examine the PK parameters of rVWF in subjects with severe VWD or type 2N VWD
• Evaluate the hemostatic efficacy, safety, and tolerability of rVWF:rFVIII and rVWF in subjects with VWD receiving the investigational product for the treatment of bleeding episodes
• Evaluate tolerability and safety of rVWF including the development of inhibitory and total binding anti-VWF antibodies and clinically significant changes in laboratory parameters following drug administration
• Assess changes in health-related quality of life (HRQoL)

Study design

Phase 3, multicenter, open-label clinical study , except for the PK50 arm (single blinded)

Intervention

• Subjects (type 3 only) participating in the crossover PK arm (PK 50 Arm) will undergo 2 PK assessments: one following an infusion of 50 IU/kg VWF:RCo rVWF and an infusion of 38.5 IU/kg FVIII, and the other following an infusion of 50 IU/kg VWF:RCo rVWF and an infusion of saline (placebo). The order in which the PK assessments will be performed will be randomized and blinded.

• Subjects participating in the PK 80 Arm will receive a single infusion of 80 IU/kg VWF:RCo rVWF at the start of the study and another after at least 6 months on study.

Treatment and Prevention of Bleeding Episodes:
An initial dose of 40-60 IU/kg VWF:RCo (+ 30-45 IU rFVIII/kg) will be infused to treat/prevent bleeding episodes. Subsequent doses, if necessary, will be 20-60 IU VWF: RCo IU/kg administered up to 24 hours apart to maintain VWF:RCo and FVIII levels of at least 30 IU/dL for as long as deemed necessary by the investigator. Additional doses of rFVIII will be administered with the rVWF product if plasma FVIII levels fall below 30 IU/dL during the treatment period.

Study burden and risks

Please refer to tabel 20.2, 20.4 and 20.5 for an overview of all study visits and procedures.
Summary of procedures:

- Informed consent: during screening visit
- Physical examination: during all visits
- Vital signs: during all visits
- ECG: during screening visit, baseline visit and PK-infusion visit
- Quality if Life Questionnaires: during baseline and completion visit
- Blood analysis and urinanalysis: during all visits
- Pregnancy test: during screening visit
- Subject diary: during all visits except for screening visit en PK-infusion visits

The most potential risks in this study are those risks associated with all new protein therapeutics:
- risk of hypersensitivity reactions (generalized itching, and tightness of the chest, shortness of breath, low blood pressure, and anaphylaxis)
- risk of formation of antibodies that will inhibit the activity of the study drug
- risk of thrombogenicity
- possible risk of infectious viruses
- fever

Based in the prior studies of rFVIII, you may experience the following side effects: a strange taste in your mouth, itching, dizziness, headache, catheter-related infection, cold shivers, hot flushes, diarrhea, sweating, nausea, pain in the upper abdomen, chest pain, prolonged bleeding after post operative drain removal, decreased hematocrit, swelling limbs, swelling of joints, shortness of breath, fever, decreased FVIII levels and post operative unspecified blood clot at the site of surgery.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

The subject has been diagnosed with:
Type 1 (VWF:RCo < 20 IU/dL) or,
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,
Type 3 (VWF:Ag <= 3 IU/dL) or,
Severe VWD with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
• The subject, who participates for the treatment for bleeding episodes, has had a minimum of 1 documented bleeds (medical history) requiring VWF coagulation factor replacement therapy during the previous 12 months prior to enrollment.
• The subject has a Karnofsky score >=60.

• The subject is at least 18 and not older than 65 years of age at enrollment.

Exclusion criteria

• The subject has been diagnosed with pseudo VWD or another hereditary or acquired coagulation
disorder other than VWD (eg qualitative and quantitative platelet disorders or elevated PT/ international normalized ratio [INR] >1.4).
• The subject has a documented history of a VWF:RCo half-life of <6 hours.
• The subject has a history or presence of a VWF inhibitor at screening.
• The subject has a history or presence of a factor VIII (FVIII) inhibitor with a titer >=0.4 BU (by Nijmegen assay) or >=0.6 BU (by Bethesda assay).
• The subject has a known hypersensitivity to any of the components of the study drugs, such as to
mouse or hamster proteins.
• The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
• The subject has a medical history of a thromboembolic event.
• The subject is HIV positive with an absolute CD4 count <200/mm3.
• The subject has been diagnosed with cardiovascular disease (New York Heart Association [NYHA] classes 1-4).
• The subject has an acute illness (eg, influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) at screening.
• The subject has been diagnosed with significant liver disease as evidenced by any of the following: serum alanine aminotransferase (ALT) 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (eg, presence of otherwise unexplained splenomegaly, history of esophageal varices).
• The subject has been diagnosed with renal disease, with a serum creatinine level >=2 mg/dL.
• In the judgment of the investigator, the subject has another clinically significant concomitant disease (eg, uncontrolled hypertension) that may pose additional risks for the subject.
• 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.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-07-2012
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Advate
Generic name:	Recombinant Factor VIII
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Recombinant von Willebrand Factor
Generic name:	N/A

Ethics review

Approved WMO

Date:	30-08-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	12-01-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	19-03-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-09-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2013
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	EUCTR2010-024108-84-NL
ClinicalTrials.gov	NCT01410227
CCMO	NL37484.078.11