Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Have Acute Major Bleeding (ANNEXA-4).

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Primary Efficacy Objectives:* To demonstrate the decrease in anti-fXa activity following andexanet treatment.* To evaluate the hemostatic efficacy following andexanet treatment.Secondary Efficacy Objective:* To assess the relationship between...

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

Summary

ID

NL-OMON45055

Source
ToetsingOnline

Brief title
ANNEXA-4

Condition

- Other condition

Synonym
Acute Major Bleeding

Health condition

Acute Major Bleeding

Research involving

Human

Sponsors and support

Primary sponsor: PORTOLA PHARMACEUTICALS, INC.
Source(s) of monetary or material Support: Portola Pharmaceuticals

Intervention

Keyword: Acute major bleeding, Andexanet alfa, Factor Xa

Outcome measures

Primary outcome

The first primary efficacy endpoint * i.e., percent change in anti-fXa activity from baseline (last measurement before administration of andexanet) to nadir (the lowest level measured between 5 minutes prior to the start of andexanet administration and 10 minutes after the end of the andexanet administration) * will be calculated for each patient as change = 100 %×(post-baseline)/baseline. Percent change from baseline in anti-fXa activity will be assessed with two-sided 95% CIs. A nonparametric CI for the median will be reported. If the nonparametric CI for the median excludes 0, the first primary objective will be considered to have been met.

The second primary efficacy endpoint * the proportion of patients who are adjudicated to have effective hemostasis (excellent or good) by the independent EAC * will be summarized as a point estimate with an asymptotic 95% confidence interval.

The primary endpoints, including the specific comparators and the specific analysis sets for the second primary endpoint, will be ordered in a fixed

sequence multiple comparisons (i.e., hierarchical) fashion.

The assessment of the relationship between effective hemostasis and percent decrease in anti-fXa activity will use the following validation procedures. An analysis of Receiver Operator Characteristics (ROC) will be the primary tool used to assess the relationship. A test of change in anti-fXa activity (percent change from baseline) in patients who do and do not achieve effective hemostasis will be used to support the ROC graph.

Secondary outcome

Two other analyses will also be presented:

1) Analysis of *Responders* (patients with a large percent decrease in anti-fXa activity) anchored to Hemostatic Efficacy.

2) Cumulative Distribution Function (CDF) Analysis.

Counts data will be summarized by observed rates and exact 95% CIs.

In addition, other analyses will be performed, allowing for adjustment of potentially confounding variables. Variables that may confound evaluation of a correlation between reversal of anti-fXa activity with effective hemostasis include anatomical location of bleeding, mechanism of injury (e.g., blunt vs. penetrating trauma; traumatic vs. spontaneous), severity of injury, severity of bleeding, presence and timing of interventions to stop bleeding (e.g., endoscopic cautery of bleeding ulcers, surgical ligation of bleeding vessel), and use of coagulation or hemostatic factors.

Further details on the analysis methods for the efficacy endpoints will be

provided in the Statistical Analysis Plan (SAP).

Study description

Background summary

FXa inhibitors, represent a new class of anticoagulants that are rapidly increasing in use. Despite their clinical benefit, however, fXa inhibitors are associated with bleeding events, some of which are life-threatening or fatal. Despite the urgent need for such an effective antidote, no such agent currently exists. Andexanet is being developed as a specific antidote for fXa inhibitors. Andexanet is a modified fXa protein that has been truncated and inactivated so that it lacks physiologic blood coagulation factor activity. Reversal of anticoagulation is achieved because andexanet retains the ability to bind fXa inhibitor drugs with high affinity, thus preventing them from binding to and inhibiting native fXa.

Study objective

Primary Efficacy Objectives:
* To demonstrate the decrease in anti-fXa activity following andexanet treatment.
* To evaluate the hemostatic efficacy following andexanet treatment.

Secondary Efficacy Objective:
* To assess the relationship between decrease in anti-fXa activity and achievement of hemostatic efficacy in patients receiving a fXa inhibitor who have acute major bleeding and reduced fXa activity.

Study design

This is a multicenter, prospective, open-label study of andexanet alfa in patients presenting with acute major bleeding who have recently received one of the following fXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin.

