# Effects of oral Levosimendan (ODM-109) on respiratory function in patients with ALS

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The primary objective of this study is to confirm that levosimendan can significantly improve respiratory function measured by supine slow vital capacity (SVC) in amyotrophic lateral sclerosis (ALS) patients.The secondary objective is to confirm...

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

## Summary

### ID

NL-OMON50701

**Source**
ToetsingOnline

**Brief title**
REFALS

### Condition

- Neuromuscular disorders

**Synonym**
ALS, Progressive neurodegenerative disease

**Research involving**
Human

### Sponsors and support

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

## Intervention

**Keyword:** Amyotrophic Lateral Sclerosis (ALS), Levosimendan (ODM-109), Phase III

## Outcome measures

**Primary outcome**

Efficacy:

* The primary efficacy variable will be the change from baseline at 12 weeks in SVC measured in supine position, SVC (supine). All SVC measurements prior to 12 weeks will be included in the statistical model. SVC is the maximum volume of air that can be exhaled slowly after slow maximum inhalation.

* ALSFRS-R will be assessed. The variables derived will be the scores of the 12 separate items, the total scores of each subdomain and the total score of ALSFRS-R.

* The *Time to respiratory event* composite endpoint will be used to validate the changes seen in supine SVC. This variable consists of the following events:

- At least 1 point decrease in ALSFRS-R respiratory function score 10, 11 or 12
- Meeting *protocolised* criteria for NIV: supine SVC * 50% predicted
- Starting NIV (actual start or attempt to start NIV)
- Invasive mechanical ventilation by intubation or tracheostomy or death

Time to respiratory event will be reached whenever any of the 4 criteria listed above has been first met.

* CGI is used to rate the severity of subjects* clinical condition. Clinical condition is assessed by the subjects themselves with a visual analogue scale (VAS).

* Perception on the intensity of dyspnoea will be assessed by Borg CR10 scale

in supine and sitting position.

* Daytime somnolence will be assessed by ESS.

* Sleep quality and disturbances will be assessed by PSQI.

* Health care and home care resource use will be assessed for possible later use in pharmacoeconomic analysis.

* Other assessments: Subject*s status for NIV support, invasive mechanical ventilation by intubation or tracheostomy and survival will be recorded at all visits.

**Secondary outcome**

Pharmacokinetics (PK): Blood samples for the determination of levosimendan, its metabolites OR-1855 and OR-1896 and riluzole concentrations in plasma will be collected.

Biomarkers: Blood samples will be collected for exploratory biomarker analyses which may give supportive data related to the disease state of the subjects.

Pharmacogenomics (PG): All subjects will provide a blood sample for determination of subjects* acetylation status (NAT polymorphisms). The DNA of subjects who have given a separate PG IC will be stored to allow possible exploratory PG research to assess whether genetic polymorphisms relate to the absorption, distribution, metabolism, excretion, pharmacodynamics or safety of levosimendan.

Safety: Safety will be assessed by adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), physical examination, weight, laboratory tests and by assessment of suicidality.

# Study description

### Background summary

see section 1.1 background in the protocol

### Study objective

The primary objective of this study is to confirm that levosimendan can significantly improve respiratory function measured by supine slow vital capacity (SVC) in amyotrophic lateral sclerosis (ALS) patients.
The secondary objective is to confirm that levosimendan improves the functionality of subjects, measured by Revised ALS Functional Rating Scale (ALSFRS-R), Clinical Global Impression (CGI), Borg Category Ratio 10 (CR10) scale on the intensity of dyspnea. Epworth Sleepiness scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). The latter two are sleep scales assessing daytime somnolence and sleep quality, respectively. In addition, the long-term tolerability and safety of levosimendan in ALS patients will be evaluated, assessing up to 48 weeks of exposure.
Other objectives: For the purposes of potential later pharmacoeconomic analysis, the use of specific health and home care resources and assistive devices will be quantified. This will include both in and outpatient care, as well as formal and informal home care.
Exploratory objectives: The plasma concentrations of levosimendan and the metabolites OR-1855 and OR-1896 will be determined. In addition, a population pharmacokinetic/pharmacodynamic (PK/PD) model between OR-1855 and OR-1896 exposure and efficacy related endpoints and heart rate (HR) will be explored. Plasma concentrations of riluzole will also be determined. The effects of levosimendan, OR-1855 and OR-1896 on plasma trough concentrations of riluzole will be evaluated. The acetylation status will be determined for all subjects to assess whether it affects the PD responses of levosimendan in patients with ALS.

