A multi-centre, phase II, randomized, double-blind, placebo-controlled study to investigate efficacy and safety of sevuparin infusion for the management of acute vaso-occlusive crisis (VOC) in subjects with sickle-cell disease (SCD)

Published: 15-04-2015
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Primary objective:The primary objective of this study is to assess the time to painful VOC resolution, measured from the first dose of sevuparine given to achievement of crises resolution, as compared to placebo. Secondary objectives: The secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Red blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON46980

Source
ToetsingOnline

Brief title
TVOC01

Condition

- Red blood cell disorders

Synonym
sickle-cell disease, vaso-occlusive crisis

Research involving

Human

Sponsors and support

Primary sponsor: Modus Therapeutics AB
Source(s) of monetary or material Support: Sponsor Modus Therapeutics AB

Intervention

Keyword: ischemic organ damage, sevuparin infusion, sickle-cell disease, vaso-occlusive crisis

Outcome measures

Primary outcome

Primary endpoint:

Time from the start of sevuparine infusion until resolution of crisis/episode

is defined as fulfilment of the following two criteria:

a. freedom from parental opioid use (in preceding 8 hours)

b. readiness for discharge as judged by the subject or physician

Secondary outcome

Secondary endpoints:

The secondary efficacy endpoints include assessment and comparison between the

2 treatment groups on the following parameters:

1. Frequency and pattern of treatment emergent adverse events (TEAEs).

2. Time to discharge (number of hours between the first study drug dose given

and discharge).

3. Time to readiness for discharge, as judged by the subject or investigator

(number of hours between the first study drug dose given and time point at which subjects feels readiness or investigator judges readiness for discharge from the hospital). The assessment will be done every 4 hours during awake time, staring from the time when the subject has been without parenteral opioids for 8 hours.

4. Time to discontinuation of IV opiods (number of hours between the first study drug dose given and discontinuation of opioids).

5. Time from start of infusion to 25%, 50% and 75% of subjects achieving VOC resolution.

6. Proportion of subjects with VOC resolution achieved at 24, 48, 72, 96 and 120 hours.

7. Clinical Global Impression of Change, measured once daily starting on day 3 until VOC resolution.

8. Patient Global Impression of Change, measured once daily starting on day 3 until VOC resolution.

9. Pain intensity assessment on VAS from the start of study treatment (first assessment within 30 minutes prior to infusion treatment) and thereafter every 4 hours during awake time, until VOC resolution.

10. Duration of severest pain, defined as time to a 30% reduction in VAS pain score from baseline (maintained during 8 hours) .

11. Amount of parenteral opioids (accumulated opioid consumption) until VOC resolution.

12. Amount of parenteral opioids (accumulated opioid consumption as average per 24h after first dose of study drug) until VOC resolution.

13. Re-occurrence of hospitalisation for VOC within 2 days, or 28 days from resolution of first VOC.

14. PK characteristics of Sevuparin administration as a continuous IV infusion (subgroup).

Exploratory endpoints:

To explore the difference between the two treatment groups on the following:

1. Need for blood transfusion during study.

2. Occurrence of acute chest syndrome.

3. Frequency of re-hospitalization due to acute complications.

4. Potential impact of sevuparin on disease mechanism by exploring biomarkers for mechanism of action and organ damage. Specific biomarkers which may be analysed (i.e. sVCAM-1, sP-selectin, sE-selectin, nucleosomes, PTX-3, sCD163, MRP8-14, nt-proBNP, S 100 B, Neuron specific enolase [NSE], TAT, D-dimer, sICAM, F1+2), in addition to general hematology and biochemistry will be used for evaluation.

Study description

Background summary

SCD is a painful, life-shortening genetic disease, caused by a mutation in the hemoglobin gene. The defect hemoglobin causes the red blood cells to, upon deoxygenation, deform into sickle-shape and causes abnormal adhesion between blood cells and the endothelium leading to microvascular obstructions. The

result is impaired blood flow in affected organs leading to organ damage and eventually a premature death. The cardinal symptom is pain that presents as intermittent very painful vaso-occlusive crisis (VOC) that often leads to hospitalization. As the patients become older, they often also suffer from chronic pain between the VOCs.

Reduced duration of the VOC in SCD patients has been observed in clinical studies with LMWHs. However, the anticoagulant effects of heparin and LMWHs limits their use in treating SCD-related VOC, due to the risk of bleeding.

Sevuparin is a novel polysaccharide drug derived from heparin through chemical depolymerization. Whereas sevuparin shares the same anti-adhesive properties as those of heparin, it lacks the pentasaccharide unit responsible for binding to anti-thrombin. Hence, the potential of sevuparin in the treatment of SCD is that significant anti-adhesive therapeutic effect can be achieved at an acceptably low risk of side-effects related to bleeding.

