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A clinical trial looking at the effectiveness and safety of a human plasma-derived antithrombin called Atenativ, for patients who are resistant to heparin (a blood thinner) and are undergoing cardiac surgery with cardiopulmonary bypass

Submission date
01/08/2024

Recruitment status
Recruiting

Registration date
24/10/2024

Overall study status
Ongoing

Last Edited
13/01/2026

Condition category
Haematological Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The study evaluates how well different doses of the drug, Atenativ work to restore and maintain participants' responsiveness to another drug called heparin. Heparin is given during cardiac surgery to prevent blood from clotting whilst on a heart and lung machine.

Who can participate?
Male and female patients aged 18-85 years old who require cardiac surgery using a heart and lung machine and who are found to be 'heparin resistant'.

What does the study involve?
Patients who consent to the study and are 'heparin resistant' will be randomised (allocated by chance) into one of three groups: 1) Atenativ at a dose of 30 International Units per kilogram body weight; 2) Atenativ at a dose 60 of International Units per kilogram body weight; 3) Placebo (a liquid that looks like the study drug but contains no medicine). Participants will be treated as per their allocated treatment group alongside the usual treatment required for cardiac surgery. During surgery, blood samples will be taken at predetermined time points to monitor levels of a compound known as 'antithrombin' and blood cell levels. In addition to the expected hospital visits for cardiac surgery patients, participants will receive a final phone call 28 days after their procedure, when they will be asked about their health. The time from consenting to the study until the final phone call will be between 1-2 months.

What are the possible benefits and risks of participating?
Taking part in this study may not result in personal medical benefit however the knowledge gained may benefit future patients.

Some risks are associated with taking part, as sometimes, people receiving medications made from human blood plasma, such as Atenativ, have allergic/hypersensitivity reactions.

Risk from the study drug: Some people treated with medications made from human blood plasma, such as Atenativ, have allergic or hypersensitivity reactions. To minimise this risk the protocol excludes the inclusion of patients with known hypersensitivity/allergic reaction to antithrombin or any of Atenativ excipients and patients with a history of anaphylactic reaction(s) to blood or blood components.
Despite Atenativ undergoing stringent treatment to render it 'safe', the risk that it may transmit infections/viruses, cannot be removed entirely. Some viruses remain and these are dangerous to the foetus and people with immune system disorders or some types of anaemia. There may also be unknown risks to the embryo/foetus. The protocol therefore excludes pregnant females and requires that females use effective contraception throughout the study and report any pregnancy immediately.

Risks from a blood draw and the infusion. Both procedures may cause pain, bruising, light-headedness, fainting, scarring, infection and clotting. To minimise this risk these procedures will be performed only by appropriately qualified staff.
The study staff will closely monitor the participants for any signs of adverse reactions during surgery, when the study drug is administered and during the participant's hospital stay; if the participants display any signs or symptoms they will be treated accordingly. Once discharged from the hospital there is a telephone call to monitor the participants' health approximately 28 days after surgery.

All the risks associated with the study are found in the Participant Information Sheet and the participants are informed to speak with their study doctor if they have any concerns.

Where is the study run from?
Octapharma AG

When is the study starting and how long is it expected to run for?
July 2024 to March 2028

Who is funding the study?
Octapharma AG

Who is the main contact?
Sigurd Knaub (Octapharma AG), sigurd.knaub@octapharma.com

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT06096116

Clinical Trials Information System (CTIS)
2023-507560-39

Integrated Research Application System (IRAS)
1009957

Study information

Scientific Title
Phase 3, double-blind, placebo-controlled, multicentre study on the efficacy and safety of human plasma derived antithrombin (Atenativ) in heparin-resistant patients scheduled to undergo cardiac surgery necessitating cardiopulmonary bypass

Acronym
ATN-108

Study objectives
The primary objective of this study is to evaluate the efficacy of two different doses of Atenativ, versus placebo, in restoring and maintaining heparin responsiveness in adult patients undergoing cardiac surgery necessitating cardiopulmonary bypass (CPB)

Secondary objectives:
1. Amounts of further therapy containing antithrombin required for restoring heparin responsiveness before CPB & maintaining it during CPB

2. Effect of Atenativ on the coagulation parameter used for evaluating heparin resistance, namely the activated clotting time (ACT)
3. Capacity of Atenativ to modify the antithrombin plasma concentration
4. The impact of Atenativ on the intraoperative use of heparin following the infusion of Atenativ or placebo
5. Any requirement for frozen plasma (FP) or antithrombin concentrates for reasons other than restoring or maintaining heparin responsiveness, both intraoperatively & postoperatively
6. Any intraoperative and postoperative use of other allogeneic blood products, coagulation factor concentrates & other haemostatic-relevant therapies
7. Volume of chest tube drainage & the need for reoperation due to bleeding
8. Safety of Atenativ
9. Any post-CPB requirement for additional therapy containing antithrombin to restore heparin responsiveness

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 15/10/2024, Yorkshire & The Humber - Sheffield Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 (0)2071048139, (0)2071048135, (0)207 104 8210; sheffield.rec@hra.nhs.uk), ref: 24/YH/0183