### Study design

This is a randomised, double-blind, placebo-controlled, parallel-group, multinational, multicentre study. The subjects will be allocated to 2 parallel groups receiving either levosimendan 1-2 mg daily or placebo in 2:1 ratio. There will be a screening visit, a baseline visit followed by visits at 2, 4, 8, 12, 24, 36 and 48 weeks, and telephone contacts during weeks 18, 30 and 42. An end-of-study visit will take place 14-25 days after the last study treatment administration for each subject. The total study duration for each subject will be about 51-52 weeks including the end-of-study visit.

### Intervention

Levosimendan 1 mg capsule/Placebo Levosimendan capsule
The daily doses of oral levosimendan will be 1-2 mg depending on the tolerability (mainly judged by HR). The subjects will start with a 1 mg dose (in the morning) for 2 weeks. Administration of placebo (1 or 2 capsules per day) will be based on the same criteria as for levosimendan.

**Study burden and risks**

A: Medicine or other interactions
The patient needs to take the study drug approx. 1 hour before food intake, since food may affect how the drug is take up by the body. Taking certain other medicines together with levosimendan (ODM-109) may increase the chance of unwanted effects. The risk will depend on how much of each medicine the patient takes every day, and on how long the patient takes the medicines together. If your study investigator instructs the patient to take these medicines together on a regular basis, follow his or her directions carefully. Report if you have taken any other medications during the study.

B: Side effects of the study medicinal product
The possible discomforts, side effects and risks related to levosimendan (ODM-109) treatment are not all known, although some may be serious and may require treatment or additional testing. This section describes how frequently side effects occurred in subjects who were treated with levosimendan (ODM-109).

Very Common: Affects more than 1 user in 10:
* Mild-moderate headache lasting for about 2-3 days.
* Increased heart rate.

Common: Affects 1 to 10 users in 100
* Rapid or irregular beating of the heart.
* Slight decrease in red blood cell count which can lead to anemia, a condition in which you don't have enough healthy red blood cells to carry adequate oxygen to the body's tissues. Having anemia may make you feel tired and weak.
* Decrease in blood value of potassium. Potassium helps carry electrical signals to cells in your body. It is critical to the proper functioning of nerve and muscles cells, particularly heart muscle cells.

Previous studies with oral levosimendan (ODM-109) have not showed any signs of more severe irregular heartbeats compared to placebo treatment. The patient will still be carefully monitored in case you would experience rapid or irregular beating of the heart, dizziness or loss of consciousness.

Because of possible drug reactions, the patient cannot enter this study if the patient is allergic or sensitive to levosimendan (ODM-109). Serious allergic reactions which could be life-threatening are rare, this could include swollen face, lips, mouth and/or throat.

Other currently unknown risks and discomforts could appear. It is therefore very important that any new health problem is quickly reported to the investigator, regardless of whether or not the patient thinks it is to do with the study.

See Appendix E of the ICF for Other Risks and discomforts

# Contacts

**Public**
Orion Corporation

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**Scientific**
Orion Corporation

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Male or female subjects with diagnosis of ALS, disease duration from symptom onset of 12-48 months, written or verbal informed consent (IC) obtained from the subject. Age at least 18 years. Able to swallow study treatment capsules,

and in the opinion of the investigator, is expected to continue to do so during the study. Sitting SVC between 60-90% of the predicted value for age, height and sex at screening visit. Able to perform supine SVC at screening and baseline visits.
Subjects with or without riluzole. If using riluzole (any daily dose up to 100 mg), the dose must have been stable for at least 4 weeks before the screening visit and
should not be changed during the study. If not on riluzole,
the respective treatments should not be started during the study.

