A Phase Ib, Dose Escalation Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients

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To assess the Pharmacokinetic and Pharmacodynamic properties of three dosages of Coagulation Factor VIIa (Recombinant) in congenital hemophilia A or B patientsTo assess the safety of three dosages of Coagulation factor VIIa (Recombinant) in...

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

Summary

ID

NL-OMON36958

Source
ToetsingOnline

Brief title
NA

Condition

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

Synonym
Haemophilia

Research involving
Human

Sponsors and support

Primary sponsor: GTC Biotherapeutics, Inc
Source(s) of monetary or material Support: GTC Biotherapeutics;Inc

Intervention

Keyword: Haemophilia A, Haemophilia B, recombinant coagulation factor VIIa

Outcome measures

Primary outcome

Pharmacokinetic variables:

Terminal half life (t1/2); area-under-the-concentration-versus-time curve from time 0 to the time of the last measurable concentration (AUC0-t); area-under-the-concentration-versus-time curve from time 0 to infinity (AUC0-inf); Mean Residence Time (MRT); Clearance (Cl); Volume of Distribution at steady state (Vss); Maximum Concentration achieved (Cmax); and time at which maximum concentration is achieved (tmax).

Pharmacodynamic variables:

Thrombin generation assay output (performed at low and high TF, and with added platelets), including lag time, time to peak, peak, and endogenous thrombin potential (ETP); activated partial thromboplastin time (aPTT); prothrombin time (PT). Besides its use in the PK analyses, FVIIa activity is also regarded a PD parameter.

Secondary outcome

Physical examinations, ECGs, vital signs, clinical laboratory tests (serum chemistry, hematology, urinalysis), immunology tests (including storage sample for potential future use), and monitoring of adverse events.

Assessment of (anti-)coagulation parameters (above listed PD markers like

prothrombin fragments F1+2 (F1+2), D-dimer, and TAT) will be used to assess the

safety of the drugs as well.

Study description

Background summary

Factor VIIa is a good therapeutic option to treat patients suffering from haemophilia who have developed antibodies against factor VIII or IX.
GTC aims with this new human recombinant factor VIIA to develop a good therapy to treat patients with haemophilia.

Study objective

To assess the Pharmacokinetic and Pharmacodynamic properties of three dosages of Coagulation Factor VIIa (Recombinant) in congenital hemophilia A or B patients
To assess the safety of three dosages of Coagulation factor VIIa (Recombinant) in congenital hemophilia A or B patients

Study design

A total of 15 adult male patients with hemophilia A or B (with or without inhibitors) will receive two administrations of rhFVIIa.
The first Cohort will consist of 10 patients who all receive a low dose. After evaluation of the safety data and some of the coagulation data up to the 24-36 hours visit by the Data Monitoring Committee, Cohort 2 will be initiated. Patients in Cohort 2 will be treated with a mid dose. Cohort 2 will consist of 5 patients that were treated in Cohort 1, and 5 newly enrolled patients. After evaluation of the safety data and some of the coagulation data up to the 24-36 hours visit by the Data Monitoring Committee, Cohort 3 will be initiated. Patients in Cohort 2 will be treated with a high dose. Cohort 3 will consist of the 5 patients that were treated in Cohort 1 but not in Cohort 2, and the 5 patients that were newly enrolled in Cohort 2. This design will result in having 10 patients treated for each dose and all patients having two administrations at two different dose levels.

Intervention

rhFVIIa will be administered at a low, mid and high dose intravenously as a 2-3 minute bolus dose. Each patient will receive two administrations (at a

different dose level).

Study burden and risks

The study day is intensive as a consequence of the relatively frequent blood sampling. The insertion of a canule can be painful and result in a bruise. There is a potential risk for disturbance of coagulation, but the risks for the volunteers are small, because they have a bleeding tendency.

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

1. be male with a diagnosis of moderate or severe congenital hemophilia A and/or B (with or

without inhibitors);2. be 18 years or older, up to and including 75 years of age;3. be capable of understanding and willing to comply with the conditions of the protocol;4. have read, understood and provided written informed consent

Exclusion criteria

1. have any coagulation disorder other than hemophilia A or B;2. have a body weight >105 kg (231 lb);3. be immuno-suppressed (i.e., the patient should not receive systemic immunosuppressive medication <30 days prior to enrollment, CD4 counts at screening should be >200/µl);4. have a known allergy or hypersensitivity to rabbits ;5. have platelet count <100,000/mL;6. have had within one month prior to first administration of the study drug in this study a major surgical procedure (e.g. orthopedic, abdominal);7. have an active, ongoing bleeding for which the patient is being treated, or treatment for a bleeding was stopped within 24 hours of the time of study drug administration;8. have received a Factor VII or FVIIa containing product (either plasma derived or recombinant) within 72 hours prior to any study drug administration;9. have received an investigational drug within 30 days of the first study drug administration, or is expected to receive such drug during participation in this study;10. have a clinically relevant hepatic (hepatic enzymes >3 times the upper limit of normal) and/or renal impairment (creatinine >2 times the upper limit of normal);11. have a history of arterial and/or venous thromboembolic events (such as myocardial infarction, ischemic strokes, transient ischemic attacks, deep venous thrombosis or pulmonary embolism) within 2 years prior to first dose of study drug, have an arterial stent in place or have clinically significant atherosclerotic disease (e.g., angina pectoris, peripheral vascular disease);12. use any anticoagulant for arterial/venous obstructions and/or atrial fibrillation within 7 daysprior to first study drug administration;13. have an active malignancy (those with non-melanoma skin cancer are allowed);14. have any life-threatening disease or other disease or condition which, according to the investigator*s judgment, could imply a potential hazard to the patient, interfere with the trial participation or trial outcome

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-11-2012
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Coagulation Factor VIIa (Recombinant)
Generic name:	Coagulation Factor VIIa (Recombinant)

Ethics review

Approved WMO Date:	31-07-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-08-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-10-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-11-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2012-002285-13-NL
CCMO	NL41575.058.12