A phase I, randomised, double-blind, placebo-controlled study in patients with amyotrophic lateral sclerosis to further assess the safety and tolerability of intracerebroventricular administration of sNN0029 infusion solution.

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The objective of the trial is to assess the safety and tolerability of i.c.v. administration of sNN0029 infusion solution at a dose of 4 µg per day delivered via a Medtronic SynchroMed® II Infusion System.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON40611

Source
ToetsingOnline

Brief title
Study of sNN0029 in ALS patients.

Condition

- Neurological disorders NEC
- Nervous system, skull and spine therapeutic procedures

Synonym
ALS, Lou Gehrig's disease

Research involving
Human

Sponsors and support

Primary sponsor: Newron Sweden AB
Source(s) of monetary or material Support: Farmaceut

Intervention

Keyword: - amyotrophic lateral sclerosis, - intracerebroventricular, - phase 1, - recombinant human vascular endothelial growth factor 165

Outcome measures

Primary outcome

• Adverse events (AE's), serious AE's (SAE's), adverse device effects (ADE's),

serious ADE's (SADE's) and withdrawals due to AE's/ADE's

• Vital signs, physical and neurological examination and ECG

• Clinical laboratory tests and anti-VEGF antibodies

• Possible pathological changes in the brain identified through MRI and MRA

• Possible pathological changes in the retina identified through fundus

photography

• Accuracy of catheter tip placement and any migration as determined by imaging

(MRI or CT-scan)

Secondary outcome

• To study the concentration-time profile of VEGF165 in the CSF, administered

as a dose of 4 µg sNN0029 infusion solution/day

• To assess the performance and tolerability of the Medtronic SynchroMed® II

Infusion system

Study description

Background summary

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig*s disease, Maladie de Charcot and motor neuron disease, is one of the most devastating diseases of the central nervous system (CNS). Although precise figures are lacking, the general incidence of ALS is approximately 2 per 100,000 with onset typically between 40 to 70 years of age. The disease is characterized by progressive muscle weakness, stiffness and fasciculation (muscle twitching) most commonly affecting muscles of the limbs. Upon histological examination, the most striking feature is a loss of upper motor neurons in the cerebral cortex and lower motor neurons in brain stem and spinal cord. In some cases muscles involved in speech and swallowing are the ones primarily affected and this variant of the disease is called Progressive Bulbar Palsy or ALS with *bulbar onset*. More commonly, symptoms first appear from the limbs (ALS with *limb onset*), which represents approximately 75% of total ALS cases. Over time, patients with both major forms of ALS lose the ability to breathe spontaneously and to swallow. The patients become immobilized and finally completely dependent on assisted ventilation and feeding. Death is often caused by untreatable infections due to the respiratory failure and cachexia. The disease progression is rapid and 95% of the patients are dead 3- to 5 years after diagnosis. The mean survival time after diagnosis is 30 months (Régal et al. 2006).
For the majority of ALS cases (90%, sporadic ALS), there is no known cause for the disease, but as for other neurodegenerative diseases, familial forms have been identified. The most common form of familial ALS (2-5%) is caused by a mutation in the superoxide dismutase (SOD) gene. Although the mechanism is not fully understood, this mutation is believed to make the SOD enzyme dysfunctional and hence the micro environment for motor neurons is not cleared from e.g. toxic free oxygen radicals. Mice and rats expressing the human SOD-1 mutation develop ALS like symptoms; muscle weakness and premature death, paralleled with a progressive loss of motor neurons. The SOD-1 rodent models are considered state of the art models in ALS research, although there is a recognized need for additional models with a clearer relevance for sporadic ALS.
There is currently no effective treatment available for ALS. The only registered drug with ALS as its therapeutic indication is Rilutek/Riluzole, which increases survival by an average of approximately 3 months. The effects appear to be more pronounced in patients presenting the bulbar onset form of sporadic ALS (Bensimon et al. 1994). The medical need for new therapeutics in this field is enormous.

Study objective

The objective of the trial is to assess the safety and tolerability of i.c.v. administration of sNN0029 infusion solution at a dose of 4 µg per day delivered via a Medtronic SynchroMed® II Infusion System.

Study design

A phase I, randomized, double-blind, placebo-controlled study in patients with amyotrophic lateral sclerosis to further assess the safety and tolerability of intracerebroventricular administration of sNN0029.

Intervention

i.c.v. administration of sNN0029 infusion solution at a dose of 4 µg per day delivered via a Medtronic SynchroMed® II Infusion System.a pump infusion system
or
i.c.v. administration of placebo solution delivered via a Medtronic SynchroMed® II Infusion System.a pump infusion system

Study burden and risks

The subject will be hospitalized twice during the study. One time for the operation of the implantation (with the standard operation risks) of the Medtronic SynchroMed® II Infusion System and the second time for observation after the operation. Further, the following items will be performed/asked with the possible associated side effects:

- MRA: Some people feel dizzy, nauseous or get a headache. In exceptional cases one can get an allergic reaction to the contrast fluid.
- A blood draw can be unpleasant, painful and might cause bruising, swelling or inflammation.
- The electrodes of the ECG apparatus may cause sensitive, considerable redness.
- The possibility exists that the catheter tip is migrating from the site of implant. The possible administration of the drug in a location other than the lateral ventricle is considered to be associated with minor risks due to the low dose administered. Accuracy of catheter tip placement and any migration as determined by imaging (MRI or CT scan).
- There is a potential risk of infection associated with the refilling of the infusion systems. However, this risk is minimized by conducting the refill procedure under aseptic conditions
- Possible unkown side effects of the investigational product.
- It cannot be excluded that already existing tumors may grow more quickly because VEGF may stimulate cell division.
- Lumbar punction: the side effects of the anaesthesia may cause in some cases headache, dizziness, stiff neck or buzzing in ears..
- Two questionnaires have to filled out.
- Standard risks of a neuro surgery:

o Complications during anesthesia. A person, who for medical reasons cannot receive anesthesia or cannot undergo this type of operation, will not be able to participate. In the absence of such complicating circumstances, anesthesia carries a low risk.
o Complications may consist of spinal fluid leak, headache, bruising, swelling, bleeding and/or blood clots, and surgical wound infection with tissue damage. In the event of bleeding, more or less serious symptoms may occur such as seizure, paralysis, loss of concentration, memory loss, loss of power of speech, loss of another function under the control of the brain, and even death. In the event of infection, it may be necessary to remove the pump and catheter and administer antibiotics.

The sponsor has achieved positive results in a former study with VEGF-165. Due to poor penetration through the blood-brain-barrier VEGF165 has been administered directly into the intracerebroventricular space using a catheter and a pump for a maximum effect. The operation for implantation of the Medtronic SynchroMed® II Infusion System might be a large burden for the subject, but seen in the light of the current supply medicines and any desired effect, this will cause the acceptance threshold is very low for him/her.

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. Ability to understand and provide written informed consent to participate in the trial before any trial-related procedures are conducted.
2. Clinical diagnosis of ALS classified as definite, or probable with or without additional laboratory evidence, according to the revised World Federation of Neurology (WFN) El Escorial criteria.
3. Male or female aged 18 to 75 years inclusive.
4. If patients are being treated with riluzole, they must have been on a stable dose for at least the past 30 days prior to screening.
5. The patient is, in the opinion of the investigator, medically fit to undergo the surgery required for stereotactic implantation of the catheter and infusion pump.

Exclusion criteria

1. Impaired respiratory function judged to pose a risk to the patient during anaesthesia for the device implantation.
2. Hypertension defined as blood pressure >160 mmHg systolic or >90 mmHg diastolic.
3. Values for coagulation parameters including platelet count, normalised prothrombin complex (PK-INR), activated partial thromboplastin time (APTT) outside normal ranges.
4. Ophthalmological examination including fundus photography, visual acuity by Early Treatment in Diabetic Retinopathy Study (ETDRS) and perimetry, with any clinically significant findings that imply safety concerns for this study.
5. Diagnosis of diabetes mellitus.
6. History of structural brain disease other than ALS, including tumours and hyperplasia.
7. An MRI of the brain and cervical spine, and an MRA of the brain with findings of tumours or potential sources of pathological bleedings, or abnormality that may interfere with the assessments of safety or efficacy or that would, in the judgment of the investigator, represent a surgical risk to the patient. If an MRI and/or MRA has been performed within 1 month prior to screening, the results from that examination can be used.
8. Any disorder that precludes a surgical procedure (e.g., signs of sepsis or inadequately treated infection), alters wound healing (e.g., including bleeding disorders), or renders chronic i.c.v. delivery or device implants medically unsuitable.
9. Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that cannot be not managed optimally due to:
i. anatomical factors at or near the implant site (e.g., vascular abnormalities, neoplasms, or other abnormalities),

ii. underlying disorders of the coagulation cascade, platelet function, or platelet count (e.g., haemophilia, Von Willebrand*s disease, liver disease, or other medical conditions)
iii. administration of any antiplatelet or anticoagulant medication in the preoperative period
10. A personal history of thromboembolic disease. A family history of thromboembolic disease will prompt a laboratory assessment to exclude hereditary liability before the patient is declared eligible.
11. Presence of additional risk factors for thromboembolism such as obesity (BMI>35) or use of oestrogens including combined contraceptive pills.
12. Presence of an implanted shunt of the drainage of CSF or an implanted CNS catheter.
13. Clinically significant abnormalities in haematology or clinical chemistry parameters as assessed by the investigator.
14. Serological evidence of Hepatitis B virus (HBV), Hepatitis C virus (HCV) or Human immunodeficiency virus (HIV)
15. Ongoing medical condition that according to the investigator would interfere with the conduct and assessments in the study. Examples are medical disability (e.g., severe degenerative arthritis, compromised nutritional state, peripheral neuropathy) that would interfere with the assessment of safety and efficacy of investigational product or device performance, or would compromise the ability of the patient to undergo study procedures (e.g., MRI), or to give informed consent.
16. Participation in another clinical trial with an investigational drug or device within 3 months prior to screening visit.
17. For women only: pregnant, breast feeding and/or for fecund women unwillingness to use adequate contraception during the trial such as:
- Established use of oral, injected or implanted hormonal methods of contraception that do NOT
contain oestrogens.
- Placement of an intrauterine device.
- Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps)
with spermicidal foam/gel/film/cream/suppository.

Study design

Design

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):	18-09-2014
Enrollment:	9
Type:	Actual

Medical products/devices used

Generic name:	Medtronic SynchroMed® II Infusion System
Registration:	Yes - CE outside intended use
Product type:	Medicine
Brand name:	Not applicable
Generic name:	Telbermin

Ethics review

Approved WMO Date:	23-04-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-06-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-08-2015
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2012-001026-10-NL
ClinicalTrials.gov	NCT01384162
CCMO	NL45580.041.13

Study results

Date completed: 30-10-2015

Summary results
Trial ended prematurely