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Title:	Effects of oral levosimendan (ODM-109) on respiratory function in patients with ALS: open-label extension for patients completing study 3119002
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CLINICAL STUDY PROTOCOL – AMENDMENT 1

[redacted]

EFFECTS OF ORAL LEVOSIMENDAN (ODM-109) ON RESPIRATORY FUNCTION IN PATIENTS WITH ALS: OPEN-LABEL EXTENSION FOR PATIENTS COMPLETING STUDY 3119002

Study code:	3119003
Study design:	Open, non-randomised, uncontrolled multicentre study
Short study title:	REFALS-ES
Phase:	III
Standard:	GCP
EudraCT number:	2018-004180-31
IND number:	134169
Study Coordinating Investigator:	Merit Cudkowicz, MD
Sponsor:	Orion Corporation Orion Pharma Orionintie 1, FI-02200 Espoo, Finland
Date:	26 March 2020

[redacted]

Sponsor approvals:

[redacted]

Development Leader: [redacted]

Clinical Study Director: [redacted]

Study Statistician: [redacted]

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SYNOPSIS

Sponsor: Orion Corporation Orion Pharma
Finished product: Not applicable
Active pharmaceutical ingredient: Oral levosimendan (ODM-109)
Study title: Effects of oral levosimendan (ODM-109) on respiratory function in patients with ALS: open-label extension for patients completing study 3119002
Study code: 3119003
Investigator: The study coordinating investigator is Merit Cudkowicz, MD
Study centres: This will be a multinational study in approximately 100 centres.
Development phase: III
Objectives: Primary: The primary objective, in addition to continuing treatment for subjects in REFALS study, is to evaluate long-term safety of oral levosimendan in amyotrophic lateral sclerosis (ALS) patients. Secondary: The secondary objective is to explore long-term effectiveness of oral levosimendan in the treatment of patients with ALS, by continuing to observe rate of disease progression during the treatment.
Methodology: Open, non-randomised, uncontrolled multicentre extension to study 3119002. Open-label levosimendan treatment will normally be started at the end-of-study visit for study 3119002. Subjects will attend the study centre at least every 3 months during the levosimendan treatment and will be reassessed (by telephone or centre visit) 2 weeks after each dose change.
Number of subjects: All subjects completing 48-weeks treatment period in the REFALS study may be eligible for this extension study. The maximum number of subjects is therefore 450.
Diagnosis and main criteria for inclusion: Subjects must meet all of the following criteria to be included into the study: 1. Written or verbal informed consent (IC) for participation in the study will be obtained from the subject. In case that the study subject him/herself cannot sign the IC, a witness may sign the consent form to indicate that the subject has given verbal consent. 2. Subjects who completed 48 weeks of treatment according to the REFALS study protocol. 3. Able to swallow study treatment capsules at the time of completing 48 weeks dosing in the REFALS study. Subjects will not be included into this study if they meet any of the following criteria: 1. Development (or significant worsening from baseline of the REFALS study) of serious cardiovascular disease (e.g. myocardial infarction, heart failure, arrhythmia, stroke, or second or third degree atrioventricular (AV) block). 2. Pulse/heart rate repeatedly > 100 bpm after 5-minute rest at baseline. If the pulse/heart rate is > 100 bpm in the first recording, then a second recording must be done after another 5 min rest to confirm pulse/heart rate > 100 bpm. 3. Systolic blood pressure (SBP) < 90 mmHg. 4. Severe renal impairment (creatinine clearance < 30 ml/min or creatinine > 170 µmol/l at 48 week visit of the REFALS study, or on dialysis. 5. Severe hepatic impairment at the discretion of the investigator. 6. Women 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. 7. Subject judged to be actively suicidal by the investigator. 8. 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.
Investigational product, dose and mode of administration: Test product will be Levosimendan 1 mg capsules administered orally. The target maintenance dose of oral levosimendan will be 2 mg/day taken as 1 mg b.i.d.

Levosimendan treatment will be started at 1 mg/day, with increase to 2 mg/day after 2 weeks treatment if well tolerated.
Frequency/duration of treatment: The subject may continue the treatment as long as clinically indicated or until the study ends.
Variables and methods of assessments: **Efficacy assessments:** Slow vital capacity (SVC): SVC will be assessed in the sitting and supine position once at each centre visit during the study including the baseline, i.e. in the morning before the study treatment administration. Revised ALS Functional Rating Scale (ALSFRS-R): ALSFRS-R will be assessed at each centre visit and telephone contact. The variables derived will be the scores of the 12 separate items, the total scores of each subdomain (bulbar, fine motor, gross motor and respiratory) and the total score of ALSFRS-R. Need for respiratory support: The use of any respiratory support, including Bilevel Positive Airway Pressure (BiPAP) and invasive mechanical ventilation, will be recorded. The time to starting or changing the degree of respiratory support will be calculated. Borg Category Ratio 10 Scale (CR 10): Borg CR 10 scale will be used in the assessment of dyspnoea. The subjects will be asked to point out a score quantifying their perception on the intensity of dyspnoea on the CR10 scale at rest in sitting and supine position (immediately before the SVC measurements). Orthostatic changes between sitting and supine positions will be calculated. Health care and home care resource use: Health care and home care resource use will be recorded for possible later use in pharmacoeconomic analysis. Other assessments: Subject's status for tracheostomy and survival will be recorded at all visits. **Safety assessments** Safety will be assessed by adverse events (AEs), vital signs, 12-lead electrocardiogram (ECG) and by assessment of suicidality.
Statistical methods: **Analysis of efficacy:** All subjects who have received at least 1 dose of study treatment will be included into the analyses. Full analysis set will also include assessments from the REFALS study from participating subjects. Analyses will be performed with and without data from the REFALS study, depending on the analysis type. When appropriate, between-subject comparisons will be performed using the randomised treatment arm in the REFALS study. Slope of decline in sitting and supine SVC and ALSFRS-R will be estimated using a random slope model. Median time to non-invasive mask ventilation (NIV) or death and to decline (by at least 1 point) in the ALSFRS-R respiratory domain will be evaluated using Kaplan-Meier estimates. Borg CR10 (sitting, supine and orthostatic changes) will be evaluated using mixed model for repeated measures. Health and home care resource use data will be summarised in the study report, but any further analysis for potential pharmacoeconomic purposes will be reported separately. **Analysis of safety:** The AEs will be displayed as event counts and subject counts in a frequency table. The number and proportion (%) of subjects having each AE as well as the AE severity (mild, moderate, severe) and causality (related, not related) to the study treatment will be given. SAEs and other significant AEs will be evaluated case-by-case. The actual values and changes from baseline in pulse/heart rate and blood pressure will be summarised using descriptive statistics. Any abnormal 12-lead ECG findings, special situations and suicidality data will be summarised using descriptive statistics.

ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	Revised ALS Functional Rating Scale
b.i.d.	Twice a day
BiPAP	Bilevel Positive Airway Pressure
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CA	Competent authority
CAFS	Combined assessment of function and survival
CHF	Chronic heart failure
CNS	Central nervous system
CR10	Category Ratio 10
CRA	Clinical research associate
CRO	Contract research organisation
CRF	Case report form
DSMB	Data and safety monitoring board
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
GCP	Good clinical practice
GMP	Good manufacturing practice
HF	Heart failure
IC	Informed consent
IRB	Institutional review board
i.v.	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities

MHRA	The Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed model for repeated measures
NIV	Non-invasive mask ventilation
PD	Pharmacodynamic(s)
PG	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SBP	Systolic blood pressure
SMA	Site management associate
SUSAR	Suspected unexpected serious adverse reactions
SVC	Slow vital capacity

Note on usage of terms:

Orion Corporation Orion Pharma is hereafter in this document called “Orion”.

