A Randomized Clinical Trial of Andexanet Alfa in acute intracranial haemorrhage in patients receiving an oral factor Xa inhibitor

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

Summary

ID

NL-OMON54049

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: Alexion Pharmaceuticals, Inc.
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Andexanet Alfa, intracranial haemorrhage

Outcome measures

Primary outcome

• Effective hemostasis 12 hours post-randomization as determined by the blinded

EAC, based on prespecified criteria documented in the Adjudication Charter (see

Appendix B).

Effective hemostasis is defined as:

1 = for patients with hemostatic efficacy rated by the EAC as excellent or

good, and

0 = for patients with hemostatic efficacy rated by the EAC as poor/none.

Secondary outcome

• Percent change from baseline to nadir in anti-fXa activity during the first 2

hours post-randomization.

• Change from baseline in NIHSS at 24 hours post-randomization.

• Change from baseline in GCS score at 24 hours post-randomization.

• Proportion of neurologic deterioration, as defined by NIHSS increase >=4 or

GCS score decrease >= 2 at 24 hours post-randomization versus

baseline

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 intracerebral 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.
To evaluate the effect of andexanet versus usual care on neurologic function.
Additional Efficacy Objectives:
To evaluate the effect of andexanet versus usual care on thrombin generation.
To assess the relationship between anti-fXa activity and the achievement of hemostatic efficacy.
To evaluate the occurrence and outcome of extracranial bleeding.
To evaluate the effect of andexanet versus usual care on health-related quality

of life.
Safety Objectives:
To evaluate the occurrence of thrombotic events (TEs) at 30 days.
To evaluate in-hospital and 30-day mortality (all-cause, cardiovascular, and bleeding).
To evaluate the occurrence of invasive intracranial procedures post-randomization.
To evaluate the length of initial hospitalization for primary bleeding event.
To evaluate the rate of re-hospitalization.
To evaluate adverse events (AEs) 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 intracerebral hemorrhage within 6 hours of symptom onset (from the baseline scan) and within 15 hours of taking an oral FXa 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 900 patients are planned to be enrolled in the study.
Once the eligibility criteria are confirmed, and baseline assessments are performed, patients will be randomized 1:1 to receive either andexanet or usual care stratified by the site*s intended-usual-care-agent response and also the time from symptomonset to baseline scan. Randomization must occur within 15 hours following the last dose of the FXa inhibitor. If a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (or over the equivalent IU/mL threshold on a Low-Molecular-Weight Heparin (LMWH) assay; see Laboratory Manual), the patient may be enrolled, irrespective of the time of the last dose, and the patient should receive the high andexanet dosing regimen. The prespecified time periods and/or anti-fXa activity levels are designed to ensure patients have sufficiently high anti-fXa activity. Usual care will consist of any treatment(s) (including no treatment) other than andexanet administered within 3 hours after randomization 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 to 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. 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, including serious AEs (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 elements: brain Magnetic Resonance Imaging (MRI) or Computed Tomography (CT), assessment using the National Institutes of Health Stroke Score (NIHSS) performed by a person blinded to treatment allocation (Appendix E), and concomitant medication entry and hospital records for rescue therapy.
The blinded, independent EAC will oversee the adjudication of hemostatic efficacy, as well as all deaths and potential TEs. All source documents will be redacted to maintain the blinding of the EAC. The independent EAC will be blinded to all anti-fXa activities and treatment assignments. An independent Data Safety Monitoring Board (DSMB) will periodically review all safety data in aggregate, and also conduct an interim analysis after 50% of the anticipated sample size has been adjudicated. The DSMB will be empowered to make recommendations regarding study modification or to suggest stopping the study early for reasons related to balance of risk and benefit. The DSMB Charter outlines all activities of this Committee.

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
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Scientific
Alexion Pharmaceuticals, Inc.