Study design
Interventional double blind randomized parallel group placebo controlled trial

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Restoring and maintaining heparin responsiveness, acquired antithrombin deficiency (heparin resistance) in adult patients undergoing cardiac surgery necessitating cardiopulmonary bypass (CPB)

Interventions
Current interventions as of 30/12/2025:
The intervention is a one-time infusion of Atenativ (a solvent/detergent and heat-treated antithrombin concentrate derived from human plasma) at a dose of 30 International Units per kilogram body weight or 60 International Units per kilogram body weight or placebo (a liquid that looks like the study drug but contains no medicine) at a volume corresponding to either the low dose or high dose of Atenativ. Atenativ or placebo will be administered during cardiac surgery before going on cardiopulmonary bypass. Computer software and an online tool (IVRS system) will be used to randomly allocate the treatment groups in a 2:2:1:1 ratio. Neither the investigator nor the participant will know to which group they have been allocated. All participants will be followed up during their post-operative hospital stay and they will receive an additional telephone call approximately 28 days after their surgery.

Previous interventions:
The intervention is a one-time infusion of Atenativ (a solvent/detergent and heat-treated

antithrombin concentrate derived from human plasma) at a dose of 15 International Units per kilogram body weight or 30 International Units per kilogram body weight or placebo (a liquid that looks like the study drug but contains no medicine) at a volume corresponding to either the low dose or high dose of Atenativ. Atenativ or placebo will be administered during cardiac surgery before going on cardiopulmonary bypass. Computer software and an online tool (IVRS system) will be used to randomly allocate the treatment groups in a 2:2:1:1 ratio. Neither the investigator nor the participant will know to which group they have been allocated. All participants will be followed up during their post-operative hospital stay and they will receive an additional telephone call approximately 28 days after their surgery.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Antithrombin III

Primary outcome(s)
Current primary outcome as of 30/12/2025:
The percentage of patients in each group in whom no further therapy containing antithrombin (i.e., frozen plasma (FP) or other antithrombin concentrates) is needed for restoring pre-CPB heparin responsiveness after administration of Atenativ or placebo, and for maintaining it until the completion of the cardiopulmonary bypass (CPB).

Previous primary outcome:
The percentage of patients in each group in whom no further therapy containing antithrombin (i.e., frozen plasma (FP) or other antithrombin concentrates) is needed for restoring pre-CPB heparin responsiveness after administration of Atenativ or placebo, and for maintaining it until the completion of the cardiopulmonary bypass (CPB). The CPB period includes any additional CPB time if a return to CPB is needed before protamine administration but excludes any additional CPB time required after protamine administration.

Key secondary outcome(s))
The following secondary outcome measures are assessed at various intraoperative and postoperative timepoints between initial heparin administration and 28 days following IMP infusion:
1. The comparison between the amounts of further therapy containing antithrombin (i.e., FP or antithrombin concentrates) needed for restoring pre-CPB heparin responsiveness after administration of Atenativ or placebo, and for maintaining it during CPB
2. The comparison between the change in ACT values following infusion of each of the Atenativ doses and placebo
3. The comparison between the change in antithrombin plasma levels following infusion of each of the Atenativ doses and placebo
4. The comparison between heparin usage following the infusion of each of the Atenativ doses and placebo
5. The comparison between the number of units of FP transfused for reasons other than restoring or maintaining heparin responsiveness, both intraoperatively (from the start of Atenativ or placebo infusion until the start of CPB, during CPB, and from the end of CPB until the end of surgery) and postoperatively (from the end of surgery until 24 hours after the start of

Atenativ or placebo infusion and until discharge or 7 days after surgery, whichever comes first), as well as cumulatively
6. The comparison between postoperative use of antithrombin concentrates for reasons other than restoring heparin responsiveness (from the end of surgery until 24 hours after the start of Atenativ or placebo infusion and until discharge or 7 days after surgery, whichever comes first)
7. The comparison between transfusion of other allogeneic blood products (e.g., red blood cells [RBCs], platelets, cryoprecipitate), both intraoperatively (from the start of Atenativ or placebo infusion until the start of CPB, during CPB, and from the end of CPB until the end of surgery) and postoperatively (from the end of surgery until 24 hours after the start of Atenativ or placebo infusion and until discharge or 7 days after surgery, whichever comes first), as well as cumulatively
8. The comparison between administration of coagulation factor concentrates such as fibrinogen concentrate, prothrombin complex concentrate (PCC), factor XIII concentrate and recombinant activated factor VII, both intraoperatively and postoperatively
9. The comparison between administration of other haemostatic-relevant therapies (e.g., tranexamic acid, protamine), both intraoperatively (from the start of Atenativ or placebo infusion until the start of CPB, during CPB, and from the end of CPB until the end of surgery) and postoperatively (from the end of surgery until 24 hours after the start of Atenativ or placebo infusion and until discharge or 7 days after surgery, whichever comes first), as well as cumulatively
10. The comparison between postoperative chest tube drainage volume at 24 hours after the start of Atenativ or placebo infusion, and the comparison between total chest tube drainage volume until discharge or 7 days after surgery, whichever comes first
11. Comparison of the need for reoperation for bleeding, including description of the cause of bleeding (surgical vs. non-surgical)
12. The comparison between cell saver volume until the end of surgery
13. Incidence of AEs in the three study groups
14. Standard haematological parameters (i.e., RBC count, white blood cell count, haemoglobin levels, haematocrit, and platelet count) following Atenativ or placebo infusion, after the end of CPB, at the end of surgery, and at 24 hours after the start of Atenativ or placebo infusion
15. Survival status in the different treatment groups
16. The comparison between the amounts of further therapy containing antithrombin (i.e., FP or antithrombin concentrates) needed for restoring heparin responsiveness from the end of CPB until 24 hours after start of Atenativ or placebo infusion and from the end of CPB until discharge or 7 days postoperatively, whichever comes first
17. Comparison of the length of ICU stay between treatment groups