The term ‘investigator’ in the text of the protocol refers to the principal investigator or co-investigator.

1. INTRODUCTION

1.1 Background

Amyotrophic lateral sclerosis (ALS) is a rare, rapidly progressive neurological disease characterised by degeneration of upper and lower motor neurons with subsequent muscle atrophy and weakness and loss of respiratory function. The latter is due to the weakness and loss of diaphragm muscle strength. The median survival time from symptom onset is approximately 3 years (Turner MR et al., 2013). No cure currently exists for ALS, the mainstay of treatment is symptom management and palliative care. The first drug product approved to treat ALS was riluzole, which has modest effect (approx. 3 months) on survival (Bensimon G et al., 1994) and no symptomatic effects. Another approved drug, edaravone has modest effects on the Revised ALS Functional Rating Scale (ALSFRS-R), but does not specifically address muscle weakness and respiratory insufficiency in ALS and is available in only few countries. In addition, dextromethorphan/quinidine is available on some markets and indicated for the symptomatic treatment of pseudobulbar affect. In later stage patients with significantly compromised respiratory function, it is a common practice to initiate non-invasive mask ventilation (NIV) to improve patients' quality of life and survival (Andersen PM et al., 2012, NICE guideline [NG42], 2016).

Levosimendan is a calcium sensitising drug that improves force generation in both cardiac and skeletal muscle through binding to troponin C, without increasing oxygen consumption. Levosimendan does not cross the blood brain barrier or cause central nervous system (CNS) adverse effects. Intravenous (i.v.) levosimendan (Simdax®) is approved for treatment of acutely decompensated heart failure in approximately 60 countries. Levosimendan improved diaphragm neuromechanical efficiency in healthy volunteers (Doorduin J et al., 2012) and had positive effects on supine slow vital capacity (SVC) in patients with ALS.

In the LEVALS phase II study (3119001), including 66 patients with ALS (sitting SVC ranging from 60 to 90% of predicted) oral levosimendan 1 or 2 mg improved supine (but not sitting) SVC after 14 days of treatment compared to placebo. Vital capacity in the supine rather than sitting position better reflects the loss of diaphragm function in ALS patients that commonly manifests in problematic orthopnoea and sleep disruption (Lechtzin N et al., 2002). Supine SVC may thus also be a better measure of diaphragm function than SVC in the sitting position. Oral levosimendan was well tolerated, the most frequent treatment-related adverse effects being headache and tachycardia, related to its known effects as an inodilator. A 6-month extension study did not identify additional safety issues.

The currently ongoing REFALS phase III study (3119002; NCT03505021; EudraCT 2017-002754-36) will evaluate whether changes in supine SVC are translated to clinical benefit for patients with ALS. A total of 450 adult patients, from Europe, Australia and North America, with definite, probable or laboratory supported probable ALS and some degree of respiratory dysfunction (sitting SVC ranging from 60 to 90%) will be treated with oral levosimendan (target 2 mg daily) or placebo for 48 weeks in a double-blind, parallel-group design. The primary endpoint will be supine SVC with important secondary endpoints including ALSFRS-R adjusted for patient survival (combined assessment of function and survival [CAFS]), the occurrence of respiratory events, clinical global impression, Borg Category Ratio 10 (CR10) scale for dyspnoea and scales assessing sleep. Safety will be assessed using standard measures including adverse events (AEs), vital signs, 12-lead electrocardiogram (ECG) and laboratory safety tests

at regular intervals throughout the 48-week treatment period. The subjects will record use of healthcare resources in a diary.

The REFALS-ES study (3119003) is an open-label extension for subjects who complete the double-blind REFALS study (3119002) and who wish to continue treatment with oral levosimendan.

1.2 Rationale of the study

1.2.1 Rationale of the study design

This study provides an opportunity for subjects in the REFALS study to continue treatment with oral levosimendan. The study will also provide more information about long-term safety and effectiveness of oral levosimendan in patients with ALS, to supplement data from the double-blind REFALS study.

This is an open-label study, so that all eligible subjects that complete the double-blind REFALS study will have the opportunity to receive oral levosimendan treatment. Apart from completing the REFALS study, eligibility criteria for REFALS-ES study are restricted to safety criteria that may have changed since the start of the REFALS study. The subjects will be able to participate in the study and receive levosimendan for as long as it is considered clinically beneficial. In addition, as a long term extension, the objective is to limit disruption to usual patient care and to reduce subject inconvenience and study commitments. Thus safety and efficacy measures and study restrictions are reduced to more closely reflect typical patient care than in the double-blind study. On completing 48 weeks double-blind treatment in the REFALS study, all subjects will stop blinded treatment, with the REFALS end-of-study visit 14-25 days later serving as the baseline visit for REFALS-ES study and re-initiation of the treatment. Since the half-life of the most important active metabolite of levosimendan, OR-1896, exceeds 60 hours, the actual drug-free period will be somewhat shorter than this. This off-treatment period allows evaluation of reversal of ongoing AEs as well as observation of the effects of withdrawal of prolonged levosimendan treatment. It also reduces any risk of unblinding occurring as a result of an abrupt change in the treatment for subjects receiving placebo in REFALS study. As levosimendan is intended for treatment of respiratory symptoms rather than preventing or delaying disease progression, the break in treatment is not expected to result in a significant risk to subject well-being.

The study will continue at least until the time of marketing approval of oral levosimendan, cessation of development of oral levosimendan for ALS, or 3 years, whichever occurs first in each participating country. Continuation after this time will be at the discretion of the sponsor. On termination of the study, an appropriate method of continued treatment supply will be sought for any subjects still requiring treatment with oral levosimendan.

1.2.2 Rationale for selected doses

The target maintenance dose of levosimendan in this study will be the same as in the REFALS study, i.e. 2 mg per day administered as 1 mg b.i.d. The subjects in the placebo-arm in the REFALS study will receive levosimendan for the first time in the REFALS-ES study. For subjects in the levosimendan-arm in the REFALS study there will be 14-25 days drug-free post-treatment period before entering the REFALS-ES study. In order to reduce the risk for headache

and marked increase in heart rate, the subjects will start the treatment at 1 mg/day, and if tolerated and considered appropriate, the treatment dose should be increased to 1 mg b.i.d. after two weeks of treatment. After that, changes to the daily dose of the study treatment are allowed at any time. It will also be possible, given the slow elimination of metabolites of levosimendan, to administer levosimendan less frequently than 1 mg daily in the event that dose is not adequately tolerated. All dose changes are re-assessed approximately 2 weeks after the change.

1.3 Benefit-risk assessment

1.3.1 Potential benefits associated with levosimendan

SVC assessed in the supine position in the LEVALS study indicated that 2 weeks treatment with levosimendan significantly improved respiratory function in ALS patients, presumably by enhancing the skeletal muscle function of the diaphragm. It is anticipated that such an effect may be larger during longer treatment and in turn improve patients' well-being and functional ability. Levosimendan is not expected to significantly affect underlying disease progression.