Study objective

Primary objective:
The primary objective of this study is to assess the time to painful VOC resolution, measured from the first dose of sevuparine given to achievement of crises resolution, as compared to placebo.

Secondary objectives:
The secondary objectives of this study are to assess the effect of Sevuparin, as compared to placebo, on:

1. Safety and tolerability by recording vital signs, physical examination, ECG, laboratory safety analyses and occurrence of adverse events.
2. Time to discharge (number of hours between the first study drug dose given and discharge).
3. Time to readiness for discharge, as judged by the subject and investigator.
4. Time to discontinuation of IV opioids.
5. Time from start of infusion to 25%, 50% and 75% of subjects achieving VOC resolution.
6. Proportion of subjects with VOC resolution achieved at 24, 48, 72, 96 and 120 hours.
7. Clinical and subject global impression of change.
8. Pain intensity assessment on VAS.
9. Duration of severest pain, defined as the time to a >30% reduction in VAS pain score from baseline (maintained during 8 hours)
10. Use of parenteral opioids (accumulated opioid consumption) until VOC resolution / readiness for discharge.
11. Use of parenteral opioids (accumulated opioid consumption as average per 24h after first dose of study drug) until VOC resolution / readiness for discharge.

12. Re-occurrence of hospitalisation for VOC within 3 days, or 28 days from resolution of first VOC.
13. PK characteristics of Sevuparin administration as a continuous IV infusion (subgroup).

Exploratory objectives:
The following exploratory objectives will be performed to assess the effect of Sevuparin, as compared to placebo, on:

1. Need for blood transfusion during study.
2. Occurrence of acute chest syndrome.
3. Frequency of re-hospitalization due to acute complications.
4. Potential impact of sevuparin on disease mechanism by exploring biomarkers for mechanism of action and organ damage. Specific biomarkers which may be analysed (i.e. sVCAM-1, sP-selectin, sE-selectin, nucleosomes, PTX-3, sCD163, MRP8-14, nt-proBNP, S 100 B, Neuron specific enolase [NSE], TAT, D-dimer, sICAM, F1+2]), in addition to general hematology and biochemistry will be used for evaluation. Biomarker samples will not be taken in adolescents who provide PK samples, so as to reduce the total blood volume to be drawn in these patients. At least two samples will be collected: at screening an at end of study / last dose for practical reasons if feasible.

Study design

This is multicentre, randomised, double-blind, placebo-controlled study designed to assess preliminary efficacy, safety and pharmacokinetics (PK) of 2-7 days continuous IV administration of Sevuparin for the management of acute VOC in subjects with SCD.

Subjects will be randomised to receive treatment with Sevuparin or placebo, at a ratio of 1:1.
The dose of sevuparin is 18mg/kg/day.
Sevuparin is compared to placebo as there is no standard therapy for VOC available.
However, a routine standard of care, including pain control management will be applied to all patients in the study.

Each study subject will be involved in the study for a maximum of 41 days (main study).
The infusion treatment of Sevuparin will be performed for a minimum of 48 hours and will then be stopped if resolution of VOC has occurred. The infusion can continue for up to 7 days in patients where VOC resolution does not occur after 48 hours. All subjects will be hospitalized during the treatment period.

A follow-up visit will be performed at 7 (± 3) and 28 (± 5) days following last dose of study medication.
A 3 and 6 months follow-up will be performed for patients exposed to Sevuparin

with HIT antibodies detected at the 28 days follow-up.

Intervention

The patients will receive sevuparin or placebo via continuous infusion.
The duration of the infusion is at least 48 hours.
The maximum duration of infusion is 7 days.

The study medication dose is 18 mg/kg/day.

Study burden and risks

Currently the standard treatment for VOC is pain relief treatment.
The sevuparin treatment will be dispensed as add-on to the standard treatment.
At the moment the patients are admitted for standard VOC treatment, they will be asked for participation in this trial.
The duration of the admittance in the hospital will not be increased because of the sevuparin treatment. Despite the burden of the many blood draws, the best case scenario is to shorten the painful episode and reduce the ischemic organ damage. In case the painful period is shortened, the hospital admission will be shortened as well.

In previous studies no significant side effects were observed.
The side effects experienced were limited to an elevation of the liver enzymes ASAT and ALAT.
Minor changes in the bloods ability to coagulate may be expected.
Within the study liver enzymes and coagulation parameters are monitored closely.
Less commonly reported side effects related to sevuparin were: diarrhea, reduced sense of touch, change of taste, sleepiness, dizziness, and pain in limb. All these events were mild to moderate.
As sevuparin is derived from heparin. There might be a very low risk for subjects on sevuparin to develop a temporary decrease in platelet counts.

