# CLINICAL TRIAL PROTOCOL

# A Phase 3, Randomised, Placebo-Controlled Trial of Arimoclomol in Amyotrophic Lateral Sclerosis

**Sponsor: Orphazyme A/S, Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark**
**Coordinating investigator: [redacted], MD PhD**
**Protocol number: ORARIALS-01**
**EudraCT No.: 2018-000137-13**
**ClinicalTrials.gov Identifier: NCT03491462**
**Trial product name: Arimoclomol Capsules**

**Date of Amendment: 08-Jun-2020**

Strengths of arimoclomol are presented throughout this document by weight of the citrate salt.



The trial will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements

# Approval Statement, Orphazyme A/S

This trial protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (1) and the guidelines on Good Clinical Practice (GCP) (2).

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# Approval Statement International Coordinating Investigator

This trial protocol was subjected to critical review and has been approved by Orphazyme A/S. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (1) and the guidelines on Good Clinical Practice (GCP) (2).

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# Acknowledgement Statement Investigators

Each participating investigator must agree to the approved clinical trial protocol and consolidated clinical trial protocol(s) (including any protocol amendments) by signing a clinical trial protocol acknowledgement form.

The investigator must be familiar with the applicable country-specific requirements as described in section 10.4.

# Protocol Amendment

This document is a Consolidated Clinical Trial Protocol, which includes protocol amendment.

The details of the amendments below are presented in a separate Summary of Changes Made to Protocol Content as Part of Protocol Amendments:

- Clinical Trial Protocol version 1.0 dated 12th March 2018 (applicable globally)
- Clinical Trial Protocol version 2.0 dated 26th June 2018 (applicable only to Canada)
- Clinical Trial Protocol version 3.0 dated 1st August 2018 (applicable globally)
- Clinical Trial Protocol version 4.0 dated 3rd February 2019 (applicable globally)
- Clinical Trial Protocol version 4.1 dated 01st April 2019 (applicable only to France)
- Clinical Trial Protocol version 5.0 dated 16th July 2019 (applicable globally)
- Clinical Trial Protocol version 6.0 dated 25th October 2019 (applicable globally)
- Clinical Trial Protocol version 7.0 dated 08th June 2020 (applicable globally)

The sponsor confirms that the changes introduced in version 7.0 qualify for classification as substantial amendments. Country specific information are contained in Section 10.4.

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## Tables in Text



## Figures in Text

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ADME | Absorption, distribution, metabolism and elimination |
| AE | Adverse event |
| ALAT | Alanine aminotransferase |
| ASAT | Aspartate aminotransferase |
| ALS | Amyotrophic lateral sclerosis |
| ALSFRS-R | ALS Functional Rating Scale-Revised |
| ANCOVA | Analysis of covariance |
| ATMP | Advanced therapy medicinal product |
| AUC | Area under the curve |
| BMI | Body mass index |
| BUN | Blood urea nitrogen |
| CAFS | Combined Assessment of Function and Survival |
| CI | Confidence interval |
| CNS | Central nervous system |
| CONSORT | Consolidated Standards of Reporting Trials |
| CMAP | Compound muscle action potential |
| Cmax | Maximum concentration |
| CMO | Contract Manufacturing Organisation |
| CRA | Clinical research associate |
| CRO | Contract Research Organisation |
| CSF | Cerebrospinal fluid |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTR | Clinical trial report |
| CTIMP | Clinical Trial of an Investigational Medicinal Product |
| DILI | Drug-induced liver injury |
| DtP | Direct to patient |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic acid |
| eCRF | Electronic case report form |
| ECAS | Edinburgh Cognitive and Behavioural Screen |
| ECG | Electrocardiogram |
| EMA | European Medicines Agency |
| EMG | Electromyography |
| EQ-5D-5L | EuroQol Five-Dimensional, Five-Level Descriptive System |
| EQ VAS | EQ Visual Analogue Scale |

| | |
|---|---|
| EU | European Union |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| $FEV_6$ | Forced expiratory volume in 6 seconds |
| GCP | Good Clinical Practice |
| GFR | Glomerular filtration rate |
| GGT | Gamma-Glutamyl Transferase |
| GMP | Good Manufacturing Process |
| hCG | Human chorionic gonadotropin |
| HDPE | High density polyethylene |
| HIV | Human immunodeficiency virus |
| HPMC | Hydroxypropyl methyl cellulose |
| HRQoL | Health-related quality of life |
| HSP70 | Heat shock protein-70 |
| ICH | International Council for Harmonisation |
| IEC | Independent ethics committee |
| IMP | Investigational medicinal product |
| INR | International Normalised Ratio |
| IRB | Institutional review board |
| ITT | Intent-to-treat |
| IRT | Interactive response technology |
| LOCF | Last observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MUNE | Motor unit number estimate |
| MRC | Medical research council |
| NASH | Non-Alcoholic Steatohepatitis |
| NOAEL | No observed adverse event level |
| Nfl | Neurofilament light chain |
| p75ECD | p75 neurotrophin receptor extracellular domain |
| Ph. Eur. | European Pharmacopeia |
| PAV | Permanent assisted ventilation |
| PIL | Patient Information Leaflet |
| PK | Pharmacokinetics |
| PP | Per protocol |
| PRO | Patient reported outcome |
| PRO-ACT | Pooled Resource Open-Access ALS Clinical Trials |

| | |
|---|---|
| QoL | Quality of life |
| QP | Qualified Person |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SEIQoL-DW | Schedule of the Evaluation of Individual QoL (direct weighting) |
| SmPC | Summary of Product Characteristics |
| SOD1 | Super oxide dismutase 1 |
| SUSAR | Serious unexpected suspected adverse reaction |
| SVC | Slow vital capacity |
| TAR | Transactive response |
| TBL | Total Bilirubin |
| TDP-43 | TAR DNA binding protein 43 |
| TEAE | Treatment-emergent adverse event |
| t.i.d. | Three times daily |
| ULN | Upper limit of normal |
| USP-NF | United States Pharmacopeia-National Formulary |
| VC | Vital capacity |

# 1. SCHEDULE OF TRIAL PROCEDURES

## Table 1 Schedule of trial procedures

| | Screening/Baseline | | Randomised treatment [i] | | | | Safety Follow Up |
|---|---|---|---|---|---|---|---|
| **Visit name** | **Screening [a]** | **Baseline** | **In person visits [b]** | **In person visits** | **Remote visits (telephone calls)** | **End of trial** | **Safety Follow Up [x] (telephone call)** |
| **Visit number** | **1** | **2** | **3, 5, 7, 9, 11, 13 15, 18** | **4, 6, 8** | **10, 12, 14, 16, 17, 19, 20** | **21** | **22** |
| **Time in relation to Baseline** | **Week -4 to Week -1** | **Day 1** | **Weeks 4, 12, 20, 28, 36, 44, 52, 64** | **Weeks 8, 16, 24** | **Weeks 32, 40, 48, 56, 60, 68, 72** | **Week 76 (or early termination)** | **2 weeks after treatment discontinuation** |
| **Visit window, days** | | | **± 7 days** | | **± 7 days** | **± 7 days** | **± 7 days** |
| **SUBJECTS** | | | | | | | |
| Written informed consent | X | | | | | | |
| Demographics [d] | X | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | |
| General medical history [e] | X | | | | | | |
| ALS characterisation | X | | | | | | |
| Body height [f] | X | | | | | | |
| Respiratory rate | X | | | | | X | |
| Use of tobacco and nicotine-containing products | X | | | | | | |
| Randomisation | | X | | | | | |
| Diary instruction | | X | | | | | |
| Diary completion [g] | | | <==========> | | | | |
| Collect diary and record diary data in eCRF | | | X | | | X | |
| Concomitant medications | X | X | X | X | X | X | X |
| **EFFICACY** | | | | | | | |
| Survival (PAV/tracheostomy/death) | | | <========== | | | | ==========> |
| ALSFRS-R [h] | X [w] | X [w] | X | X | X | X | |

| | Screening/Baseline | | Randomised treatment [i] | | | | Safety Follow Up |
|---|---|---|---|---|---|---|---|
| **Visit name** | **Screening [a]** | **Baseline** | **In person visits [b]** | **In person visits** | **Remote visits (telephone calls)** | **End of trial** | **Safety Follow Up [x] (telephone call)** |
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| **Visit window, days** | | | **± 7 days** | | **± 7 days** | **± 7 days** | **± 7 days** |
| SVC | X [w] | X [w] | X | | | X | |
| ECAS | X | | | | | X | |
| **HEALTH-RELATED QUALITY OF LIFE** | | | | | | | |
| SEIQoL-DW (subject) | | X | X | | | | |
| SEIQoL-DW (primary caregiver) | | X | X | | | | |
| EQ-5D-5L | | X | X | | | X | |
| **SAFETY [j]** | | | | | | | |
| Physical examination [k] | X | | X | | | X | |
| Neurological examination [k] | X | | X (Weeks 20 and 52 only) | | | X | |
| Vital signs [l] | X | X | X | | | X | |
| Body weight [f] | X | | X (Week 52 only) | | | X | |
| ECG [k] | X | | X (Weeks 20 and 52 only) | | | X | |
| C-SSRS [m] | X | X | X | X | X | X | |
| Adverse events | X [n] | X [n] | X | X | X | X | X [o] |
| Pregnancy test [p] | X | X | X | | | X | |
| Clinical safety laboratory test [q y z] | X | X | X | X | | X | |
| **BIOLOGICAL SAMPLE ASSESSMENT** | | | | | | | |
| **GENOMICS** | | | | | | | |
| Blood sample genetics [r] | X | | | | | | |
| **BIOMARKERS** | | | | | | | |
| CSF sampling [s k] | | X | X (Weeks 20 and 52 only) | | | X | |
| Blood sampling [t] | | X | X (Weeks 20 and 52 only) | | | X | |
| Urinalysis [u] | | X | X (Weeks 20 and 52 only) | | | X | |

| | Screening/Baseline | | Randomised treatment [i] | | | | Safety Follow Up |
|---|---|---|---|---|---|---|---|
| **Visit name** | **Screening [a]** | **Baseline** | **In person visits [b]** | **In person visits** | **Remote visits (telephone calls)** | **End of trial** | **Safety Follow Up [x] (telephone call)** |
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| **Visit window, days** | | | **± 7 days** | | **± 7 days** | **± 7 days** | **± 7 days** |
| **PHARMACOKINETICS** | | | | | | | |
| Blood sampling (arimoclomol) [v] | | | X (Weeks 20 and 52 only) | | | | |
| CSF sampling (arimoclomol) [k] | | | X (Weeks 20 and 52 only) | | | | |
| **INVESTIGATIONAL MEDICINAL PRODUCT** | | | | | | | |
| Dispensing of IMP | | X | X | | | | |
| Drug accountability | | | X | | | X | |

**Abbreviations**: AE = adverse event; ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale-Revised; CSF = cerebral spinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; ECAS = Edinburgh Cognitive and Behavioural Screen; ECG = electrocardiogram; eCRF = electronic case report form; EQ-5D-5L = EuroQol Five-Dimensional, Five-Level Descriptive System; F/U = follow-up; HSP70: heat shock protein 70; IMP = investigational medicinal product; MUNIX: Motor unit number index; NfL: Neurofilament light chain; P75ECD: p75 neurotrophin receptor extracellular domain; PAV = permanent assisted ventilation; SAE = serious adverse event; SEIQoL-DW = Schedule of the Evaluation of Individual QoL (direct weighting); SVC = slow vital capacity; t.i.d.= 3 times daily.

**Footnotes:**

a. Screening may be up to 4 weeks prior to Baseline if a washout period for an investigational treatment is required and to allow for laboratory re-tests (if required).
b. At Weeks 4, 12, 20, 28, 36, 44, 52, 64, and 76 (end of randomised treatment), subjects will visit the site. If a subject is no longer able to attend the site, appropriate trial site staff (e.g. nurse, sub-investigator as required) will assess the subject by conducting a home visit.
c. Visit 21 (end of trial) is applicable for all randomised subjects. Subjects discontinuing treatment prior to Week 76 should continue in the trial up to Week 76 according to the visit schedule and should also have Visit 22 (Safety Follow Up) 2 weeks after IMP discontinuation. For subjects withdrawing from the trial prematurely, the investigator should conduct the last in-person visit as per the end of trial visit. Subjects discontinuing treatment prior to Week 76 yet remaining in the trial will have telephone calls in place of the scheduled in-clinic visits with only the following assessments completed:

ALSFRS-R, AE, Concomitant Medication and survival. Clinical safety laboratory tests may be required if there are any clinically significant parameters out of range due to an AE possibly or probably related to the IMP; samples should be collected until resolution.

d. Demographics include age, sex, race and ethnicity.
e. General medical history, as well as the history of any diagnostic testing such as electromyography and nerve conduction studies; imaging; muscle biopsy; and antibodies.
f. Assessment to be completed only when possible.
g. The diary consists of logs to record: IMP compliance, mode of administration, concomitant medication and non-invasive ventilation support.
h. The ALSFRS-R will be performed over the telephone for remote visits. If the scale is administered over the telephone and the patient is unable to respond because of significant bulbar impairment the caregiver should relay the questions and responses.
i. If a visit is missed, every effort should be made to ensure that as much information as practically possible is collected at a telephone contact as close to the scheduled visit date as possible. If the missed visit was expected to be in person, the assessments and procedures scheduled for remote visits should be followed.
j. At any time during the trial, the IMP may be temporarily halted for up to 4 weeks for an intolerable AE. Following re-challenge at the intended dose, de-escalation from 1200 mg/day (400 mg t.i.d.) to 600 mg/day (200 mg t.i.d.) may be considered. The subject will remain on this decreased dose for the remainder of the trial. Re-challenge with IMP in cases of elevation of transaminases should only be done in accordance with section 6.5 Dose Modification and IMP Discontinuation.
k. Examinations will only be conducted in those subjects able to attend the trial site.
l. Vital signs include blood pressure (supine; seated if supine is not possible) pulse and body temperature.
m. The C-SSRS “Screening/Baseline” assessment will be used at the Screening visit and the “since the last visit” version at all other visits.
n. Signs and symptoms occurring during the screening period will be collected and entered on the AE form
o. Only stop dates for ongoing AEs and new SAEs will be collected.
p. Women of childbearing potential only. Serum test at Screening and urine test on all other occasions.
q. Clinical safety laboratory tests include haematology, chemistry (including Cystatin C) and urinalysis.
r. Profiling for common genes associated with ALS.
s. Biomarker assessments for HSP70, NfL and chitotriosidase.
t. Biomarker assessments for HSP70 and NfL.
u. Biomarker assessments in urine for p75ECD.
v. At Week 20, PK samples will be collected pre-dose and at 0.5 hours post-dose. At Week 52 PK samples will be collected pre-dose and at 1.5 hours post-dose. The time of the dose prior to the visit should be recorded in the subject diary and transcribed to the eCRF.
w. ALSFRS-R and SVC are assessed at Screening and Baseline. The assessment at the Screening visit is used for determination of subject eligibility. The assessment at the Baseline visit is used for analysis purposes and the value will not exclude the subject.
x. Visit to be conducted in case of a) premature IMP discontinuation or b) subject completing trial, but not continuing into open label extension trial

y. At screening a blood sample will be sent to the central laboratory for testing of HIV, HBV and HCV status. The result must be available in time for the Baseline visit where final eligibility is confirmed.
z. At the first sign of elevated transaminases (ASAT or ALAT > 3 x ULN), a single serum sample should be taken for use and stored frozen (shipment may be ambient) at the central laboratory at the earliest opportunity.

# 2. INTRODUCTION AND RATIONALE

## 2.1 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig's disease, is a progressive, fatal neurodegenerative disorder. The loss of motor neurons causes the muscles under their control to weaken and waste away, leading to paralysis and death, usually due to respiratory failure, within 3-5 years of symptom onset. Symptoms include loss of motor control in hands, arms and legs, tripping and falling and bulbar symptoms with difficulty speaking, swallowing and/or breathing, persistent fatigue, and twitching and cramping of the muscles. In addition, cognitive and behavioural changes are often seen.

Several mechanisms have been implicated in the pathogenesis of ALS. These include excitotoxicity, oxidative stress, neuro-inflammation, mitochondrial dysfunction, disrupted nucleocytoplasmic transport and impaired proteostasis characterised by protein misfolding and aggregation. Of these, the latter two are increasingly recognised as general molecular hallmarks of ALS (3).

While rare in prevalence, ALS is considered one of the most common neuromuscular diseases worldwide. The incidence of ALS is estimated at between 1-3 per 100,000 individuals per year globally. The patient population in Europe and the United States is estimated to be approximately 50,000 patients and about 10 percent of ALS cases are inherited. While the mean age of onset is between 55 and 65 years, symptoms can begin at any adult age. The disease occurs more frequently in men than women, whereas prevalence is roughly the same throughout the world (4-5.4 per 100,000 individuals) with no ethnic, racial or socioeconomic differences.

Around 10 percent of patients with ALS have ALS associated with pathogenic mutations (commonly referred to as ‘familial ALS’) and the remaining 90 percent are isolated or sporadic in nature and are denoted ‘sALS’.

The focus of medical care is to give symptomatic management of patients with mild to moderate disease and easing (palliative) intervention in patients with severe or terminal disease. The care of ALS patients is often provided in multidisciplinary clinics, with a team comprised by respiratory therapist, physiotherapist, occupational therapist, dietician, speech consultant and social worker.

There is significant unmet medical need for further treatment options as current therapies convey only modest treatment benefit. The only approved treatment for ALS in EU, riluzole (Rilutek®), has been granted a marketing authorisation in the EU in 1996 to extend life or the time to mechanical ventilation for patients with ALS. According to the product’s Summary of Product Characteristics (Rilutek® SmPC), clinical trials have demonstrated that Rilutek® extends survival for patients with ALS. Survival was defined as patients who were alive, not intubated for mechanical ventilation and tracheotomy-free. The mode of action of riluzole is not fully understood. It may exert its effect via an inhibitory effect on glutamate release, inactivation of voltage-dependent sodium channels, and/or ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors.

Riluzole has since been approved as a 5 mg/mL oral suspension (Teglutik®, Tiglutik®) with a recommended dose of 100mg daily (50 mg every 12 hours).

In May 2017, the Food and Drug Administration (FDA) approved edaravone (Radicava®, Radicut®), which is the first approved ALS treatment option for more than 20 years. Edaravone is thought to act as a free-radical scavenger which prevents oxidative stress damage to neurones. It is an intravenous infusion treatment for ALS and has been shown to reduce functional decline as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) by 33%. As the clinical trials were of short duration (6 months), there is no information available on the effect on survival.

## 2.2 Arimoclomol

Orphazyme A/S (hereafter referred to as Orphazyme) is developing arimoclomol for treatment of ALS.

Arimoclomol amplifies the heat shock response under conditions of cellular stress (3). The heat shock response promotes natural folding of nascent proteins and refolding of damaged or mutated proteins via enhanced heat shock protein expression, a mechanism of action that is thought to be highly relevant to an essential and early pathophysiological event that leads to neurodegeneration in ALS (4,5).

Notably, in super oxide dismutase 1 (SOD1) mutant mice that model some of the features of human SOD1 ALS, arimoclomol amplifies the production of heat shock proteins, rescues motor neurons, improves neuromuscular function and extends lifespan, even when treatment is initiated after the emergence of clinical and pathological manifestations of disease (6, 7).

A major hallmark of sporadic and most forms of familial ALS, is the presence of mis-localised transactive response (TAR) DNA binding protein 43 (TDP-43) in cytoplasmic inclusions in affected areas of the central nervous system (CNS) (9). TDP-43 belongs to a group of ribonucleic acid (RNA) binding proteins, several of which have been shown to be mutated in different forms of ALS (9), and is involved in regulation of RNA splicing and modulation of microRNA biogenesis (11). TDP-43 plays an important role in neuronal plasticity by regulating protein synthesis in dendrites (12), and mutated and misfolded forms are prone to toxic fibrillization in stress granules (11). Importantly, arimoclomol ameliorates TDP-43 pathology in a mouse model for multisystem proteinopathy, a disease that is tightly linked to ALS on a genetic level (13). Additional evidence of the relevance of heat shock response in ALS comes from preclinical data demonstrating that activation of the heat shock response leads to clearance of TDP-43 inclusions (14). Thus, augmentation of the heat shock response might remedy the mis-localisation and inclusion of TDP-43 and other ALS related proteins, and thereby be a promising target for new treatment (summarised in (15)).

See the current version of the Investigator's Brochure for further information (19).

In conclusion, the mode of action of arimoclomol addresses fundamental pathophysiological processes of ALS and by doing so, arimoclomol may potentially slow the progression of the disease and the associated symptoms with or without riluzole treatment.

Strengths of arimoclomol are presented throughout this document by weight of the citrate salt.

## 2.3 Experience with Arimoclomol

### 2.3.1 Non-clinical Experience

[redacted]

A package of nonclinical studies has been performed to evaluate the safety of arimoclomol. Nonclinical safety studies support chronic dosing of arimoclomol 400 mg three times daily (t.i.d.). Refer to the current version of the Investigator's Brochure for detailed information (19).

### 2.3.2 Clinical Experience

Clinical experience with arimoclomol in ALS originates from seven Phase 1 trials in healthy subjects and two Phase 2a trials (trial AALS-01 (16) and trial AALS-01 OL(17)) in patients with ALS. Moreover, one investigator-led Phase 2 trial has been conducted in ALS patients with pathogenic SOD1 mutations (18).

In addition, 50 patients with Niemann-Pick disease type C (NPC) have also been exposed to arimoclomol (CT-ORZY-NPC-002).

The Phase 1 trials were conducted in healthy subjects for evaluation of single-dose, multiple-doses, food effects, absorption, distribution, metabolism and elimination (ADME), as well as renal safety. A total of 106 healthy subjects were exposed to arimoclomol and 24 received placebo in these trials. Arimoclomol was safe and well-tolerated in all trials.

Based on data from the clinical pharmacology trials in healthy subjects and from clinical trials in ALS (AALS-001) and Niemann-Pick disease type C (NPC) patients (CT-ORZY-NPC-002), arimoclomol may lead to an increase in serum creatinine and/or a decrease in mean creatinine clearance without effects on glomerular function or renal haemodynamics. This suggests an inhibitory effect of arimoclomol on tubular secretion of creatinine and is supported by the finding that arimoclomol is an inhibitor of organic cation transporter 2 (OCT-2) and the multidrug and toxin extrusion (MATE) transporters responsible for creatinine secretion in the kidneys.

