A randomized, placebo-controlled study to evaluate the effects of intravenous sevuparin on dermal and systemic LPS responses and the interaction between subcutaneous enoxaparin and sevuparin on coagulation responses in healthy volunteers.

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Part 1:• To evaluate the effect of IV sevuparin on inflammatory responses following an intradermal (ID) LPS challenge.Part 2:• To evaluate the effect of IV sevuparin on safety and tolerability and inflammatory responses following an intravenous (IV...

Ethical review	Approved WMO
Status	Completed
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON52250

Source
ToetsingOnline

Brief title
Inhibition of LPS responses by sevuparin

Condition

- Bacterial infectious disorders

Synonym
Sepsis, Septic shock

Research involving
Human

Sponsors and support

Primary sponsor: Modus therapeutics Inc.
Source(s) of monetary or material Support: Biotechnology industry

Intervention

Keyword: Heparin, LPS, Sepsis, Sevuparin

Outcome measures

Primary outcome

Part 1

• Microvascular function

- Laser speckle contrast imaging, basal flow and with heating protocol

- Multispectral imaging

• Blister exudate

- Flow cytometry (Neutrophils, monocyte subsets, T cells, B cells, NK cells,

dendritic cells)

- Cytokines (including IL-1b, IL-6, IL-8 and TNF-a)

• Safety and tolerability

- Vital signs

- Treatment-Emergent Adverse Events

- Electrocardiography

- Haematology and chemistry blood panels, including HIT antibodies

Part 2

• Microvascular function

- Laser speckle contrast imaging, with heating protocol

- Sidestream Darkfield Imaging

- Passive limb movement

• Blood

- Leucocyte differential

- Cytokines (including IL-6, IL-8, IL-10 and TNF-a)

- Flow cytometry (Neutrophils, monocyte subsets, T cells, B cells, NK cells, dendritic cells, including neutrophil extracellular traps)

- Explorative biomarkers: acute phase reactants and components measurable in blood, serum and plasma of relevance for septic inflammation may be measured and reported separately.

• Pharmacokinetics

• Safety and tolerability

- Vital signs

- Treatment-Emergent Adverse Events

- Electrocardiography

- Haematology and chemistry blood panels, including HIT antibodies

- NRS (self-rated sickness feeling)

Part 3

• Coagulation parameters (including APTT, PT, INR, anti-fXa, anti-fIIa and D-dimer)

• Safety and tolerability

- Vital signs

- Treatment-Emergent Adverse Events

- Electrocardiography

- Haematology and chemistry blood panels, including HIT antibodies

Secondary outcome

Not applicable

Study description

Background summary

In search for novel treatments for 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 and has been shown to impede neutrophil adhesion and degranulation, as well as inhibiting neutrophil effector functions, although the anticoagulant properties of both unfractionated heparin and low-molecular weight heparins (LMWHs) have reduced their application in this setting. To decrease the risk of bleeding associated with heparins, modifications to the structure have led to a reduction in the anticoagulant properties while retaining anti-inflammatory effects, including inactivation of neutrophil-derived proteins.

Sevuparin (DF02) is a low-anticoagulant heparin derivative from which the high-affinity anti-thrombin III-binding pentasaccharide motif has been removed, resulting in a lack of direct effect on factor Xa and thrombin. Sevuparin has been explored clinically as a treatment for malaria and sickle cell disease and is thought to possess properties suitable for treatment of vascular hyperpermeability in sepsis

Study objective

Part 1:
• To evaluate the effect of IV sevuparin on inflammatory responses following an intradermal (ID) LPS challenge.

Part 2:
• To evaluate the effect of IV sevuparin on safety and tolerability and inflammatory responses following an intravenous (IV) LPS challenge.

Part 3:
• To evaluate the interaction between subcutaneous (SC) enoxaparin and SC

sevuparin on coagulation parameters
• To evaluate the safety/tolerability of sevuparin in interaction with enoxaparin

Study design

Parts 1 and 2:
A randomized, placebo-controlled, inflammatory challenge study in healthy volunteers during IV infusion of sevuparin:
Part 1: ID LPS challenge,
Part 2: IV LPS challenge,
Study Parts will be executed in the order 1-2.

Part 3:
A randomized, placebo-controlled, 2-way cross over study to investigate the interaction effect of SC injection of sevuparin with enoxaparin.

Intervention

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 and intravenous LPS.

Part 3 volunteers will receive subcutaneous injections of sevuparin (or placebo) and enoxaparin

Study burden and risks

A study population of healthy male and female volunteers is deemed appropriate for this study examining the effects of sevuparin of dermal and systemic LPS responses and the interaction between subcutaneous enoxaparin and sevuparin on coagulation responses. Although there are significant differences in the immune response between males and females, the study will also allow enrolment of female volunteers to provide generalization of study data across sexes, and is also expected to aid volunteer recruitment. Furthermore, sevuparin effects on LPS responses are expected not to differ between sexes. Importantly, females have previously been safely exposed to LPS challenges exceeding a 1 ng/kg dose. For coagulation responses, no significant differences between males and females are anticipated.

The risk to the subjects can be assessed as acceptable and it is not expected that the subjects participating in this study will benefit from it.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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, a minimum body weight of 50 kg and a maximum body weight of 112 kg;
3. Be able to abstain from smoking from 24 hours prior to dosing until study discharge visit;
4. No history of alcohol or drug abuse;
5. No history of trauma with likely damage to the spleen or surgery to spleen;
6. Free from any clinically significant febrile illness 30 days preceding study Day 1;

7. Non-atopic constitution, including non-asthmatic;
8. Fitzpatrick skin type I-III (applicable to Part 1 and 2 only);
9. No use of any prescription drugs, including aspirin or other non-steroid anti-inflammatory drugs;
10. Able to give written informed consent and willing to comply with all study-related procedures;
11. Female subjects of childbearing potential and male subjects who have sexual intercourse with a woman of childbearing potential must be willing to practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
Women of childbearing potential are defined as all women physiologically capable of becoming pregnant, unless they meet one of the following conditions:
• Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy;
• Posthysterectomy.
For the purposes of the study, effective contraception is defined as follows:
• Females: Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge or cervical cap).
• Males: Effective male contraception includes a vasectomy with negative semen analysis at follow up, or the use of condoms.
Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

Exclusion criteria

1. History of sepsis or history of clinically significant 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 un-fractioned heparin
6. Subjects who have received prophylactic/therapeutic LMWH or un-fractioned 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).
8. Subject is female and is pregnant (based upon serum pregnancy test at screening and urine pregnancy test pre-dose to the first sevuparin/placebo administration), breast-feeding, or planning to become pregnant during the study or within 90 days after last dose of study treatment.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	24-11-2021
Enrollment:	64
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Enoxaparin
Generic name:	Enoxaparine Becat
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sevuparin
Generic name:	NA

Ethics review

Approved WMO Date:	27-09-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-11-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	29-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2021-004977-29-NL
CCMO	NL79064.056.21

Study results

Date completed:	24-10-2022
Results posted:	06-06-2024

First publication
29-05-2024