The patient will be exposed to the following study related procedures:
- Continuous infusion of study medication/placebo (min. 48 hours, max. 7 days).
- During the study the patient will be subjected to a number of non-invasive procedures.
- This concerns a physical examination at screening, day 2, end of study medication administration and 7 days post last dose.
- ECGs will be assessed at screening and thereafter daily throughout the treatment days and 7 days post last dose.
- The vital signs (temperature, heart rate, respiratory rate, bloodpressure and pulse oximetry) will be assessed at screening, at start of study medication infusion, and thereafter every 8 hours until stop of study medication administraton, and 7 days post last dose.
- Urinalysis will be assessed at screening, end of study medication

administration and 7 days post last dose.
- A VAS questionnaire has to be completed 30 minutes prior to start of infusion and every 4 hours (during awake time) until VOC resolution.
- A Global Impression of Changes questionnaire has to be completed once daily during treatment and at VOC resolution.

The number of blood draws is depending on the duration of the hospital admission.
The venapunctures can be painful and can lead to bleeding or bruising (in case a catheter is used, this will be a one time experience).
For hematology this concerns a minimum 4 blood draws.
For clinical chemistry this concerns a minimum of 4 and a maximum of 6 blood draws.
For biomarkers this concerns 2 blood draws.
For HIT antibodies this concerns at least 2 blood draws. If a patient is positive for HIT antibodies, this concerns 3 to 4 blood draws.
For PK analysis: 1 blood draw on day 2.
Coagulation analysis is performed at screening and then for coagulation monitoring during the first 24 hours of infusion 4 blood draws will be performed. On days 3-8 for coagulation monitoring 2 blood draws will be performed (every 12 hours). After the infusion of IMP has stopped 1 blood draw must be performed and the reslult should be <1.5 ULN before discharge of the patient. During the 7days follow up visit 1 sample will be drawn.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Sign a written informed consent.
2. Male or female, age 12 - 50 years.
3. Diagnosis of sickle cell disease, types HbSS, HbSC, Hb O Arab, HbSß0-thalassemia or HbSß+-thalassemia (SCD type to be confirmed by HPLC confirmed or other method of comparable reliability durin the study, if confirmation is not available at time of inclusion).
4. Subjects admitted for an acute, painful VOC to be treated / or treated with parenteral opiod analgesia at the time of admission. VOC is defined as an episode of pain that led to a clinic or emergency department visit, and cannot be explained except by SCD. Please note: Study treatment should start as soon as possible and at the latest within 24 hours from the time of the decision to hospitalize the subject.
5. Expectancy of the need for hospitalization for at least 48 hours.
6. Be at least 1 year postmenopausal, surgically sterile, or if WOCBP use an effective method of birth control during study drug administration and one month following treatment completion.

Exclusion criteria

1. Severe hepatic failure/disease, or liver enzyme tests (AST and ALT) above 2 times the upper limit of normal (ULN) range, or clinically significant impairment of liver function due to HBV, HCV or other liver diseases.
2. Conjugated (direct) bilirubin 3 fold above ULN.
3. History of clinically significant bleeding in vital organs (not due to relevant trauma), or pathological bleeding.
4. Current clinically significant bleeding, as judged by the investigator
5. Current use of ASA, anti-platelet therapy, anticoagulant therapy and prophylactic and therapeutic LMWH or un-fractioned heparin.
6. APTT above normal range, and INR above 1.4.
7. A platelet count <75,000/µL.
8. BMI >35

9. Subjects with more than 5 hospitalizations for VOC during the last 6 months (to exclude subjects with exacerbations of chronic pain rather than true vaso-occlusion).
10. Evidence of acute SCD complications other than VOC at screening (CVA, ACS, multi-organ failure).
11. The use of strong opiods for >3 consecutive days during the last 15 days before presenting to the hospital.
12. History of chronic drug abuse.
13. Renal dysfunction (GFR< 60 ml/min)
14. Known infection (positivity) with HIV, and active infection with HBV or HCV.
15. Significant ECG abnormality including QTcf > 450 msec (for details please see Section 8.3.3.)
16. History of a clinically significant drug allergy to heparin, LMWH*s, or Sevuparin.
17. Use of any investigational agent during the 30 days prior to the first dose.
18. For females: pregnancy, lactating or intention of becoming pregnant within the next 40 days.
19. Evidence of clinically significant disorders that might interfere with the study aim or safety of the subject, as judged by the Investigator: e.g. neurological, psychiatric (depression, psychosis or schizophrenia), cardiovascular (including arrhythmia), pulmonary, metabolic, gastrointestinal, endocrine diseases, coagulation or malignancies.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2015
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sevuparin
Generic name:	Sevuparin

Ethics review

Approved WMO Date:	15-04-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-08-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	20-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2019
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	EUCTR2014-004416-11-NL
CCMO	NL51673.018.15