One elderly patient with inclusion body myositis experienced severe tubulointerstitial nephritis with acute tubular injury and acute tubular necrosis approximately 1 month after initiation of arimoclomol. The patient had autoimmune disease (Sjögren's syndrome) and was treated with omeprazole, both of which may have contributed to the event. The investigator

judged this event to be probably related to the IMP and Orphazyme considered the causality to be possibly related.

See the current version of the Investigator's Brochure (IB) for further information (19).

Trial AALS-001 was a multicentre, double-blind, placebo-controlled 12-week trial with the objective to assess the safety, tolerability, and pharmacokinetics (PK) of arimoclomol in ALS (16).

A total of 62 subjects with ALS received arimoclomol at 75, 150, or 300 mg/day (25, 50, or 100 mg t.i.d.) and 22 subjects received placebo t.i.d. A total of 9 serious adverse events (SAEs) (all on active treatment) were reported, including 3 deaths, none of which were assessed as related to the investigational medicinal product (IMP) by the investigator. Arimoclomol was safe and well-tolerated. No clinically significant abnormal changes were reported in vital signs or electrocardiogram (ECG) assessments with treatment. There were small statistically significant changes in mean laboratory tests, including increased serum creatinine and decreased creatinine clearance. The mean changes in serum creatinine were neither time nor dose-dependent, within the clinically accepted normal range and returned to pre-dose levels after completion of the dosing regimen. Arimoclomol resulted in dose-linear pharmacologic exposures and the half-life did not change with continued treatment. At steady state, the mean CSF-to-serum ratios ranged between 0.4 and 0.6 across dose levels at the 3 hour post-dose time point and between 0.9 and 1.1 at the 6 hour post-dose time point.

In the open-label extension to this trial (17), the long-term (6 months) safety and exploratory efficacy of arimoclomol treatment was evaluated. In total, 69 ALS patients from the AALS 001 trial were treated with arimoclomol 300 mg/day (100 mg t.i.d.) for up to 6 months. Arimoclomol 300 mg/day was safe and well-tolerated. One participant discontinued treatment due to an adverse event (AE) (respiratory failure). There were no trial medication-related clinically meaningful changes in vital signs, ECGs, or laboratory safety tests. In particular, serum creatinine levels did not increase with treatment. Seventeen (17) SAEs were reported in 14 patients. One SAE, pulmonary embolism, was rated by the site investigator as possibly related to the IMP. All other SAEs were assessed as not related or unlikely related to the IMP. Exploratory efficacy assessment of the open-label extension part of the trial showed a slower reduction in ALSFRS-R compared to a historical placebo control group (approximately 30% difference in decline, p=0.034). There was no treatment effect on vital capacity, body weight or body mass index (BMI).

In the investigator-led randomised, double-blinded, placebo-controlled clinical trial, ALS patients with pathogenic SOD1 mutations associated with aggressive disease course were treated with arimoclomol (17 patients) or placebo t.i.d. (19 patients) for 12 months (18). The patients randomised to arimoclomol were initially treated with 300 mg/day (100 mg t.i.d.), however this dose regimen was later amended to 600 mg/day (200 mg t.i.d.) following an interaction with the FDA. Albeit not powered for efficacy, consistent directional benefit was observed across the predefined efficacy endpoints survival function (ALSFRS-R) and pulmonary function (forced expiratory volume in 6 seconds, $FEV_6$). Arimoclomol was safe and well-tolerated and a consistent directional benefit of arimoclomol over placebo across predefined efficacy endpoints was observed. In a post hoc analysis, a clear dose response

relationship in this trial between 300 mg/day (100 mg t.i.d.) and 600 mg/day (200 mg t.i.d.) was not observed, possibly due to the low number of patients.

In conclusion, given the results from these two Phase 2 trials with preliminary indication of effectiveness at doses of 300-600 mg/day (100 to 200 mg t.i.d.) and favourable tolerability, it appears justified to further increase the dose to 1200 mg/day (400 mg t.i.d.) to investigate whether a higher dose may result in greater efficacy and acceptable tolerability.

For further information on experience with arimoclomol, see the current edition of the IB (19).

## 2.4 Trial Rationale

### 2.4.1 Justification for the Trial

To date, only two drugs (riluzole and edaravone) are approved for the treatment of ALS in the US and one drug (riluzole) is approved in the EU. Nuedexta® is used for symptomatic treatment of pseudobulbar effect in ALS patients. The high unmet medical need persists despite these treatment options and ALS still to date is a rapidly progressive neurodegenerative disease that leads to progressive weakness and ultimately to death due to respiratory failure. The mode of action of arimoclomol is expected to be relevant across the disease spectrum of both familial and sporadic ALS.

The trial has been designed to conform with the recommendations of the FDA draft guidance document for industry (20) and the European Medicines Agency (EMA) guideline on clinical investigation of medicinal products for the treatment of ALS (21).

### 2.4.2 Justification for Selected Dose

Seven clinical pharmacology studies have been performed in healthy volunteers with daily doses ranging from 50 mg to 1800 mg. The maximum single dose administered is 800 mg and the maximum repeated dose is 1800 mg daily (600 mg t.i.d.) for 5 days (Study AALS-005). During these studies the maximum tolerated dose was not reached. In the renal safety study, 1200 mg/day (400mg t.i.d.) or matching placebo were administered for 28 days (Study AALS-010). No tolerability or safety issues were identified.

Two clinical phase 2 trials have been completed in ALS (AALS-001 and SOD1-ALS). In the 12-week dose ranging trial (AALS-001), 84 ALS patients were randomised in a 1:1:1:1 ratio to placebo, 25 mg, 50 mg or 100 mg t.i.d., respectively. There were no significant increases in treatment-related adverse events or serious adverse events as compared to placebo. Sixty-nine patients from AALS-01 continued into the open label extension trial of 6 months duration and were all administered 300 mg/day (100 mg t.i.d.). Disease progression, as measured by ALSFRS-R, was slower in the trial population compared to a historical placebo control group, indicating a potential treatment benefit (16).

Data from the placebo-controlled investigator initiated SOD1-ALS trial indicate that 600 mg/day arimoclomol (200 mg t.i.d.) is safe and well-tolerated in ALS. The trial was not powered for efficacy however, there was a positive trend across the pre-specified endpoints; survival, ALSFRS-R and pulmonary function (measured by $FEV_6$) in favor of arimoclomol in a population of ALS patients with a very aggressive disease course.

In the preclinical repeat toxicology studies, the dog was the most sensitive species. NOAEL was established at 160 mg/kg/day in the 52 weeks toxicity study corresponding to a safety margin to the intended human dose of 1200 mg/day (400 mg t.i.d.) of 13.55 and 7.6 for Cmax and AUC, respectively.

**Table 2 Estimated Safety Margin Based on Exposure at NOAEL in 52-week Toxicity Study in Dog and Steady State Exposure in Healthy Subjects at 400 mg t.i.d. (Study AALS-005)**

| Study | Dose | $C_{max}$ (µg/mL) | Mean $AUC_{(0-24)}$ (µg h/mL) | Safety margin based on $AUC_{(0-24)}$ | Safety margin based on $C_{max}$ |
|---|---|---|---|---|---|
| **52-week repeat dose toxicity in dogs** | 80 mg/kg b.i.d. (NOAEL) | 18.94 | 124.87 | 7.6 | 13.55 |
| **MAD study Human** | 400 mg t.i.d. | 1.398 | 16.42 (3*5.47) | _ | _ |

*In vitro protein binding is low and similar between species with free fractions about 90% and 87% in human and dog, respectively (Study PRE-SK-007-0018).

**Abbreviations**: AUC = area under the time/concentration curve; b.i.d = twice a day; $C_{max}$ = maximum serum concentration; MAD = multiple ascending dose; NOAEL = no observed adverse effect level; t.i.d. = three times a day.

In summary, a relevant mouse model has confirmed measures of efficacy at doses equivalent to the intended clinical dose. Non-clinical long-term studies support the use of arimoclomol up to 1200 mg/day, which is the selected dose in the ongoing confirmatory trial in IBM. Safety and tolerability have been demonstrated in multiple phase 1 trials, for a dose range covering the intended dose, and in two phase 2 clinical trials in ALS which also provided preliminary indication of efficacy (albeit at a lower dose). Collectively, these data suggest that

a higher dose than that studied in phase 2 clinical trials may be safe, well tolerated and efficacious. Therefore, the dose of 1200 mg/day (400 mg t.i.d.) is selected for the present phase 3 trial in ALS to maximise chances of the individual subject to receive an efficacious treatment.

### 2.4.3 Justification for Placebo

The use of placebo in confirmatory trials in ALS is supported by the FDA draft guidance document for industry (20) and the EMA guideline on clinical investigation of medicinal products for the treatment of ALS (21) where background treatments with approved products are also favoured. The present trial includes placebo control to demonstrate the benefit of arimoclomol in the treatment of ALS. Subjects will be randomly assigned to active or placebo treatment in a disproportionate ratio weighted 2:1 towards active therapy. Subjects may also be treated with a background stable dose of riluzole. Riluzole use will be a stratification factor meaning that there is a chance that subjects without background riluzole therapy may also receive placebo. The probability of receiving placebo will be explained clearly in the informed consent form.

### 2.4.4 Justification for Endpoints

The proposed primary endpoint in the present trial is the measurement of Combined Assessment of Function and Survival (CAFS) in the arimoclomol treatment arm as compared to the placebo after treatment for 18 months. The CAFS is used to compare each trial subjects' outcome to others in the trial in a series of pairwise comparisons, based on function and survival (22). For each pairwise comparison, a trial subject is assigned a score and then the summed scores are ranked for all participants.

While historically ALS clinical trials have assessed survival and function as independent endpoints, the CAFS combines the endpoints and thereby decreases the confounding effect of mortality on analysis of functional outcomes. Thus, the CAFS is a robust statistical tool for ALS clinical trials and appropriately accounts for and weights mortality in the analysis of function. The individual components of CAFS (function and survival) will also be analysed separately as secondary outcome measures.

The secondary efficacy assessment of arimoclomol in the present trial will be completed by the following evaluations:

#### 2.4.4.1 Permanently Assisted Ventilation (PAV)- and Tracheostomy-Free Survival

In accordance with the completed SOD1-ALS Phase 2 trial (18) this endpoint is defined as permanently assisted ventilation (PAV)- and tracheostomy-free survival. This endpoint is commonly used in ALS clinical trials and, given the rapidly progressing disease course in the population to be studied, represents a relevant "hard" endpoint. PAV will be defined as the first of 7 consecutive days on which PAV was used for >22 hours/day.

#### 2.4.4.2 Disease Progression, as Measured by Change from Baseline on the ALSFRS-R

The ALSFRS and the revised version that includes respiratory function (ALSFRS-R) is the most widely used instrument to measure function in ALS clinical trials. It is a validated and disease specific questionnaire (23,24,25,26) The functional decline averages about 1 point per month in untreated patients (27).

#### 2.4.4.3 Decline of Respiratory Function, as Quantified by Change From Baseline on the Slow Vital Capacity (SVC) as % of Predicted

Vital capacity (VC) has been most thoroughly studied, and has been shown to decline by about 3% per month throughout much of the disease course (28). The rate of decline of VC is strongly correlated with survival, as would be expected given the close relationship between respiratory function and survival in ALS. VC was used as a primary outcome measure in one xaliproden Phase 3 trial in ALS patients (29), and showed a statistically significant positive effect in the treated group. This effect was not seen in patients simultaneously taking riluzole, however. In many other clinical trials, VC has been employed as a secondary outcome measure, without a clear demonstration of difference between active treatment and placebo. Patients on topiramate showed a modestly increased rate of progression compared to those on placebo, though this difference was not statistically significant, suggesting that vital capacity can be impacted by treatments. The SVC is a valid and robust measurement of the pulmonary function and is highly correlated with survival.

### 2.5 Risk-Benefit Assessment

Arimoclomol has shown an acceptable safety profile in ALS patients as well as in healthy subjects. Preliminary evidence of benefit has been established in two Phase 2 trials at doses up to 600 mg/day (please see Section 2.3.2). The clinical trial in mutant SOD1 ALS patients lacked the statistical precision to conclude efficacy, however the consistency of results across the range of prespecified efficacy outcome measures suggests a possible therapeutic benefit of arimoclomol. Data from the open label extension of the Phase 2 trial in sporadic ALS was suggestive of an effect in reducing the decline of ALSFRS-R when comparing to historical controls. Therefore, the present trial will be conducted in the general ALS population, i.e. including both patients with sporadic and familial ALS and irrespective of genotype.

Clinical trials in healthy subjects and patients with ALS and NPC indicate that arimoclomol is associated with a reversible increase in serum creatinine/decreased in creatinine clearance, most likely due to inhibition of OCT-2 and MATEs, without any effects on renal function, although. One event of severe tubulointerstitial nephritis with acute tubular injury and acute tubular necrosis with arimoclomol have been reported.

Increases in transaminases (ALAT/ASAT) have been observed in a minority of patients treated with blinded IMP in ongoing trials with arimoclomol. The maximum increase has been above 20x upper limit of normal (ULN). The values have returned to baseline either during treatment or after discontinuation of blinded IMP.

In conclusion, current risk with arimoclomol can be handled within a clinical trial context and appropriate measures have been instituted in this trial to protect subjects from possible risks.

The current benefit-risk ratio is favourable and supports the administration of arimoclomol for the purposes of achieving the objectives of this trial.

## 2.6 Ethical Considerations

No paediatric patients or other vulnerable subject's, including individual's incapable of giving informed consent at the time of enrolment, will be included in this clinical trial. Furthermore, women who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled in this clinical trial. Women of child-bearing potential must agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial and until 1 month after discontinuation of treatment with the IMP. All female subjects of child-bearing potential will have a pregnancy test performed before treatment, during treatment and at End of Trial to ensure that no fetuses are exposed to the IMP.

Since ALS is a rapidly progressing neurological condition, the ability of a trial subject to confirm ongoing or provide new consent may be diminished (i.e. the trial subject may decline to a legal status of an incapacitated adult). Since there is the possibility of needing to reconsent subjects in the clinical trial due to unforeseen circumstances, a legal representative will be nominated by the time of the Baseline visit to ensure that this occurs while the subject is competent. In this circumstance (and in accordance with local legislation or guidelines) a legal representative will ensure the subject's best interests and legal rights are protected throughout the trial should the subject become incompetent. Legal representation certificate must be obtained as per applicable country legal requirements and procedures. While the subject is competent, informed consent for any research procedure or intervention is sought from the subject only. The subject may freely decline consent and the legal representative will not be consulted. Based on the selection criteria, this trial will not prompt legislation regarding enrolment of incapacitated adults into clinical trials in emergency situations.

Additionally, this individual will give consent to be contacted during the conduct of the trial should contact with the subject become challenged.

Altogether, the risks associated with participating in this clinical trial are considered outweighed by the benefit of a potential future treatment option for ALS.

In accordance with the current version of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, qualified medical personnel will be appointed by Orphazyme and will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial. Safety data will be reviewed regularly by Orphazyme, and an independent Data Monitoring Committee (DMC; see Appendix 10.2.10) to ensure that prompt action is taken, if needed, to ensure subject safety.

In conclusion, the trial design chosen for this efficacy and safety trial on arimoclomol is regarded as ethically justified and adherent with ethical requirements.

# 3. OBJECTIVES AND ENDPOINTS

## Table 3 Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| Primary objective | Primary endpoint |
| To determine the efficacy of chronic treatment with 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo over 76 weeks in subjects with ALS as assessed with CAFS | • CAFS over a treatment period of 76 weeks (or end-of-trial) |
| Secondary objectives | Secondary endpoints |
| To evaluate the impact of 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo on:<br>• Time to PAV/tracheostomy free (PAV)/tracheostomy free survival<br>• Disease progression as measured by change from Baseline of the ALSFRS-R<br>• Progression of respiratory dysfunction as measured by change from Baseline of SVC | • Time to PAV/tracheostomy/death from Baseline<br>• Change from Baseline to Week 76 (or end-of-trial) in ALSFRS-R<br>• Change from Baseline to Week 76 (or end-of-trial) in SVC |
| Safety objective | Safety endpoints |
| To assess the safety and tolerability of 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo | • Incidence and severity of TEAEs over a treatment period of 76 weeks<br>• Mean and change from Baseline to Week 76 (or end-of-trial) in clinical safety laboratory tests, and vital signs<br>• Incidence of potentially clinically significant abnormalities in clinical safety laboratory tests and vital signs over a treatment period of 76 weeks<br>• C-SSRS over a treatment period of 76 weeks |
| Exploratory objectives | Exploratory endpoints |
| ***Efficacy*** | |
| To explore the potential effect of 1200 mg/day arimoclomol (400 mg t.i.d.) to placebo on cognitive and behavioural changes | • Change from Screening to Week 76 in cognitive and behavioural changes as evaluated by ECAS |

| Objectives | Endpoints |
|---|---|
| ***Health-Related Quality of Life*** | |
| To evaluate the effect of 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo on health-related quality of life | • The SEIQoL-DW for the subject over a treatment period of 76 weeks<br>• The SEIQoL-DW for the caregiver over a treatment period of 76 weeks<br>• EQ-5D-5L over a treatment period of 76 weeks |
| ***Pharmacokinetics (will be reported separately from the main Clinical Trial Report)*** | |
| To investigate CSF and plasma levels of arimoclomol following administration of 1200 mg/day arimoclomol (400 mg t.i.d.) | • Plasma and CSF concentrations of arimoclomol at weeks 20 and 52 |
| ***Biomarkers (will be reported separately from the main Clinical Trial Report )*** | |
| To evaluate the effect of 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo on candidate biomarkers of target engagement, disease activity (markers reflecting ongoing neurodegeneration), and disease progression in blood, urine, and CSF compared to placebo. | Absolute values and change from Baseline to Week 20, Week 52, and Week 76 for 400 mg t.i.d. arimoclomol compared to placebo in blood, urine, and CSF for the following biomarker endpoints:<br>• HSP70 in CSF and blood<br>• NfL in CSF and blood<br>• Urinary p75ECD<br>• Chitotriosidase in CSF |

**Abbreviations**: ALS: amyotrophic lateral sclerosis; ALSFRS-R: ALS functioning rating scale revised; CAFS: Combined Assessment of Function and Survival; CSF: cerebrospinal fluid; C-SSRS: Colombia Suicide Severity Rating scale; ECAS: Edinburgh Cognitive and Behavioural Screen; EQ-5D-5L:EuroQol Five-Dimensional, Five-Level Descriptive System; HSP70: heat shock protein-70; NfL: neurofilament light chain; p75ECD: p75 neurotrophin receptor extracellular domain; PAV: permanent assisted ventilation; SCV: slow vital capacity; SEIQoL-DW: the schedule for the evaluation of individual quality of life (direct weighting); TEAE: treatment-emergent adverse event; t.i.d.. three times daily

# 4. TRIAL DESIGN

## 4.1 Overall Trial Design

This is a multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of 1200 mg/day arimoclomol (400 mg t.i.d.) over a 76 weeks' treatment period).

Patients diagnosed with ALS who had first appearance of symptoms (weakness) within the previous 18 months will be eligible for screening.

In accordance with the eligibility criteria (see Sections 5.2 and 5.3), subjects participating in the present trial may be on a stable background treatment with riluzole. Additionally, a subset of up to 18 subjects on stable (i.e. minimum 6 months') treatment with edaravone and who otherwise fulfil the eligibility criteria are planned for enrolment (see exclusion criterion 5).

Following confirmation of eligibility during the Screening/Baseline period (Day -28 to Day 1), subjects will be randomised in a 2:1 ratio to receive either 1200 mg/day arimoclomol (400 mg t.i.d.) or placebo orally t.i.d. Randomisation will be stratified by background riluzole use. The first post-baseline assessment will take place in-person at the investigator site 4 weeks after the Baseline visit; subsequent assessments will consist of a combination of in-person visits and remote visits (telephone calls).

Subjects will attend the investigator site for an in-person visit on a 4-weekly basis for the initial 6 months of treatment (on Weeks 4, 8, 12, 16, 20, 24, 28), followed by an 8-weekly basis to 12 months (on Weeks 36, 44 and 52), and then for the following 6 months of treatment in-person visits are scheduled on a 12-weekly basis until the Safety Follow Up (on Weeks 64 and 76). Assessments will include those for efficacy and safety, as well as sampling of biofluids for clinical safety laboratory tests, biomarkers, and PK according to the schedule of procedures (Table 1). If a subject is no longer able to attend the site, appropriate trial site staff (e.g. nurse, sub-investigator or contract nursing services as required) may assess the subject by conducting a home visit.

On the remaining weeks of the treatment period (Weeks 32, 40, 48, 56, 60, 68 and 72) a remote visit will be conducted by the subject receiving a telephone call from the trial site staff. Assessments will therefore be limited to efficacy and safety evaluations according to the schedule of procedures.

All visits should be scheduled within the visit window (+/- 7 days) relative to the Baseline visit. Every effort should be made to ensure that the in-person visits at Week 52 and Week 76 are arranged as close as possible to the scheduled time-point.

An independent DMC will be established to monitor benefit:risk and ensure that subjects are not unnecessarily exposed to the IMP in the event that the expected benefit:risk should change. The DMC will act in accordance with the DMC charter and may have access to unblinded data (see Appendix 10.2.10).

At any time during the trial, the IMP may be temporarily halted for up to 4 weeks for an intolerable AE. Following re-challenge at the intended dose, de-escalation from 1200 mg/day (400 mg t.i.d.) to 600 mg/day (200 mg t.i.d.) may be considered. The subject will continue on this decreased dose for the remainder of the trial. Re-challenge with IMP in cases of elevation of transaminases should only be done as specified in Section 6.5 regarding dose modification and IMP discontinuation. Subjects who discontinue treatment will be encouraged to attend all planned visits as per protocol after drug discontinuation. Additionally, these subjects will have remote visit 2 weeks after the premature IMP discontinuation.

