Effects of ODM109 on respiratory function in patients with ALS. A randomised, double blind, placebocontrolled, crossover, 3 period, multicentre study with openlabel followup extension.

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The primary objective of this study will investigate the effect of oral levosimendan on the respiratory function of patients with Amyotrophic Lateral Sclerosis.

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

Summary

ID

NL-OMON42507

Source
ToetsingOnline

Brief title
Levals

Condition

- Neuromuscular disorders

Synonym
ALS, Amyotrophic Lateral Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Orion Corporation Orion Pharma
Source(s) of monetary or material Support: Orion Corporation Orion Pharma

Intervention

Keyword: ALS, MND, Respiratory, Symptomatic

Outcome measures

Primary outcome

Efficacy of levosimendan on respiratory functions.

The primary efficacy variable will be the upright slow vital capacity (SVC) measured in sitting position with a spirometer. SVC is the maximum volume of air that can be exhaled slowly after slow maximum inhalation. The best read from 3 assessments will be chosen. The volume is measured in letres and the SVC variable will be % of predicted (normal) value for age, height and sex/ SVC is measured once during screening, three times during each treatment period in the cross-over part of the study and three time during the 6 months open-label part of the study.

Secondary outcome

Effect oral levosimendan on hand grip strength, hand grip endurance as well as quality of life and daily functions.

Safety and tolerability of the IMP.

Effects of the IMP on Riluzole.

Study description

Background summary

Levosimendan has been shown to increase skeletal muscle force and endurance as well as human diaphragm function. Hence, Levosimendan may be useful in the treatment for ALS.

Study objective

The primary objective of this study will investigate the effect of oral levosimendan on the respiratory function of patients with Amyotrophic Lateral Sclerosis.

Study design

This is a two part study.
The first part is a double blind, cross over study with three distinct treatment periods that are separated by a wash out period.

The second part of the study is a supportive 6month open label followup period. Each patient will transition to part two of the study at the end of part one.

Intervention

During each 2 week treatment period either a 1mg dose, a 2 mg dose or placebo capsules.
At the beginning of part two on a 1mg dose, which may be titrated after 2 weeks to 2mg for the remainder of the open label part.

Study burden and risks

Levosimendan is currently approved in several countries as an intravenous (IV) formulation to treat acutely worsened serious heart failure. Known possible adverse events for IV Levosimendan in heart failure patients include arrhythmias and heart attack which sometimes may be serious or life threatening. Other reported adverse events for the IV formulation include lightheadedness, nausea and vomiting, decreased blood pressure and changes in laboratory tests such as decreased potassium values. The most common side effects of oral Levosimendan in earlier studies have included: headache (usually mild or moderate in intensity and which may last for a couple of days) and palpitations (feeling of increased heart rhythm) If such events occur, careful monitoring of the subject will be performed and supportive care

administered as appropriate.

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. Written informed consent (IC) for participation in the study will be obtained from the subject (or from the subject*s next of kin, caregiver, or other legally acceptable representative in case the study subject him/herself cannot sign the IC due to severe muscle weakness).
2. Age of at least 18 years.
3. Male or female subjects with diagnosis of laboratory supported probable, probable or definite Amyotrophic Lateral Sclerosis (ALS) according to El Escorial revised criteria (Brooks BR et al., 2000). Full electromyogram report available consistent with ALS (but not necessarily fulfilling electrodiagnostic criteria for ALS) according to an experienced

neurophysiologist.
4. Ability to swallow the study treatment capsules.
5. An upright (sitting position) Slow Vital Capacity between 60-90% of the predicted value for age, height and sex at screening visit.
6. Normal oxygen saturation during daytime (measure of >= 95% when steady state has been reached with a reliable read) in sitting position measured by pulse oximetry.
7. Disease duration from symptom onset. This is defined by first muscle weakness or difficulty speaking (dysarthria) of 12-48 months at the time of baselin/day 1 of the first treatment period.
8. Patients with or withour riluzole. If using riluzole, the dose must have been stable for at least 4 weeks prior to screening and should not be changed during the cross-over, double blind part of the study.

Exclusion criteria

1. Subject in whom other causes of neuromuscular weakness have not been excluded.
2. Subject with a diagnosis of another neurodegenerative disease
3. Assisted ventilation or gastrostomy of any type during the preceding 3 months prior to screening or predicted to be required within the randomised, doubleblind crossover
part of the study
4. Recorded diagnosis or evidence of major psychiatric diagnosis, significant cognitive impairment or clinically evident dementia
5. Haemodynamically significant uncorrected valve disease or hypertrophic cardiomyopathy or restrictive cardiomyopathy
6. Acute myocardial infarction or any other acute coronary event within 1 month before the screening visit
7. Any major surgery within 1 month before the screening visit or patients who are scheduled for any major surgery during the planned study period
8. History of Torsades de Pointes, family history of long QTsyndromeor history of lifethreatening
ventricular arrhythmia within 3 months before screening
9. Heart Rate of less than 50 or greater than 100 beats per minute as an average over the 24hour ambulatory HolterECG recording at screening
10. Systolic blood pressure (SBP) less than 100 mmHg or greater than 180 mmHg, or diastolic blood pressure (DBP) greater than 100 mmHg at screening.
11. Ventricular tachycardia (wide complex tachycardia greater than 100/min, greater than 5 consecutive beats) in the 24hour ambulatory HolterECG recording at screening.
12. Episode of atrial fibrillation or atrial flutter lasting greater than 60 seconds in 24hour ambulatory HolterECG recording at screening.
13. Second or third degree atrioventricular (AV) block in the 12lead ECG or in the 24hour ambulatory HolterECG recording at screening.
14. Potassium less than 3.7 mmol/l or greater than 5.5 mmol/l at screening
15. Creatinine greater than 170 µmol/l at screening or on dialysis.
16. Blood haemoglobin less than 10 g/dl at screening.
17. Clinically significant hepatic impairment at the discretion of the investigator.

18. Women of reproductive age without a negative pregnancy test and without a commitment to using an acceptable method of barrier or hormonal contraception (e.g. condoms, diaphragms, oral contraceptives and long acting progestin agents), if sexually active during the study, and for 1 month after the last dose of the study treatment. Women who are
postmenopausal (1 year since last menstrual cycle), surgically sterilised or who have undergone a hysterectomy are considered not to be reproductive and can be included.
19. Known hypersensitivity to levosimendan.
20. Administration of levosimendan within 30 days prior to screening visit.
21. Any botulinum toxin use within 3 months from screening. Use of botulinum toxin is not allowed during double-blind, cross-over part of the study.
22. Patients with known history of human immunodeficiency virus (HIV) infection.
23. Any other clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, neurological or psychiatric disorder or any other major concurrent illness that in the opinion of the investigator could interfere with the interpretation of the study results or constitute a health risk for the subject if he/she took part in the study.
24. Blood donation or loss of significant amount of blood within 60 days prior to screening.
25. Participation in a clinical trial with any experimental treatment within 30 days prior to the screening visit or previous participation in the present study.
26. Any other condition that in the opinion of the investigator could interfere with the interpretation of the study results or constitute a health risk for the subject if they took part in the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-12-2015

Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Levosimendan
Generic name:	Levosimendan

Ethics review

Approved WMO Date:	04-08-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-11-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-06-2017
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	EUCTR2014-004567-21-NL
ClinicalTrials.gov	NCT02487407
CCMO	NL54036.041.15