1.3.2 Potential risks associated with levosimendan

Safety data with oral levosimendan are primarily based on treatment of patients with heart failure and extensive experience with the i.v. preparation, although 66 patients with ALS received levosimendan in the LEVALS study. Available data indicate that levosimendan or its active metabolites do not typically cause clinically significant direct CNS effects. Headache (due to vasodilatation), increased heart rate and palpitations have been the most commonly reported adverse drug reactions in healthy subjects and/or ALS patients treated with levosimendan. Myocardial and arterial changes such as hypertrophy, myocarditis and vasculitis have been observed in toxicity studies in animal species, dog being the most sensitive species with first signs of toxicity appearing at 2-5 fold clinical exposure. The clinical relevance of these findings is not known. Based on the safety data originating from the completed clinical studies with oral levosimendan in chronic heart failure (CHF) (administered 1-2 mg daily for longer than 180 days), safety signals of increased heart rate and palpitations have been detected and are considered as potential risks for oral levosimendan use. No other safety concerns related to cardiac function have been identified from these data. Arrhythmias are known AEs for i.v. levosimendan in patients with severe CHF. However, there is no such evidence for oral levosimendan in healthy subjects. In addition, in the LEVALS, phase IIa study conducted in ALS patients, no differences in supraventricular or ventricular tachyarrhythmias were seen between placebo and levosimendan treatments. There were no differences either in the numbers of severe AEs or serious adverse events (SAEs) between the treatments. However, special attention should be paid to symptoms potentially connected with cardiac arrhythmias, such as palpitations, dizziness and loss of consciousness. In laboratory parameters, slight decreases in red cell parameters and serum potassium have been observed in some studies.

1.3.3 Potential risks associated with the study assessments

Blood samples may be collected for safety laboratory and levosimendan concentration analyses can be conducted, if clinically indicated. The risks of blood sampling include fainting and pain, bruising, swelling or rarely infection of the injection site. Respiratory assessments may be burdensome for patients with ALS.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective, in addition to continuing treatment for subjects in REFALS study, is to evaluate long-term safety of oral levosimendan in ALS patients.

2.2 Secondary objective

The secondary objective is to explore long-term effectiveness of oral levosimendan in the treatment of patients with ALS, by continuing to observe rate of disease progression during the treatment.

3. OVERALL STUDY DESIGN AND PLAN

This is an open, non-randomised, uncontrolled, multicentre phase III extension study to the REFALS study.

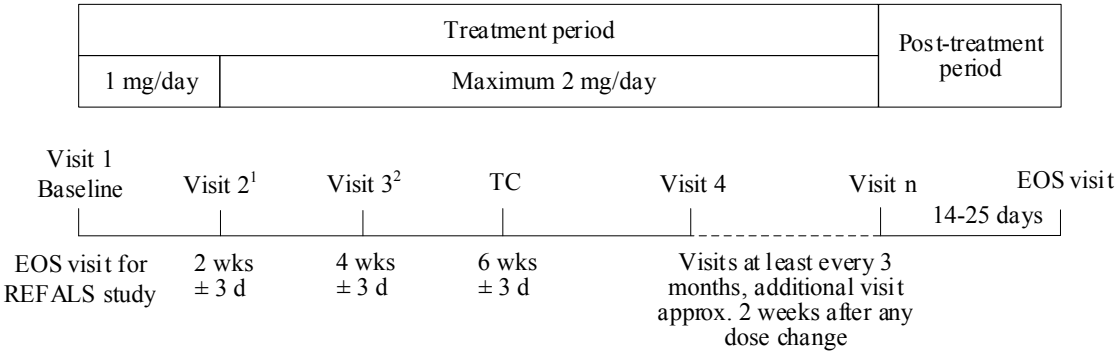
The subjects will give informed consent (IC) to continue in this open-label extension study at the 48-week or end-of-study visit of the REFALS (or between these visits). The REFALS end-of-study visit will double as the REFALS-ES baseline visit. Visits to the study centre are flexible but occur at least every 3 months. Subject assessments will be conducted 2 weeks after starting the study treatment and after each change in the dose: such visits may be at study centre or conducted remotely where feasible (see section 6.1.3). A telephone contact will be performed for all subjects 6 weeks after starting the treatment.

The subject may continue the treatment as long as clinically indicated (see withdrawal criteria in section 4.5) or until the study ends.

An end-of-study visit will take place 14-25 days after the last study treatment administration for each subject.

The study design is presented in Figure 1.

Figure 1. Study design



TC = telephone contact, EOS = end-of-study

[1] Dose increased to 1 mg b.i.d. if the 1 mg/day dosing was well tolerated

[2] Additional visit approx. 2 weeks after any dose change at visit 2

4. SELECTION OF STUDY POPULATION

4.1 Number of subjects

All subjects completing 48-weeks treatment period in the REFALS study may be eligible for this extension study. The maximum number of subjects is therefore 450.

4.2 Inclusion criteria

Subjects must meet all of the following criteria to be included into the study:

1. Written or verbal IC for participation in the study will be obtained from the subject. In case that the study subject him/herself cannot sign the IC, a witness may sign the consent form to indicate that the subject has given verbal consent.
2. Subjects who completed 48 weeks of treatment according to the REFALS study protocol.
3. Able to swallow study treatment capsules at the time of completing 48 weeks dosing in the REFALS study.

4.3 Exclusion criteria

Subjects will not be included into this study if they meet any of the following criteria:

1. Development (or significant worsening from baseline of the REFALS study) of serious cardiovascular disease (e.g. myocardial infarction, heart failure, arrhythmia, stroke, or second or third degree atrioventricular [AV] block).
2. Pulse/heart rate repeatedly > 100 bpm after 5-minute rest at baseline. If the pulse/heart rate is > 100 bpm in the first recording, then a second recording must be done after another 5 min rest to confirm pulse/heart rate > 100 bpm.

3. Systolic blood pressure (SBP) < 90 mmHg.
4. Severe renal impairment (creatinine clearance < 30 ml/min or creatinine > 170 µmol/l at 48 week visit of the REFALS study, or on dialysis.
5. Severe hepatic impairment at the discretion of the investigator.
6. Women 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.
7. Subject judged to be actively suicidal by the investigator.
8. 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.

4.4 Information collected on screening failures

For subjects screened but not included in the study, the following case report forms (CRFs) will be completed: date of the screening visit, IC, demography (birth year, sex and race), criteria causing the exclusion and decision of entry. In addition, all information (including concomitant treatments and medical history) about AEs related to study assessments and SAEs must be collected.

4.5 Removal of subjects from treatment or assessment

Study subjects are free to discontinue the study at any time without providing a reason. However, the investigator should try to identify the reason and document it in the CRF.

A subject must discontinue the study for the following reasons:

- The subject starts another study with investigational medicinal product.
- Uncontrolled pulse/heart rate increase from baseline (visit 1) despite maximal dose reduction (see section 5.2.2).
- Life-threatening supraventricular or ventricular arrhythmia.
- Pregnancy.
- The investigator judges that it is in the best interest of the subject to stop the study treatment due to any other abnormality compromising subject safety. However, the investigator should consult the medical monitor whenever possible in these instances.

Irrespective of the reason for discontinuation, the subject should be invited to complete the end-of-study assessments. As long as the subject consents, all relevant assessments, at least those of

safety, should be performed, preferably according to the schedule for the end-of-study assessments.

The study monitor must be notified about premature discontinuations by email/phone/fax within 24 hours in the event of discontinuation due to an SAE (see section 6.4.1.3) or within 7 days in the event of discontinuation due to another reason.

Discontinued subjects are not allowed to re-enter the study.

5. STUDY TREATMENTS

Manufacturing, packaging, and labelling of the study treatments will comply with good manufacturing practice (GMP) regulations (Annex 13 of EU guide to GMP). The capsules will be stored below 30°C and the container kept tightly closed.

5.1 Investigational medicinal product

5.1.1 Test product

Test product will be Levosimendan 1 mg capsules administered orally.

5.1.2 Control product

No control product will be used.

