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A study to investigate the effects of sevuparin on lipopolysaccharide responses and the interaction between enoxaparin and sevuparin in healthy volunteers

Submission date
11/09/2023

Recruitment status
No longer recruiting

Registration date
02/10/2023

Overall study status
Completed

Last Edited
02/10/2023

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
In search for novel treatments for systemic inflammation disorders such as endotoxemia and sepsis, heparin and its derivatives have been suggested as potential candidates. Heparin, aside from its anticoagulant properties, is also known to possess anti-inflammatory properties, although its anticoagulant properties have reduced its possible applications in this setting. To decrease the risk of bleeding associated with heparins, modifications to the structure of sevuparin (DF02) have led to a reduction in the anticoagulant properties while retaining anti-inflammatory and other effects typical for heparinoids. Sevuparin is also under development clinically as a treatment for severe malaria and was also explored as a treatment for sickle cell disease. Sevuparin is believed to possess properties suitable for treatment of vascular hyperpermeability in systemic inflammations such as endotoxemia and sepsis. The study will assess the effects of sevuparin on inflammatory responses following local and systemic lipopolysaccharide (LPS) reactions. In addition, the study will assess the type and degree of any interactions in terms of coagulation parameters when sevuparin is given together with enoxaparin.

Who can participate?
Healthy males and females, aged 18 to 55 years.

What does the study involve?
In Parts 1 and 2, a total of 48 male healthy volunteers are planned to be enrolled and randomized over 4 treatment groups (sevuparin low, intermediate or high dose or matching placebo). Each treatment group will comprise 12 healthy volunteers. All subjects will undergo intradermal LPS challenge during Part 1, and an intravenous LPS challenge during Part 2. In Part 3, 16 subjects will receive two single doses of enoxaparin and two single doses of sevuparin or placebo.

What are the possible benefits and risks of participating?
There are no direct health benefits for the participating volunteers, but results will help in developing in the treatment for systemic inflammations such as endotoxemia and sepsis. Possible side effects or risks that can occur during the study are side effects of the administered treatments and LPS, inconveniences of the invasive measurements, in-house stays and lifestyle restrictions.

Where is the study run from?
Centre for Human Drug Research (Netherlands)

When is the study starting and how long is it expected to run for?
January 2021 to October 2022

Who is funding the study?
Modus Therapeutics AB (Sweden)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2021-004977-29

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CHDR2124

Study information

Scientific Title
A randomized, placebo-controlled study to evaluate the effects of intravenous sevuparin on dermal and systemic lipopolysaccharide responses and the interaction between subcuteneous enoxaparin and sevuparin on coagulation responses in healthy volunteers

Study objectives
This exploratory study will evaluate the effect of intravenous sevuparin on inflammatory responses following an intradermal and intravenous lipopolysaccharide challenge and the interaction between subcutaneous enoxaparin and subcutaneous sevuparin on coagulation parameters in healthy volunteers.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 09/11/2021, Stichting BEBO (Doctor Nassaulaan 10, Assen, 9401 HK, Netherlands; +31 592-405871; info@stbebo.nl), ref: NL79064.056.21

Study design
Randomized double blind placebo-controlled study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format. Please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Novel treatment for systemic inflammation disorders such as endotoxemia and sepsis.

Interventions
Part 1 and Part 2 volunteers will either receive sevuparin (low dose, intermediate dose or high dose) or placebo. This will be administered by IV infusion (bolus loading dose followed by continuous infusion over 6 hours). Subjects of Part 1 will also receive 4 intradermal injections of LPS and subjects in Part 2 will receive LPS intravenously.
In Part 3 volunteers will receive either sevuparin or placebo and enoxaparin by subcutaneous injection om a cross-over fashion.