## Exclusion criteria

Subject in whom other causes of neuromuscular weakness have not been excluded.
Subject with a diagnosis of another neurodegenerative disease (e.g. Parkinson*s or Alzheimer*s disease).
Assisted ventilation of any type within 3 months before the screening visit or at screening.
Any use of a diaphragm pacing system (DPS) within 3 months before the screening visit.
Any form of stem cell or gene therapy for the treatment of ALS.
Known hypersensitivity to levosimendan.
Administration of levosimendan within 3 months before the screening visit or previous participation in the present phase III study or earlier study with oral levosimendan in ALS patients (LEVALS).
Any use of tirasemtiv or reldesemtiv within 1 month before the screening visit.
Participation in a clinical trial with any experimental treatment within 30 days or within 5 half-lives of that treatment (whichever is longer) before the screening visit.
Any botulinum toxin use within 3 months before the screening visit.
Recorded diagnosis or evidence of major psychiatric diagnosis, significant cognitive impairment or clinically evident dementia that may interfere with the patient*s ability to comply with study procedures.
Pulmonary illness (e.g. asthma or COPD) requiring regular treatment.
Haemodynamically significant uncorrected valve disease or hypertrophic cardiomyopathy or restrictive cardiomyopathy.
Any cardiovascular event (e.g. myocardial infarction, HF, arrhythmia or stroke) requiring hospitalisation within 3 months before the screening visit.
History of Torsades de Pointes (TdP) or diagnosed long QT-syndrome.
History of life-threatening ventricular arrhythmia, unless treated with reliable measures to prevent recurrence (e.g. with placement of implantable cardioverter defibrillator [ICD] or catheter ablation).
History of second or third degree atrioventricular (AV) block or sinus node disease at screening, if not treated with pacemaker.
HR repeatedly > 100 bpm in the 12-lead ECG after a 5-minute rest at screening. If the HR is > 100 bpm in the first recording, then the second recording must

be done after another 5 min rest to confirm HR > 100 bpm.
Systolic blood pressure (SBP) < 90 mmHg at screening.
Potassium < 3.7 mmol/l or > 5.5 mmol/l at screening.
Several renal impairment (creatinine clearance < 30 ml/min at screening), creatinine > 170 *mol/l at screening or on dialysis.
Blood haemoglobin < 10 g/dl at screening or blood donation or loss of significant amount of blood within 60 days before the screening visit.
Clinically significant hepatic impairment at the discretion of the investigator.
Body mass index (BMI) * 18.5kg/m2 (BMI = weight/height2).
Women who are lactating or of reproductive age without a negative pregnancy test and without a commitment to using a highly effective method of contraception (e.g. oral hormonal contraceptives associated with inhibition of ovulation, intrauterine devices 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.
Patient judged to be actively suicidal by the investigator during 3 months before the screening visit.
Patients with known history of human immunodeficiency virus (HIV) infection.
Any other clinically significant cardiovascular, 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.

# Study design

## Design

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|---|---|
| Study phase: | 3 |
| 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): | 14-11-2018 |
| Enrollment: | 16 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Simdax |
| Generic name: | Levosimendan |

## Ethics review

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|---|---|
| Approved WMO Date: | 22-05-2018 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 30-08-2018 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 11-09-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 08-10-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 07-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 03-02-2020 |
| Application type: | Amendment |

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|---|---|
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 26-02-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 28-04-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 07-05-2020 |
| 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 | EUCTR2017-002754-36-NL |
| ClinicalTrials.gov | NCT03505021 |
| CCMO | NL64706.041.18 |