5.2 Dosing

5.2.1 Selection and timing of doses

All subjects will receive levosimendan in this study. The target maintenance dose of oral levosimendan will be 2 mg/day (see section 5.2.2) taken as 1 mg b.i.d. Levosimendan treatment will be started at 1 mg/day. The subject should be reviewed 2 weeks after initiation of levosimendan at which time the dose should be increased to 2 mg/day, if considered appropriate and the 1 mg/day dose was well tolerated. Since OR-1896 has a very long elimination half-life, it is permitted to use also less frequent dosing than 1 mg once daily (e.g. 1 mg on alternate days) if levosimendan 1 mg/day is not well tolerated. The subject should be re-assessed 2 weeks after each dose change.

Single daily doses should be taken in the morning. It is recommended to take the study treatment about 1 hour before food intake or on an empty stomach. The morning dose of study treatment will be administered at the study centre during the visit days.

5.2.2 Dose adjustment

The levosimendan dose will be adjusted according to tolerability, including pulse/heart rate. It is recommended to reduce the daily dose of the study treatment (or discontinue the treatment if no further dose reduction is possible) if resting pulse/heart rate is repeatedly > 30 bpm more than the pre-treatment value or the subject has marked symptoms related to tachycardia (see section

6.4.4). It is further advised not to increase the dose at week 2 visit or any later time point if the resting pulse/heart rate change is close to this recommended limit.

After the initial two weeks of treatment with levosimendan 1 mg/day, changes in dose can take place at any time but it should be remembered that the full effect of a dose change may take 2 weeks to develop, at which point the subject should be reassessed before making any further dosing decision.

5.3 Method of assigning study subjects to treatment groups

No randomisation will be applied in this study. The subjects will receive their subject numbers in the REFALS study and the same subject numbers will be used in this study.

5.4 Blinding

This is an open-label study.

5.5 Emergency procedures

5.5.1 Treatment of emergencies

Emergencies will be treated according to the decision of the physician in charge or the investigator, when available.

5.6 Prior and concomitant treatments

All relevant concomitant treatments during the study (including all medical treatments for ALS), including the post-treatment period, must be recorded. Subjects may not take part in another clinical study while participating in this extension study.

5.6.1 Prohibited treatments during the study

Other medications are not restricted, except as part of another clinical study.

5.6.2 Permitted treatments during the study

Supplements and other treatments for ALS are not prohibited during this study, although possibility of drug interactions should always be considered. Botulinum toxin is not excluded if considered clinically required. Treatment with riluzole and edaravone can be started, discontinued or adjusted as indicated.

Any other treatments, except as part of another clinical study, which are considered necessary for the subject's welfare, and which will not interfere with the study treatment, may be given at the discretion of the investigator.

If the permissibility of a specific drug/treatment is questionable, the medical monitor must be contacted.

5.7 Treatment compliance and exposure

Treatment compliance will be assessed by study treatment accountability. The morning dose of study treatment will be administered at the study centre during the visit days. Treatment deviations must be recorded. Subjects should be asked about the reason for non-compliance.

Drug accountability records will be kept. The investigator must maintain accurate records demonstrating the date and amount of study treatments received, to whom and by whom dispensed (drug dispensing list) and accounts of study treatments accidentally or deliberately destroyed.

At the end of the study, any remaining study treatments will be collected and returned to the sponsor. Any discrepancies between the returned and expected returned study treatments should be explained.

5.8 Availability of investigational medicinal product after termination of study

On termination of the study, an appropriate method to continue treatment will be sought for any subjects still requiring treatment with oral levosimendan.

6. STUDY PROCEDURES AND ASSESSMENTS

6.1 Study procedures

Table 1 lists all study procedures and indicates with an ‘x’ during which visit a particular procedure is performed.

Table 1. Schedule of study events

Protocol activities	Baseline		Treatment period		Post-treatment period
	REFALS End-of-study visit	Visit 1 Baseline D1	Telephone contact	Study centre visit	End-of-study visit 14-25 d after last study treatment administration
IC		x[1]			
Weight	x			x	x
Height and BMI	x				
Physical examination	x				
Heart rate and BP	x				
Pulse/heart rate and BP		x	x (only pulse/heart rate)	x	x
12-lead ECG	x			x	x
Pregnancy test for females of childbearing potential	x			x	x
Laboratory safety assessments					
Haematology	x				
Chemistry	x				
Urinalysis	x				
SVC sitting		x[2,3]		x[4]	x[3]
SVC supine	x[2]	x[3]		x[4]	x[3]
Eligibility criteria and decision of entry		x			
Study treatment		x			
ALSFRS-R		x	x	x	x
Borg CR10 scale	x			x	x
Use of health care and home care resources and non-medical assistive devices		x	x	x	
Assessment of suicidality	x			x	x
Status for NIV support, invasive mechanical ventilation by intubation or tracheostomy and survival	x		x	x	x
AEs and SAEs	x				
Concomitant treatments	x				

[1] If not given earlier [2] Using MasterScope [3] Local equipment
[4] MasterScope will be used for all study centre visits up to 3 months, all subsequent visits use local equipment

6.1.1 Procedures during the baseline visit

A prospective subject will receive both written and verbal information about the study at the 48-week or end-of-study visit for the REFALS study (or between these visits) and will have an opportunity to ask questions and sufficient time to decide whether or not to participate in the extension study. A signed and dated written IC will be obtained (a witness may sign the consent form to indicate that the subject has given verbal consent) before any study specific procedures will be performed.

End-of-study visit assessments for the REFALS study will be used as baseline for this study. The following procedures for the REFALS study will be carried forward to this extension study:

- Weight will be recorded.
- SVC supine will be assessed using the MasterScope.
- The Borg CR10 scale to assess the intensity of dyspnoea will be completed at rest in sitting and supine positions (immediately before SVC measurement).
- Blood pressure (supine) will be recorded.
- A pregnancy test will be performed for females of childbearing potential.
- Suicidality will be assessed.
- AEs, SAEs and concomitant treatments will be recorded.

In addition the following procedures will be performed before starting the study treatment in the REFALS-ES:

- Inclusion and exclusion criteria for this extension study will be assessed.
- SVC sitting and supine (local equipment) will be assessed. Baseline SVC sitting will also be performed with the MasterScope.
- ALSFRS-R will be assessed.
- Pulse/heart rate will be recorded.
- Use of health care and home care resources and non-medical assistive devices will be recorded.

If the subject is eligible, the study treatment will be dispensed. The first dose of the study treatment will be administered at the study centre, and blood pressure (supine) and pulse/heart rate will be recorded approximately 1 hour after the administration. It is recommended that subjects remain at the study centre for at least 2 hours after the first dose of levosimendan.

6.1.2 Procedures during the treatment period

Visits will be performed either by telephone or attendance at the study centre. For simplicity, all visits of the same type involve the same procedures.

Any planned follow-up may take place at the study centre and may occur at any time, but should not be less frequent than every 3 months. The only fixed follow-up points are dose assessment at 2 weeks and telephone contact 6 weeks after start of the study treatment.

Any visit may be performed by telephone provided:

- A reliable measure of resting pulse/heart rate can be obtained and documented.
- The minimum 3-monthly study centre visit schedule is maintained.

In case a subject is no longer able to travel to the study centre, but levosimendan is considered to still be of clinical value, wholly remote monitoring by telephone contacts may be acceptable. This must be agreed in advance by the sponsor and the medical monitor, and an acceptable method of dispensing study treatment must be established.

Procedures during visits are presented in Table 2. The morning dose of study treatment will be administered at the study centre during the study centre visit days. In addition, additional visits or contacts approximately 2 weeks after dose change can occur at any time (see section 6.1.3).

