A phase 4 Randomized Clinical Trial of Andexanet Alfa [Andexanet Alfa for injection] in acute intracranial haemorrhage in patients receiving an oral factor Xa inhibitor

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON49173

Source
ToetsingOnline

Brief title
ANNEXA-I

Condition

- Central nervous system vascular disorders
- Vascular haemorrhagic disorders

Synonym
intracranial bleeding

Research involving
Human

Sponsors and support

Primary sponsor: Portola Pharmaceuticals Inc.
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Andexanet Alfa, intracranial haemorrhage

Outcome measures

Primary outcome

Primary Efficacy Endpoint

• Effective hemostasis as determined by the blinded EAC.

Effective hemostasis is defined as no greater than a 35% increase from baseline

in hematoma volume/thickness at 12 hours post randomization, AND less than a 7

point increase from baseline NIHSS score at 12 hours post randomization

Secondary outcome

Secondary Efficacy Endpoints

• Maximum reduction in anti-fXa activity.

• Minimum value of anti-fXa activity post randomization.

Study description

Background summary

Andexxa® (andexanet) has been approved for use in the United States as a reversal agent for patients who have taken the blood thinning drugs, rivaroxaban or apixaban and who are experiencing a serious or life-threatening bleeding episode. Andexanet is only conditionally (or provisionally) approved, which means it has not been fully demonstrated that andexanet actually helps to stop bleeding. This study is intended to determine whether andexanet is more effective than usual care to stop bleeding in this setting.

Andexanet is not approved in other regions, such as the European Union or Canada, but is available for use in clinical research studies. In all regions, andexanet is considered an experimental drug for patients who are taking the blood thinner edoxaban (also known as Savaysa® or Lixiana®) and who are experiencing a serious or life-threatening bleeding episode.

Andexanet was specifically made for Factor Xa inhibitors. Andexanet is a recombinant, modified human protein and inactive form of factor Xa, a protein in the blood that plays a key role in normal blood clotting. Andexanet works by binding to the blood thinner drug so the blood thinner drug is no longer able to interfere with the blood clotting process.

Andexanet has been studied in animals, in approximately 416 healthy volunteers, most of whom have been treated with andexanet after receiving a blood thinner drug, and in 185 patients who have experienced a serious or life-threatening bleed while taking a Factor Xa blood thinner drug.

Study objective

In oral FXa inhibitor-treated patients with acute intracranial bleeding, the objectives of this study are as follows:
Primary Efficacy Objective:
• To evaluate the effect of andexanet versus usual care on the rate of effective hemostasis.

Secondary Efficacy Objective:
• To evaluate the effect of andexanet versus usual care on anti fXa activity.

Additional Efficacy Objectives:
• To evaluate the effect of andexanet versus usual care on thrombin generation.
• To evaluate the effect of andexanet versus usual care on clinical and functional neurologic status.
• To assess the relationship between anti-fXa activity and the achievement of hemostatic efficacy.

Safety Objectives:
• To evaluate the occurrence of thrombotic events at 30 days.
• To evaluate in-hospital and 30-day mortality (all-cause, cardiovascular, and bleeding).
• To evaluate the length of initial hospitalization for primary bleeding event.
• To evaluate the rate of re-hospitalization.
• To evaluate adverse events and vital signs.
• To evaluate the immunogenicity of andexanet.

Study design

This is a randomized, multicenter clinical trial designed to determine the efficacy and safety of andexanet compared to usual care in patients presenting with acute intracranial hemorrhage within 12 hours of symptom onset (from the baseline scan) and within 15 hours of taking an oral factor Xa inhibitor (from randomization). The study will use a prospective, randomized, open label design, as it is unfeasible to blind the Investigator to the treatment assignment given the many potential therapeutic options available under usual care treatment. The primary efficacy outcome will be adjudicated by a blinded Endpoint Adjudication Committee (EAC). To support the adjudication of hemostatic efficacy, a blinded Imaging Core Laboratory will review all available scans. Approximately 440 patients are planned to be enrolled in the study.

Once the Informed Consent Form (ICF) is signed and eligibility is confirmed, patients will be randomized to receive either andexanet or usual care. Randomization must occur within 15 hours following the last dose of the FXa inhibitor. If the time from last dose of FXa inhibitor is unknown, the patient is not eligible. If a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL, the patient may be enrolled, irrespective of the time of the last dose (as long as it is known). The prespecified time periods and/or anti-fXa activity levels are designed to ensure patients have therapeutic anti-fXa activity levels. Usual care will consist of any treatment(s) (including no treatment) other than andexanet that the Investigator and/or other treating physicians consider to be appropriate. For andexanet treatment, patients will receive one of two dosing regimens of andexanet based on which FXa inhibitor they received and the amount and timing of the most recent dose. Andexanet will be given via an intravenous (IV) bolus administered over ~15-30 minutes followed immediately by a continuous infusion administered over ~120 minutes. There will be no cross-over between treatment groups.

It is intended that all patients initiate treatment as soon as possible after the treatment allocation is known (this will necessitate preparation of andexanet for all patients prior to randomization, with wastage of andexanet product for those randomized to usual care). For: 1) anti-fXa activity; and 2) diagnostic evaluations to support hemostatic efficacy (i.e., imaging tests), baseline is defined as the most recent assessment within 15 minutes and 120 minutes prior to randomization, respectively. For post-baseline efficacy assessments, time 0 is defined as randomization.