If a subject reaches a trial survival endpoint (e.g. tracheostomy or PAV), the IMP will be permanently discontinued. The subject will be offered to participate in an open-label extension trial which will be conducted as a separate trial.

Subjects who complete 76 weeks of randomised treatment will be offered participation in a separate open-label extension which will be conducted as separate clinical trial.

**Figure 1: Trial Design**

## 4.2 Number of Subjects

The anticipated disposition of subjects is as follows;

Number of subjects planned to be screened: Approximately 298

Estimated screen failure rate: 25%

Number of subjects planned to be randomised: Approximately 231

Estimated trial discontinuation rate: 40%

Number of subjects expected to complete 76 weeks of treatment: 128

Within the total number of subjects to be randomised up to 18 subjects will be on stable (i.e. minimum 6 months') treatment with edaravone (see exclusion criterion 5).

The statistical power considerations for the sample size are described in Section 8.1.

The trial will be conducted at approximately 32 sites in approximately 13 countries in North America and Europe.

## 4.3 End of Trial Definition

The end of the trial is defined as the date of the last visit of the last subject in the trial globally.

# 5. TRIAL POPULATION AND WITHDRAWAL

## 5.1 Subject Eligibility

The investigator should only enrol subjects who meet all inclusion and none of the exclusion criteria, are not put at undue risk by participating in the trial and can be expected to comply with the protocol.

The subject's eligibility for the clinical trial must be checked according to the inclusion and exclusion criteria listed in Sections 5.2 and 5.3.

In addition, section 10.4 should be consulted for any country-specific eligibility criteria.

Any implementation of national requirements/law for the subject's participation in the clinical trial will be ensured and described in the submission documentation to regulatory authorities/ethics committees, as applicable.

## 5.2 Inclusion Criteria

1. Capable of- and willing to- provide written informed consent and comply with trial procedures.

2. Subject is male or female ≥18 years of age.

3. Subject meets revised El Escorial criteria for clinically possible, clinically probable / clinically probable ALS laboratory-supported, clinically definite ALS or clinically definite familial ALS laboratory-supported.

4. 18 months or less since first appearance of weakness (e.g. limb weakness, dysarthria, dysphagia, shortness of breath).

5. ALSFRS-R ≥35 and erect (seated) SVC % predicted ≥ 70% at Screening.

6. Able and willing to travel to the site, and in the investigator's opinion is likely to attend visits for at least 24 weeks.

7. All sexually active female subjects of child-bearing potential (postmenarchal)* must agree not to intend to become pregnant and use a highly effective method of contraception** during the trial through 1 month after the last dose of trial medication. If the subject is a sexually active male with female partners of child-bearing potential (postmenarchal) he must use a condom with or without spermicide in addition to the birth control used by their partners during the trial until 3 months after the last dose of trial medication.

8. Stable dose of riluzole (50 mg twice daily) for a minimum of 14 days prior to Day 1 (Baseline) or has not taken it for 14 days prior to Day 1.

** Non child-bearing potential is defined as post-menopausal (minimum of 12 months with no menses and follicle-stimulating hormone in the post-menopausal range) or sterilisation (hysterectomy, oophorectomy, or bilateral tubal ligation).*

*** Highly effective methods of contraception include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; and vasectomised partner.*
*According to the recommendations from the Clinical Trial Facilitation Group (CTFG, 2014), sexual abstinence is considered a highly effective birth control method only if it is defined as refraining from heterosexual intercourse during the trial until 1 week after the last dose of trial medication (for female subjects of child-bearing potential) and for 3 months after the last dose of trial medication (for male subjects with female partners of child-bearing potential). The reliability of sexual abstinence needs to be evaluated by the investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.*

## 5.3 Exclusion Criteria

1. Tracheostomy or use of non-invasive ventilation for more than 2 hours during waking hours at the time of Screening and Baseline visits.
2. Pregnant or breast-feeding.
3. Current or anticipated use of diaphragmatic pacing during the trial.
4. Exposure to any investigational treatment within 4 weeks or <5 half-lives of the Screening visit, whichever is longest and/or advanced therapy medicinal product (ATMP), i.e. treatments based on genes, cells or tissues and/or participated in any prior ALS clinical trial receiving active drug treatment (with the exception described in exclusion criterion 5).
5. Treatment with edaravone within 4 weeks of the Baseline visit. However, up to 18 subjects on stable (i.e. minimum 6 months') treatment with edaravone and who otherwise fulfil the eligibility criteria are planned for enrolment (limited to countries where edaravone has a marketing authorisation for treatment of ALS).
6. Any of the following medically significant conditions:
    a. Neurological impairment/dysfunction or unstable psychiatric illness that in the investigator's opinion is likely to interfere with assessment of ALS disease progression.
    b. Clinically significant unstable medical condition other than ALS, which would present a risk to a subject to participate in the trial.
    c. Presence of dementia that impairs the ability of the subject to provide informed consent, according to the PI decision.
    d. Known or suspected allergy or intolerance to the IMP (arimoclomol or constituents).

e. Chronic infection particularly HIV or Hepatitis B or C.

f. Clinically significant renal or hepatic disease.

g. Aspartate aminotransferase and/or alanine aminotransferase, and/or lactate dehydrogenase ≥3 times the upper limit of normal [ULN], bilirubin≥2 times the ULN, or creatinine ≥1.5 times the ULN. Laboratory tests may be repeated once at Screening. Reasons to repeat laboratory tests may include that the medication causing laboratory abnormality was suspended, any other suspected cause may no longer exist, or to rule out laboratory error.

h. Cancer that is currently under active treatment or is likely to require treatment during the trial that may alter the subject´s function and thereby interfere with assessment of ALS disease progression.

i. Any other condition that in the investigator's opinion would present a risk to a subject to participate in the trial, interfere with the assessment of safety or has an increased risk of causing death during the trial.

## 5.4 Screening, Screening Failures and Randomisation Procedure

Trial participation begins once written informed consent is obtained (see Appendix 10.2.2 for details on the informed consent process). Once informed consent is obtained, a subject identification number (subject ID) will be assigned by a central interactive response technology (IRT) and the screening evaluations to assess eligibility criteria may begin. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. A master log of all consented subjects will be maintained at the trial site.

Screening may be up to 4 weeks prior to Baseline if a washout period for an investigational treatment is required (see exclusion criterion 4). The minimum screening period is set as one week for practical reasons (to ensure all results are available to determine eligibility at Baseline). If laboratory re-tests are required, these should be completed within the maximal 4 weeks' screening period.

Screening failures are defined as subjects who consent to participate in the trial but are not subsequently randomly assigned to trial treatment. A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (30) and to respond to queries from regulatory authorities. Minimal information includes demography, screening failure details, eligibility criteria, and any AEs and SAEs. Follow-up of SAEs must be carried out according to Section 7.5.7.6.

In principle subjects may not be rescreened however if the reason for screen failure is deemed to be due to acute illness, the subject may be rescreened following recovery. Likewise, screen failure due to safety laboratory abnormality may be repeated on one occasion. Subjects who have failed to qualify for trial participation due to the requirements for SVC according to eligibility criteria contained in protocol version 1.0 and 2.0 may be re-screened for all

eligibility criteria of this protocol (amendment 4.0). The appointed medical monitor should be notified of such occurrence. In the event of rescreening, the subject should be marked as a screen failure in IRT, electronic case report form (eCRF) for the first screening attempt and a new Subject ID should be generated for the second screening attempt. A cross reference between the two Subject IDs will be prompted in the IRT/eCRF.

Only the assessment of ALSFRS-R and SVC at the Screening visit is used for determination of subject eligibility. The result of these assessments at the Baseline visit is used for analysis purposes and the value will not exclude the subject from trial participation.

## 5.5 Discontinuation

A subject may withdraw from trial or from treatment at any time (prior to first dose or during treatment period) at his/her own request. A subject may be withdrawn at any time at the discretion of the investigator. Discontinued subjects will not be replaced.

### 5.5.1 Discontinuation from Treatment

Reasons for permanent discontinuation of IMP are given in Section 6.5.

If a subject discontinues treatment and does not meet any of the survival endpoint definitions the subject should be invited to attend the remaining trial visits as per the schedule of procedures. Additionally, a remote follow-up (Safety Follow Up) phone call should be scheduled for 2 weeks after the last treatment.

Subjects who remain on the trial and do not take IMP will have telephone calls in place of in-clinic visits and only the following assessments will be completed: ALSFRS-R, AE and concomitant medication (based on patient recall), and survival status. If the subject has an ongoing AE possibly or probably related to an AE requiring clinical safety laboratory tests, in-clinic visits may be used to collect a central laboratory sample; samples should be collected until resolution or following agreement with the medical monitor.

For subjects discontinuing treatment, the end of trial form must be completed in the eCRF and the final drug accountability must be performed. The reason for discontinuation of trial product must be recorded in subject's medical records and the eCRF.

### 5.5.2 Discontinuation from the Trial

Subjects who move to another CTIMP shall be withdrawn from this trial. Subjects who enter registry trials do not need to be withdrawn from this current trial.

If a subject withdraws from the trial, the last in-person visit should be conducted as per the schedule of assessments for the End of Trial Visit and recorded as this visit in the eCRF. If the subject has not already discontinued treatment, the Safety Follow Up visit should also be scheduled for 2 weeks after the last treatment.

If a subject withdraws from the trial, he/she may request the destruction of any samples taken and not tested however data and samples collected up to the point of withdrawal may not be

removed from the clinical database. The investigator must record this in the site's trial records and notify the clinical research associate (CRA) and appointed medical monitor.

Subjects and/or caregiver may be asked to sign an additional informed consent form prior to trial discontinuation to allow follow-up of the survival endpoints (PAV/tracheostomy/death) at the scheduled week 76.

## 5.6 Missed Visits and Lost to Follow-Up

If a visit is missed, every effort should be made to ensure that as much information as practically possible is collected at a telephone contact as close to the scheduled visit date as possible. If the missed visit was expected to be in person, the assessments and procedures scheduled for remote visits should be followed. The subject should be advised to use IMP as supplied from the spare bottle and where the subject does not have sufficient IMP for the remaining visit interval, site staff should ensure that additional spare IMP is allocated via IRT and provided to the subject (by direct to patient shipment, as required). Subjects will be invited for the next scheduled visit according to visit schedule (Table 1).

Subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled in-person visits and are unable to be contacted by the trial site (including remote visits or other appropriate means of follow-up). The threshold for being considered lost-to follow-up is set as 3 consecutive missed visits.

The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial. If a subject is no longer able to travel to the trial site an in-person visit may be conducted in the subject's home/residency (see section 7.1.7)
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

As the subject has not withdrawn consent, a telephone call will be attempted at the scheduled week 76, and the following assessments will be completed: ALSFRS-R, AE, concomitant medication (based on patient recall), and survival status.

# 6. TREATMENTS

## 6.1 Trial Products

The following trial products for oral administration either in whole or sprinkled and dispensed in liquid or food stuff will be manufactured and supplied by Orphazyme, Denmark:

- Arimoclomol, formulated into size "0", white hard capsules for oral administration.
- Placebo, formulated into size "0", white hard capsules for oral administration.

Both trial products are considered IMPs.

Each trial site will be supplied with sufficient IMP for the trial on an on-going basis as controlled via an interactive response technology (IRT). The Contract Manufacturing Organisation (CMO) selected for this trial is Catalent Pharma Solutions who will control IMP with regards to Good Manufacturing Practice (GMP) and release by qualified person (QP).

The description of IMPs is provided in Table 4 and the quantification of ingredients in Table 5.

**Table 4: Description of investigational medicinal products**

| | **Active treatment** | **Placebo** |
|---|---|---|
| **Name of active ingredient** | Arimoclomol citrate | 1ppm denatonium benzoate |
| **Chemical name** | N-[(2R,Z)-2-hydroxy-3-(1-piperidyl)propoxy]pyridine-3-carboximidoyl chloride, 1-oxide, citrateArimoclomol citrate | Denatonium benzoate |
| **Pharmaceutical form** | Capsule | Capsule |
| **Appearance** | White capsule with white to off-white powder | White capsule with white to off-white powder |
| **Strength (calculated as salt)** | 200 mg | 0 |
| **Stability** | Stable in original container | Stable in original container |
| **Storage** | Room temperature (15-25°C) in original container | Room temperature (15-25°C) in original container |
| **Shelf-life** | 24 months* | 24 months* |
| **Manufacturer** | Catalent Pharma Solutions | Catalent Pharma Solutions |
| **Batch number(s)** | To be printed on the label | To be printed on the label |
| **Expiry date(s)** | To be printed on the label | To be printed on the label |

* The shelf-life may be extended based on available stability data

The capsules are packed in 185 mL high density polyethylene (HDPE) bottles each containing 84 capsules. The bottles are heat sealed and closed with a HDPE child resistant closure.

**Table 5: Quantities of ingredients in trial product**

| Ingredient | Function | Grade | Content mg/capsule |
|---|---|---|---|
| OR 003 (BRX-345) arimoclomol citrate[1] | Active | - | 200.0 |
| [redacted] | [redacted] | Ph.Eur./USP-NF | [redacted] |
| [redacted] | [redacted] | Ph.Eur./USP-NF | [redacted] |
| [redacted] capsule shells (Size 0, white) | [redacted] | Ph.Eur./USP-NF | - |

**Abbreviations:**
Ph. Eur.: European Pharmacopeia
USP-NF: United States Pharmacopeia-National Formulary
HPMC: Hydroxypropyl methyl cellulose

**Footnote:**
[1] In placebo capsules, the active is replaced by 1ppm denatonium benzoate as bitter tasting agent

## 6.2 Administration of Investigational Medicinal Products

Arimoclomol 2 x 200 mg or matching placebo capsules will be taken orally t.i.d. for up to 76 weeks. If required, the capsules can be opened and dispersed in 10-20 mL (i.e. 1-2 tablespoons) of liquid (water or apple juice) or in a tablespoon of soft food material (yoghurt or apple puree). Once dispersed in water, the IMP can also be administered via a gastric tube (as applicable). For full administration, the tube should be flushed with 5 mL of water.

The method of oral administration (swallowed whole, sprinkled/dispersed into liquid, sprinkled/dispersed into food or sprinkled/dispersed in water and fed via gastric tube) will be recorded in a subject diary and a summary transcribed into the eCRF.

The investigator must document that verbal direction for use and the Patient Information Leaflet (PIL) is provided at the first dispensing visit (Day 1). At the later dispensing visits the investigator or delegate should ensure that subjects comply with treatment procedure and dispersion, if needed additional instruction should be provided, including provision of a further copy of the PIL.

At Weeks 20 and 52, the subject must not administer IMP within 8 hours of the site visit to allow for a trough PK sample to be taken. The time of the dose prior to the visit should be recorded in the subject diary and transcribed to the eCRF.

The first administration of IMP on the day of the Week 20 and Week 52 visit will be administered while at the site to allow for PK assessment.

At any time during the trial, dose de-escalation from 1200 mg/day (400 mg t.i.d.) to 600 mg/day (200 mg t.i.d.) for tolerability may be considered (see Section 6.5). The subject will continue on this decreased dose for the remainder of the trial.

## 6.3 Interactive Web Response System

A trial-specific IRT will be used for (amongst others); forward logistics of the supply chain, inventory management and randomised treatment assignment. A full description of functionalities will be included in an IRT user manual which will be provided to each trial site. This IRT can be accessed at any time via the internet with a telephone helpdesk back-up solution for emergency situations. Access to the IRT must be restricted to and controlled by authorised persons.

## 6.4 Treatment Assignment

### 6.4.1 Randomisation

Subjects found to be eligible will be randomised via the IRT in a 2:1 ratio to one of the following treatments:

a. 1200 mg/day arimoclomol (400 mg t.i.d.)
b. Placebo (matching)

Treatment assignment will also be stratified by the presence or absence of a background treatment with riluzole.

### 6.4.2 Blinding

This is a double-blinded trial in which arimoclomol and placebo are visually identical and matched for taste.

Neither the subject nor any of the investigator site staff or Orphazyme staff (included Contract Research Organisation (CRO) delegated staff) who are involved in the treatment or clinical evaluation and monitoring of the subjects will be aware of the treatment received. The packaging and labelling of the IMPs will contain no evidence of their identity.

The DMC may have access to unblinded data.

### 6.4.3 Emergency Unblinding of Individual Subject Treatment

The randomisation code for an individual subject may be broken if knowledge of the assigned treatment would influence the care of the subject in a medical emergency. Facility to unblind individual subject is provided for investigators. The circumstances under which an individual subject is unblinded should be discussed with the appointed medical monitor however the

immediate management of the subject should take precedence in an emergency situation and the final decision to unblind a subject is the sole responsibility of the investigator.

Emergency unblinding is performed in the IRT. For clinicians outside of the clinical trial who do not have access to this system, unblinding will occur by proxy by the investigator. Investigator contact details will be provided via the subject trial card.

Immediately after an unblinding event, the IRT will automatically distribute an unblinding notification email. This notification will be unblinded to the requester and will be blinded for all other nominated recipients; medical monitor and selected other representatives of the sponsor e.g. clinical safety, medical director, trial manager.

Whenever a code is broken, the investigator must print the unblinding notification email, sign and date the document to acknowledge awareness of the event and file in the investigator site file. The reason for code break should be documented in the medical record.

If the code has been broken, the subject must be discontinued from the trial.

End of trial procedures should be observed, see Section 5.5.

## 6.5 Dose Modification and IMP Discontinuation

### 6.5.1 Permanent Discontinuation of IMP

In case of a safety concern or unacceptable intolerability, the IMP may be permanently discontinued at the investigator's discretion. In case of pregnancy or intention to become pregnant the trial product must be discontinued (see section 7.5.7.7 for reporting of pregnancies in the trial). The primary reason for discontinuation of the IMP must be specified in the eCRF.

According to the FDA Guidance for Industry on Drug-Induced Liver Injury (DILI) (39), IMP must be permanently discontinued in the case of the following:

- ALAT or ASAT >8 x ULN
- ALAT or ASAT >5 x ULN for more than 2 weeks
- ALAT or ASAT >3 x ULN and bilirubin >2 x ULN or International Normalised Ratio (INR) >1.5)
- ALAT or ASAT >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

If a subject reaches a trial survival endpoint (e.g. tracheostomy or PAV), the IMP will be permanently discontinued. The subject will be offered to participate in an open-label extension which will be conducted as a separate trial.

If a subject is no longer able to attend the clinic, nor have the option of a home visit via an appropriate trial site staff (e.g. nurse, sub-investigator or contract nursing services) for safety

monitoring, the IMP will be permanently discontinued. The subject may remain on the trial without IMP.

For procedures related to discontinuation, see Section 5.5.

### 6.5.2 Temporary Halt of IMP and Dose Modification

A temporary halt of IMP treatment of up to 4 weeks is permitted if a subject experiences an intolerable AE. The interruption of IMP should be as short as possible, and the appointed medical monitor should be consulted prior to re-initiation of the intended 1200 mg/day (400 mg t.i.d.) dose.

If the subject experiences the same intolerable AE after re-challenge with the intended dose, dose de-escalation from 1200 mg/day (400 mg t.i.d.) to 600 mg/day (200 mg t.i.d.) may be considered following consultation with the appointed medical monitor. The subject will continue this decreased dose for the remainder of the trial. If this reduced dose is not tolerated, the IMP must be discontinued permanently.

This sequence of events can be implemented only once for intolerable AEs within a given organ/body system. If the subject experiences a different intolerable adverse event within a different organ/body system, this sequence of events can be repeated for that AE.

Likewise, a temporary halt of IMP treatment of up to 4 weeks is permitted in circumstances where a concurrent procedure or concomitant treatment for an acute condition requires withdrawal of IMP administration. The circumstances under which a temporary halt is initiated should be discussed with the appointed medical monitor.

**Re-Challenge in Case of Increased Transaminases**

If in the Investigator's judgement, a temporary halt in IMP is instituted because of elevated transaminases, a re-challenge **must not** occur if the patient had the following:

- ALAT or ASAT > 5 x ULN
- ALAT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALAT or ASAT > 3 x ULN AND TBL >2 x ULN

IMP must also be discontinued for subjects with elevated transaminases where close observation (repeated laboratory tests) is not possible, see Section 7.5.10.2.

The missed doses must be recorded in the eCRF.

An Safety Follow Up visit should not be conducted when a temporary halt of IMP is initiated.

## 6.6 Treatment logistics and accountability

### 6.6.1 Labelling and packaging of IMPs

The IMPs will be packaged into bottles containing 84 capsules. Each bottle will be given a unique number (bottle code).

The labelling of IMPs will be in accordance with Annex 13 (31), local regulations and trial requirements. Label text will be translated into local languages, as required.

### 6.6.2 Storage of IMPs

All IMPs must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

The IMP must be stored at room temperature (15-25°C) at the site. The temperature during storage must be monitored by a calibrated, stationary and continuously recording system. Minimum requirement is a calibrated min/max thermometer.

A temperature log must be kept documenting the storage within the permitted temperature interval. Storage facilities should be checked at least every working day.

Storage of IMP may be delegated, e.g. to a hospital pharmacy, as locally applicable.

Note that in the cases listed below, IMP should be placed into quarantine and should not be used. Site staff should immediately document the bottle status in IRT (refer to the IRT manual for further details) and contact their CRA for further guidance:

- Temperature excursion upon receipt or during storage at the trial site.
- Damaged kit upon receipt or during storage at the trial site.

All excursions from the permitted storage conditions should be reported in accordance with the trial specific Pharmacy Manual.

The sponsor will decide if the affected bottles may be released back into the inventory, returned to the depot or destroyed locally.

### 6.6.3 Drug Distribution and Dispensation

At each in-person visit IMP will be dispensed according to the bottle codes allocated by the IRT. On each dispensing occasion, an adequate number of bottles will be dispensed to allow for the 2 x 200 mg t.i.d. dosing regimen across the visit interval (range: 4 to 12 weeks) unless dose de-escalation has occurred, in which case the IRT will adjust the number of bottles dispensed.

A spare bottle will be assigned to the subject to cover the additional doses needed should visit scheduling require the +/- 7 day visit windows. All spare bottles used will have accountability performed on a capsule level by the end of the trial.

In the event that a subject is unable to attend the trial site for a scheduled in-person site visit (e.g. due to ALS progression), a 'direct-to-patient' (DtP) logistics service may be used in accordance with local legislation or guidelines. This service will only be implemented where all required permissions are obtained.