Table 2. Procedures during the treatment period

Time	Study centre visit[1]	Telephone contact
Weight	x	
Pulse/heart rate and BP	x	Pulse/heart rate only
12-lead ECG	x	
Pregnancy test for females of childbearing potential	x	
SVC supine and sitting	x[2]	
Study treatment	x	
ALSFRS-R	x	x
Borg CR10 scale	x	
Use of health care and home care resources use and non-medical assistive devices	x	x
Assessment of suicidality	x	x
Status for NIV support, invasive mechanical ventilation by intubation or tracheostomy and survival	x	x
AEs and SAEs	x	x
Medical history and current medical conditions	x	x
Concomitant treatments	x	x

[1] All procedures will be performed pre-dose
[2] MasterScope used up to 3 months

During the telephone contact a caregiver can take the telephone contact on behalf of the subject in case the subject is unable to communicate verbally due to disease progression.

6.1.3 Additional visits

Additional centre visits or telephone contacts will be performed after changing the dose of the study treatment (see section 5.2.2), approximately 2 weeks after the dose change. Procedures at these visits/contacts will be the same as described in Table 2.

6.1.4 Procedures during the post-treatment period

An end-of-study visit will take place 14-25 days after the last study treatment administration for each subject. The following procedures will be performed:

- Pulse/heart rate and BP will be recorded.
- SVC supine and sitting will be assessed.
- A pregnancy test will be performed for females of childbearing potential.
- AEs, current medical conditions and concomitant treatments will be recorded.
- Status for NIV support, invasive mechanical ventilation by intubation or tracheostomy and survival will be recorded
- Suicidality will be assessed.

In case it is not possible for the subjects to travel to the study centre, the end-of-study visit may be performed by telephone (except pregnancy test, BP and SVC).

6.2 Efficacy assessments

6.2.1 Slow Vital Capacity

SVC is the maximum volume of air that can be exhaled slowly after slow maximum inhalation. The best read from 3 attempts will be chosen. The volume is measured in litres and the SVC variable will be % of predicted (normal) value for age, height and sex.

SVC will be assessed in the sitting and supine position once at each centre visit during the study including the baseline (visit 1), i.e. in the morning before the study treatment administration. The MasterScope (used in the REFALS study) will be used in all study centre visits during the first 3 months (so that all subjects have at least 1 post-baseline assessment with the device), after which each centre will use its own standard pulmonary function test equipment. At baseline (visit 1), the SVC will be assessed by using both MasterScope and the local equipment.

6.2.2 Revised ALS Functional Rating Scale

ALSFRS-R (Cedarbaum JM et al., 1999) will be assessed at each centre visit and telephone contact. This scale includes 12 items: speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting sheets, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. Each item will be scored from 0 to 4. The variables derived will be the scores of the 12 separate items, the total scores of each subdomain (bulbar, fine motor, gross motor and respiratory) and the total score of ALSFRS-R.

6.2.3 Need for respiratory support

The use of any respiratory support, including Bilevel Positive Airway Pressure (BiPAP) and invasive mechanical ventilation, will be recorded. The time to starting or changing the degree of respiratory support will be calculated.

6.2.4 Borg Category Ratio 10 Scale

Borg Category Ratio 10 (CR 10) scale will be used in the assessment of dyspnoea (Borg GA, 1982). The subjects will be asked to point out a score quantifying their perception on the intensity of dyspnoea on the CR10 scale at rest in sitting and supine position (immediately before the SVC measurements). Orthostatic changes between sitting and supine positions will be calculated.

6.2.5 Health care and home care resource use

For possible later use in pharmacoeconomic analysis, any hospital inpatient days, other institutional care, any additional hospital emergency unit visits, days in other institutional care, and the amount of formal and informal home care received, will be recorded.

In addition, all non-medical assistive devices which the subjects have in use at baseline are recorded and thereafter all new devices that they start using due to ALS will be recorded.

6.2.6 Other assessments

Subject's status for tracheostomy and survival will be recorded at all visits.

6.3 Pharmacokinetic assessments

No formal PK assessments samples will be taken. Levosimendan concentration sample may be taken for later analysis if clinically indicated e.g. in assessment of an AE.

Instructions for the collection, handling, storage and transportation of samples will be provided before the start of the study.

6.4 Safety assessments

6.4.1 Adverse events

6.4.1.1 Definitions

An AE is any untoward medical occurrence in a study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

Thus, an AE may be an appearance or worsening of any undesirable sign or symptom, any worsening of the current medical conditions or onset of a new disease, compared with the previous observations or a clinically significant adverse change in a laboratory variable or other diagnostic finding (e.g. ECG).

In this study, symptoms that the investigator considers to be due to expected progression of ALS are not considered as an AE, except for disease progression leading to death during the study.

An SAE is any untoward medical occurrences that at any dose

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation (see section 6.4.1.3 for exclusions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect, or
- is an important medical event jeopardizing the patient or requiring intervention to prevent serious outcome (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; development of drug dependency or drug abuse; overdose or interaction).

Other significant AEs are marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that lead to an intervention, including

- withdrawal of the investigational product
- reduction of its dose
- significant additional concomitant therapy

6.4.1.2 Assessment of adverse events

All AEs must be elicited, documented and reported by the investigator to the sponsor from the time that a study subject signs the IC form until the end-of-study visit (14-25 days after the last study treatment administration).

SAEs and other significant AEs should be followed up until resolved or until the event is considered a chronic or stable outcome, or both.

AE may be notified to the investigator by the study subject (or his/her caregiver) or observed by the investigator clinically, or be an adverse change in laboratory assessment results. The investigator will evaluate the subject's AEs at each visit by asking a standard question such as "Since you were last asked, have you felt unwell or different from the usual in any way?"

The investigator will assess and record the causality and severity of the AEs. Causality should be assessed in relation to the investigational medicinal product (see criteria for causality and severity below).

Causality criteria:

Related: The temporal relationship of the AE/SAE onset to the administration of the investigational medicinal product makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the AE/SAE.

Not related: The temporal relationship of the AE/SAE onset to the administration of the investigational medicinal product makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Severity criteria:

Mild: Discomfort noticed, but it does not affect normal activity.

Moderate: Discomfort sufficient to reduce or affect normal daily activity.

Severe: Incapacitating with inability to work or perform normal daily activity.

From the time that a study subject candidate signs the IC form, newly appearing diagnosed diseases will be recorded on the AE CRF.

Investigators must report all AEs to the sponsor on a specific AE CRF irrespective of their assessment of the causal relationship of the investigational medicinal product to the event.

6.4.1.3 Reporting of serious adverse events by the investigator

The investigator must report all SAEs within 24 hours of becoming aware of an SAE. SAEs must be reported within 24 hours regardless of the time that may have elapsed since the time the event occurred and regardless of the causal relationship of investigational medicinal product to the event.

In this study, the following events will not be reported as SAEs:

- hospitalisation and elective surgery for treatment of pre-existing condition that has not exacerbated during the study
- hospitalisation for procedures and/or evaluations in connection with ALS such as evaluation for the need or initiation of ventilatory support (e.g. NIV) or gastrostomy.
- symptoms that the investigator considers to be due to expected progression of ALS, except for disease progression leading to death during the study

All SAEs should be reported electronically by the investigator or other relevant study centre personnel and submitted by the investigator. Optionally, if the investigator is not able to submit the SAE electronically, the paper version of the SAE form can be completed and sent by e-mail or fax. The SAE reporting contact information can be found on the SAE form and will be filed in the investigator's study file.