In all Parts, the duration of the follow-up will be 7-9 days after dosing. The randomization code will be generated by a study independent unblinded statistician and provided to the unblinded pharmacist. The code will be kept strictly confidential. Sealed individual randomization codes, per subject and per treatment, will be placed in a sealed envelope with the label 'emergency decoding envelopes' in a safe cabinet at CHDR. The code will be broken after study closure for data analysis or if required for subject safety.

Intervention Type
Drug

Pharmaceutical study type(s)
Dose response

Phase
Phase I

Drug/device/biological/vaccine name(s)
Sevuparin, enoxaparin

Primary outcome measure
Part 1 (ID LPS) basal cutaneous perfusion measured using a laser speckle contrast imager on day -1, day 1 and day 2.
Part 2 (IV LPS) safety and tolerability measured using the following:
2.1. Vital signs on day 1 to 3 and day 8 (up to day 10)
2.2. Treatment-Emergent Adverse Events on day 1 to day 8 (up to day 10)
2.3. Electrocardiography on day 1 to 2 and day 8 (up to day 10)
2.4. Haematology and chemistry blood panels, including heparin-induced thrombocytopenia antibodies, at day 1 to 3 and day 8 (up to day 10)
2.5. Subjective assessment of feeling sick on a numeric rating scale on day 1 and 2.
Part 3 is to assess magnitude of any pharmacodynamic interactions in terms of coagulation parameters measured using APTT, PT, INR, fibrinogen, anti-factor Xa activity, anti-factor IIa activity and D-dimer concentration on day 1 and 2.

Secondary outcome measures
1. Changes in immune cells and inflammatory cytokines measured using flow cytometry and MesoScale Discovery from baseline up to 48 h post-dose (Part 1 and Part 2).
2. Safety and tolerability endpoints measured using vital signs, Treatment-Emergent Adverse Events, electrocardiography and haematology and chemistry blood panels, including heparin-induced thrombocytopenia antibodies (if indicated), at baseline and up to 8-10 days post-dose (Part 1 and Part 3).
3. Pharmacokinetic endpoints measured using a heparin red assay method at baseline and up to 24 h post-dose (Part 2).

Overall study start date
20/01/2021

Completion date
31/10/2022

Eligibility

Key inclusion criteria
1. Healthy male and female volunteers aged 18 to 55 years, inclusive. Health status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry, and urinalysis;
2. BMI in the range of 18 to 30 kg/m², and a minimum body weight of 50 kg and a maximal body weight of 112 kg;
3. No history of trauma with likely damage to the spleen or surgery to spleen;
4. Free from any clinically significant febrile illness 30 days preceding study Day 1.

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Both

Target number of participants
64

Total final enrolment
83

Key exclusion criteria
1. History of sepsis, cardiovascular disease, syncope or malignancy;
2. Haemorrhagic diathesis (easy bruising, epistaxis, gastro-intestinal bleeding);
3. First degree family history of premature cardiovascular disease event (if diagnosed before 50 years of age);
4. Previous participation in a systemic (i.v./inhaled) LPS challenge trial or prior exposure to systemic endotoxin within a year before the first study day (applicable to Part 1 and 2 only) or previous exposure to sevuparin in study Part 1 or 2 (applicable to Part 3 only);
5. Subjects who have received any of the following excluded medications within prescribed 14 days of the first dose administration: aspirin, anti-platelet therapy, anticoagulant therapy and prophylactic and therapeutic LMWH or unfractioned heparin;
6. Subjects who have received prophylactic/therapeutic LMWH or unfractioned heparin within the last year;
7. Subjects who have any current and / or recurrent pathologically, clinically significant skin condition at the lower forearms (i.e. atopic dermatitis); including tattoos (applicable to Part 1 and 2 only).

Date of first enrolment
17/11/2021

Date of final enrolment
22/09/2022

Locations

Countries of recruitment
Netherlands

Study participating centre
Centre for Human Drug Research
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Sponsor information

Organisation
Modus Therapeutics (Sweden)

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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
Modus Therapeutics

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
31/12/2023

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date