Once it is determined that a subject is unable to attend the trial site, a request for the use of the DtP shipment will be made to the service provider by a site staff member. Use of the service requires sponsor approval. The IMP should be dispensed per the schedule of procedures, via the IRT. The site will schedule for the approved courier to collect the IMP from the trial site and distribute directly to the subject's home/residence. Accountability logs and temperature monitoring will be maintained throughout the chain of custody. The service should be used for reverse logistics to ensure that used and unused IMP (including empty packaging material) is returned to the trial site.

The subject (or the primary caregiver) must acknowledge receipt of the IMP, using their trial specific subject ID as signature to ensure that their identity is not transferred to the sponsor via the paper records.

Deviations from this process must be agreed with the Sponsor.

### 6.6.4 Drug Accountability and Destruction

The IMP must be accounted for throughout the duration of the trial. The responsibility for the IMP is transferred from Orphazyme to the investigator from the time of IMP receipt to time of destruction. The investigator is fully responsible for the IMPs at the trial site and for maintaining adequate control of the IMPs and for documenting all transactions with them.

The IMPs will be dispensed to each subject as required according to treatment group. The IRT will allocate IMP bottles to be dispensed to a subject in compliance with the trial randomisation code and packing list at randomisation and at each subsequent dispensing transaction (each in person visit).

The investigator or delegated person is responsible for ensuring that:

- Drug accountability is performed using paper-based accountability logs for all IMP transactions and the IRT drug accountability module for forward logistics.
- Subjects are instructed to return all used, partly used and unused IMP including empty packaging material at each dispensing visit and at End of Treatment visit.
- Returned IMP (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product.
- Destruction will be performed in accordance with local procedures after accountability is finalised and verified by the CRA. If local destruction procedures or services are not adequate for clinical trial standards, IMP may be sent to a returns depot for destruction by the CMO. Destruction of products must be documented.

### 6.6.5 Treatment Compliance

The subject or their nominated primary caregiver will maintain a diary record of compliance with t.i.d. IMP administration. These data (summarised as the number of missed applications per visit interval) will then be transcribed into the eCRF by site staff at the next in-person visit including the reason for non-adherence. If a subject is found to be non-compliant, the investigator should remind the subject of the importance of following the treatment instructions.

If a dose of IMP is missed, the subject should not adjust their dosing schedule to accommodate the missed administration. The subject therefore should not reschedule dosing to achieve the t.i.d. dosing regimen or add the missed dose to the next scheduled administration.

A compliance rate of 80% (visit interval and total trial) will be used as the threshold for protocol deviation reporting.

## 6.7 Mode of Administration

The subject or their nominated primary caregiver will record the method of administration of IMP in the subject diary (swallowed whole, sprinkled/dispersed into liquid, sprinkled/dispersed into food or sprinkled/dispersed in water and fed via gastric tube). The data will then be summarised and transcribed into the eCRF.

## 6.8 Concomitant Medication and Procedures

Any medication or vaccine that the subject receives from 3 months prior to Screening and until the End of Trial visit (Week 76) must be recorded in the subject's medical record and the eCRF along with details such as:

- Trade name or generic name
- Reason for use (indication)
- Dates of administration including start and stop dates
- Dosage information including dose, route and frequency

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 6.9. The appointed medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant medication for conditions other than ALS may be continued throughout the trial without any change in dosage whenever possible.

Arimoclomol is an in vitro inhibitor of the OCT2, MATE-1, and MATE-2K transporters and consequently may inhibit the elimination of cationic drugs that are significantly eliminated by tubular secretion. In addition, arimoclomol is an in vitro substrate of the MATE-1 and MATE-2K transporters. Arimoclomol undergoes renal tubular secretion and concomitant treatment with drugs that are MATE1 or MATE-2K inhibitors may therefore lead to increased exposure of arimoclomol. Consequently, the concomitant use cationic drugs that are significantly eliminated by tubular secretion as well as drugs which are MATE1 or MATE-2K inhibitors should be administered with caution. These include but are not limited to: amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin, dofetelide, trimetroprim, verapamil, levofloxacin, ciprofloxacin, moxifloxacin, pyrimethamine, ondansetron and quinidine.

Additionally, in vitro studies show that arimoclomol is a direct inhibitor of CYP2D6 and may potentially cause increase in exposure of co-administered medications that are substrates of CYP2D6 when arimoclomol is dosed at 400 mg t.i.d (40).

Since the magnitude of the potential increase cannot be predicted from in vitro data, caution is advised if arimoclomol is co-administered with medicinal products that are metabolised by CYP2D6. This may, for example, be relevant for Class I anti-arrhythmic, tricyclic antidepressants, betablockers, tramadol and selective serotonin reuptake inhibitors (SSRI's) particularly if they are known to be sensitive and moderate sensitive CYP2D6 substrates and/or have a narrow therapeutic index.

The product information for co-administered medicinal products should be consulted for guidance on concomitant treatment with a CYP2D6 inhibitor as dose adjustment of the CYP2D6 substrate may be appropriate. For compounds metabolised by CYP2D6 the dose may be reduced and for pro-drugs that are converted to the active compound by CYP2D6 the dose may be increased to ensure efficacy.

Nuedexta® (or compounded equivalent) is a treatment for pseudo-bulbar effect which is a combination of dextromethorphan and an ultra-low dose quinidine 20 and 10 mg, respectively. The main effect of Neudexta® is exerted by dextromethorphan which is metabolised by CYP2D6. The intended effect of quinidine as a strong inhibitor of the CYP2D6 isoenzyme is to reduce the metabolism of dextromethorphan. The collective information available to date on potential drug-drug interactions suggests that Neudexta® should be co-administered with arimoclomol with caution, since arimoclomol may inhibit the excretion of quinidine. Nuedexta® is known to prolong the QTc interval in a dose dependent matter (less than moxifloxacin) and concomitant therapy with medications that prolong the QT interval and are metabolized by CYP2D6 should be done with caution.

Animal studies have indicated a possible pharmacodynamic interaction with furosemide increased urinary volume and increased urinary creatinine, potassium, sodium, phosphorus and calcium; additive effect) at high doses. Consequently, concomitant treatment with furosemide should be done with caution. The following concomitant medications related to ALS treatment are permitted from Screening and throughout the trial:

- Stable dose of riluzole (50 mg twice daily) for a minimum of 14 days prior to Baseline (see inclusion criterion 8)
- Stable dose of edaravone i.e. minimum 6 months of treatment (only applicable for subjects enrolled into the edaravone sub-population, limited to countries where edaravone has a marketing authorisation for treatment of ALS (see exclusion criterion 5). The number of subjects in this sub-population will be tracked via eCRF data and investigators will be pro-actively notified when recruitment under this criterion will be closed.
- Other medication or treatments that are deemed necessary to provide adequate supportive care.

The use of non-invasive ventilation is permitted during the trial.

Concomitant medication and non-invasive ventilation will be recorded in the subject diary in the interval between trial visits.

### 6.9 Prohibited Medication and Procedures

The following medications are prohibited during the trial from the Screening or Baseline visit (see specific case) until the end of the trial defined as either the completion of 76 weeks of treatment or meeting a survival endpoint (PAV or tracheostomy):

- Treatment with edaravone within 4 weeks of the Baseline visit (unless the subject is enrolled as part of the sub-population).
- Commencement of riluzole treatment at any time throughout the trial if not established on a stable dose at Baseline (see inclusion criterion 8). Adjustment of riluzole dose,

including temporary halt due to tolerability may be permitted at the investigator's discretion.

- Other investigational treatments within 4 weeks or <5 half-lives of the Screening visit (whichever is longest).
- ATMP (i.e. treatments based on genes, cells or tissues) at any time

Diaphragmatic pacemakers are not permitted for the duration of the trial (see exclusion criterion 3).

The use of non-invasive ventilation is not permitted at Screening or Baseline but may be commenced during the trial.

The appointed medical monitor must be notified if a subject receives any of these therapies during the trial.

### 6.10 Provision for Subject Care Following Trial Completion

To ensure appropriate treatment of the subjects after they have completed the trial, the subjects will be treated at the investigator's discretion or referred to other physician(s) according to standard practice. Subjects who complete the 76 weeks of treatment will be offered participation in a separate open-label trial.

Patients who complete the 76 weeks of treatment, but do not continue in the open-label trial will attend the Safety Follow Up visit.

If a subject reaches a trial survival endpoint (e.g. tracheostomy or PAV), the IMP will be permanently discontinued. The subject will be offered to participate in an open-label extension which will be conducted as a separate trial.

# 7. TRIAL ASSESSMENTS AND PROCEDURES

## 7.1 General Principles

### 7.1.1 Investigator's or Delegate's Responsibilities

The investigator may delegate responsibility for performance of clinical assessments and trial procedures to adequately trained and experienced site staff members. This delegation of authority must be documented prior to the individual undertaking any trial specific tasks.

In addition to general experience and training, selected clinical assessment and procedures require trial specific rater-certification (see Section 7.1.3).

Subjective measures for a specific subject should be administered by the same rater throughout the course of the trial.

ALS diagnosis according to El Escorial criteria and neurological examination may only be delegated to qualified neurologists.

The following clinical assessments and procedures may only be delegated to site staff with recognised medical qualification or similar as permitted according to local regulation; taking informed consent, interpretation of clinical safety laboratory reports, vital signs, ECGs, physical examination, lumbar puncture for CSF sampling and assessment of AEs.

For clinical safety laboratory tests, values outside the reference range, the investigator must specify whether the value is clinically significant or not. All laboratory report printouts must be signed and dated by the investigator or delegate. The evaluation of screening results must be dated and signed prior to Visit 2 (Baseline) in order to confirm subject's eligibility. For the subsequent laboratory sampling, all reports must be reviewed prior to the next subject visit.

Review of ECGs must be documented as described in Section 7.5.5.

Review of diaries must be documented either on the documents and/or in the subject's medical record. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned, and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

### 7.1.2 Nomination of Primary Caregiver and Legal Representative

The subject must nominate a primary caregiver and a legal representative (may be the same person). This will be by the time of the Baseline visit where possible, although for the legal representative this may be deferred to the appropriate time as per applicable country legal requirements and procedures.

The primary caregiver should be a friend, family or spouse (i.e. not a healthcare professional assigned to care for the subject) and must be a regular caregiver who has substantial contact

with the subject. If the caregiver does not cohabitate with the subject, he/she ideally should have a minimum of 10 hours total and at least 3 days contact with the subject per week.

The primary caregiver should be willing to attend visits with the subject where the Schedule of the Evaluation of Individual QoL (direct weighting) (SEIQoL) and Edinburgh Cognitive and Behavioral Screen (ECAS) questionnaires are administered. They should also oversee the subject's compliance with protocol-specified procedures and IMP and report on subject's status. Although day-to-day care of the subject is not expected at the time of trial inclusion, the primary caregiver may support the subject in completion of trial assessments such as interpretation of responses or completion of the subject diary in the event of deteriorating motor function or communication as considered appropriate by the investigator.

The primary caregiver will be asked to complete the SEIQoL (see Section 7.4.2) and provide information about the subject by completing the behavior and psychosis screens as part of the ECAS (see Section 7.3.4).

If on any occasion the subject is accompanied to site by a different caregiver, they will not be asked to complete these assessments. If the nominated primary caregiver must change, the informed process must be repeated with this individual. In this circumstance the SEIQoL will not be completed but the ECAS behavior and psychosis screens are required. Caregiver non-attendance at clinics resulting in missed SEIQoL and ECAS does not constitute a protocol deviation.

Likewise, a legal representative should be nominated by the subject by the time of the Baseline visit. The legal representative will agree to make decisions regarding use of clinical trial data and biological samples during the trial in the event of diminished capacity of the trial subject. The legal representative must be consulted should re-consent processes be required due to unforeseen circumstances during trial conduct (e.g. new emerging safety information or a change to trial procedures) at a time where the subject is not capable of giving consent or in matters relating to trial participation in after-life situations. Legal representation certificate must be obtained as per applicable country legal requirements and procedures.

### 7.1.3 Rater Training and Certification

To ensure consistency in administration and interpretation of subjective clinical outcome measures, a customised rater training program (described in separate rater training plans) will be delivered to qualified site staff. Management of rater training will be provided by the Clinical Assessment Technologies group of Worldwide Clinical Trials.

For scales where the rater may be the subject or the subject's nominated primary caregiver, the training of site staff will focus on instruction.

Site staff delegated the responsibility of performing clinical assessment who hold accreditation from other recognised groups must undergo the trial specific training and certification program to ensure consistency between raters.

Training will be provided at face to face meetings and will also be available through the course of the trial as remediation including an on-line learning portal.

Raters will be trained by completing the specific training courses for each scale. Certification will be issued as appropriate to each scale.

### 7.1.4 Subject Instruction

#### 7.1.4.1 Investigational Medical Product

IMP must be dispensed to subjects at the specified visits (see Table 1). IMP will be dispensed to the subject by the site, hospital pharmacy or equivalent. At the randomisation visit, the subjects will be instructed in the handling and administration of IMP (Section 6.2).

#### 7.1.4.2 Subject Diary

The subject must be provided with diaries to record IMP compliance, mode of administration, concomitant medication uses and use of non-invasive ventilation at the specified visits (see Table 1) the investigator or delegate should instruct the subjects on how to complete the diary at the Baseline visit and provide ongoing instruction as necessitated by data quality. The diaries dispensed to subjects should be collected at the specified visits (see Table 1) and data used to complete the eCRF.

#### 7.1.4.3 Patient Reported Outcomes (PROs)

Site staff who have undergone training will instruct subjects on the completion of questionnaires, measurements and assessments as described in Section 7.1.3. Education materials on minimising placebo response/ research alliance will be provided to all subjects and reviewed at the Screening visit.

### 7.1.5 Sequence of Assessments

Assessments should be conducted in a sequence which allows for best clinical practice and patient experience while also ensuring protocol compliance.

Patient and caregiver health-related quality of life (HRQoL) assessments should be completed prior to investigator efficacy assessments to minimise responder fatigue on most sensitive HRQoL scales and to limit investigator influence over patient and caregiver responses.

Sequence of scale assessments;

1. ALSFRS-R
2. ECAS
3. EuroQol Five-Dimensional, Five-Level Descriptive System (EQ-5D-5L)
4. SEIQOL-DW

5. Columbia Suicide Severity Rating Scale (C-SSRS)

### 7.1.6 Visit Scheduling

All visits should be scheduled within the visit window (+/- 7 days) relative to the date of the Baseline visit. Every effort should be made to ensure that the in-person visits at Week 52 and Week 76 are arranged as close as possible to the scheduled time-point.

### 7.1.7 Subject Assessment when Unable to Travel to the Trial Site

Following baseline, if a subject is still on IMP and is unable to attend the trial site for a scheduled in-person visit (e.g. due to ALS progression) or at Weeks 8, 16 and 24, a sub-set of clinical assessments as listed below in Table 6 will be conducted, in accordance with Table 1, Schedule of Trial Procedures.

The visit will be conducted both in attendance at the subject's home/residency and by telephone call. If the subject does not give consent for attendance to their home/residency, only the telephone call will be conducted and the appropriateness for the subject to continue trial participation will be assessed by the investigator, considering the ability to assess safety.

Clinical assessment in the subject's home/residency may be performed by site staff or contract nursing service, according to Table 1, Schedule of Trial Procedures.

**Table 6 Clinical Assessments when an In-Person Visit is Conducted at the Subject's Home / Residency**

| **Weeks: 8, 16, 24** | |
|---|---|
| **Telephone call** | **In-Person at Subject's home/residency** |
| Conducted by by investigator (or designee) and rater | Conducted by trial site staff or via contract nursing services |
| • Adverse Events & concomitant medication<br>• ALSFRS-R<br>• C-SSRS | • Adverse Events & concomitant medication *<br>• Clinical safety laboratory sampling |
| **All other weeks** | |
| **Telephone call** | **In-Person at Subject's home/residency** |
| Conducted by by investigator (or designee) and rater | Conducted by trial site staff or via contract nursing services |
| • Adverse Events & concomitant medication<br>• ALSFRS-R<br>• EQ-5D-5L<br>• C-SSRS | • Adverse Events & concomitant medication *<br>• SVC<br>• Vital signs<br>• Clinical safety laboratory sampling<br>• Pregnancy test (urine)<br>• Collection of subject diary and provision of new diary<br>• Confirmation of DtP IMP shipment (as applicable) |

*information about potential adverse events noticed during a home visit, must be provided to the PI within 24 hours.

Note: Biomarker, Biorepository and PK samples will not be collected when the visit is conducted in the subject's home/residency due to sample handling requirements.

## 7.2 Baseline Characteristics

### 7.2.1 Demographics

Demographic data will be recorded at Screening and consist of:

- Age
- Sex
- Race (according to local regulation)
- Ethnic origin (according to local regulation)

### 7.2.2 General Medical History

Relevant past and concurrent medical history, as judged by the investigator, must be recorded.

General medical history may include the history of any diagnostic testing such as electromyography and nerve conduction studies, imaging, muscle biopsy and antibodies.

The following data should be recorded in the eCRF:

- Diagnosis
- Date of onset
- Date of resolution or ongoing

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

### 7.2.3 ALS Characterisation

Information on ALS characteristics will be recorded at Screening and consist of:

- Date of symptom (weakness) onset
- Date of diagnosis
- Familial history of ALS
- Riluzole use
- Edaravone use
- Site of onset (limb, bulbar [includes respiratory], both limb and bulbar, other)
- ALS diagnosis (according to el Escorial diagnostic criteria)
- Information on pathogenic mutation (if available)

### 7.2.4 El Escorial Diagnostic Criteria for ALS

The investigator (or delegate that is a neurologist by training) must use the ALS diagnostic criteria set forth at the El Escorial World Federation of Neurology. As part of the trial eligibility criteria, the subject must meet the criteria for clinically possible, clinically probable / clinically probable ALS laboratory-supported, clinically definite ALS or clinically definite familial ALS laboratory-supported at Screening to be included in the trial (38).

For a subject to meet the diagnostic criteria for clinically definite familial ALS laboratory-supported, the following must apply;

- Family history of ALS
- Known pathogenic mutation

- Progressive UMN and/or LMN signs in at least a single region (in the absence of another cause for the abnormal neurological signs).

However, in genetically determined cases where the gene has not been identified (even if linkage is established), the criteria for the diagnosis of sporadic ALS apply.

### 7.2.5 Respiratory Rate

The respiratory rate (breaths per minute) will be recorded at the Screening visit and end-of-trial visit only. This will be determined by manual visualisation and count.

### 7.2.6 Body Height

The body height will be measured at Screening only, to be used for calculation of BMI in combination with body weight. Height should be measured without shoes in centimetres or inches and recorded in the eCRF to nearest ½ cm or 1/4 inch. For subjects where measurement of height is not possible (e.g. unable to stand), self-reported height will be accepted.

### 7.2.7 Use of Tobacco and Nicotine-Containing Products

At Screening, the subject's use of tobacco and nicotine-containing products should be recorded in the eCRF. The subject will be categorised as follows:

- Never smoked; a subject who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime.
- Former smoker; a subject who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview. Cessation date and calculation of pack-years will also be recorded in the eCRF.
- Current smoker; a subject who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes. Calculation of pack-years will be recorded in the eCRF.

A pack-year is calculated by multiplying the number of packs of cigarettes (quantity 20) smoked per day by the number of years the subject has smoked e.g. 1 pack-year is equal to smoking 20 cigarettes (1 pack) per day for 1 year or 40 cigarettes (2 packs) for half a year etc.).

## 7.3 Efficacy Assessments

### 7.3.1 Survival (PAV/Tracheostomy/Death)

Should the subject reach one of the survival endpoints (permanent assisted ventilation (PAV), tracheostomy or death) this event and the date will be recorded (on the end-of-trial form) in

the eCRF. The time from Day 1 to PAV/tracheostomy/death or trial completion (at Week 76), whichever comes first will be derived.

PAV will be defined as the first of 7 consecutive days on which PAV was used for >22 hours/day as a direct consequence of symptom progression related to ALS. This will not apply for intercurrent acute reversible illness requiring temporary assisted ventilation for 7 consecutive days or longer.

### 7.3.2 ALS Functional Rating Scale – Revised (ALSFRS-R)

The ALSFRS-R is a short (5 minute) ordinal rating scale used to determine subjects' subjective assessment of their capability and independence with 12 functional activities ('speech', 'salivation', 'swallowing', 'handwriting', 'cutting food and handling utensils', 'dressing and hygiene', 'turning in bed and adjusting bed clothes', 'walking', 'dyspnoea', 'orthopnoea' and 'respiratory insufficiency'). Each activity is rated on a 5-point scale (from 0 to 4), giving a maximal ALSFRS-R score of 48.

An ALSFRS-R assessment will be performed as scheduled in Table 1.

Only the assessment of ALSFRS-R at the Screening visit is used for determination of subject eligibility. The result of this assessments at the Baseline visit is used for analysis purposes and the value will not exclude the subject from trial participation.

The assessment may be made by a trained site staff member either in person or over the telephone. Rater certification is described in Section 7.1.3. The ALSFRS-R will be performed over the telephone for remote visits. If the scale is administered over the telephone and the patient is unable to respond because of significant bulbar impairment the caregiver should relay the questions and responses. If a subject is no longer able to travel to the site to attend the in-person visits, a certified rater will perform the assessment over the telephone as per a remote visit.

The assessment outcome will be recorded on a source document and transcribed into the eCRF.

### 7.3.3 Slow Vital Capacity (SVC)

SVC measures the volume that can be exhaled from a full inhalation after exhaling to a maximum as slowly as possible. Measurements of SVC will be performed via standardised Flowscreen CT ™ spirometer as scheduled in Table 1. SVC analysis will include SVC, predicted SVC and % of predicted SVC. Calibration of the spirometry equipment must be completed in accordance with user guides and spirometry manual.

The SVC should be measured in the seated erect position. Before onset of measurement, the subject should be instructed to breathe normally through the pneumotach. After obtaining a stable breathing pattern with a minimum of four tidal breaths, the subject should be instructed to inspire slowly and maximally then exhale slowly and maximally. The subject should be instructed to return to normal breathing upon which the measurement is complete.