Intervention

All patients receive a 15-30 minutes bolus infusion immediately followed by an infusion during 2 hours. The dosing of both type of infusion is dependent on the type of anticoagulant they used and the time elapsed between last intake of anticoagulant and occurrence the bleeding.

Study burden and risks

Of the side effects that have been reported, those most common, which are thought to be related or possibly related to andexanet, include:
* Infusion reactions
* Abnormal taste during the infusion
* Leg twitching
* Sensation of the heart beating rapidly
* Generalized itching
* Fatigue

Another possible risk that may occur with any drug that reverses blood thinning is the formation of blood clots. Blood clots can cause strokes, heart attacks, leg swelling, and difficulty breathing. Several test tube experiments showed that there is a possibility that andexanet interacts with blood proteins which then makes the blood easier to clot. No animals or people that have received andexanet in past studies have developed blood clots.

Andexanet is a protein drug and as such, may cause allergic reactions that could be mild or severe (anaphylaxis). Anaphylaxis (severe allergy) has not been seen in any of the 211 subjects that have been treated with andexanet. Symptoms of allergic reactions might include hives, swelling of the face or throat, and low blood pressure. Allergic reactions might need medical treatment with drugs, fluids, or if breathing problems develop, with a plastic tube to protect your windpipe.

Because andexanet is similar to one of your natural clotting factors, it is possible that an antibody against andexanet could also recognize your natural clotting factor and perhaps interfere with normal blood clotting for an unknown period of time. No people receiving andexanet have developed antibodies against clotting factors.

Contacts

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Either the patient or his or her medical proxy (or legally acceptable
designee) has been adequately informed of the nature and risks of the study and has given written
informed consent prior to Screening;
2) The patient must be at least 18 years old at the time of Screening;
3) The patient must have an acute overt major bleeding episode requiring urgent reversal of anticoagulation; Acute major bleeding requiring urgent reversal of anticoagulation is defined by at
least ONE of the following:
- Acute overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of haemodynamic compromise, such as severe
hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise
explained;
- Acute overt bleeding associated with a fall in haemoglobin level by * 2 g/dL, OR a Hgb * 8 g/dL
if no baseline Hgb is available;
- Acute bleeding in a critical area or organ, such as, intra-spinal, pericardial or intracranial.
4) The patient, for whom the bleeding is intracranial or intraspinal must have undergone a CT or
MRI scan demonstrating the bleeding.
5) The patient received or is believed to have received one of the following within 18 hours prior
to andexanet administration: apixaban, rivaroxaban, edoxaban or enoxaparin (dose of enoxaparin
*1mg/kg/d).

6) For patients with ICH, there must be a reasonable expectation that andexanet treatment will
commence within 2 hours of the baseline
imaging evaluation.

Exclusion criteria

1) The patient is scheduled to undergo surgery in less than 12 hours with the exception of minimally invasive surgery/procedures (e.g., endoscopy, bronchoscopy, central lines, Burr holes);
2) A patient with ICH has any of the following:
* Glasgow coma score < 7
* Estimated intracerebral haematoma volume >60 cc as assessed by the CT or MRI.
3) Patients with visible, musculoskeletal, or intra-articular bleeding as the qualifying bleed.
4) The patient has an expected survival of less than 1 month;
5) The patient has a recent history (within 2 weeks) of a diagnosed thrombotic event (TE) as follows: venous thromboembolism (VTE; e.g., deep venous thrombosis, pulmonary embolism, cerebral venous thrombosis), myocardial infarction, disseminated intravascular coagulation (DIC), cerebral vascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to Screening;
6) The patient has severe sepsis or septic shock at the time of Screening;
7) The patient is pregnant or a lactating female;
8) The patient has received any of the following drugs or blood products within 7 days or Screening:
* Vitamin K antagonist (VKA) (e.g., warfarin);
* Dabigatran;
* Prothrombin Complex Concentrate products (PCC, e.g., Kcentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®);
* Whole blood, plasma fractions
Note: Administration of platelets or packed red blood cells (PRBCs) is not an exclusion criterion;
9) The patient was treated with an investigational drug <30 days prior to Screening.

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):	16-07-2016
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Andexanet alfa
Generic name:	N/A

Ethics review

Approved WMO Date:	18-08-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2016

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2018
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	EUCTR2015-001785-26-NL
ClinicalTrials.gov	NCT02329327
CCMO	NL53914.018.15