If the initial report is reported by phone or e-mail to the study monitor or other contract research organisation (CRO) personnel and the study centre personnel are unable to report it electronically or to fill in the SAE form within 24 hours, the person receiving the report will forward the information to Orion Drug Safety. The investigator must report the SAE electronically as soon as possible.

The minimum criteria for SAE reporting are: the event or outcome meets the SAE definition, the event happens to an identifiable study subject, and the event is reported by an identifiable and qualified reporter (usually an investigator or other qualified study centre personnel).

A follow-up report to an SAE should be prepared if any relevant change in the condition of the study subject occurs after the initial report. The follow-up report should be documented as an update to the initial report.

SAEs that occur after the end-of-study visit (14-25 days after the last study treatment administration), should be reported, if the investigator feels that there is a reasonable possibility for the event to have been caused by the study subject's participation in the study.

6.4.1.4 Reporting of serious adverse events to competent authorities and ethics committees

The sponsor is responsible for expediting all suspected unexpected serious adverse reactions (SUSARs) as well as other safety issues requiring expedited reporting to the relevant authorities within applicable timelines. These tasks can also be carried out by a delegate of the responsible sponsor.

Notification of the ECs and IRBs about all relevant events (SUSARs, other relevant safety information) will be performed by the sponsor or delegate of the responsible sponsor and/or by the investigator according to applicable regulations.

The Sponsor will inform all investigational sites about SUSARs as well as other safety issues according to all applicable regulations.

The expectedness evaluation is required for regulatory reporting and it is performed by the sponsor. The expectedness in this study is evaluated against the Reference safety information section in the current ODM-109: oral levosimendan capsule for treatment of ALS investigator's brochure.

6.4.2 Special situations

The special situations with study treatment are defined as:

- medication error
- overdose
- abuse
- misuse
- interaction

These special situations with study treatment are reported on the Special situations with study treatment CRF even if there is no accompanying AE. All clinical manifestations in relation to these special situations will be reported as AEs or SAEs at the same time using the corresponding section of the CRF.

6.4.3 Pregnancy during the study

Whenever it becomes known that a study subject or a partner of a study subject was pregnant during the exposure to study treatments, the outcome of the pregnancy, delivery, postpartum recovery and the clinical condition of the offspring during the neonatal period should be reported, subject to the study subject's or the partner's consent. A pregnancy follow-up form

will be provided to the investigator for completion after the sponsor has received the initial report.

Any case of pregnancy during a clinical study should be reported by the investigator in the same way as an SAE.

6.4.4 Clinical safety assessments

Pulse/heart rate, and systolic and diastolic blood pressure will be measured in a supine position after at least 5 minutes at rest before morning dose of study treatment at all study centre visits. For telephone contacts a pulse/heart rate assessment measured in a supine position after at least 5 minutes at rest before morning dose up to 3 days prior to the contact will be accepted.

Pulse rate will normally be assessed by manual palpation over at least 30 seconds by a qualified healthcare professional. Alternatively, mean heart rate as measured by the 12-lead ECG or a continuous ECG monitor may be used, however heart rate values measured by an automated sphygmomanometer are not accepted. Where possible, abnormal values should be re-checked (ensuring the subject is at rest) before making a decision concerning the levosimendan dose.

A standard 12-lead ECG will be recorded in a supine position after at least 5 minutes at rest at each centre visit during the treatment period, before the morning dose of the study treatment.

6.4.5 Laboratory safety assessments

A pregnancy test for female subjects of childbearing potential will be performed at baseline and at each study centre visit during the treatment period and at the end-of-study visit.

Local safety laboratory tests may be performed if clinically indicated (for example in assessment of an AE).

Instructions for the collection, handling, storage and transportation of samples will be provided before the start of the study.

6.4.6 Assessment of suicidality

Suicidality will be assessed by asking the following standard questions at each visit:

1. Since the last visit, have you wished you were not alive anymore or had any thoughts about ending your life?
2. Since the last visit, have you done anything or prepared to do anything to end your life?

The second question (2) will be asked only in cases where the answer to the first question (1) has been ‘yes’.

6.5 Changes implemented due to COVID-19 pandemic

The following arrangements should be applied in the event that the subjects are not able to attend the study centre, either for baseline or treatment period visits, as a direct result of the COVID-19 pandemic.

All arrangements described in this section apply only to the extent that protocol requirements cannot be met because of COVID-19 restrictions. Study centre visits should take place to the extent possible and usual protocol requirements adopted for all subjects as soon as COVID-19 limitations permit. SVC and weight will not be assessed while these arrangements apply.

Exceptional measures taken in response to COVID-19 and their impact on study results, such as tests done in a local laboratory, will be explained, assessed and reported in the clinical study report following ICH E3.

Baseline visit

It will be possible for subjects to enter the study provided all eligibility criteria can be verified. In case baseline procedures described in Table 1 and in section 6.1.1 cannot be performed at the study centre due to restrictions related to COVID-19, a telephone visit (could also be a home visit or video call) should be arranged (see table below). 12-lead ECG, laboratory safety assessments, pregnancy test and vital signs are essential for the evaluation of eligibility and must be obtained locally if they cannot be performed at the study centre.

All the eligibility criteria should be reviewed and discussed with the subject. In case all data needed to evaluate eligibility are not available, entry of the subject may be delayed until the tests can be performed.

Procedures at remote visits

Time	REFALS End-of-study visit	Visit 1 Baseline	Telephone visit to replace 3-monthly centre visit
IC (in case not collected at the study centre prior to the baseline visit)		x[1]	
Pulse/heart rate and BP (supine)	x[2]	x[2]	x[8]
12-lead ECG	x[3]	x[3,7]	x[3]
Laboratory safety assessments[4]			
Haematology	x	x[7]	
Chemistry	x	x[7]	
Urinalysis	x	x[7]	
Pregnancy test for females of childbearing potential	x[5]	x[7]	x[5]
Eligibility criteria and decision of entry		x	
Study treatment		x[6]	x[6]
ALSFRS-R		x	x
Borg CR10 scale	x	x[7]	x
Use of health care and home care resources and non-medical assistive devices		x	x
Assessment of suicidality	x	x[7]	x
Status for NIV support, invasive mechanical ventilation by intubation or tracheostomy and survival	x	x	x
AEs and SAEs	x	x	x
Medical history and current medical conditions			x
Concomitant treatments	x	x	x

[1] If IC is taken over the phone, it should be documented and confirmed by normal consent procedures as soon as possible.

[2] Performed in supine position after at least 5 min rest before the morning dose of the study treatment. The assessment should normally be done by a health care professional. The use of alternative methods, including home devices are subject to sponsor approval.

[3] The measurement should be taken using the local ECG device after at least 5 min rest. A copy of the trace (paper or electronic) will be provided.

[4] Standard biochemical, electrolyte and haematological test panels of the local laboratory will be accepted (at least Creatinine needed, exclusion criterion 4). A copy of the laboratory report with local reference range should be provided.

[5] Test kits for urine pregnancy test should be provided to the subject for testing at home (unless taken in a local laboratory).

[6] Study treatment shipped to subject's home.

[7] Performed only in case not performed at REFALS end-of-study or study entry is delayed.

[8] Performed locally.

Visits during the treatment period

During the treatment period any visit may be performed by telephone (see section 6.1.2). In case the first dose of study treatment is taken at the subject's home instead of the study centre,

arrangements should be made for the pulse rate to be measured before and 1 h after the first study treatment administration.

If the subjects are unable to attend the study centre at least once every 3 months, a specific telephone assessment as described in the table above should be performed. A 12-lead ECG recording should be performed along with blood pressure and heart rate measurement. A pregnancy test should also be obtained where applicable. In case these assessments cannot be obtained at the specified time, the benefit:risk ratio for the subject to continue in the study should be reassessed.