An acceptable manoeuvre has the following characteristics:

- No hesitation or false start
- Stable breathing pattern before onset of measurement
- No cough
- No glottis closure or obstruction by tongue or dentures
- No early termination and no forced exhalation

The quality of data generated will be analysed against recognised spirometry standards (32). Data will be subject to centralised analysis by spirometry experts.

Only the assessment of SVC at the Screening visit is used for determination of subject eligibility. The result of this assessments at the Baseline visit is used for analysis purposes and the value will not exclude the subject from trial participation.

If a subject is no longer able to travel to the site to attend the in-person visits, a member of trial site staff or the contract nursing service may instead perform this assessment at an in-person visit at the subject's home/residency. Measurement of SVC will be performed via the SpiroSphere™ spirometer. The source data from the machine will be provided to the clinical site for transcription into the eCRF and will not be subject to centralized over-read analysis.

The reason for a missed spirometry measurement will be recorded in the eCRF to capture data on whether this is due to ALS progression. Missed spirometry measurements due to ALS progression do not constitute a protocol deviation.

### 7.3.4 Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

ECAS determines cognitive and behavioural changes of patients suffering from ALS. It is a global measure for the evaluation of cognitive impairments in ALS patients.

ECAS consists of 15 individual tasks, which rely on standard procedures and tests used in neuropsychology. These 15 individual tasks correlate with certain cognitive functions which are split up into 5 different subdomains of which; 3 are ALS-specific ('language', 'verbal fluency' and 'further executive functions') and 2 are non-specific functions ('memory' and 'visuospatial'). The ECAS-total score of 136 points is the sum of scores of all 15 individual tasks.

ECAS evaluations will be performed as scheduled in Table 1.

The assessment will be performed by a trained trial site staff member. Rater certification is described in Section 7.1.3.

The ECAS may be performed in oral or written form. An adapted version of the scale is not available for general use in clinical trials however the simple completion is expected to allow subjects with significant impairment due to ALS to be able to adequately respond to the rater.

It will be up to the investigator's discretion if the subject is unable to provide responses to the scale.

If a subject is no longer able to travel to the site to attend the in-person visits this assessment will not be conducted since it requires administration by a certified rater and is not validated for use over the telephone.

The primary caregiver will complete the behaviour screen and the psychosis screen (the latter is not to be completed in the vicinity of the subject). If the nominated primary caregiver changes during the trial, these assessments should continue to be collected.

The scale will be available in all major recognised languages of the countries participating in the trial.

The assessment will be recorded on a source document. The total score for each task and both screens will be transcribed into the eCRF.

## 7.4 Health-Related Quality of Life Assessment

The following HRQoL questionnaires will be used in this trial:

- EQ-5D-5L (subject, clinician-led)
- SEIQoL-DW (subject and primary caregiver)

The questionnaires should be completed according to the schedule of procedures (Table 1).

All results from the HRQoL questionnaires will be recorded on a source document and transcribed into the eCRF.

### 7.4.1 EuroQol, Five-Dimensional, Five-Level Descriptive System (EQ-5D-5L)

The EQ-5D5L will be used for exploratory assessments of the subject's health-related quality of life. The EQ-5D-5L consists of 2 sections; the EQ-5D descriptive system and the health scale, an adaption of the EQ Visual Analogue Scale (EQ VAS).

The descriptive system comprises 5 dimensions: 'mobility', 'self-care', 'usual activities', 'pain/discomfort' and 'anxiety/depression'. Each dimension has 5 levels: 'no problems', 'slight problems', 'moderate problems', 'severe problems' and 'extreme problems'. The subject is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the subject's health state.

The health scale records the subject's self-rated health reported as an integer between 0 and 100 where 0 represents 'the best health you can imagine' and 100 represents 'the worst health you can imagine'. This health score can be used as a single quantitative measure of health status that reflects the subject's own judgement based on a same day recall period.

The EQ-5D-5L scale adapted for interview (over the telephone) will be used from the outset despite the ability of subjects to self-report HRQoL on this scale from inclusion. The adapted version will ensure consistent utilisation of the scale, preventing the need to transfer from self-reported to clinician-led modes for subjects who develop significant impairment due to ALS.

The assessment will be performed by a trained trial site staff member. Rater certification is described in Section 7.1.3. If a subject is no longer able to travel to the site to attend the in-person visits, a certified rater will perform the assessment over the telephone as per a remote visit.

The scale will be available in all major recognised languages of the countries participating in the trial.

### 7.4.2 Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW)

The SEIQoL-DW is a semi-structured interview for assessment of quality of life (QoL) of the individual. The interviewer first elicits the 5 areas of life considered most important by the individual in determining his/her QoL. The level of satisfaction/functioning in each area is recorded followed by the SEIQoL-DW task which allows the interviewer to determine the relative importance of each QoL area.

This HRQoL interview will be administered to both the subject and their nominated primary caregiver.

If the primary caregiver has any significant medical condition (e.g. cancer or significant co-morbidities) which, in the opinion of the investigator, would prevent them from being able to distinguish the impact of caring for a patient with ALS on their personal QoL, this questionnaire may be omitted from the visit schedule. Missed assessments for this reason will not be considered protocol deviations.

If the nominated primary caregiver changes during the trial, this assessment should not be completed.

If a subject is no longer able to travel to the site to attend the in-person visits, this assessment will not be conducted since it requires administration by a certified rater and is not feasible for use over the telephone due to the tactile elements required during administration.

The scale will be available in all major recognised languages of the countries participating in the trial.

## 7.5 Safety Assessments

### 7.5.1 Physical Examination

A physical examination including general appearance, head/neck, eyes, ears, nose/throat, cardiovascular, lungs, abdomen, musculoskeletal, CNS (non-ALS) extremities and skin will be carried out as scheduled in Table 1 and only for subjects who are able to attend the trial site.

The outcome of each area evaluated will be recorded as either normal, abnormal or not done. If a result is abnormal at Screening and considered by the investigator to be clinically significant, it should be recorded as medical history or AE, as applicable. It will be up to the investigator's discretion if the subject should be enrolled into the trial; if such a subject is enrolled, the investigator will provide a justification in the medical record.

Any new clinically significant findings or deterioration of previous findings observed during the trial are to be recorded as AEs (see Section 7.5.7).

If a subject is no longer able to travel to the site to attend the in-person visits, this assessment will not be done at patient's home/residency.

### 7.5.2 Neurological Examination

A neurological examination including general, cranial nerves, reflexes, motor system, coordination/cerebellar function and sensation (see Appendix 10.2.13 for full criteria) will be carried out as scheduled in Table 1 and only for subjects who are able to attend the trial site.

The outcome of each area tested will be recorded as either normal/none, abnormal or not done. If an abnormality is secondary to ALS this should be indicated. If a result is abnormal at Screening and considered by the investigator to be clinically significant it should be recorded as medical history or AE, as applicable. It will be up to the investigator's discretion if the subject should be enrolled into the trial; if such a subject is enrolled, the investigator will provide a justification in the medical record.

Any new clinically significant findings or deterioration of previous findings observed during the trial are to be recorded as AEs (see Section 7.5.7). Worsening of symptoms (e.g. progression of weakness) of ALS will not be recorded as an AE.

If a subject is no longer able to travel to the site to attend the in-person visits, this assessment will not be performed in the subject's home/residency.

### 7.5.3 Vital Signs

Vital signs (resting blood pressure, pulse, and body temperature) must be assessed as scheduled in Table 1. Vital signs will be measured in supine position (seated, if supine is not possible), with the legs uncrossed, the back and arms supported following at least 5 minutes rest.

If an abnormal vital sign at Screening is considered by the investigator to be clinically significant, it should be recorded as medical history or AE, as applicable. It will be up to the investigator's discretion if the subject should be randomised into the trial (respecting exclusion criterion 6). Any clinically significant changes observed during the trial are to be recorded as AEs (see Section 7.5.7).

If a subject is no longer able to travel to the site to attend the in-person visits, a member of trial site staff or the contract nursing service may instead perform this assessment at an in-person visit at the subject's home/residency.

### 7.5.4 Body Weight

The body weight will be measured as scheduled in Table 1, and only when possible. Body weight should be measured and recorded in the eCRF in kilogram or pound [kg or lb], with one decimal (without shoes and only wearing light clothing).

If a subject is no longer able to travel to the site to attend the in-person visit at week 52 or week 76, this assessment will not be performed.

### 7.5.5 Electrocardiogram – 12 lead

12-lead ECGs will be performed as scheduled in Table 1 according to local procedure.

At a minimum, date of ECG collection and assessment of clinical significance will be recorded in the source documents.

The investigator must ensure evaluation of all ECGs by medically trained site staff with the interpretation recorded on the trace accompanied by signature and date. Where a cardiologist is delegated the responsibility of ECG interpretation a pre-evaluation of the ECGs must be performed by the investigators to assess immediate subject safety. The investigator has the final decision on the clinical significance of ECG abnormalities ('clinically significant' or 'not clinically significant'). If a result is abnormal at Screening and considered by the investigator to be clinically significant, it should be recorded as medical history or AE, as applicable. It will be up to the investigator's discretion if the subject should be enrolled into the trial; if such a subject is enrolled, the investigator will provide a justification in the medical record. Refer to Appendix 10.2.6.3 for principles for data entry in the eCRF.

Any clinically significant new findings or deterioration of previous findings observed during the trial are to be recorded as AEs (see Section 7.5.7).

If a subject is no longer able to travel to the site to attend the in-person visits, this assessment will not be conducted in the subject's home/residency. The Investigator should review AEs and vital signs with particular attention to signs related to conduction disorders to allow for appropriate follow-up, and to ensure that the subject is safe to continue trial participation.

### 7.5.6 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation through a series of simple, plain-language questions (33). The questionnaire will be administered as an interview by the investigator or a qualified delegate according to the schedule of procedures (Table 1). All results from the questionnaire must be transcribed into the eCRF.

Two versions of the scale will be used: a 'Screening/Baseline' version (lifetime assessment and recent history, used at Screening) and a 'since last visit' version (used on all subsequent occasions).

The scale will be available in all major recognised languages of the countries participating in the trial.

If a subject is no longer able to travel to the site to attend the in-person visits, a certified rater will perform the assessment (may be over the telephone).

### *7.5.7* Adverse Events

#### 7.5.7.1 Definitions of Adverse Events and Serious Adverse Events

**Adverse Event Definition**
*An AE is defined as any untoward medical occurrence in a subject or clinical investigation 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 a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.* (ICH Harmonized Tripartite Guideline for Good Clinical Practice, E6 (R1)).

This definition includes (but is not limited to):

accidental injuries, clinically significant changes in safety laboratory tests, events related to trial procedures, reasons for any unfavourable and unplanned change in medication (drug and/or dose), clinically significant worsening of pre-existing conditions other than the disease under study, or reasons for admission to hospital or surgical procedures unless these were planned before enrolment. It also includes AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.

**Serious Adverse Event Definition**

An SAE is any AE that;

- results in death.
- is life-threatening.
- requires inpatient hospitalisation or prolongation of existing hospitalisation. (Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE but should be documented in the subject's medical record).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.

or

- is a medically important condition.

A medically important condition is an event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias and convulsions that do not result in hospitalisation, development of drug dependency or drug abuse.

If there is any doubt as to whether an adverse event meets the definition of an SAE, a conservative viewpoint must be taken, and the adverse event must be reported as an SAE.

### 7.5.7.2 Collection of adverse events

Adverse Events should be obtained through observation of the patient, from any information volunteered by the patient and through asking non-leading questions such as "How have you been doing since your last visit?"

Adverse events (including pre-treatment adverse events) must be recorded in the eCRF. The investigator must provide information on the adverse event, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates and start and stop time; severity; causal relationship to the IMP; action taken; and outcome. If the adverse event is not related to the IMP, an alternative aetiology must be recorded, if available.

If the adverse event is serious, this must be indicated on the Adverse Event Form. Furthermore, the investigator must fill out a Serious Adverse Event Form and report the SAE to the Safety vendor immediately (within 24 hours) after becoming aware of it (see section 7.5.7.6.). If individual adverse events are later linked to a specific diagnosis, the diagnosis should be reported instead of the symptoms.

**Severity**

The *severity* of the AE will be graded according to the following categorisation:

| | |
|---|---|
| Mild | An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. |
| Moderate | An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. |
| Severe | An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. |

**Causality**

The *causal relation* of the AE to the use of the IMP should be described in terms of probable, possible or not related according to the following:

| | |
|---|---|
| Probably related | AEs that are temporally linked and for which the study product is more likely to be the explanation than other causes, which may improve when not using study product or recurs on re-challenge |
| Possibly related | AEs that could equally well be explained by study product or other causes, which are usually temporally linked and may improve when not using study product but do not reappear when using study product |
| Not related | AEs that can be clearly explained by other causes or for which there is no plausible association with study product, or AEs for which there is no temporal relationship |

An AE is considered related to IMP if it is at least possibly related.

**Outcome**

The *outcome* of the event should be classified and handled as follows:

| | |
|---|---|
| Recovered/ resolved | The event has stopped. The stop date of the event must be recorded. |
| Recovering/ resolving | The subject is clearly recovering from an event. The event is not yet completely resolved. |
| Not recovered/ not resolved | Event is still ongoing. |
| Recovered/resolved with sequelae | The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke.<br><br>The stop date of the event must be recorded. In case of a SAE, the sequelae should be specified. |
| Fatal | The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE. |
| Unknown | Unknown to investigator, e.g. subject lost to follow-up. |

#### 7.5.7.3 Disease Progression

Disease progression can be considered as a worsening of a patient's condition that is being studied. It may be reflected by an increase in the severity of the condition or an increase in the symptoms. Disease progression and any events that are unequivocally due to disease progression should not be reported as an AE or SAE.

Any AE or SAE which is secondary to ALS must always be reported (e.g. secondary lung infection in respiratory compromised subjects).

#### 7.5.7.4 Death

All deaths that occur during the AE reporting period must be reported as follows:

- Death clearly due to disease progression should be documented in the eCRF but should not be reported as an SAE.
- Death that is not clearly due to disease progression should be documented in the eCRF and the reason for death should be reported as an SAE within 24 hours.

Refer to Appendix 10.2.6.3 for principles for data entry in the eCRF.

#### 7.5.7.5 Follow-Up for Final Outcome of Adverse Events

The investigator should follow up for final outcome on all AEs until resolution or the Safety Follow Up visit whichever comes first. SAEs must be followed up until a final outcome has been established, i.e. the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilised and cannot be expected to recover during the trial, for example chronic illnesses, the final outcome should be considered 'recovered with sequalae' or 'not recovered' and a statement that the SAE has stabilised should be added to the narrative in the SAE form.

#### 7.5.7.6 Reporting of Serious Adverse Events

Any SAE must be reported to the Safety vendor on the (paper) SAE Form immediately (within 24 hours) of first knowledge.

This report should contain as much information as possible and include an assessment of available information on seriousness, severity, causal relationship to the IMP or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

Photocopies of the subject's medical records should not be sent in lieu of completion of the SAE Form. Medical records, laboratory reports etc. should only be sent to the Safety vendor upon request. Importantly, when subject records are shared outside the site, all subject identifiers, with the exception of the subject number, shall be redacted on the copies of the medical records before submission.

The completed SAE form must be faxed or scanned and e-mailed to the Safety vendor. Please refer to the SAE Reporting Contact Details document.

Follow-up information received by the investigator concerning an SAE should be reported to the Safety vendor using the same time line (24 hours) as for the initial report.

The Safety vendor may request further information in order to fully assess the SAE. The investigator must forward such information to the Safety vendor upon request by fax or e-mail (see contact details above).

SAEs occurring after the completion of the clinical trial (i.e., after the Safety Follow Up visit) should not be routinely sought or collected. However, such events should be reported to the Safety vendor if the investigator becomes aware of them and considers them at least possibly related to IMP.

**Reporting to Competent Authorities and IRBs/IEC**

The *investigator* is responsible for reporting SAEs to the institutional review board(s) (IRB[s])/ independent ethics committee(s) (IEC[s]) as required by current applicable legislation for the concerned country.

Orphazyme is responsible for assessing whether or not an SAE is expected. The reference safety information for this clinical trial is the current version of the Investigator's Brochure.

Oprhazyme is responsible for reporting all SAEs which are assessed as causally related to the IMP(s) by either the investigator or Orphazyme, and which are unexpected (suspected, unexpected serious adverse reactions [SUSARs]), in an expedited manner to regulatory authorities according to the current applicable legislation in the concerned countries. Investigators will be notified of such SUSARs and the evolving safety profile on an ongoing basis.

Orphazyme is also responsible for reporting to the IRB(s)/IEC(s) that require unblinded reporting.

### 7.5.7.7 Pregnancies

Any pregnancy occurring during the clinical trial must be reported to the Safety vendor immediately (within 24 hours) of first knowledge using the (paper) Pregnancy Form. All pregnancies must be followed up until delivery or termination and final outcome must be reported on the (paper) Pregnancy Follow Up Form within 24 hours of first knowledge.

The completed Pregnancy (Follow Up) Forms must be faxed or scanned and e-mailed to the Safety vendor. Please refer to the SAE Reporting Contact Details document.

#### 7.5.7.8 Overdose

Overdose is a dose taken by a subject that exceeds the dose prescribed to that subject. All cases of overdose will be recorded in the subject diary (and transcribed into the compliance section of the eCRF) as an excursion from the prescribed dose.

Any associated symptoms of an overdose must, as a minimum, be recorded as an AE.

#### 7.5.7.9 Handling of an Urgent Safety Measure

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined within the EU Directive as *"...the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard*." (34).

If the investigator becomes aware of information that necessitates an immediate change in the clinical trial procedure or a temporary halt to the clinical trial in order to protect clinical trial subjects from any immediate hazard to their health and safety, the investigator must immediately inform Orphazyme of this change to; Orphazyme Clinical Safety at [redacted]

Orphazyme must act immediately upon receipt of the notification in accordance with the internal procedures.

### 7.5.8 Pregnancy Test

A serum pregnancy test must be taken at Screening in female subjects of child-bearing potential as scheduled in Table 1.

A urine pregnancy test (human chorionic gonadotropin (hCG)) must be performed at the trial site at Day 1 prior to randomisation in female subjects of child-bearing potential. The test must be repeated during the trial as scheduled in Table 1. In addition, urine pregnancy tests must be performed at home for females of childbearing potential if a menstrual period is missed or if pregnancy is suspected. hCG urine pregnancy tests will be provided to the subjects.

Note that pregnant subjects must discontinue IMP immediately (Section 6.5.1) and the pregnancy report must be expedited in accordance with Section 7.5.7.7.

If a subject is no longer able to travel to the site to attend the in-person visits, a member of trial site staff or the contract nursing service may instead perform this assessment at an in-person visit at the subject's home/residency.

### 7.5.9 Clinical Safety Laboratory Assessments

#### 7.5.9.1 Central Laboratory

The clinical safety laboratory parameters (chemistry, haematology, virology and serum pregnancy) analysed by a central laboratory are presented in Table 7. Urine samples will be tested at the trial site with a dipstick and the result recorded in the eCRF.

The subject's fasting status will be recorded in the eCRF to aid the interpretation of the results.

A laboratory manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information specific to this trial.

Samples for laboratory testing will be collected according to the schedule of procedures (Table 1). Clinical safety laboratory tests may be repeated once at Screening. Reasons to repeat laboratory tests may include that the medication causing laboratory abnormality was suspended, any other suspected cause may no longer exist or to rule out laboratory error.

If an abnormal clinical safety laboratory finding at Screening is considered by the investigator to be clinically significant, it should be recorded as medical history or AE, as applicable. It will be up to the investigator's discretion if the subject should be randomised into the trial (respecting exclusion criterion 6). Any clinically significant new findings or deterioration of previous findings observed during the trial are to be recorded as AEs (see Section 7.5.7.2)

If an abnormal clinical safety laboratory value is found when using the urine dipstick, further urine sampling and analysis may be performed locally according to normal local practice and at the investigator's discretion.

Clinical safety laboratory findings will be classified as potentially clinically significant abnormalities based on pre-defined thresholds for laboratory alert reporting. These potentially clinically significant abnormalities will be used for analysis purposes.

If a subject is no longer able to travel to the site to attend the in-person visits, a member of trial site staff or the contract nursing service may instead perform this assessment at an in-person visit at the subject's home/residency.

**Table 7 Clinical Safety Laboratory Parameters**

| Biochemistry | Haematology |
|---|---|
| • Creatinine<br>• Alanine aminotransferase (ALAT)<br>• Aspartate aminotransferase (ASAT)<br>• Alkaline phosphatase (ALP)<br>• Sodium<br>• Potassium<br>• Albumin<br>• Bilirubin (direct, indirect and total)<br>• Total protein<br>• Blood urea nitrogen (BUN)<br>• Creatine kinase (CK)<br>• Calcium (total, albumin corrected (calcium, ionised)<br>• Cystatin C<br>• Lactate dehydrogenase (LDH)<br>• Gamma- Glutamyltransferase (GGT)<br>• Glucose<br>• Low density lipoprotein (LDL)<br>• High density lipoprotein (HDL)<br>• Triglycerides<br>• Cholesterol | • Haemoglobin<br>• Haematocrit<br>• Thrombocytes<br>• Erythrocytes<br>• Leucocytes<br>• Differential count (% )(eosinophils, neutrophils, basophils, monocytes and lymphocytes) |
| | **Serum pregnancy test [a b]** |
| | • Choriogonadotropin beta |
| | **Virology [b]** |
| | • HIV<br>• HBV<br>• HCV |
| | **Urinalysis** (dipstick) |
| | • Blood<br>• Protein<br>• Glucose |
| | **Urine Pregnancy Test [a]** |
| | • hCG |

a. Females of child-bearing potential only
b. Screening visit only

#### 7.5.9.2 Local Laboratory

In addition to the above clinical safety laboratory parameters which are analysed and reported by a central laboratory, local laboratory services are required for the analysis and reporting of coagulation parameters and thrombocytes prior to performing lumbar puncture. Local safety laboratory assessments may also occur in case of close monitoring for increased transaminases (see Section 7.5.10.2).

