A multi-centre, open-label, follow-on study to assess long-term safety and tolerability of intracerebroventricular administration of sNN0029 in patients with amyotrophic lateral sclerosis

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The objective of the trial is to assess the long-term safety and tolerability of intracerebroventricular administration of sNN0029 infusion solution at a dose of 4 µg/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-OMON42272

Source
ToetsingOnline

Brief title
Follow on study of sNN0029 with ALS patients.

Condition

- Neurological disorders NEC

Synonym
ALS, Lou Gehrig's disease

Research involving
Human

Sponsors and support

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

Intervention

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

Outcome measures

Primary outcome

The primary objective of the trial is to assess the safety and tolerability

through assessment of:

• AEs, SAEs, ADEs, SADEs and withdrawals due to AEs/ADEs

• Vital signs, physical and neurological examination and ECG

• Clinical laboratory tests and anti-VEGF antibodies

• Possible pathological changes in the brain identified through MRI

• 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

The secundary objective of the trial is to assess the safety and tolerability

through assessment of:

• 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

Some exploratory objectives of the trial are:

• To explore the changes from baseline (study 003; day 85) and at regular

intervals (every 6 months) in relevant efficacy related variables

o Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R)

o Slow Vital Capacity (SVC)

o Quality of Life (EQ-5D including EQ visual analogue scale [VAS])

o Motor Unit Number Index (MUNIX)

• To explore biomarkers in plasma and CSF

o IL-6, IL-8, Hepatocyte growth factor, Angiopoietin-2, Neurofilament light

chain, Tau, sAPP, S100beta, Cystatin C, Complement C3

The exploratory biomarker analyses listed above are planned but may not be

conducted if deemed as obsolete during later stages of the trial; other

exploratory analyses may be added to explore based on emerging new findings.

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 characterised 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 immobilised and finally completely dependent on assisted ventilation and feeding. Death is often caused by untreatable infections due to the respiratory failure and cachexia. The median survival time from onset of symptoms for bulbar onset cases is 2-3 years and 3-5 years for limb onset cases (see review Wijesekera and Leigh 2009). 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 as a consequence 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 recognised 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 long-term safety and tolerability of intracerebroventricular administration of sNN0029 infusion solution at a dose of 4 µg/day delivered via a Medtronic SynchroMed® II Infusion System.

Study design

Shortly before the end of trial treatment administration in study sNN0029-003 (Visit 9, Day 85), patients will be asked whether they would like to continue sNN0029 treatment after end of study. Information on the content of the follow-on study will be given and an informed consent signed for the follow-on study. Eligible patients will roll over to study sNN0029-004 immediately after completion of study sNN0029-003, i.e. the last day of the sNN0029-003 study will constitute the first in the sNN0029-004 study.

The assessments performed at the last visit in study sNN0029-003 will serve as the baseline values for patients included in study sNN0029-004 and be the start

of sNN0029 treatment for all patients (Study Day 1; Visit 1). Patients who have received placebo in the previous sNN0029-003 study will start administration of IMP at a higher flow rate than those who have received active treatment (see Section 10.4.9). In order not to reveal the blind, an unblinded study nurse will be specifically assigned to handle pump refill and programming in the sNN0029-004 study. For the same purpose, all patients, and not only those who have previously received placebo, will return to hospital on Day 3 and stay to Day 6 (Visit 2). During these days, the sNN0029 begins to exit the i.c.v. catheter tip in the ventricle of the brain for patients who have previously received placebo.
Patients will return to the hospital on Day 11 (Visit 3) for a refill of sNN0029 and adjustment of the infusion pump flow rate. After this, the patient will return to the clinic on Day 39 (Visit 4) for a sNN0029-refill and assessments. Thereafter the patients will visit the hospital on a monthly basis (every 28 days ± 2) to perform refills and every 3 months for the assessment of clinical parameters.
Treatment in study sNN0029-004 may continue unless safety concerns warrant discontinuation of therapy, until patients choose to withdraw from the study, experience treatment related toxicity or intolerance, are deemed to be unsuitable to continue treatment by the investigator, or die.

Intervention

Intercerebrovascular administration of sNN0029 infusion solution at a dose of 4 µg sNN0029 per day delivered via a Medtronic SynchroMed® II Infusion System.

Study burden and risks

The patient will be hospitalized once during the study for observation of the first administration of the study drug into the cavity of the brain.
Further, the following items will be performed/requested with the possible side effects:
- Blood drawing can be unpleasant, painful and might cause bruising, swelling or inflammation.
- Stickers used to adhere the ECG electrodes may cause sensitive and red skin after removal.
- There is a possible risk that the intracerebrovascular catheter tip may move from its intended position within the cavity of the brain. The possible administration of the study drug in a location other than the ventricle is considered to be associated with minor risks due to the low dose administered. Regular MRI scans during the study ensures close monitoring of this.
- A potential risk of infection assocatied with refilling of the infusion system exists. The risk is minimized by conducting the refill procedure under aseptic conditions.
- Not all side effects of the study drug may be known at this moment.
- It cannot be excluded that already existing tumors may grow more quickly

because VEFG may stimulate cell division. Patients with history of tumors will therefore be excluded from the study. MRIs performed regularly during the study will monitor for any signs of tumor formation.
- The local anesthetics used for lumbar puncture may cause headache of mild intenstiy, and dizziness, stiff neck or buzzing in the ears can occur.
- Two questionnaires have to be completed (4 times in the first year and then 2 times per year).

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. Previous participation in sNN0029-003 with completion of 12 weeks treatment without clinically significant safety concerns
2. Intact continuity of the Medtronic SynchroMed® II Infusion System as judged by X-ray of

head and abdominal area
3. Clinical diagnosis of ALS classified as definite, or probable with or without additional laboratory evidence, according to the revised WFN El Escorial criteria
4. Patient has been given written and verbal information about the continuation study, has had the opportunity to ask questions about the study, and understands the time and procedural commitments
5. Patient has given oral and / or signed consent (written) to participate in the study. In the event that a patient who gives oral informed consent is not physically able to sign the informed consent form (ICF) due to disease progression, a witness may sign the informed consent form on the patient*s behalf

Exclusion criteria

1. Hypertension defined as blood pressure >160 mmHg systolic or >90 mmHg diastolic
2. Ophthalmological examination (fundus photography, visual acuity and perimetry) with any clinically significant findings that imply safety concerns for this study.
3. Diagnosis of diabetes mellitus
4. Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that cannot be not managed optimally due to:
a. anatomical factors at or near the implant site (e.g., vascular abnormalities, neoplasms, or other abnormalities)
b. underlying disorders of the coagulation cascade, platelet function, or platelet count (e.g., haemophilia, Von Willebrand*s disease, liver disease, or other medical conditions)
5. Presence of additional risk factors for thromboembolism such as obesity (Body mass index [BMI] > 35) or use of oestrogens including combined contraceptive pills
6. Clinically significant abnormalities in haematology or clinical chemistry parameters as assessed by the investigator
7. 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
8. For women only: pregnant, breast feeding and/or for fecund women unwillingness to use adequate contraception during the trial such as:
a. Established use of oral, injected or implanted hormonal methods of contraception that do NOT contain oestrogens
b. Placement of an intrauterine device
c. 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

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-01-2015
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:	01-12-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	06-01-2015
Application type:	First submission
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	EUCTR2012-005034-11-NL
ClinicalTrials.gov	NCT02269436
CCMO	NL51030.041.14