Adverse Events (AEs), including SAEs and survival will be followed through the Day 30 post-treatment visit for all patients. The study Schedule of Activities can be found in Appendix A.

The primary efficacy endpoint will be adjudicated based on data collected through 12 hours post randomization. The following data are planned to be captured: imaging and clinical modalities: brain Magnetic Resonance Imaging (MRI) or Computed Tomography (CT), and assessment using the National Institutes of Health Stroke Score (NIHSS) performed by a person blinded to treatment allocation (Appendix E).

The blinded, independent EAC will adjudicate hemostatic efficacy, as well as

all deaths and potential thrombotic events. All source documents will be redacted to maintain the blinding of the EAC. The independent EAC will be blinded to all anti-fXa levels and treatment assignments. An independent Data Safety Monitoring Board (DSMB) will periodically review all safety data in aggregate. In addition, an interim efficacy analysis will be conducted when 50% of the patient population has been adjudicated. Based on the above, DSMB will be empowered to recommend alterations or stoppage of the study if warranted.

Intervention

Andexanet will be administered as an IV bolus, immediately followed by a continuous infusion. There are two possible dosing regimens:
Dose Initial IV Bolus
* Follow-on IV Infusion *

Low 400 mg at a target rate of 30 mg/min for ~15
minutes 480 mg at a target rate of 4 mg/min for 120 minutes

High 800 mg at a target rate of 30 mg/min for up to ~30 minutes 960
mg at a target rate of 8 mg/min for 120 minutes

Study burden and risks

Not applicable

Contacts

Public
Portola Pharmaceuticals Inc.

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South San Francisco, CA 94080
US
Scientific
Portola Pharmaceuticals Inc.

East Grand Avenue 270
South San Francisco, CA 94080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Written informed consent. 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.
In the Netherlands, deferred consent procedure is allowed. In cases of deferred consent,
the time of the study physician*s documented decision to include the patient into the
study will serve as *time of consent* with respect to protocol-specific procedures.
In all cases where the patient does not sign informed consent for prior to study entry,
informed consent from the patient will be obtained as soon as realistically possible after
inclusion in the trial and in accordance with the Declaration of Helsinki, ICH-GCP, the
Data Protection Directive (Directive 95/46/EC) and national and local regulations.
2. Age 18 years old or greater at the time of consent.
3. An acute intracranial bleeding episode, defined as any amount of blood acutely observed radiographically within the cranium. Patients may have extracranial bleeding (e.g., gastrointestinal, intraspinal) additionally, but the intracranial hemorrhage must be considered the primary bleed.
4. Performance of a head CT or MRI scan demonstrating the intracranial bleeding within 2 hours prior to randomization (the baseline scan may be repeated to meet this criterion).
5. Treatment with an oral FXa inhibitor (apixaban, rivaroxaban, or edoxaban) within 15 hours prior to randomization. If the time of last dose is unknown, the patient is not eligible for the study. If a patient is documented to have an anti-fXa activity > 100 ng/mL within 2 hours prior to consent, they may be

enrolled irrespective of the time since last dose (as long as it is known).
6. Time from bleeding symptom onset < 12 hours prior to the baseline imaging scan. Time of trauma (if applicable) or time last seen normal may be used as surrogates for time of symptom onset.

Exclusion criteria

If a patient meets any of the following criteria, he/she is not eligible to participate in this trial.
1. Planned surgery, including Burr holes for hematoma drainage, within 12 hours after randomization. Minimally invasive surgery/procedures not directly related to the treatment of intracranial bleeding are allowed (e.g., Burr holes for intracranial pressure monitoring, endoscopy, bronchoscopy, central lines* see Section 7.3 and Appendix F).
2. Glasgow Coma score < 7 at the time of consent. If a patient is intubated and/or sedated at the time of consent, they may be enrolled if it can be documented that they were intubated/sedated for non-neurologic reasons within 2 hours prior to consent.
3. Estimated intracerebral hematoma volume > 60 mL assessed by the baseline CT or MRI.
4. Any bleeding into the (intracranial) epidural space.
5. Anticipation that the baseline and follow up brain scans will not be able to use the same imaging modalities (i.e., patients with a baseline CT scan should have a CT scan in follow up; similarly for MRI).
6. Expected survival of less than 1 month.
7. Recent history (within 2 weeks) of a diagnosed Thrombotic Event (TE) or clinically relevant symptoms of the following: 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, acute coronary syndrome, or arterial systemic embolism within 2 weeks prior to Screening (see Appendix G for DIC scoring algorithm).
8. Acute decompensated heart failure or cardiogenic shock at the time of randomization (see Appendix H for cardiogenic shock definition).
9. Severe sepsis or septic shock at the time of randomization (see Appendix H for sepsis definition).
10. Pregnant or lactating.
11. Receipt of any of the following drugs or blood products within 7 days prior to consent:
a. Vitamin K Antagonist (VKA) (e.g., warfarin).
b. Dabigatran.
c. Prothrombin Complex Concentrate products (PCC, e.g., Kcentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®), or anti-inhibitor coagulant complex (e.g., FEIBA®).
12. Past or planned use of andexanet.

13. Treatment with an investigational drug < 30 days prior to consent.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-11-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Recombinant Factor Xa Inhibitor Antidote
Generic name:	Andexanet

Ethics review

Approved WMO Date:	30-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2019

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Not approved Date:	15-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2022
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	EUCTR2018-002620-17-NL
ClinicalTrials.gov	NCT03661528
CCMO	NL69515.018.19