### 7.5.10 Follow-up for Specific Laboratory Abnormalities

#### 7.5.10.1 Increased Serum Creatinine

Serum creatinine values > 2-3-fold compared to the subject's baseline value should be further investigated for signs of kidney injury. Estimation of the subject's GFR based on BUN, creatinine, and cystatin C should be performed. Follow-up may include measurement of oliguria, urine analysis, glomerular filtration rate, vital signs, ultrasound of the kidney, blood sampling for parathyroid hormone, metabolic status, and investigation of other markers of kidney dysfunction and alternative causes of increased creatinine.

In addition, follow-up should be done according to local hospital guideline (if applicable) or may include the consultation of a local nephrologist if required in the opinion of the investigator.

#### 7.5.10.2 Increased Transaminases

Transaminases (ASAT, ALAT) > 3 x ULN must be further investigated in line with the FDA Guidance on Drug-Induced Liver Injury (39).

Upon first observation of transaminases (ASAT, ALAT) > 3 x ULN, a repeat test must be performed within 48-72 hours (ALAT, ASAT, ALP, bilirubin) and the subject should be enquired for presence of symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash).

If the increase is confirmed, close observation must be performed:

- Repeating of ALAT, ASAT, ALP, GGT, bilirubin, eosinophils (differential count) 2-3 times weekly. Frequency of retesting may be decreased to once a week or less (after agreement with the medical monitor) if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining/confirming detailed history of symptoms and prior or concurrent diseases.
- Obtaining/confirming concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease (e.g.

performing an abdominal ultrasound or Magnetic resonance cholangiopancreatography (MRCP)).
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

If close observation is not possible, IMP must be interrupted or discontinued (see section 6.5 Dose modification and IMP discontinuation).

If the subject cannot attend the trial site for close monitoring, the analyses may be conducted at a local laboratory.

At the earliest possible opportunity, a single serum sample should be taken for use in case further analyses to explore possible mechanisms behind the transaminase elevations are conducted.

The sample may be processed and shipped under ambient or frozen conditions and will be stored frozen at the central laboratory. This sample will be discarded as soon as it is decided that such analyses are not warranted or after sample processing and analysis is completed which will be no longer than 2 years after the completion of the trial.

All local laboratory assessments and other assessment performed in relation to increased transaminases must be recorded in the eCRF including the appropriate reference ranges.

For scenarios where a permanent halt in the IMP is required, please see Section 6.5.

## 7.6 Biological Sample Assessments

### 7.6.1 Genomic Assessments

At Screening, blood samples will be drawn to test for the presence of genetic mutations identified and described in subjects with ALS.

The analysis of these samples will be reported in a specific genomic assessment report, separate to the clinical trial report.

The subjects and/or caregivers will not be informed of the results of this genomic assessment unless mandated by local regulation or law.

The genomic assessment will only be performed where all required permissions are granted and in accordance with local regulation or law.

### 7.6.2 Pharmacokinetics Assessments

The plasma and CSF samples will be analysed for arimoclomol using a bioanalytical method validated in accordance with the US FDA Guidance for Industry (35) and EMA Guideline on bioanalytical method validation (36). If other ongoing research studies identify significant metabolites, these may be analysed in samples collected from this trial using a scientifically validated bioanalytical method or by a method validated in accordance with the US FDA Guidance for Industry (35).

The bioanalysis will be performed by Covance (see Appendix 10.3.6.3) according to a protocol approved by Orphazyme before the samples are analysed.

Selected plasma samples will be subject to incurred sample re-analysis (ISR) as part of the in-study validation of the bioanalytical method.

The plasma concentration values will be reported in the clinical trial report and the results will be used for population PK analyses. In addition to the population PK analysis an exposure response analysis, evaluating correlation between exposure of arimoclomol and e.g. change in biomarker levels, will be performed. A separate modelling analysis plan will be issued before DBL and results will be reported separately.

If a subject is no longer able to travel to the site to attend the in-person visits, samples required for PK assessment will not be drawn in the subject's home/residency.

#### 7.6.2.1 Blood Samples

Blood samples will be taken for bioanalysis of concentrations of arimoclomol in plasma at Week 20 and Week 52 (see Table 1).

At Week 20 a blood sample will be drawn pre-dose and at 0.5 hours post-dose. At Week 52 blood samples will be drawn pre-dose and at 1.5 hours post-dose.

The exact time for drawing the samples must be recorded in the eCRF.

The first dose of IMP will be administered while at the site to allow for PK assessment on the day of the Week 20 and Week 52 site visit.

The subject must not administer IMP within 8 hours of the site visit to allow for a trough PK sample to be taken. The time of the last dose administered prior to the visit should be recorded in the subject diary and transcribed to the eCRF.

Blood sampling and handling procedures will be described in a separate laboratory manual.

#### 7.6.2.2 Cerebrospinal Fluid (CSF) Samples

Lumbar puncture will be taken for bioanalysis of concentrations of arimoclomol in CSF according to the schedule of procedures in Table 1. Lumbar puncture will only be performed in subjects who are able to attend the trial site.

The CSF sample should be drawn at 3 hours post-dose at Week 20 and Week 52 (see Table 1).

The exact time for drawing the samples must be recorded in the eCRF.

CSF sampling and handling procedures are described in a separate laboratory manual.

Lumbar puncture will be performed by the investigator (or delegate that is a physician by training) in accordance with local clinical practice including procedural guidelines and/or regulation. CSF sample handling procedures are described in a separate laboratory manual.

Coagulation parameters and thrombocytes should be reviewed via local laboratory services prior to performing lumbar puncture. The results of the local analysis will not be recorded in the eCRF. Subjects should not undergo lumbar puncture if local laboratory results indicate an abnormality, the subject is receiving concomitant therapy with anti-coagulants or if in the opinion of the investigator the procedure is not appropriate (including for reasons related to ALS progression or practical reasons).

Examinations will only be conducted in those subjects able to attend the trial site. If a lumbar puncture is missed it will not be considered a protocol deviation.

### 7.6.3 Biomarker Assessments

Blood samples, urinalysis and CSF samples will be taken for exploratory bioanalysis of biomarkers in blood, urine and CSF according to the schedule of procedures in Table 1.

For details regarding lumbar puncture see Section 7.6.2.2.

The biomarkers (see Table 8) will be analysed at the bioanalysis laboratory (see Appendix 10.3.6.3) using a validated method.

Guidance for biomarker sample handling are provided in the laboratory manual.

If a subject is no longer able to travel to the site to attend the in-person visits, samples required for biomarker assessment will not be drawn in the subject's home/residency.

**Table 8 Biomarker Sampling**

| | CSF | Blood | Urinalysis |
|---|---|---|---|
| HSP70 | X | X | |
| Chitotriosidase | X | | |
| NfL | X | X | |
| p75ECD* | | | X |

*Urine creatinine will be used to normalize the value for p75ECD.

**Abbreviations**: CSF: cerebrospinal fluid; HSP70: heat shock protein 70; NfL: neurofilament light chain; p75ECD: p75 neurotrophin receptor extracellular domain

The biomarker analysis will only be performed where all required permissions are granted and in accordance with local regulation or law.

### 7.6.4 Biorepository

If consent is given by the subject, Orphazyme will submit samples of biological fluids to a biorepository for long-term storage to allow for future genetic testing of novel genes associated with ALS and disease-specific biomarker testing. The location of the biorepository is detailed in Appendix 10.3.6.3.

The samples will be used for future research approved by Orphazyme. Donation of the samples for future research is voluntary and subjects must give their written consent to expressly confirm donation and storage and the terms associated herewith. The samples will be transferred from the central laboratory to the biorepository at the end of the trial. The samples will be labelled with the trial ID, subject ID, and the sample date to protect the privacy of the subjects and to allow continued blinding for future analyses. The samples from this trial will be stored for up to 15 years after the end of the trial and will then be destroyed.

Samples will only be submitted to the biorepository where all required permissions are granted and in accordance with local regulation or law.

If a subject is no longer able to travel to the site to attend the in-person visits, sample collection with the specific purpose of submission to the biorepository will not be drawn in the subject's home/residency (i.e. residual volume from clinical safety laboratory assessment may continue to be submitted to the biorepository).

### 7.6.5 Estimate of Total Blood Volume and CSF Volume Collected

Blood samples will be drawn for analysis of safety (chemistry, haematology, pregnancy test), genome, PK and biomarkers. The total volume of blood drawn for a subject competing all trial visits and procedures will not exceed 250 mL which is less than the volume of blood drawn during a blood donation (approximately 500 mL). The maximum blood volume on a

single occasion will not exceed 30 mL. The expected CSF sampling volume will not exceed 5 mL on a single occasion.

### 7.6.6 Destruction of Biological Material

All biological material, except material collected for the biorepository, will be retained until the results have been reported. The material will subsequently be destroyed by the responsible laboratory. For destruction of samples collected for the biorepository, see Section 7.6.4.

## 7.7 Home Visit / Contract Nursing Service

Following the baseline visit, if a subject is no longer able to attend the site, appropriate trial site staff (e.g. nurse, sub-investigator or contract nursing service as required) may assess the subject by conducting a home visit, as permitted by local laws and regulations.

# 8 STATISTICAL METHODS

Prior to unblinding, a separate statistical analysis plan (SAP) will be finalised, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final clinical trial report (CTR).

Planned analyses will be described and justified in the SAP and the CTR.

## 8.1 Sample Size

Two hundred and thirty-one (231) subjects are planned for randomisation This number includes 213 subjects according to the main trial eligibility criteria and up to an additional 18 subjects on stable (i.e. minimum 6 months') treatment with edaravone and who otherwise fulfil the eligibility criteria. The sample size calculation has been made for the 213 subjects in the main trial population (not including the additional subjects in the edaravone sub-population).

The primary endpoint is the CAFS over a 76 weeks' treatment period comparing 1200 mg/day arimoclomol 400 mg t.i.d. vs. placebo. The trial will be powered for the primary endpoint.

In the Phase 2 trial in ALS patients with pathogenic SOD1 mutation associated with rapid progression (please see Section 2.3.2), the effect size in CAFS between arimoclomol and placebo ranged between 0.41 (entire subject population) to 0.5 (subjects with baseline ALSFRS-R ≥35). An examination of the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database reveals that the effect of active drugs versus placebo increases from 12 to 18 months on both survival and change in ALSFRS-R. While the precise magnitude of the increase in the comparative efficacy from 12 to 18 months is difficult to assess, the rate of increase appears to be greater than a linear increase. Applying this observation to the effect of arimoclomol compared to placebo, it is expected that the effect size (which is estimated to be at least 0.41 at 12 months) will be no less than 0.48 assuming a minor increase from 12 to 18 months, and as high as 0.61 with a linear increase from 12 to 18 months. Assuming an effect size of 0.48, 213 subjects randomised 2:1 to arimoclomol and placebo will provide 90% power to detect a statistically significant difference between arimoclomol and placebo, at a two-sided type-1 error of 0.05.

Table 9 provides scenarios for power and sample sizes. The power shown are:

**Table 9 Sample Size Calculation**

| Effect size at 76 weeks | Power at final analysis |
|---|---|
| 0.44 | 85% |
| Assumed 0.48 | 90% |
| 0.54 | 95% |
| 0.61 | 98% |

The assumed effect size of 0.48 will provide a 90% power with a final analysis done with a two-sided type-1 error of 0.0446.

## 8.2 Trial Analysis Sets

The 'intent-to-treat' (ITT) analysis population will include all randomised subjects, excluding subjects on edaravone, who received at least one dose of IMP. The ITT population will be the primary population for all efficacy analyses. Patients whose dose is de-escalated will be included in the ITT population. The primary population for safety will be the ITT population. Since subjects that discontinue treatment should attend all trial visits, a cut-off date of 2 weeks after the date of the last treatment will be applied to the safety analysis. If more than 20% of the patients have their dose de-escalated, safety analyses may be conducted for these subjects in addition to the analysis of the ITT subjects.

The per-protocol (PP) population will include all subjects in the ITT population who do not exhibit any major protocol violations that could affect efficacy. The definition of major violations that could affect efficacy will be included in the SAP. Subjects excluded from the PP Population will be determined before unblinding the database. The PP population will be used for supportive analyses of the primary and secondary efficacy endpoints.

Patients receiving concomitant edaravone will be summarised separately for safety and efficacy.

## 8.3 Statistical Analysis

### 8.3.1 Disposition of Subjects

Trial completion status and reasons for discontinuation will be summarised by treatment group with frequencies and percentages.

### 8.3.2 Demographics and Other Baseline Characteristics

Continuous demographic and baseline parameters will be summarised by treatment group, by the number of non-missing observations, mean, standard error, median, minimum, and maximum. Categorical parameters will be summarised by frequencies and percentages.

### 8.3.3 Exposure and Treatment Compliance

#### 8.3.3.1 Exposure

Treatment exposure will be summarised by treatment group, by mean number of days exposed, mean daily dose and standard errors.

#### 8.3.3.2 Treatment Compliance

Compliance data will be summarised for each subject by treatment group overall and by trial visit.

### 8.3.4 Analysis of Efficacy

#### 8.3.4.1 Primary Efficacy Analysis

The primary efficacy endpoint is the Combined Assessment of Function and Survival (CAFS) (22). The CAFS will be calculated over a treatment period of 76 weeks for 1200 mg/day arimoclomol 400 mg t.i.d. compared to placebo. The CAFS compares each trial subject's outcome to others in the trial in a series of pairwise comparisons, based on function and survival (22). For each pairwise comparison, a trial patient is assigned a score and then the summed scores are ranked for all participants. The score is assigned based on the change in ALSFR-S from baseline and the survival endpoint (PAV, tracheostomy or death) where a shorter survival corresponds to a lower rank. In the pairwise comparisons a score of 1 is assigned when the subject has a better function or reached the survival endpoint later than the comparison. A score of 0 is assigned when the subject and the comparison have the same function or reached the survival endpoint at the same time, A score of –1 is assigned when the subject has a worse function or reached the survival endpoint earlier than the comparison. The mean rank score for each treatment group is calculated. A higher mean CAFS score indicates a better group outcome. The CAFS will be analysed using nonparametric rank analysis of covariance (37), adjusting for baseline ALSFRS-R, SVC and riluzole use (Yes/No).

#### 8.3.4.2 Secondary Efficacy Analysis

The endpoint 'PAV/tracheostomy-free survival over treatment period of 76 weeks for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo' will be analysed using a log-rank test stratified by riluzole use. Subjects who drop-out prior to Week 76 will be censored.

The endpoint 'ALSFRS-R change from Baseline to Week 76 for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo' will be analysed using an analysis of covariance (ANCOVA). The model will include treatment, baseline ALSFRS-R, baseline SVC, and riluzole use.

The endpoint 'SVC change from Baseline to Week 76 for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo' will be analysed using an ANCOVA. The model will include treatment, baseline ALSFRS-R, baseline SVC, and riluzole use.

Secondary endpoints will be tested sequentially at a two-sided 0.025 level of significance. Testing for treatment difference will stop if no treatment difference in favour of arimoclomol is found. See section 8.3.6 for details.

### 8.3.5 Analysis of Safety

#### 8.3.5.1 Adverse Events

AEs will be coded by system organ class (SOC) and preferred term from the current version of Medical Dictionary for Medical Activities (MedDRA). TEAEs will be summarised overall, by seriousness, severity, and relationship to treatment. AEs causing premature treatment discontinuation, and incidence of SAEs will be summarised.

All AEs, severe AEs, SAEs, AEs causing premature treatment discontinuation, will be listed by subject.

#### 8.3.5.2 Other Safety Parameters

The C- SSRS will be summarised at each visit and overall by treatment using descriptive statistics.

Vital signs and clinical safety laboratory values will be summarised by visit and changes from Baseline using descriptive statistics.

The incidence of potentially clinically significant abnormal values for vital signs and safety laboratory values will be summarised.

### 8.3.6 Exploratory Analysis

#### 8.3.6.1 Efficacy

Change from Baseline to Week 76 for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo in cognitive and behavioural changes as evaluated by ECAS, sub-group analyses by demographic, baseline, and regional differences may be conducted.

Change in ALSFRS-R and SVC will be evaluated for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo on a longitudinal basis.

#### 8.3.6.2 Health-related Quality of Life

The EQ-5D-5L, SEIQOL for subject and SEIQOL for caregiver will be summarised at each visit by treatment using descriptive statistics.

#### 8.3.6.3 Pharmacokinetics

CSF and plasma concentrations of arimoclomol will be listed. The pharmacokinetic results will be used for population PK analyses and reported separately.

#### 8.3.6.4 Biomarkers

Absolute values and changes from Baseline in biomarkers will be summarised by treatment at Weeks 20, 52, and 76, using means and standard errors, minimum and maximum for continuous variables or by frequency and percentages. Correlations by biomarkers and efficacy measures will be explored.

### 8.3.7 General Principles

Unless otherwise stated, all significance tests will be two-sided using the 5% significance level. All confidence intervals (CIs) will be presented with 95% degree of confidence.

An observed-cases approach will be used for tabulations of data by visit (i.e. involving only those subjects who attended each specific visit).

Categorical data will be summarised using the number and percentage of subjects in each category and treatment group. Continuous data will be summarised using the mean, median, standard deviation (SD), minimum and maximum values.

All the analyses specified in the protocol will be reviewed in relation to the blinded data actually obtained and the statistical analysis plan will be finalised before breaking the randomisation code.

Any changes from the statistical analysis planned in this clinical trial protocol will be described and justified in a protocol amendment, the statistical analysis plan and/or in the CTR dependent on the type of deviation and when it occurs.

### 8.3.8 Handling of Missing Values

The primary efficacy endpoint, the CAFS, will handle missing data in a manner that allows the comparison of each subject to another subject at time when each of the two subjects compared have an ALSFRS-R evaluable result. Thus, for the CAFS analysis, no missing data imputation is needed. The first secondary endpoint, PAV/tracheostomy-free survival, will be analysed using survival analysis methods (log-rank test) in which subjects who drop-out from the trial will be censored at their last visit. No data imputation will be used for the analysis of this endpoint. For change from Baseline in ALSFRS-R and SVC, the multiple imputation method will be used as the primary method of handling missing data. Other methods for handling missing data such as observed case, last observation carried forward (LOCF) and others will be used as sensitivity analyses for this endpoint.

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# 10 APPENDICES

## 10.1 Protocol summary

| | |
|---|---|
| **Title** | A Phase 3, Randomised, Placebo-Controlled Trial of Arimoclomol in Amyotrophic Lateral Sclerosis |
| **ICI** | [redacted], MD, PhD |
| **Phase** | 3 |
| **Indication** | Arimoclomol in Amyotrophic Lateral Sclerosis (ALS) |
| **Design** | A multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of 1200 mg arimoclomol (400 mg t.i.d.) over a 76 weeks' treatment period<br><br>**Screening period**<br>Screening may be up to 4 weeks prior to Baseline if a washout period for an investigational treatment is required. The minimum screening period is set as one week for practical reasons (to ensure all results are available to determine eligibility at Baseline).<br><br>Following confirmation of eligibility during the Screening/Baseline period (Day -28 to Day 1), subjects will be randomised in a 2:1 ratio to receive either 1200 mg/day arimoclomol (400 mg t.i.d.) or placebo orally t.i.d. Randomisation will be stratified by background riluzole use.<br><br>**Treatment period**<br>The first post-baseline assessment will take place in-person at the investigator site 4 weeks after the Baseline visit; subsequent assessments will consist of a combination of in-person visits and remote visits (telephone calls).<br><br>Subjects will attend the investigator site for an in-person visit on a 4-weekly basis for the initial 6 months of treatment (on Weeks 4, 8, 12, 16, 20, 24, 28), followed by an 8-weekly basis to 12 months (on Weeks 36, 44 and 52) and then for the following 6 months of treatment in-person visits are scheduled on a 12-weekly basis until the Safety Follow Up (on Weeks 64 and 76). |

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| | On the remaining weeks of the treatment period (Weeks 32, 40, 48, 56, 60, 68 and 72) a remote visit will be conducted by the subject receiving a telephone call from the trial site staff.<br><br>Following baseline, if a subject is unable to attend the trial site for a scheduled in-person visit (e.g. due to ALS progression) or at Weeks 8, 16 and 24, a sub-set of clinical assessments as listed in Table 6 of the main body of the protocol should be conducted by trial site staff or via contract nursing service.<br><br>At any time during the trial, the IMP may be temporarily halted for up to 4 weeks for an intolerable AE. Following re-challenge at the intended dose, de-escalation from 1200 mg/day (400 mg t.i.d.) to 600 mg/day (200 mg t.i.d.) may be considered. The subject will remain on this decreased dose for the remainder of the trial. Re-challenge with IMP in cases of elevation of transaminases should only be done as specified in Section 6.5 of the main clinical trial protocol which relates to dose modification and IMP discontinuation.<br><br>**Safety Follow Up**<br>Subjects who discontinue treatment will be encouraged to attend all planned visits as per protocol after drug discontinuation.<br><br>A Safety Follow Up visit is to be conducted 2 weeks after last administration of IMP in case of a) premature IMP discontinuation or b) subject completing trial but not continuing into open label extension trial<br><br>**End of trial**<br>All randomised subjects will attend an end of trial visit.<br><br>If a subject reaches a trial survival endpoint (e.g. tracheostomy or PAV), the IMP will be permanently discontinued. The subject will be offered to participate in an open-label extension trial which will be conducted as a separate trial.<br><br>Subjects who complete the 76 weeks randomised treatment period will be offered participation in a separate open-label extension trial through means of a separate clinical trial protocol. |
| **IMP** | Subjects found to be eligible will be randomised via the IRT in a 2:1 ratio to one of the following treatments:<br>a. 1200 mg/day arimoclomol (400 mg t.i.d.)<br>b. Placebo (matching) |

