A Phase III case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0g idarucizumab (BI 655075) in patients treated wtih dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures.

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to investigate the safety and efficacy of idarucizumab in reversing the anticoagulation effect of dabigatran, in patients who have uncontrolled bleeding or require emergency surgery or invasive procedures.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON42113

Source
ToetsingOnline

Brief title
Dabigatran Antidote

Condition

- Other condition
- Vascular therapeutic procedures

- Vascular injuries

Synonym
emergency surgery/procedure + uncontrolled bleeding

Health condition

hemorragisce stroke

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer Ingelheim b.v.

Intervention

Keyword: emergency surgery/procedure, monoclonal antibody, reversal anticoagulant effect, uncontrolled bleeding

Outcome measures

Primary outcome

the primairy endpoint for this study is to demonstrate the reversal of the

anticoagulant effect of dabigatran.

Secondary outcome

The secundary objectives are the assessment of bleeding, safety, and the

pharmacokinetics of dabigatran in the presence of idarucizumab.

Study description

Background summary

currently there is no commercially available drug to reverse the anticoagulation effect of dabigatran.
for emergency situations with subjects using dabigatran, there is need for a drug to quickly reverse the anticoagulation effect of dabigatran.

An antidote was developed, acting on the dabigatran in the blood, and reversing the the anticoagulation effect of dabigatran.
this drug is called idarucizumab.

during previous studies in toal 110 subjects were treated with idarucizumab (doses between 20 mg and 8000 mg), administered in 5 to 60 minutes by intravenous injection.

From this studies it showed that the effect was nearly direct, and no observations nor laboratory parameters indicated that it would be possible to overdose a subject.
Based on these results 5 gram idarucizumab was chosen as the best dose to investigate within this trial, for all subjects.

Study objective

to investigate the safety and efficacy of idarucizumab in reversing the anticoagulation effect of dabigatran, in patients who have uncontrolled bleeding or require emergency surgery or invasive procedures.

Study design

Based on the results mentioned in chapter "background" this trial will investigate 5 gram idarucizumab (or 10 gram, if applicable) for all patients.
This trial will thus be open-label, single arm.
Subjects will be evaluated as their own control group (instead of more arms within a study) by means of labevaluations prior to the administration of antidote, between the 2 antidote vials, and at various timepoints after the antidote administration.

A lot of the patients suitable for the trial, will be brought into the hospital through Emergency Room (ER). few will already be admitted and might require unplanned emergency procedures. to make sure all subjects potentially suitable for the trial are described correctly here, they will be referred to as "brought in" from now on.

within the protocol there is a distinction between population A (patients who are taking dabigatran, and have uncontrolled/life threatening bleeding requiring urgent medical intervention) and B (patients who are taking dabigatran who may not be bleeding, but do require an emergency surgery or precedure for a condition other than bleeding). regardless of population A or B, all subjects will have the possibility to be treated with a participating site.

when subjects are brought in, their condition will be evaluated by a physician, to determine the need for an antidote (inclusion/exclusion criteria) + the use

of dabigatran is confirmed.
When the need for treatment is decided and consented upon (see section informed consent process) the antidote will be administered.

Prior, during and after administration of the antidote, labparameters will be taken for PK/PD and safety determinations. all details could be found in protocol flowchart. In the rare case an additional dose of 5 gram idarucizumab is administered labparameters will again be taken or PK/PD and safety analysis.

After approximately 24 hours (visit 3) restart of anticoagulation can be evaluated + the selected drug/dose will be documented.

Patients will be followed up untill 90 days (visit 6) after administration of vial 2 for safety and labevaluations.

Intervention

every patient will receive 1 administration of open label treatment with 5 gram idarucizumab, to reverse the anticoagulation effect of dabigatran.
this dose will be intravenously administered through 2 vials of 50ml each, max 15 minutes apart.

In rare cases in which the bleeding does not seize after 5 gram idarucizumab the investigator may administer an additional dose of 5 gram idarucizumab.

Study burden and risks

Burden for patients will mainly be caused by the first 24 hours after being brought in.
Burden will consist of frequent blood draws surrounding the administration of the antidote

Patients will be given the choice to participate, or not to participate tot his trial. There is no comparable alternative for the study drug with the same effect within the same timeframe.
Subjects might experience this as a burden.

Patients might be brought in, in a condition that somebody else (see section informed consent) will decide for them about study participation. Subjects might experience this as a burden.

Patients will be under extra care of their research physician for 90 days following the administration of the antidote. The first 24 hours will be most time consuming, but as this coincides with the admission a subject is exposed to anyway due to it*s condition, this will not take more time than whilst not participating into the study.

Depending on a subject*s condition, the time investment expected after visit 3 is fairly little, but this may vary from subject to subject.

The to be expected risks are low, as described in the patient information sheet.
The consist of risks with blood draws, ECG, allergic reactions, interactions with other drugs, early discontinuation, pregnancy&breastfeeding and unforeseen risks.

Increasing the dose to 10 gram did not show any effect on adverse event numbers based on pre-clinical and clinical data.

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

Group A (Bleeding patients)
-- Overt bleeding judged by the physician to require a reversal agent
-- Currently taking dabigatran etexilate
-- At least 18 years of age
-- Written informed consent;- Group B (Patients who are taking dabigatran who may not be bleeding, but do require an emergency surgery or invasive procedure for a condition other than bleeding
-- Condition requiring emergency surgery or procedure where adequate hemostasis is required. Emergency is defined as within the next 8 hours.
-- Current treatment with dabigatran
-- At least 18 years of age
-- Writen Informed consent.

Exclusion criteria

- Group A (Bleeding Patients);-- Patients with minor bleeds (epistaxis, hematuria) who can be managed with standard supportive care. ;-- Patients with no clinical signs of bleeding ;-- Contraindications to study medication including known hypersensitivity to the drug or its excipients. (patients with hereditary fructose intolerance may react to sorbitol);- Group B (Patients who require emergency surgery or procedure);-- A surgery or procedure which is elective or where the risk of uncontrolled or unmanageable bleeding is low.;-- Contraindications to study medication including known hypersensitiity to the drug or its excipients. (patients with hereditary fructose intolerance may react to sorbitol)

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):	13-02-2015
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PraxBind
Generic name:	Idarucizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-004813-41-NL
CCMO	NL48017.018.14