7. DATA COLLECTION AND MANAGEMENT

The investigators and study centre personnel will prepare and maintain accurate source data for each study subject about clinical findings specified in the protocol. Source data include patient records and laboratory results, if applicable. The data from source documents will be recorded into an electronic data capture (EDC) system, Medidata Rave (Medidata Inc), using eCRFs at the study centre. All data on the eCRFs must be verifiable in the source data or patient records unless eCRF data are declared as source data.

Investigators and other relevant study centre personnel will be trained to use the eCRFs. After completion of training, they are provided with user names and authorised access to enter and correct data on the eCRFs.

Electronic queries about missing, misleading, incomplete or illogical data will appear in the EDC system. An audit trail within the system will track all changes/corrections made. The investigator has to confirm the content of the eCRF with an electronic signature.

Individual data fields in the EDC system may be locked on an ongoing basis during the study. The fields may be unlocked if further updates are needed. When all data have been entered and all queries resolved, the whole database will be locked. Only authorised and well-documented updates to the study data are possible after the database lock.

An authorised person will code medical history, current medical condition and AEs using standard coding dictionaries. Prior and concomitant treatments will be coded.

Further details regarding data collection and management are presented in the data management plan.

Statistical analyses, tables and subject data listings will be performed with SAS® for Windows (SAS Institute Inc., Cary, NC, USA).

8. STATISTICAL METHODS

8.1 Statistical hypotheses

No formal hypothesis will be made

8.2 Estimation of sample size

No formal sample size calculation will be performed.

8.3 Analysis populations

All subjects who have received at least 1 dose of study treatment will be included into the analyses. Full analysis set will also include assessments from the REFALS study from participating subjects. Analyses will be performed with and without data from the REFALS study, depending on the analysis type.

8.4 Statistical analyses

Statistical analyses are described in more detail in the statistical analysis plan.

8.4.1 Demographic and other baseline characteristics

All relevant demographic and baseline characteristics will be summarised using descriptive statistics. The summary will be based on data collected at initiation of study 3119002 and covering all relevant changes prior to initiation of this study. The number and reasons for discontinuations will be listed and tabulated by treatment groups.

8.4.2 Treatment compliance and extent of exposure

The number of exposed subjects, the number of dispensed and returned study treatments and the duration of study treatment exposure will be tabulated with descriptive statistics.

8.4.3 Analysis of efficacy

Slope of decline in sitting and supine SVC and ALSFRS-R will be estimated using a random slope model. Estimation will be performed with and without the data collected in the REFALS study. When appropriate, between-subject comparisons will be performed using the randomised treatment arm in the REFALS study including a treatment-by-study interaction term.

Median time to NIV or death and to decline (by at least 1 point) in the ALSFRS-R respiratory domain will be evaluated using Kaplan-Meier estimates. Estimation will be performed with and without the data collected in the REFALS study. When appropriate, between-subject comparisons will be performed using the randomised treatment arm in the REFALS study, and Cox' proportional hazard regression model including treatment by study interaction term.

Borg CR10 (sitting, supine and orthostatic changes) will be evaluated using mixed model for repeated measures (MMRM) with and without the data collected in the REFALS study. When appropriate, between-subject comparisons will be performed using the randomised treatment arm in the REFALS study and appropriate MMRM including treatment by study interaction term.

Health and home care resource use data will be summarised in the study report, but any further analysis for potential pharmacoeconomic purposes will be reported separately.

To avoid selection bias in estimations, sensitivity analyses including all the subjects enrolled in the REFALS study will be considered. No imputation for missing data is planned. All efficacy data will be listed and summarised over time using appropriate descriptive statistics.

8.4.4 Pharmacokinetic analysis

In case PK samples are taken, levosimendan, OR-1855 and OR-1896 concentrations will be summarised using descriptive statistics. Metabolites OR-1855 and OR-1896 will be further summarised by subject acetylation status collected in the main study.

8.4.5 Safety analysis

8.4.5.1 Analysis of adverse events

AEs reported during the study will be classified by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. The AEs will be displayed as event counts and subject counts in a frequency table. The number and proportion (%) of subjects having each AE as well as the AE severity (mild, moderate, severe) and causality (related, not related) to the study treatment will be given. SAEs and other significant AEs will be evaluated case-by-case.

When appropriate, between-subject comparisons will be performed using the randomised treatment arm in the REFALS study. AEs reported as part of the REFALS study may be used to complement the safety profile.

8.4.5.2 Clinical safety analysis

The actual values and changes from baseline in pulse/heart rate and blood pressure will be summarised using descriptive statistics. Any abnormal 12-lead ECG findings and special situations will be summarised.

8.4.5.3 Laboratory safety analysis

In case recorded, laboratory values and changes from baseline will be summarised using descriptive statistics.

8.4.5.4 Analysis of prior and concomitant treatments

The number and percentage of subjects using concomitant treatments will be summarised by pharmacological subgroup and chemical substance. The summary of prior medications will be based on data collected at initiation of the REFALS study and covering all relevant changes prior to initiation of this study.

8.4.5.5 Analysis of Suicidality

Suicidality will be summarised using descriptive statistics.

8.5 Interim analyses

No interim analysis is planned for this study.

9. DATA QUALITY ASSURANCE

9.1 Training

An initiation meeting will be arranged for the investigators and other relevant study centre personnel. This meeting will include a review of the protocol, CRF completion and study procedures.

The investigators will ensure that appropriate training relevant to the study is given to the medical, nursing and other personnel involved in the study. The investigators will also ensure that any information relevant to the conduct of the study is forwarded to other relevant study centre personnel.

9.2 Case report forms

Electronic queries about missing, misleading, incomplete or illogical data will appear in the EDC system. An audit trail within the system will track all changes/corrections made. The investigator has to confirm the content of the eCRF with an electronic signature.

9.3 Monitoring, audits and inspections

The CRO will implement a risk based monitoring strategy which will combine a centralised monitoring team of site management associates (SMAs) supported by a clinical research associate (CRA) who will perform on site visits.

In this innovative real world research model, the site relationship is streamlined from onsite and in-house CRAs to centralised (regional) SMAs. The SMAs use state-of-the-art analytical tools to combine site management, data review, query processing, and central monitoring into a single role, which reduces resource allocation and site burden. During the last interim monitoring visit for pivotal phase activities, PRA will conduct a hand-off call (Site Initiation for OLE) for each site, which would include site staff and the CRA and SMA assigned to the site.

The CRA will perform on site visits if needed in line with the risk management assessment plan and to perform close out activities at the end of the study.

The SMA/CRA will ensure that the study complies with good clinical practice (GCP) and applicable regulatory requirements and that the protocol is followed in all aspects, accurate recording of results, reporting of AEs, drug accountability and record keeping.

The study may be audited by independent representative(s) of the sponsor or inspected by the CAs. For these purposes, the study monitor, auditors and inspectors will be allowed direct access to hospital or patient records/source data of the study subjects, original laboratory data etc., as far as they are related to the study.

It is essential that the investigator and other relevant members of the study centre team are available during the monitoring visits, audits and inspections, and that they devote sufficient time to these processes.

9.4 Laboratories and other vendors

A local laboratory will be used for possible laboratory safety measurements and ECG analyses.

Details regarding spirometry and possible laboratory safety measurements and ECG analyses are presented in the separate instructions. Quality certificates are required from all safety laboratories.

In case levosimendan concentration samples are taken, bioanalytics will be performed using validated methods.

10. FURTHER REQUIREMENTS AND GENERAL INFORMATION

10.1 Investigators and study administrative structure

10.1.1 Investigators

Should the investigator transfer one of his/her responsibilities to other members of the study centre team, he/she must have this documented.

