The Effect of Voxelotor on Cerebral Perfusion and Oxygenation (ESR-C005)

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To study the effect of voxelotor on the hemodynamics of the cerebral vasculature (CBF and CVR)

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

Summary

ID

NL-OMON52775

Source
ToetsingOnline

Brief title
COVERAGE

Condition

- Red blood cell disorders
- Blood and lymphatic system disorders congenital

Synonym
sickle cell disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Global Blood Therapeutics (GBT)

Intervention

Keyword: cerebral perfusion, oxygenation, sickle cel disease, voxelotor

Outcome measures

Primary outcome

To assess the effect of voxelotor on the cerebral vascular reserve capacity

(CVR)

Secondary outcome

- To assess the effect of voxelotor on cerebral blood flow (CBF)

- To determine the effect of voxelotor on neurocognitive function (processing

speed).

- To determine the effect of voxelotor on the Quality of Life.

Exploratory outcomes:

- To determine the effect of voxelotor on cerebral oxygen utilization and

oxygen extraction fraction (CMRO and OEF).

- To determine the effect of voxelotor on cardiovascular biomarkers (NTproBNP

and TRV).

- To determine the effect of voxelotor on biomarkers of oxidative stress and

endothelial damage (AGE*s, VWFag and VCAM-1).

- To determine the effect of voxelotor on P-selectin mediated

neutrophil-platelet adhesion as measure of neutrophil adhesiveness.

- To determine the effect of voxelotor on neutrophil activity, pro-inflammatory

properties and oxidative burst capacity.

- To determine the effect of voxelotor on hypoxia-induced RBC deformability

(Oxyscan).

- To determine the effect of voxelotor on the development of white matter

lesions.

Study description

Background summary

Sickle cell disease is known to be associated with brain damage. This often happens without patients noticing it. The MRI makes such unnoticed damage easily visible and it has been determined that brain abnormalities are common in sickle cell patients. It is also known that blood vessels of patients with sickle cell disease do not work as proper as those of healthy patients. We hypothesize this has to do with one another.
An important risk factor in the development of this abnormal brain blood flow is the severity of anemia. In our department we are researching the effect of new treatments against sickle cell disease on the function of the blood flow of the brain. You should think of treatments such as Hydrea, blood transfusions, but also stem cell transplantation and new medicines that will come on the market for sickle cell disease. In the current study, we are looking at the effect of a new drug, Voxelotor, on blood flow to the brain.

Study objective

To study the effect of voxelotor on the hemodynamics of the cerebral vasculature (CBF and CVR)

Study design

Single center, open label intervention study of the treatment of voxelotor. In this study, 24 adult patients with SCD (homozygous or compound heterozygous SCD) and with Hb <10.5 g/dl will be treated with voxelotor for 12 months, followed by an extension phase for patients who experience benefit of voxelotor, up until voxelotor is reimbursed by the health insurance companies in the Netherlands. The study procedures consists of MRI, echocardiography and laboratory assessments that will be performed at baseline, 3, 6 (no MRI and no echocardiography), 12, 18 months upon voxelotor administration. Quality of Life and processing speed as measure of neurocognitive function will be performed at baseline and 12 months following voxelotor initiation. Due to retraction of

voxelototor, measuremetns after 24 months will be performed without voxelotor.

Intervention

Voxelotor administration daily, at a dose of 1500 mg for a period of 12 months, followed by an extension phase for patients who experience benefit of voxelotor, up until voxelotor is reimbursed by the health insurance companies in the Netherlands. However, voxelotor has been retracted due to a negative risk to benefit ratio.

Study burden and risks

Voxelotor has demonstrated to induce an increase in the Hb concentration due to strong inhibition of hemolysis. In a previous phase 2 and phase 3 study voxelotor has demonstrated to be safe. MRI is harmless, Diamox infusion has proven to be save in patients with SCD and venipuncture is routine in patients with SCD. Parameters obtained by blood drawn in this study will be used clinically as well. Presumably, participation is associated with minimal burden and risks. As cranial MRI is not routinely performed in adults with SCD, coincidental findings are potentially beneficial. The studied population represents the group of patients with the highest disease severity, and is, thus, representable.

Contacts

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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. Documented severe SCD genotype (HbSS, HbS-β) which must be based on previous or confirmed by high performance liquid chromatography (HPLC) testing during screening.
2. Age 18 and above
3. Hemoglobin (Hb) <=10.5 g/dL
4. For participants taking hydroxyurea (HU), the dose of HU (mg/kg) must be stable for at
least 90 days prior to participation and with no anticipated need for dose adjustments
5. Participants, who if female and of child bearing potential, are using highly effective
methods of contraception from study start to 30 days after the last dose of study drug, and who if male are willing to use barrier methods of contraception, from study start to 30
days after the last dose of study drug.
6. Participant has provided documented informed consent or assent (the informed consent
form [ICF] must be reviewed and signed by each participant; the participant*s legal representative or legal guardian, and the participant*s assent must be obtained).
7. For extension phase: clinical benefit being apparent, clinical benefit is defined as an increase in Hb of > 0.62 mmol/L (1 g/dL) and or clinical response assessed by the investigator or reported by patient (e.g. increased endurance, diminished fatigue, improved well-being).

Exclusion criteria

1. No informed consent has been given
2. Contra-indication for MRI or acetazolamide
3. Female who is breast feeding or pregnant.
4. Patients who are receiving regularly scheduled blood (RBC) transfusion

therapy (also
termed chronic, prophylactic, or preventive transfusion) or have received a RBC transfusion for any reason within 90 days before participation.
5. Hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days prior participation.
6. Hepatic dysfunction characterized by alanine aminotransferase (ALT) >4 × ULN.
7. Participants with clinically significant bacterial, fungal, parasitic or viral infection which
require therapy:
• Participants with acute bacterial infection requiring antibiotic use should delay
screening/enrollment until the course of antibiotic therapy has been completed.
• Participants with known active hepatitis A, B, or C or who are known to be human immunodeficiency virus (HIV) positive.
8. Severe renal dysfunction (estimated glomerular filtration rate <30mL/min).
9. History of malignancy within the past 2 years prior to participation requiring chemotherapy and/or radiation (with the exception of local therapy for non-melanoma
skin malignancy).
10. History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior
to consent including but not limited to the following:
• Unstable angina pectoris or myocardial infarction or elective coronary intervention.
• Congestive heart failure requiring hospitalization.
• Uncontrolled clinically significant arrhythmias.
11. Any condition affecting drug absorption, such as major surgery involving the stomach or
small intestine (prior cholecystectomy is acceptable).
12. Participated in another clinical trial of an investigational agent (or medical device) within
30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently
participating in another trial of an investigational agent (or medical device)
13. Medical, psychological, or behavioral conditions, which, in the opinion of the
Investigator, may preclude safe participation, confound study interpretation, interfere
with compliance, or preclude informed consent.
14. Receipt of erythropoietin or other hematopoietic growth factors within 28 days of signing
ICF or anticipated need for such agents during the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-02-2021
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Voxelotor
Generic name:	Voxelotor
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-07-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2022
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:	21-06-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2025
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	EUCTR2019-003766-41-NL
CCMO	NL72598.018.20