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| | Treatment assignment will also be stratified by background treatment with riluzole. |
| **Primary objective** | To determine the efficacy of chronic treatment with 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo over 76 weeks in subjects with ALS as assessed with Combined Assessment of Function and Survival (CAFS) |
| **Primary endpoint** | Combined assessment of function and survival (CAFS) over a treatment period of 76 weeks (or end-of-trial) |
| **Secondary objective** | To evaluate the impact of 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo on:<br>• Time to permanent assisted ventilation (PAV)/tracheostomy free survival<br>• Disease progression as measured by change from Baseline of the ALSFRS-R<br>• Progression of respiratory dysfunction as measured by change from Baseline of the slow vital capacity (SVC) |
| **Secondary endpoints** | • Time to PAV/tracheostomy/death from Baseline<br>• Change from Baseline to Week 76 (or end-of-trial) in ALSFRS-R<br>• Change from Baseline to Week 76 (or end-of-trial) in SVC |
| **Safety objective** | To assess the safety and tolerability of 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo |
| **Safety endpoints** | • Incidence and severity of treatment-emergent adverse events (TEAEs) over a treatment period of 76 weeks<br>• Mean and change from Baseline to Week 76 (or end-of-trial) in clinical safety laboratory tests, and vital signs<br>• Incidence of clinically significant abnormalities in clinical safety laboratory tests and vital signs over a treatment period of 76 weeks<br>• Columbia Suicide Severity Rating Scale (C-SSRS) over a treatment period of 76 weeks |
| **Exploratory objectives** | **Efficacy**<br>To explore the potential effect of 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo on cognitive and behavioural changes |

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| | **Health-related quality of life**<br>To evaluate the effect of 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo on health-related quality of life<br><br>**Pharmacokinetics**<br>To investigate CSF and plasma levels of arimoclomol following administration 1200 mg/day arimoclomol (400 mg t.i.d.).<br><br>**Biomarkers**<br>To evaluate the effect of 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo on candidate biomarkers of target engagement, disease activity (markers reflecting ongoing neurodegeneration), and disease progression in blood, urine, and CSF compared to placebo. |
| **Exploratory endpoints** | **Efficacy**<br>• Change from Screening to Week 76 in cognitive and behavioural changes as evaluated by ECAS<br><br>**Health-related quality of life**<br>• The SEIQoL-DW for the subject over a treatment period of 76 weeks<br>• The SEIQoL-DW for the caregiver over a treatment period of 76 weeks<br>• EQ-5D-5L over a treatment period of 76 weeks<br><br>**Pharmacokinetics**<br>• Plasma and CSF concentrations of arimoclomol at weeks 20 and 52.<br><br>**Biomarkers**<br>Absolute values and change from Baseline to Week 20, Week 52, and Week 76 for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo in blood, urine, and CSF for the following biomarker endpoints:<br>• HSP70 in CSF and blood<br>• Neurofilament light chain (NfL) in CSF and blood<br>• Urinary p75 neurotrophin receptor extracellular domain (p75ECD)<br>• Chitotriosidase in CSF |
| **Sample size** | Two hundred and thirty-one (231) subjects are planned for randomisation This number includes 213 subjects according to the main trial eligibility criteria and up to an additional 18 subjects on stable (i.e. minimum 6 months') treatment with edaravone and who otherwise fulfil the eligibility criteria. |

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| | The sample size calculation has been made for the 213 subjects in the main trial population (not including the additional subjects in the edaravone sub-population). |
| **Anticipated disposition** | Number of subjects planned to be screened: Approximately 298<br>Estimated screen failure rate: 25%<br>Number of subjects planned to be randomised: Approximately 231<br>Estimated trial discontinuation rate: 40%<br>Number of subjects expected to complete 76 weeks of treatment: 128<br><br>Within the total number of subjects to be randomised up to 18 subjects will be on stable (i.e. minimum 6 months') treatment with edaravone |
| **Statistical methods** | **Primary analysis**<br>The CAFS will be calculated over a treatment period of 76 weeks for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo. The CAFS will be analysed using nonparametric rank analysis of covariance (29), adjusting for Baseline ALSFRS-R, SVC and riluzole use (Yes/No).<br><br>**Secondary analysis**<br>The endpoint 'PAV/tracheostomy-free survival over treatment period of 76 weeks for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo' will be analysed using a log-rank test stratified by riluzole use. Subjects who drop-out prior to Week 76 will be censored.<br><br>The endpoint 'ALSFRS-R change from Baseline to Week 76 for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo' will be analysed using an analysis of covariance (ANCOVA). The model will include treatment, baseline ALSFRS-R, baseline SVC, and riluzole use.<br><br>The endpoint 'SVC change from Baseline to Week 76 for 1200 mg/day arimoclomol (400 mg t.i.d.) compared to placebo' will be analysed using an ANCOVA. The model will include treatment, baseline ALSFRS-R, baseline SVC, and riluzole use.<br><br>Secondary endpoints will be tested sequentially at a two-sided 0.025 level of significance. Testing for treatment difference will stop if no treatment difference in favour of arimoclomol is found. |

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| | **Safety analysis**<br>Adverse events (AEs) will be coded by system organ class (SOC) and preferred term from the current version of MedDRA. Treatment emergent adverse events (TEAEs) will be summarised overall, by seriousness, severity, and relationship to treatment. AEs causing premature treatment discontinuation, and incidence of SAEs will be summarised.<br><br>All AEs, severe AEs, SAEs, AEs causing premature treatment discontinuation, will be listed by subject.<br><br>The Columbia Suicide Severity Rating Scale (C- SSRS) will be summarised at each visit and overall by treatment using descriptive statistics.<br><br>Vital signs and safety laboratory values will be summarised by visit and changes from Baseline will be summarised using descriptive statistics.<br><br>The incidence of potentially clinically significant abnormal values for vital signs and safety laboratory values will be summarised. |
| **Trial committees** | An independent Data Monitoring Committee (DMC) will be established to monitor benefit:risk and ensure that subjects are not unnecessarily exposed to the investigational medical product (IMP) in the event that the expected benefit:risk should change.<br><br>The DMC will act in accordance with the DMC charter and may have access to unblinded data. |
| **Eligibility criteria** | **Inclusion criteria**<br>1. Capable of- and willing to- provide written informed consent and comply with trial procedures.<br>2. Subject is male or female ≥18 years of age.<br>3. Subject meets revised El Escorial criteria for clinically possible, clinically probable / clinically probable ALS laboratory-supported, clinically definite ALS or clinically definite familial ALS laboratory-supported.<br>4. 18 months or less since first appearance of weakness (e.g. limb weakness, dysarthria, dysphagia, shortness of breath).<br>5. ALSFRS-R ≥35 and erect (seated) SVC % predicted ≥ 70% at Screening.<br>6. Able and willing to travel to the site, and in the investigator's opinion is likely to attend visits for at least 24 weeks. |

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| | 7. All sexually active female subjects of child-bearing potential (postmenarchal)* must agree not to intend to become pregnant and use a highly effective method of contraception** during the trial through 1 month after the last dose of trial medication. If the subject is a sexually active male with female partners of child-bearing potential (postmenarchal) he must use a condom with or without spermicide in addition to the birth control used by their partners during the trial until 3 months after the last dose of trial medication.<br>8. Stable dose of riluzole (50 mg twice daily) for a minimum of 14 days prior to Day 1 (Baseline),or has not taken it for 14 days prior to Day 1.<br><br>**Exclusion criteria**<br>1. Tracheostomy or use of non-invasive ventilation for more than 2 hours during waking hours at the time of Screening and Baseline visits.<br>2. Pregnant or breast-feeding.<br>3. Current or anticipated use of diaphragmatic pacing during the trial.<br>4. Exposure to any investigational treatment within 4 weeks or <5 half-lives of the Screening visit, whichever is longest and/or advanced therapy medicinal product (ATMP), i.e. treatments based on genes, cells or tissues and/or participated in any prior ALS clinical trial receiving active drug treatment (with the exception described in exclusion criterion 5).<br>5. Treatment with edaravone within 4 weeks of the Baseline visit. However, up to 18 subjects on stable (i.e. minimum 6 months') treatment with edaravone and who otherwise fulfil the eligibility criteria are planned for enrolment (limited to countries where edaravone has a marketing authorisation for treatment of ALS).<br>6. Any of the following medically significant conditions:<br>a. Neurological impairment/dysfunction or unstable psychiatric illness that in the investigator's opinion is likely to interfere with assessment of ALS disease progression.<br>b. Clinically significant unstable medical condition other than ALS, which would present a risk to a subject to participate in the trial<br>c. Presence of dementia that impairs the ability of the subject to provide informed consent, according to the PI decision. |

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| | d. Known or suspected allergy or intolerance to the IMP (arimoclomol or constituents)<br>e. Chronic infection particularly HIV or Hepatitis B or C.<br>f. Clinically significant renal or hepatic disease<br>g. Aspartate aminotransferase and/or alanine aminotransferase and/or lactate dehydrogenase ≥3 times the upper limit of normal [ULN], bilirubin ≥2 times the ULN, or creatinine ≥1.5 times the ULN). Laboratory tests may be repeated once at Screening. Reasons to repeat laboratory tests may include that the medication causing laboratory abnormality was suspended, any other suspected cause may no longer exist, or to rule out laboratory error.<br>h. Cancer that is currently under active treatment or is likely to require treatment during the trial that may alter the subject´s function and thereby interfere with assessment of ALS disease progression.<br>i. Any other condition that in the investigator's opinion would present a risk to a subject to participate in the trial, interfere with the assessment of safety or has an increased risk of causing death during the trial.<br><br>** Non child-bearing potential is defined as post-menopausal (minimum of 12 months with no menses and follicle-stimulating hormone in the post-menopausal range) or sterilisation (hysterectomy, oophorectomy, or bilateral tubal ligation).*<br><br>*** Highly effective methods of contraception include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; and vasectomised partner.*<br><br>*According to the recommendations from the Clinical Trial Facilitation Group (CTFG, 2014), sexual abstinence is considered a highly effective birth control method only if it is defined as refraining from heterosexual intercourse during the trial until 1 week after the last dose of trial medication (for female subjects of child-bearing potential) and for 3 months after* |

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| | *the last dose of trial medication (for male subjects with female partners of child-bearing potential). The reliability of sexual abstinence needs to be evaluated by the investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.* |
| **Anticipated trial period** | First Subject First Visit: Jul 2018<br>Last Subject First Visit: May 2019<br>Last Subject Last Visit: Dec 2020 |
| **Countries & centres** | The trial will be conducted at approximately 32 sites in approximately 13 countries in North America and Europe. |

## 10.2 Trial governance considerations

### 10.2.1 Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Current version of applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The appropriate regulatory authority(ies) must be notified of/approve the clinical trial as required.

The protocol, protocol amendments, subject information leaflet including the informed consent form (ICF), Investigator's Brochure, and other relevant documents (for example advertisements) must be submitted to an IRB/IEC by the investigator (in collaboration with Orphazyme, if applicable) and reviewed and approved by the IRB/IEC prior to enrolment of subjects.

Any amendments to the protocol must be approved by/receive favourable opinion from relevant regulatory authorities and IRBs/IECs as required prior to the implementation.

The investigator or the assigned responsible CRO will be responsible for ensuring the following:

- Provision of written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notification of the local IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Oversight of the conduct of the trial at the trial site and adherence to applicable national and international legislation.

### 10.2.2 Informed consent process

Subjects shall receive written and verbal information concerning the clinical trial. This information will emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

The subject's signed and dated informed consent to participate in the clinical trial must be obtained prior to any clinical trial related procedure being carried out in accordance with ICH

GCP (4.8) and all applicable laws and regulations. The authorised person obtaining the informed consent must also sign the ICF.

Subjects unable to provide informed consent prior to the commencement of the screening and baseline visits cannot participate in the trial.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

Since ALS is a rapidly progressing neurological condition, the ability of a trial subject to confirm ongoing / provide new consent may be diminished (i.e. the trial subject may decline to a legal status of an incapacitated adult). Since there is the possibility of needing to reconsent subjects in the clinical trial due to unforeseen circumstances, a primary caregiver will be nominated as a legal representative prior to commencement of the trial will be nominated by the time of the Baseline visit to ensure that this occurs while the subject is competent. In this circumstance (and in accordance with local legislation or guidelines) a legal representative will ensure the subject's best interests and legal rights are protected throughout the trial should the subject become incompetent. Legal representation certificate must be obtained as per applicable country legal requirements and procedures. While the subject is competent, informed consent for any research procedure or intervention is sought from the subject only. The subject may freely decline consent and the legal representative will not be consulted. Based on the selection criteria, this trial will not prompt legislation regarding enrolment of incapacitated adults into clinical trials in emergency situations.

Additionally, this individual will give consent to be contacted during the conduct of the trial should contact with the subject become challenged.

For competent trial subjects who have lost dexterity in the hands and cannot personally sign and date the informed consent form, an impartial witness signature may be used to document that the participant understands the study, the consent process, and has consented to continue to participate in the trial (if permitted by local regulations).

### 10.2.3 Subject card

At Screening, subjects will be provided with a card stating that they are participating in a clinical trial and which contains contact address(es) and telephone number(s) of relevant trial site staff. The subject will use this card to notify non-investigator physicians of their trial participation. The contact details of the appointed medical monitor will be included on the card should medical information be required by the non-investigator physician. These contact details are not provided for use by the subject.

### 10.2.4 Subject and data confidentiality

This clinical trial protocol as well as all other information, data and results relating to this clinical trial and/or to the IMP is confidential information of Orphazyme and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that Orphazyme may use any and all information, data and results from this clinical trial in connection with the development of the IMPs and, therefore, may disclose and/or transfer information, data and/or results to other investigators, regulatory authorities and/or commercial partners.

Subjects will be assigned a unique identifier (subject ID) by Orphazyme. Any subject's records or datasets that are transferred to Orphazyme will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

Subjects must be informed that their personal trial-related data will be used by Orphazyme in accordance with local data protection law.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by Orphazyme, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### 10.2.5 Processing of personal data

This protocol specifies the personal data on trial subjects (for example age, gender, health condition, height, medical history, test results, etc.) which shall be collected as part of the clinical trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator, Orphazyme and third parties acting on behalf of Orphazyme.

Processing of personal data on behalf of Orphazyme requires a written agreement between Orphazyme and the relevant party which covers collection, processing and transfer of personal data in the clinical trial. In certain cases an agreement on transfer of personal data may also be required.

Investigators and Orphazyme must ensure that collection, processing and transfer of personal data are in compliance with applicable legislation on data protection and privacy.

Subjects (or their legally acceptable representative) must be asked to consent to the collection, processing and transfer of their personal data to EU and non-EU countries for the purpose of conducting the clinical trial, research and development of new or existing products/services, improving existing products/services, applying for marketing authorisations for products/services, marketing of products/services and other related activities.

Orphazyme has obtained the necessary authorisations for the processing of personal data collected in the trial.

### 10.2.6 Record keeping, quality control and data handling

#### 10.2.6.1 Investigator Logs

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from IRT.

In addition, the investigator must keep a log of staff and a delegation of task(s) list at the trial site. Investigator must sign the log of staff and the delegation of task(s) at the trial site prior to the delegation of tasks.

#### 10.2.6.2 Case report forms

Data will be collected by means of electronic data capture unless transmitted to Orphazyme or designee electronically (e.g., laboratory data). The investigator or staff authorised by the investigator will enter subject data into eCRFs. Data recorded in the eCRFs will be accessible to the trial site and Orphazyme personnel immediately after entry. The eCRFs must be maintained in an up-to-date state by the trial site at all times.

The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require the re-signature by the investigator. The person making the change to the data, and the date, time and reason for the change will be identified in the audit trail.

#### 10.2.6.3 Principles for data entry

Clinically significant abnormal findings at the (first) Screening visit will be documented as medical history in the eCRF.

If an abnormal finding (vital signs, physical examination, laboratory tests, ECG) at any other visit than the (first) Screening visit is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with Section 7.5.7. Further, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom or illness observed after Screening will be reported as an AE in accordance with Section 7.5.7.

#### 10.2.6.4 Source data

For all data recorded, the source document must be defined in a source document agreement or similar document at each trial site. There must only be one source defined at any time for any data elements.

Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a

routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed by medically qualified investigators.

If the worksheet does not become part of the subject's medical record, the following should as a minimum be added to the subject's medical record:

- Date(s) of conducting the informed consent process, including date of provision of subject information.
- A statement from the investigator to verify that each of the eligibility criteria are met.
- Subject ID.
- The fact that the subject is participating in a clinical trial in ALS with arimoclomol for up to 76 weeks.
- Other relevant medical information.

Source records used to document assessments conducted in the subject's home/residency and local laboratory reports will be retained at the trial site and handled as per all other source records.

#### 10.2.6.5 Trial monitoring

During the course of the trial, CRA(s) will visit the trial site. These visits have the following objectives: (i) to perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; (ii) to confirm that the safety and rights of subjects are being protected; and (iii) to confirm that the trial is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The monitoring visit intervals will depend on the trial site's recruitment rate, the compliance of the trial site with the protocol and GCP.

In order to perform their role effectively, CRAs and persons involved in quality assurance and inspections will need direct access to source data, e.g. medical records, laboratory reports, appointment books, etc. If the electronic medical record does not have a visible audit trail, the investigator must provide the CRA with signed and dated printouts. In addition, relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

#### 10.2.6.6 Protocol compliance

Protocol deviations will be documented and notified to the investigator. Protocol deviations will be assessed by Orphazyme and those considered important (and fulfilling the ICH E6 guideline definition) will be included in the CTR.

#### 10.2.6.7 Sponsor audits, IRB/IEC review and regulatory agency inspections

The clinical trial will be subject to audits conducted by Orphazyme or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Orphazyme staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify and reproduce any records and reports that are important to the evaluation of the trial.

If the trial site is contacted for an inspection by competent authorities, Orphazyme must be notified immediately.

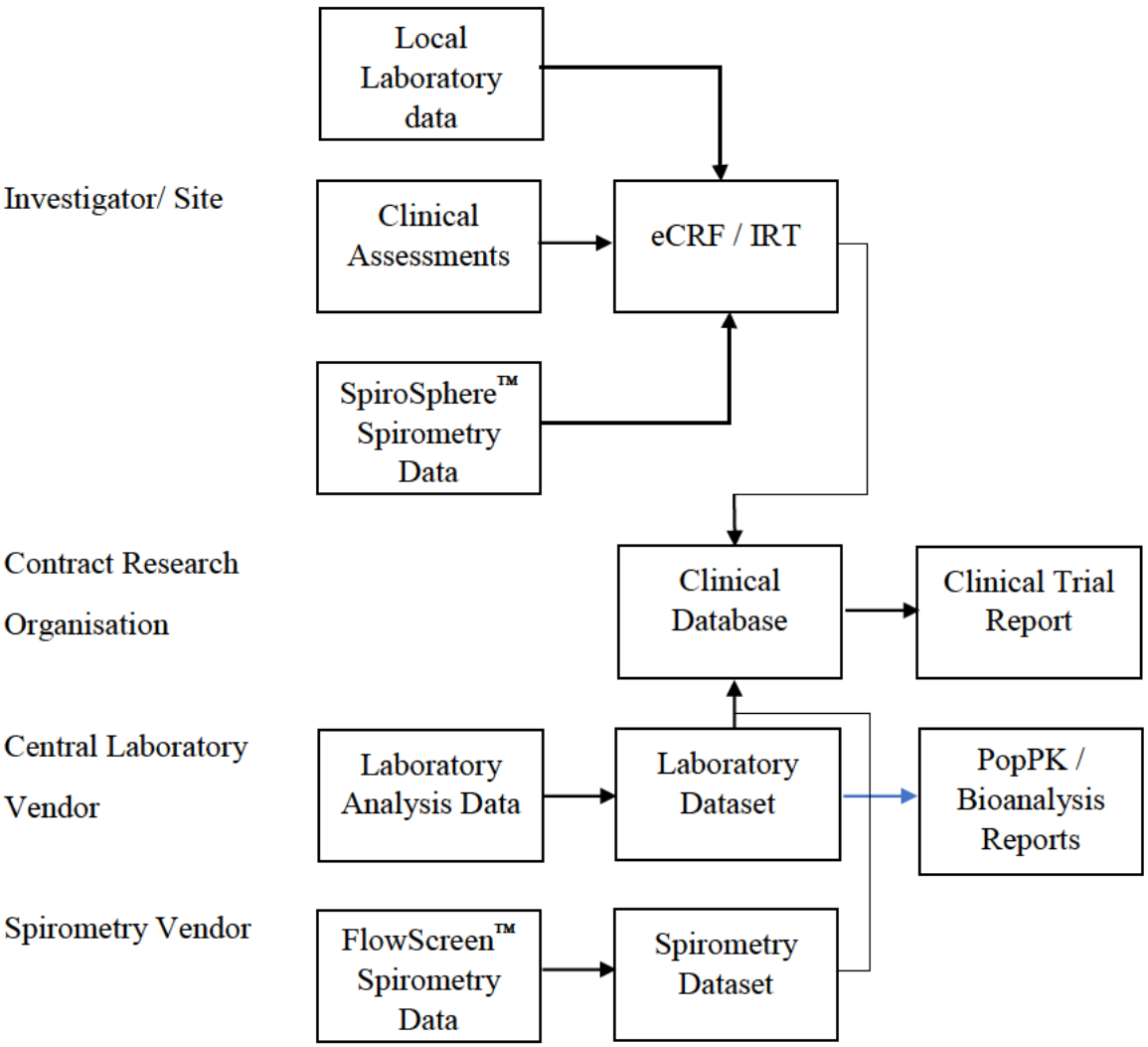
#### 10.2.6.8 Data handling

Subject data should be entered into the eCRF no later than 5 business days after each visit or in accordance with the requirements described in the Clinical Trial Agreement, if applicable. Queries for discrepant data will be generated automatically by the system upon entry or manually by the CRA, sponsor's medical expert, or the data manager. All queries will be raised electronically within the electronic data capture system. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

External data transfers between databases including from vendors to Orphazyme will be transmitted and handled via a secure file transfer protocol site.

Transmissions of electronic data from external data providers (centralised spirometry and central laboratory) to the clinical database are illustrated in Panel 1.

**Panel 1 Transmission of electronic data**



#### 10.2.6.9 Archiving of trial documentation

The investigator at each trial site must make arrangements to store the essential trial documents including the Investigator Trial File (ICH E6, Guideline for Good Clinical Practice) for a retention period of approximately 15 years or in accordance to national/local standards as stated in the clinical trial agreement or until Orphazyme informs the investigator that the documents are no longer to be retained or longer if required by local regulations.

In addition, the investigator is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after the completion of the trial (for example in case of an inspection from regulatory authorities).

The investigator is required to ensure the continued storage of the documents even if the investigator leaves the trial site or retires before the end of the required storage period.