Completion date
31/03/2028

Eligibility

Key inclusion criteria
1. Planned cardiac surgery with CPB
2. Heparin-resistant patients: pre-CPB Hemochron ACT less than 480 seconds in the measurement performed between 2 and 5 minutes following intravenous administration of 500 U/kg BW UFH
3. Patients ≥18 and ≤85 years of age
4. Freely given written or electronic informed consent

5. In female patients of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile), a pre-existing negative pregnancy test within 14 days before surgery

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
85 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current key exclusion criteria as of 30/12/2025:
Key exclusion criteria
1. Receiving or have received one or more of the following medications within the specified time frames before the start of the surgery: a) vitamin K antagonist (within 3 days) b) direct oral anticoagulants (within 2 days) c) thienopyridines (ticlopidine within 14 days, prasugrel within 7 days, or clopidogrel within 5 days), unless platelet function is satisfactory according to local standard of care assessment d) ticagrelor (within 5 days) unless platelet function is satisfactory according to local standard of care assessment e) glycoprotein IIb/IIIa antagonist (within 24hrs)
2. Pre-existing coagulopathy, a history of bleeding problems or a laboratory-diagnosed bleeding disorder (e.g., von Willebrand disease, platelet disorder)
3. Renal insufficiency, defined as serum creatinine level >2.0 mg/dL
4. Thrombocytosis, defined as platelet count >400,000 per µL
5. Known hypersensitivity or allergic reaction to antithrombin or any of the excipients in Atenativ, i.e., human albumin, sodium chloride, acetyl tryptophan and caprylic acid
6. History of anaphylactic reaction(s) to blood or blood components
7. Refusal to receive a transfusion of blood or blood-derived products
8. Current participation in another interventional clinical trial with an investigational medicinal product (IMP) or previous participation in the current trial
9. Treatment with any IMP within 30 days before the screening visit

Previous key exclusion criteria:
1. Receiving or have received one or more of the following medications within the specified time frames before the start of the surgery: a) warfarin (within 3 days) b) direct oral anticoagulants (within 2 days) c) ticlopidine (within 14 days) d) prasugrel (within 7 days) e) clopidogrel (within 5 days) f) ticagrelor (within 5 days) g) glycoprotein IIb/IIIa antagonist (within 1 day)

2. Pre-existing coagulopathy, a history of bleeding problems or a laboratory-diagnosed bleeding disorder (e.g., von Willebrand disease, platelet disorder)
3. Renal insufficiency, defined as serum creatinine level >1.5 mg/dL
4. Known hypersensitivity or allergic reaction to antithrombin or any of the excipients in Atenativ, i.e., human albumin, sodium chloride, acetyl tryptophan and caprylic acid
5. History of anaphylactic reaction(s) to blood or blood components
6. Refusal to receive a transfusion of blood or blood-derived products
7. Current participation in another interventional clinical trial with an investigational medicinal product (IMP) or previous participation in the current trial
8. Treatment with any IMP within 30 days before the screening visit

Date of first enrolment
21/08/2024

Date of final enrolment
29/02/2028

Locations

Countries of recruitment
United Kingdom

England

Austria

Canada

Czech Republic

Kazakhstan

Lithuania

Poland

Romania

Serbia

Slovenia

Spain

Türkiye

United States of America

Study participating centre

Royal Papworth Hospital
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England
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Study participating centre
James Cook University Hospital
Marton Road
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England
TS4 3BW

Study participating centre
University Hospital (coventry)
Clifford Bridge Road
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CV2 2DX

Sponsor information

Organisation
Octapharma (Austria)

ROR
https://ror.org/022k50n33

Funder(s)

Funder type
Industry

Funder Name
Octapharma

Alternative Name(s)
Octapharma AG

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository (Medidata Rave: https://www.medidata.com/). A summary of the results will be shared in the clinical study report, at scientific conferences, and in public databases. There is a clause in the Informed Consent Form for participants to optionally consent to their data, saved from this study, to be used in future research. Additionally, data rendered anonymous from this study may be shared with other researchers.

IPD sharing plan summary
Published as a supplement to the results publication, Stored in non-publicly available repository