Phase 1 trial of mutant proUK: HisproUK

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON45609

Source
ToetsingOnline

Brief title
Phase 1 trial of HisproUK

Condition

- Coronary artery disorders
- Central nervous system vascular disorders
- Embolism and thrombosis

Synonym
Healthy volunteers [occlusive thrombotic diseases; any disease with a clot impairing blood flow to organ(s)]

Research involving
Human

Sponsors and support

Primary sponsor: Thrombolytic Science International
Source(s) of monetary or material Support: Thrombolytic Science International

Intervention

Keyword: HisproUK, ProUK, tPA

Outcome measures

Primary outcome

* The maximum degree of fibrinogen degradation per dose levels of HisproUK with and without tPA;

* The maximum degree of plasminogen consumption per dose levels of HisproUK with and without tPA;

* The maximum degree of *2-antiplasmin decrease per dose levels of HisproUK with and without tPA;

* The effect of HisproUK on circulating cytokines (TNFa, IL-6, IL-8 and IL-1b), with or without tPA.

* Nature, frequency, and severity of adverse events;

* Changes to vital signs, routine safety laboratory results, or ECG-findings.

Secondary outcome

* The pharmacokinetic profile of HisproUK (with or without exogenous tPA); the following parameters

* Maximum plasma concentration (Cmax)

* Time of maximum plasma concentration (tmax)

* Area under the plasma concentration time curve from time 0 to the last quantifiable point (AUCt)

* Area under the plasma concentration time curve from time 0 to infinity (AUC*)

* Apparent terminal phase rate constant (*z)

* Apparent elimination half-life (t1/2)

* Mean residence time (MRT);

Study description

Background summary

Single-chain urokinase-type plasminogen activator (pro-urokinase) is a highly effective thrombolytic drug, however, at pharmacologic concentrations it is converted to nonspecific urokinase, limiting its therapeutic use. Mutant pro-urokinase (HisproUK) is more stable. HisproUK targets primarily degraded fibrin, which is why concomitant administration with tissue plasminogen activator is proposed.

Study objective

The primary objective of the study is:
* To evaluate the overall safety and tolerability related to systemic plasminogen activation of single doses of HisproUK (part 1) and sequential administration of tPA and HisproUK (part 2)
The secondary objectives of the study is:
* To evaluate the pharmacokinetic and pharmacodynamic properties of HisproUK with (part 2) and without (part 1) tPA pretreatment.

Study design

26 healthy male volunteers will randomly and in a double-blinded manner receive a single dose of HisproUK or placebo intravenously (part 1) or a single dose of HisproUK or placebo preceded by a single mini bolus of tPA (part 2). Subjects will be divided among cohorts of 4 subjects (5 subjects in cohort 1 and 2) with alternating doses.

Intervention

Single dose of HisproUK or placebo, with (part 2) or without (part 1) a preceding single dose of tPA

Study burden and risks

Although thrombolytic drugs can impair normal haemostasis, this study is designed to maintain all participants at an adequate haemostatic level.
There is no direct benefit to subjects participating in this study as they are healthy man, however they contribute to the development of a novel drug in its class for occlusive thrombotic diseases, which are a major health burden.

Subjects will be finally compensated for their participation.

Contacts

Public
Thrombolytic Science International

Concord Ave 763D
Cambridge MA 02138
US
Scientific
Thrombolytic Science International

Concord Ave 763D
Cambridge MA 02138
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

To be eligible for inclusion a volunteer must meet all of the following criteria:
1. Male, aged between 18 and 35 years inclusive, and with a body weight of at least 60 kg and a body mass index (BMI) between 18.5 and 25 kg/m2 inclusive.
2. Be without clinical significant abnormalities according to the investigator*s judgment, based on a detailed medical history, a complete physical examination (including vital signs), a standard 12-lead electrocardiogram, urinalysis, and routine clinical laboratory tests.
3. Have normal endogenous C1-inhibitor, *2-antiplasmin, and fibrinogen levels.
4. Have a negative serology for HIV, HBsAg, and HCV.
5. Have a negative test for alcohol and drugs of abuse at screening and on study day -1.

6. Be capable of understanding and willing to comply with the conditions and restrictions of the protocol.
7. Have read, understood and provided written informed consent.

Exclusion criteria

A volunteer will not be included if he fulfils one or more of the following criteria:
1. Has a known or suspected inherited, congenital, or acquired disease or condition that affects the haemostatic or coagulation pathways or that is associated with an increased bleeding tendency.
2. Has a reasonable chance of developing a clinically significant bleeding event or a bleeding event that may go undetected for a considerable amount of time during the study, for example:
a. Has undergone major (internal) surgery or trauma within the last three months of the anticipated dosing day;
b. Has an intestinal or cerebral vascular malformation;
c. Has participated in high impact contact sports, such as kick-boxing, within two weeks of the anticipated dosing day.
3. Has received any systemically absorbed drug or substance (including prescription, over-the-counter, or alternative remedies) that is not permitted by this protocol prior to dosing without undergoing a wash-out period of at least seven times the elimination half-life of the product. For aspirin or other products inhibiting thrombocyte-aggregation the wash-out period must not be less than 28 days.
4. Has smoked tobacco in any form within three months of dosing, or has ever smoked more than five cigarettes per day (or equivalent) on average.
5. Has received blood or plasma derivatives in the year preceding the administration day.
6. Has lost blood or plasma outside the limits of the local blood donation service (i.c. Sanquin) three months prior to dosing.
7. Has a known hypersensitivity to any of the investigational material or related compounds.
8. Has a history of severe hypersensitivity or of an allergy with severe reactions.
9. Has a history of substance abuse tobacco, or alcohol.
10. Has a condition or demonstrates an attitude that in the opinion of the investigator might jeopardise the subject*s health or well-being, or the scientific integrity of the study results.
11. Is mentally or legally incapacitated to provide informed consent.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-03-2017
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Actilyse
Generic name:	alteplase
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	HisproUK
Generic name:	Single site mutant single-chain urokinase-type plasminogen activator (prourokinase)

Ethics review

Approved WMO

Date:	09-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	24-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	10-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-05-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-004851-55-NL
CCMO	NL60133.056.16