No records may be destroyed during the retention period without the written approval of Orphazyme. No records may be transferred to another location or party without written acceptance from Orphazyme.

The destruction process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

For archiving purposes, each investigator will be supplied with a copy of the eCRFs (including audit trail, closed queries and metadata), centralised spirometry and laboratory data for all subjects enrolled at the trial site. This is done after completion of the trial and before access to the eCRF is revoked. Audit trail information will be included. eCRFs and centralised spirometry and laboratory data must be available for inspection by authorised representatives from Orphazyme, from regulatory authorities and/or IEC/IRBs.

### 10.2.7 Registration, reporting and publication policy

Basic information of this clinical trial will be registered in the global data registry, www.clinicaltrials.gov before the first subject enters into the trial. The trial may also become registered in other online data registries, according to applicable law and regulations.

Orphazyme will report the results of this trial on www.ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination. Results may also be posted on the corporate website of Orphazyme or be otherwise communicated as deemed appropriate by the Orphazyme Management Team.

The first publication will be a joint multi-centre publication. Multi-centre publications will be prepared in collaboration between Orphazyme and the members of a writing group, which shall be appointed by Orphazyme. The Chair of the Arimoclomol in ALS Advisory Committee will lead the writing group.

Publication by an investigator of his/her trial results shall not be made public before the first multi-centre publication.

If no multi-centre publication has been submitted for publication within 18 months (or in accordance with national/local standards) after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as database lock of the clinical trial, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

At least 60 days prior to submitting or presenting a manuscript relating to the clinical trial to a publisher, reviewer or other outside person, or in accordance with national/local standards as agreed in the Clinical Trial Agreement, the investigator shall provide to Orphazyme a copy of all such manuscripts, and Orphazyme shall have rights to review and comment. Upon the request of Orphazyme, the investigator shall remove any confidential information (other than results generated by the investigator) prior to submitting or presenting the manuscripts.

The investigator shall, upon the request of Orphazyme, delay the publication or presentation for up to 90 days (or in accordance with national/local standards, as agreed in the Clinical Trial Agreement) to allow Orphazyme to protect its inventions and other intellectual property rights described in any such manuscripts. In case the first multi-centre publication is still ongoing and has not been made public at the time of notification, Orphazyme and the writing group may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-centre publication.

In case of publications made by the investigator after the first multi-centre publication has been published, the above-mentioned requirements must still be followed.

### 10.2.8 Insurance

Orphazyme has taken out relevant insurances covering the subjects in the present clinical trial in accordance with applicable laws and regulations.

### 10.2.9 Financial disclosure

Investigators will provide Orphazyme with sufficient, accurate financial information as requested to allow Orphazyme to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities as required by local legislation. Investigators are also responsible for providing information on financial interests during the course of the clinical trial and for 1 year after completion of the clinical trial, or for a longer period of time if required by local legislation.

### 10.2.10 Data Monitoring Committee

Subject safety will be carefully assessed by an independent DMC. All members will be independent of the trial (i.e. they will not be participating investigators or employees at participating sites) and of Orphazyme (i.e. they will not be Orphazyme employees). The DMC members are experienced with clinical trials and will be responsible for assessing the safety of the subjects through assessment of the safety of the treatment regimen during the trial and

through monitoring the overall conduct of the trial. Further specification and operational procedures are included in the DMC Charter.

### 10.2.11 Trial and site disclosure

#### 10.2.11.1 Premature termination of trial or trial site

Orphazyme, the investigator, the IRB/IECs or competent authorities may decide to stop the clinical trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a clinical trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. As specified by applicable regulatory requirements, the investigator or Orphazyme must promptly inform IRB/IECs and provide a detailed written explanation. Relevant competent authorities must be informed.

The trial must be terminated if the perception of the benefit/risk ratio (judged from clinical signs and symptoms, (S)AEs and/or remarkable safety laboratory changes) becomes unfavourable for the continuation of the trial.

Reasons for the early closure of a trial site by Orphazyme or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Orphazyme's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further IMP development.

#### 10.2.11.2 Completion of trial

Investigators will be informed when subject recruitment is to cease. Trial enrolment will be stopped at a trial site when the total requested number of subjects for the clinical trial has been obtained, irrespective of the specific site's planned inclusion number.

Trial sites will be closed upon trial completion. Orphazyme will undertake arrangements for the collection and disposal of any unused trial material that the investigator is not required to keep in his/her files. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

When the randomisation code has been broken, the investigators will receive information about the treatment allocation for the subjects randomised at their respective sites and will be asked to record this in the subject's medical record.

### 10.2.12 Responsibilities

**The international coordinating investigator (ICI)** is responsible for the approval of the (consolidated) clinical trial protocol, including any amendment(s) and the CTR on behalf of all clinical trial investigators as agreed to in an International Coordinating Investigator Agreement.

**The national coordinating investigator (NCI)** is responsible for the representation of the trial at IEC/IRB meetings (if required) as agreed to in a National Coordinating Investigator Agreement. Appointment of an NCI will only be made if required by local regulation. The ICI will also serve as an NCI.

**Each participating investigator** is responsible for all aspects of the clinical trial conduct at his/her trial site as agreed to in a Clinical Trial Agreement.

### 10.2.13 Neurological examination criteria

A neurological examination will be made by a neurologist in accordance with the schedule of procedures (Table 1). The examination parameters presented in Table 10 will be considered as either normal or abnormal. Abnormalities will be described and indicated if secondary to ALS.

## Table 10 Parameters for neurological examination

| | |
|---|---|
| General | Level of Consciousness |
| | Level of Appearance/ Facial/Motor Expression |
| | Mental Status |
| | Language |
| Cranial Nerves | Vision (II) |
| | Eye Movements (III, IV, VI) |
| | Jaw movement and facial sensation (V) |
| | Facial motion (VII) |
| | Hearing (VIII) |
| | Swallowing, pharynx, larynx (IX, X) |
| | SCM, trapezious (XI) |
| | Tongue (XII) |
| Reflexes | Biceps |
| | Brachioradialis |
| | Triceps |
| | Knee Jerk |
| | Achilles tendon |
| Motor System | General Movement |
| | Muscle Bulk/ Mass |
| | **Muscle Strength:** |
| | Trunk |
| | Upper Extremities |
| | Lower Extremities |
| | **Muscle Tone:** |
| | Upper Extremities |
| | Lower Extremities |
| Coordination / Cerebellar Function | Gait |
| | Romberg |
| | Nystagmus |
| | Tremor |
| | Finger-Nose |
| | Heel-shin |
| | Rapid Rhythmic Movement |
| Sensation: | **Upper Extremities** |
| | Pain/ Temperature |
| | Light Touch |
| | Position |
| | Vibration |
| | **Lower Extremities** |
| | Pain/ Temperature |
| | Light Touch |
| | Position |
| | Vibration |

## 10.3 Contact list

### 10.3.1 International coordinating investigator

[redacted], MD, PhD, Professor of Neurology, Walter Bradley Chair in ALS Research, Chief, Neuromuscular Division, Chief, Neuromuscular Division, University of Miami, 1120 NW 14th St CRB1318, Miami FL 33136 USA, Phone: [redacted], email: [redacted]

### 10.3.2 National coordinating investigator

A national coordinating investigator may be appointed as required by local regulation.

### 10.3.3 Investigators

The list of investigators is maintained outside of the protocol.

### 10.3.4 Data Monitoring Committee

See the DMC Charter.

### 10.3.5 Sponsor

#### 10.3.5.1 Sponsor

Orphazyme A/S, Ole Maaløes Vej 3, DK-2200, Copenhagen N, Denmark, [redacted], [redacted] www.orphazyme.com

The following individuals have been appointed to act on behalf of the sponsor in the conduct of this clinical trial:

**Medical Expert**
[redacted], MD, Medical Director, Orphazyme A/S, Copenhagen, Phone: [redacted], email [redacted]

**Biostatistician (consultant representative of Sponsor)**
[redacted], PhD, Statistician, President ProSoft Clinical, Phone: [redacted], email: [redacted]

**Data Manager**
[redacted], Senior Data Manager, Copenhagen, Tel: [redacted], email: [redacted]

**Clinical Safety**
[redacted], Clinical Safety Operations Manager, Orphazyme A/S, Copenhagen, Phone: [redacted], email: [redacted]

**Clinical Trial Supply**
[redacted], Senior Clinical Trial Supply Coordinator, Orphazyme A/S, Copenhagen, Phone [redacted], email: [redacted]

**Trial Manager**
[redacted], Senior Clinical Trial Manager, Orphazyme A/S, Copenhagen, Phone: [redacted], email: [redacted]

### 10.3.6 Service Providers

The following service providers have been appointed to collaborate with the sponsor in the conduct of this clinical trial:

#### 10.3.6.1 Contract Research Organisations

**Worldwide Clinical Trials**
1st Floor Waterfront House, Beeston Business Park, Beeston, Nottingham, NG9 1LA, UK

Responsible for project management, site feasibility, clinical assessment technologies, clinical monitoring, data management, statistical analysis and reporting as agreed in a contract

**ERT**
eResearchTechnology Limited, Peterborough Business Park Lynch Wood, Peterborough PE2 6FZ UK

Responsible for centralised spirometry assessment as a third-party provider to Worldwide Clinical Trials

**(Safety vendor)**
Responsible for pharmacovigilance services including safety database management and safety reporting as agreed in a contract. Please refer to the SAE Reporting Contact Details document.

#### 10.3.6.2 Contract Manufacturing Organisations

**Catalent Pharma Solutions**
Responsible for secondary packaging and labelling, import, distribution and destruction as agreed in a contract.

***Packaging, Distribution and Returns, EU;***
Catalent Germany Schorndorf GmbH, Steinbeisstraße 1-2, 73614 Schorndorf, Germany

***Depot and distribution, North America;***
Catalent Pharma Solutions, 10381 Decatur Road, Philadelphia, Pa 19154

***Returns depot and destruction, North America;***
Catalent CTS (Kansas City), LLC, Attn: Returned Goods Dock 10, 10245 Hickman Mills Drive, Kansas City, Missouri 64137-9724

**World Courier**

Responsible for 'direct to patient' (DtP) distribution and logistics as agreed in a contract.

World Courier Denmark A/S, Avedøreholmen 96-98, Hvidovre, DK-2650, Denmark

#### 10.3.6.3 Contract Laboratory Services

**Covance Laboratories**
Responsible for centralised bioanalysis of safety laboratory parameters (biochemistry, haematology and urinalysis), PK and biomarkers and biorepository management as agreed in a contract.

***Pharmacokinetic analysis;***
Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire, HG3 1PY England

***Biomarker analysis;***
Covance Laboratories Inc., Translational Biomarker Solutions, 220 Building/Dock 229, 671 South Meridian Road, Greenfield IN 46140

Covance Laboratories Inc., 3635 Concorde Parkway, Suite 100, Chantilly, VA 20151

***Biorepository;***
Covance Laboratories Inc., Covance Biorepository, Building 210, 671 South Meridian Road, Greenfield IN 46140

***Clinical Safety Laboratory, North America;***
Covance Inc., 8211 SciCor Drive, Indianapolis, IN 46214 USA

***Clinical Safety Laboratory, EU;***
Covance Central Laboratory Sàrl, 7 rue Marcinhes, 1217 Geneva, Meyrin Switzerland

## 10.4 Country-Specific Requirements

The following provisions account for national requirements where the competent authorities have mandated such content be included in the Clinical Trial Protocol.

### 10.4.1 Canada

**Reporting of Serious Adverse Events**
Orphazyme will inform Health Canada, in an expedited manner, of any serious and unexpected adverse drug reaction, regardless of whether the event has occurred inside or outside of Canada.

a) Where it is neither fatal nor life-threatening, report will be submitted within 15 days after becoming aware of the information;

b) Where it is fatal or life-threatening, report will be submitted within 7 days after becoming aware of the information. Orphazyme will submit as complete a report as possible within 8 days of the initial report. Follow-up reports of fatal or life-threatening reactions must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

**Archiving of Trial Documentation**
Under Canadian Law, the retention period for clinical trial records is 25 years. This will be enforced via the clinical trial agreement with each site and furthermore each subject will be made aware of this retention period via the informed consent form.

### 10.4.2 France

**Inclusion Criteria**
An additional eligibility criterion for subjects recruited in France is mandatory under this protocol. Criterion number nine as described below is required to ensure compliance with this additional national requirement.

9. Affiliated to a social security system (requirement for France only)

**Temporary halt of IMP and Dose Modification**
For subjects in France, the following process should be adhered to for subjects with an intolerable AE;

A temporary halt of IMP treatment of up to 4 weeks is permitted if a subject experiences an intolerable AE. The interruption of IMP should be as short as possible and the appointed medical monitor should be consulted prior to re-initiation of the intended 1200 mg/day (400 mg t.i.d.) dose.

If the subject experiences the same intolerable AE after re-challenge with the intended 1200 mg/day (400 mg t.i.d.) dose, the IMP must be discontinued permanently.

If a subject discontinues treatment and does not meet any of the survival endpoint definitions the subject should be invited to attend the remaining trial visits as per the schedule of procedures. Additionally, an in-person follow-up visit should be scheduled for 2 weeks after the last treatment.

**ECG Assessments**
For subjects in France, the ECG examinations should be conducted in all subjects for visits at week 20, 52 and 76 regardless of whether the visit is at the trial site or a home visit. Hence footnote k is not applicable.

**Adverse Events**
For subjects in France, the wording below on AE collection is added to the protocol. The wording was removed in error as the actual data collection is performed as requested in the sentence.

AEs must be collected from the time that the subject has signed the informed consent.

## 10.5 Coronavirus (COVID) operational changes

The document *ORARIALS-01 (COVID-19) Addendum 1.0 dated 24-Mar-2020* shall remain in effect with this Clinical Trial Protocol. The Addendum to the Clinical Trial Protocol is designed to mitigate the operational impact resulting from COVID-19, and shall only be applied as an interim solution during the period that normal Clinical Trial Protocol logistics cannot be adhered to. Once containment measures have ceased and operations return to normal on both a site and subject level, procedures will resume as per the site's currently approved Clinical Trial Protocol.

# (CYP2D6 DDI) Addendum 1.0 to Clinical Trial Protocol v7.0 dated 08-Jun-2020

# A Phase 3, Randomised, Placebo-Controlled Trial of Arimoclomol in Amyotrophic Lateral Sclerosis

**Sponsor: Orphazyme A/S, Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark**
**Coordinating investigator: [redacted], MD PhD**
**Protocol number: ORARIALS-01**
**EudraCT No.: 2018-000137-13**
**ClinicalTrials.gov Identifier: NCT03491462**
**Trial product name: Arimoclomol Capsules**

**Date of Addendum: 16-Sep-2020**



The trial will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements

## Approval Statement, Orphazyme A/S

This trial protocol was subjected to critical review by Orphazyme. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP).

[redacted] 21SEP2020

[redacted] MD Date
Medical Director, Orphazyme A/S

Phone: [redacted]

## Acknowledgement Statement Investigators

Each participating investigator must agree to the approved clinical trial protocol Addendum and consolidated clinical trial protocol(s) (including any protocol amendments) by signing a clinical trial protocol acknowledgement form.

# Contents

# Justification for Addendum

Results from an in vitro study showed that arimoclomol is a direct inhibitor of CYP2D6 with an IC50 of190 µM which is > 25 times higher than clinical exposure (Cmax)

The investigator's Brochure was previously updated with these findings and correspondingly the Clinical trial Protocol (CTP) was updated to indicate that concomitant treatment with CYP2D6 substrates should be done with caution (since their exposure could increase as a result of their metabolism being inhibited).

By using mechanistic static modelling, instead of basic equations, it has since been evaluated that the in vitro CYP2D6 inhibition is not clinically relevant. These findings have been included in the annual update of the Investigator's Brochure and the updated guidance on use of concomitant medications are included in this CTP addendum.

The changes described are done to ensure continued safety and well-being of the subjects and the integrity of the clinical trial. A sponsor risk assessment has concluded that the changes in this addendum are not likely to affect the safety and well-being of the participants or the scientific value of the trial. Therefore, the Sponsor confirms that the benefit-risk evaluation for arimoclomol in ALS is not changed.

# Modification to the Clinical Trial Protocol due to update of Investigator Brochure version 4.0 dated 15-SEP-2020

The following changes shall be made to the respective sections of the Clinical Trial Protocol version 7.0. In countries where version 7.0 is not yet fully in effect, the same principles will apply based on the country's currently approved version.

The below table provides a detailed description of changes made to protocol content as part of this protocol amendment.

Text in *italics* represents additions

Text in ~~strikethrough~~ represents deletions

| ***Section*** | ***Modification*** | ***Rationale (including risk/benefit justification)*** |
|---|---|---|
| 6.8 Concomitant Medication and Procedures | Any medication or vaccine that the subject receives from 3 months prior to Screening and until the End of Trial visit (Week 76) must be recorded in the subject's medical record and the eCRF along with details such as:<br>• Trade name or generic name<br>• Reason for use (indication)<br>• Dates of administration including start and stop dates<br>• Dosage information including dose, route and frequency<br><br>Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 6.9. The appointed medical monitor should | There is no change the benefit-risk evaluation as a result of this change.<br><br>Information is provided to the investigators to ensure guidance in line with the Investigators Brochure update.<br><br>The guidance text on Nuedexta® has been added back in as a result of the above, based on the original guidance in the previously approved Clinical Trial Protocol. |

| *Section* | *Modification* | *Rationale (including risk/benefit justification)* |
|---|---|---|
| | be contacted if there are any questions regarding concomitant or prior therapy.<br><br>Concomitant medication for conditions other than ALS may be continued throughout the trial without any change in dosage whenever possible.<br><br>Arimoclomol is an in vitro inhibitor of the OCT2, MATE-1, and MATE-2K transporters and consequently may inhibit the elimination of cationic drugs that are significantly eliminated by tubular secretion. In addition, arimoclomol is an in vitro substrate of the MATE-1 and MATE-2K transporters. Arimoclomol undergoes renal tubular secretion and concomitant treatment with drugs that are MATE1 or MATE-2K inhibitors may therefore lead to increased exposure of arimoclomol. Consequently, the concomitant use cationic drugs that are significantly eliminated by tubular secretion as well as drugs which are MATE1 or MATE-2K inhibitors should be administered with caution. These include but are not limited to: amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin, dofetelide, trimetroprim, verapamil, levofloxacin, ciprofloxacin, moxifloxacin, pyrimethamine, ondansetron and quinidine.<br><br>~~Additionally, in vitro studies show that arimoclomol is a direct inhibitor of CYP2D6 and may potentially cause increase in exposure of co-~~ | |

| *Section* | *Modification* | *Rationale (including risk/benefit justification)* |
|---|---|---|
| | ~~administered medications that are substrates of CYP2D6 when arimoclomol is dosed at 400 mg t.i.d (40).~~<br><br>~~Since the magnitude of the potential increase cannot be predicted from in vitro data, caution is advised if arimoclomol is co-administered with medicinal products that are metabolised by CYP2D6. This may, for example, be relevant for Class I anti-arrhythmic, tricyclic antidepressants, betablockers, tramadol and selective serotonin reuptake inhibitors (SSRI's) particularly if they are known to be sensitive and moderate sensitive CYP2D6 substrates and/or have a narrow therapeutic index.~~<br><br>~~The product information for co-administered medicinal products should be consulted for guidance on concomitant treatment with a CYP2D6 inhibitor as dose adjustment of the CYP2D6 substrate may be appropriate. For compounds metabolised by CYP2D6 the dose may be reduced and for pro-drugs that are converted to the active compound by CYP2D6 the dose may be increased to ensure efficacy.~~<br><br>Nuedexta® (or compounded equivalent) is a treatment for pseudo-bulbar effect which is a combination of dextromethorphan and an ultra-low dose quinidine 20 and 10 mg, respectively. *Quinidine in low doses inhibits the CYP2D6 metabolism of dextromethorphan.*<br>~~The main effect of Neudexta® is exerted by dextromethorphan which is metabolised by CYP2D6. The intended effect of quinidine as a strong inhibitor of the CYP2D6 isoenzyme is to reduce the metabolism of~~ | |

| *Section* | *Modification* | *Rationale (including risk/benefit justification)* |
|---|---|---|
| | ~~dextromethorphan. The collective information available to date on potential drug-drug interactions suggests that Neudexta® should be co-administered with arimoclomol with caution, since arimoclomol may inhibit the excretion of quinidine~~. Nuedexta® is known to prolong the QTc interval in a dose dependent matter (less than moxifloxacin) and concomitant therapy with medications that prolong the QT interval and are metabolized by CYP2D6 should be done with caution. *Arimoclomol may inhibit the excretion of quinidine (as described above) but has no effect at the CYP2D6 enzyme. Thus, Nuedexta® can be administered concomitantly with arimoclomol using appropriate caution.*<br><br>*Based on in vitro studies, drug interactions related to cytochrome P450 (CYP) enzymes are not expected. Even though CYP2D6 inhibition was observed in vitro, the mechanistic static model predicts that it will not be clinically relevant. Consequently, concomitant use of drugs that are CYP2D6 substrate is not considered to of concern.*<br><br>Animal studies have indicated a possible pharmacodynamic interaction with furosemide increased urinary volume and increased urinary creatinine, potassium, sodium, phosphorus and calcium; additive effect) at high doses. Consequently, concomitant treatment with furosemide should be done with caution. The following concomitant medications related to ALS treatment are permitted from Screening and throughout the trial:<br>• Stable dose of riluzole (50 mg twice daily) for a minimum of 14 days prior to Baseline (see inclusion criterion 8) | |

| *Section* | *Modification* | *Rationale (including risk/benefit justification)* |
|---|---|---|
| | • Stable dose of edaravone i.e. minimum 6 months of treatment (only applicable for subjects enrolled into the edaravone sub-population, limited to countries where edaravone has a marketing authorisation for treatment of ALS (see exclusion criterion 5). The number of subjects in this sub-population will be tracked via eCRF data and investigators will be pro-actively notified when recruitment under this criterion will be closed.<br>• Other medication or treatments that are deemed necessary to provide adequate supportive care.<br><br>The use of non-invasive ventilation is permitted during the trial.<br><br>Concomitant medication and non-invasive ventilation will be recorded in the subject diary in the interval between trial visits. | |