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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. Written informed consent. Either the patient or his or her legally authorized representative (LAR) if permissible by local or regional laws and regulations has been adequately informed of the nature and risks of the study and has given written informed consent prior to Screening.
-Deferred consent procedure is allowed where approved by local ethics committees. 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 prior to study entry, informed consent from the patient (or LAR) will be obtained as soon
as realistically possible after inclusion in the study 18-513 and in accordance with
the Declaration of Helsinki, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP), the EU General Data Protection Regulation (GDPR) and national
and local regulations.
2. Age >=18 years old at the time of consent.
3. An acute intracranial bleeding episode, defined as an estimated blood volume >=0.5 mL to <=60 mL acutely observed radiographically within the cranium. Patients may have extracerebral (e.g., subdural, subarachnoid, epidural) or extracranial bleeding (e.g., gastrointestinal, intraspinal) additionally, but the intracebral hemorrhage must be considered the significant bleed at the time of enrollment.
4. Performance of a head CT or MRI scan demonstrating the intracerebral bleeding within 2 hours prior to randomization (the baseline scan may be repeated only once to meet this criterion).
5. Treatment with an oral FXa inhibitor (apixaban [last dose 2.5 mg or greater], rivaroxaban [last dose 10 mg or greater], or edoxaban [last dose 30 mg or greater]):
-<=15 hours prior to randomization.
-> 15 hours prior to randomization or unknown time of last dose, if 1) the local anti-fXa activity > 100 ng/mL (for direct fXa inhibitors (apixaban, rivaroxaban or edoxaban); and
2) the local anti-fXa activity level is obtained within 2 hours prior to consent, performed as per standard care. Note: Patients enrolled in this manner should
receive a high andexanet dosing regimen.
6. Time from bleeding symptom onset < 6 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.(If the baseline scan is repeated to meet Inclusion Criterion #4, the time from bleeding symptom onset must be < 6 hours prior to the repeated baseline imaging scan.)
7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy for 30 days after the last dose of study drug.
8.Have a negative pregnancy test documented prior to enrollment (for women of childbearing potential).
9. NIHSS score <= 35 at the time of consent.

Exclusion criteria

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 and that are not expected to significantly affect haematoma volume are allowed (e.g., Burr holes for intracranial pressure monitoring, endoscopy, ronchoscopy, central lines*see Section 7.2 and 7.3 and Appendix G).
2. Glasgow Coma score (GCS) < 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 nonneurologic
reasons within 2 hours prior to consent.
3. Purposefully left blank to align with the programmed database.
4. 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).
5. Expected survival of less than 1 month (not related to intracranial bleed).
6. Recent history (within 2 weeks) of a diagnosed TE or clinically relevant symptoms of the following: -Venous Thromboembolism (VTE: e.g., deep venous thrombosis, pulmonary embolism [PE], cerebral venous thrombosis), myocardial infarction [MI], Disseminated Intravascular Coagulation (DIC), cerebral vascular accident, transient ischemic attack [TIA], acute coronary syndrome, or arterial systemic embolism (see Appendix H for DIC scoring algorithm).
7. Acute decompensated heart failure or cardiogenic shock at the time of randomization (see Appendix A for cardiogenic shock definition).
8. Severe sepsis or septic shock at the time of randomization (see Appendix A for sepsis definition).
9. The patient is a pregnant or lactating female.
10. 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®), FFP and whole blood.
11. Past use of andexanet (or planned use of commercial andexanet).
12. Treatment with an investigational drug < 30 days prior to consent.
13. Any tumor-related bleeding.
14. Known hypersensitivity to any component of andexanet.

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:	Completed
Start date (anticipated):	02-11-2020
Enrollment:	45
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ondexxya (R)
Generic name:	Andexanet
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-11-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2020
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2022
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2023
Application type:	Amendment
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Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	NL75568.018.20

Study results

Date completed: 05-06-2023

Results posted: 06-08-2024

First publication
22-11-2023