In the event of changes in key study centre team members, the responsible investigator must ensure that the successor is fully informed and capable of following the procedures.

A curriculum vitae in English must be obtained from all investigators who sign the protocol and from other relevant persons.

10.1.2 Data and safety monitoring board

No formal data and safety monitoring board (DSMB) reviews specifically for this study are planned. The DSMB of the REFALS study will review the data from this extension study until completion of the REFALS study. The DSMB may also decide to conduct further meetings to review safety data from this extension study, if clinically indicated. The duty of the DSMB is to protect the ethical and safety interests of the study subjects and all others who may possibly be exposed to study treatments.

Further details regarding the composition and responsibility of the REFALS study DSMB are presented in the DSMB charter.

10.2 Amendments to study protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, and when required by the EC or CA. Only in the event of a need to eliminate an immediate hazard(s) to study subjects, the investigator may implement deviation from the protocol without prior approval.

Any change or addition to the approved study protocol may lead to suspension of the study or its results.

Any changes to the study protocol are subject to prior discussion with, and approval by, the sponsor and the principal investigator. As a general rule, protocol amendments should be approved according to the same procedures as the study protocol.

Amendments are regarded as substantial, where they are likely to have a significant impact on the safety, physical or mental integrity of the study subjects, or the scientific value of the study. An approval of the responsible EC or CA shall be obtained before substantial amendments may be implemented, unless local regulations are different.

If an amendment contains only minor changes (typically administrative) not affecting the safety, physical or mental integrity of the study subjects, or the scientific value of the study, the EC or CA need not to be notified and in-house approval (including approval by the principal investigator) is adequate.

10.3 Insurance

The sponsor will provide clinical trial liability insurance for study subjects in all participating countries according to local regulations.

10.4 Financial disclosure

The investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; any significant payments of other sorts from the sponsor, such as a grant to fund on-going research, compensation in the form of equipment, retainer for on-going consultation, or honoraria; any proprietary interest in oral levosimendan; any significant equity interest in the sponsor as defined in the US Code of Federal Regulations [21 CFR 54 2(b)].

In consideration of participation in the study, the sponsor will pay the investigator, or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

10.5 Retention of records

The investigator agrees to keep the following documentation in the investigator's study file: study subject records, a subject identification list, all original signed IC forms, a copy of CRFs and records of drug dispensing.

The study files at the study centres will be stored in the respective archives for 15 years, after which the sponsor will be contacted and the possibility of future archiving will be mutually agreed upon.

10.6 Completion of the study

The end of the study is defined as the date of the last subject's last visit or last contact with the study site.

Study centres will be closed upon study completion. A study centre is considered closed when all required documents and study supplies have been collected and a study completion/termination visit has been performed.

The sponsor reserves the right to prematurely terminate the study, or recruitment to the study, for valid scientific or administrative reasons. After decision to prematurely terminate the study, the investigator must contact all participating study subjects within 7 days, and invite them for an end-of-study visit.

10.7 Reports, publications and communication of results

Statistical analysis will be performed by or under the supervision of the sponsor according to the statistical analysis plan.

The study report will be prepared by or under the supervision of the sponsor. The final report will be approved by the appropriate representatives of the sponsor and the investigators.

Orion wishes to collaborate with the investigators to publish the results as timely as possible, without compromising accuracy or industrial property rights. The preparation, submission and authorship for publications containing the study results shall be in accordance with a process determined by mutual written agreement among the sponsor and participating investigators/institutions, and in accordance with international criteria for authorship; see International Committee of Medical Journal Editors recommendations, available at http://www.icmje.org.

Orion remains the exclusive owner of the study data defined by the protocol.

This study will be registered in one of the acceptable registries before the enrolment of the first subject.

11. ETHICS

11.1 Ethics committee

The study protocol, subject information sheet, IC form, and all other necessary documents will be submitted to an independent EC/IRB for review according to local regulations.

The investigator is responsible for obtaining a favourable opinion from the EC/IRB for the study, submitting any amendment(s), and communicating study-related safety issues as requested by the EC/IRB. The investigator should file all correspondence with the EC/IRB in the investigator's study file. Relevant copies of this correspondence should be forwarded to the sponsor.

11.2 Ethical conduct of the study

The study will be conducted in accordance with the Declaration of Helsinki guiding physicians in biomedical research involving human subjects.

The study shall not be initiated before favourable opinion from the EC and approval from the CA has been obtained for the study.

The study will be conducted in compliance with the protocol, GCP (ICH E6[R2]) and applicable regulatory requirements. A substantial amendment shall not be implemented until the protocol amendment has received a favourable opinion from the EC and approval from the CA. Only in

case of the need to eliminate an immediate hazard(s) to study subjects, the investigator may implement deviation from the protocol without prior favourable opinion from the EC and approval from the CA for the protocol amendment.

In case of serious breaches, the MHRA GCP Inspectorate must be notified according to MHRA Guidance for the notification of serious breaches of GCP or the study protocol (see http://www.mhra.gov.uk).

11.3 Subject information and informed consent

The investigator will ensure that each subject candidate is fully informed about the objectives and procedures of the study. The investigator will also explain any possible risks with participating in the study and answer all questions regarding the study. After this, the subject will be given sufficient time to make a decision regarding participation in the study. In the case that the subject is unable to sign the consent form due to muscular weakness, a witness may sign the form to indicate that the subject has given oral consent to participate in the study. In such cases, the investigator must also explain the study to the witness at the same time as they explain the study to the participant. After this, the subject will be given sufficient time to make a decision regarding participation in the study.

Subjects will be informed of their right to discontinue the study at any time without their medical care or legal rights being affected. Subjects will also be informed that representatives of the sponsor or CA may inspect relevant parts of their medical records and study data.

The investigator will obtain a signed and dated consent from each subject before any study related procedures are performed. A copy of each signed and dated IC will be given to the subject. The investigator should confirm the receipt of every IC by entering the date of the consent both on the subject's CRF and also on the subject screening log and identification list.

11.4 Subject data protection

Information collected during the course of the study will be stored in a database and used in the further development of oral levosimendan and thereafter for as long as the information is relevant to patient care. The use includes the transfer of data to CAs in the European Union, the United States or other countries for the purpose of obtaining and maintaining marketing authorisations. All information is handled confidentially and according to local laws and regulations.

The study subjects can be identified in the CRFs only by study subject number, birth year and sex.

12. REFERENCE LIST

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Turner MR et al. (2013) Controversies and priorities in amyotrophic lateral sclerosis. Lancet Neurol. 12 (3): 310-22.

13. SUMMARY OF CHANGES TO AMENDMENT 1

13.1 Revision history

Protocol and amendments	Date	Applies to
Clinical study protocol	07 January 2019	Global
Amendment 1	26 March 2020	Global

Country specific amendments	Date	Applies to
Amendment 1	30 April 2019	Sweden

13.2 Summary of changes

The changes incorporated in this amended protocol from the original protocol dated 07 Jan 2019 are described in the following. The modifications of the text are indicated by ~~strikethrough~~ (for deletions) and underline (for additions).

The following changes were made due to COVID-19 pandemic:

Section	Previous text	New text	Rationale for the change
6.5 Changes implemented due to COVID-19 pandemic	-	Whole text is new, see the section 6.5.	New sections describing changes due to COVID-19 pandemic added

In addition,

- the table of contents was updated to reflect the headings and pagination of the current document.
- the title page, header and footer sections were updated to reflect the version details of the current document

14. APPENDICES

Appendix 1. Investigator signature