CLINICAL TRIAL PROTOCOL

Arimoclomol in ALS – Open-Label Extension Trial

Open-label, Non-randomised Extension Trial to Assess the Long-Term Safety and Efficacy of 1200 mg/day Arimoclomol 400 mg Three Times a Day (t.i.d.) in Subjects with Amyotrophic Lateral Sclerosis (ALS) who have Completed the ORARIALS-01 Trial

Sponsor: Orphazyme A/S, Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark
Coordinating investigator: [redacted], MD PhD
Protocol number: ORARIALS-02
EudraCT No.: 2019-000374-39
Trial product name: Arimoclomol Capsules
Date of protocol amendment: 08 June 2020

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

Clinicaltrials.gov ID: NCT03836716

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).

[redacted] 10JUN2020

Medical Director, Orphazyme A/S Date

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Biostatistician, President, ProSoft Clinical Date

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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 10.3.

Protocol Amendment

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

The details of content amended from the Clinical Trial Protocol versions 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 12-Feb-2019
- Clinical Trial Protocol version 2.0 dated 08-Apr-2019
- Clinical Trial Protocol version 2.1 dated 04-Jun-2019 (applicable only in France)
- Clinical Trial Protocol version 3.0 dated 19-Jul-2019
- Clinical Trial Protocol version 4.0 dated 04-Nov-2019
- Clinical Trial Protocol version 5.0 dated 28-Feb-2020
- Clinical Trial Protocol version 6.0 dated 08-Jun-2020 (this latest version)

The sponsor confirms that the changes introduced in version 6.0 qualify for classification as substantial amendments.

This Consolidated Clinical Trial Protocol, version 6.0 is applicable globally. Country specific information are contained in Section 10.3.

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List of Abbreviations and Definitions of Terms

AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
ATMP	Advance therapy medicinal product
CI	Confidence interval
CNS	Central nervous system
CMO	Contract Manufacturing Organisation
CRA	Clinical research associate
CRO	Contract Research Organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTR	Clinical trial report
CYP2D6	Cytochrome P450 2D6
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DtP	Direct-to-patient
eCRF	Electronic case report form
ECG	Electrocardiogram
EQ-5D-5L	EuroQol Five-Dimensional, Five-Level Descriptive System
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
hCG	Human chorionic gonadotropin
HDPE	High density polyethylene
HPMC	Hydroxypropyl methylcellulose
HRQoL	Health-related quality of life
HSP70	Heat shock protein-70
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICI	International coordinating investigator
ID	Identification
IEC	Independent ethics committee

IMP	Investigational medicinal product
INR	International Normalised Ratio
IRB	Institutional review board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
MATE	Multidrug and toxin extrusion
NASH	Non-Alcoholic Steatohepatitis
NCI	National coordinating investigator
NPC	Niemann-Pick disease type C
OCT	Organic cation transporter
OLE	Open-label extension
Ph. Eur.	European Pharmacopeia
PAV	Permanent assisted ventilation
PIL	Patient Information Leaflet
PK	Pharmacokinetics
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOD1	Superoxide 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 a day
ULN	Upper limit of normal
US	United States
USP-NF	United States Pharmacopeia-National Formulary
VC	Vital capacity

1 SCHEDULE OF TRIAL PROCEDURES

Table 1-1: Schedule of Trial Procedures

	Baseline [a]	Open-label treatment [b]				Safety Follow Up
Visit name	**Baseline [c]**	**In-person visits [c]**	**In-person visits**	**Remote visits (telephone calls)**	**End of trial [d] (in person)**	**Safety Follow Up [e] (telephone call)**
Visit number	**1**	**2, 4, 6, 8, 11, 14 and 17**	**3, 5, 7,**	**9, 10, 12, 13, 15, 16, 18 and 19**	**20**	**21**
Time in relation to Baseline	**Day 1**	**Weeks 4, 12, 20, 28, 40, 52, 64**	**8, 16, 24**	**Weeks 32, 36, 44, 48, 56, 60, 68 and 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 [r]					
Inclusion/Exclusion Criteria	X					
Demographics [f]	(X)					
Medical History [g]	(X)					
Respiratory rate	(X)				X	
Diary instruction [h]	X					
Diary completion [h]	<==========>					
Collect diary and record diary data in eCRF [h]	(X)	X			X	
Concomitant Medication	(X)	X	X	X	X	X
EFFICACY						
Survival (PAV/ tracheostomy/ death)	<==========>					
ALSFRS-R[i]	(X)	X	X	X	X	
SVC	(X)	X			X	
SAFETY						

	Baseline [a]	Open-label treatment [b]				Safety Follow Up
Visit name	**Baseline [c]**	**In-person visits [c]**	**In-person visits**	**Remote visits (telephone calls)**	**End of trial [d] (in person)**	**Safety Follow Up [e] (telephone call)**
Visit number	**1**	**2, 4, 6, 8, 11, 14 and 17**	**3, 5, 7,**	**9, 10, 12, 13, 15, 16, 18 and 19**	**20**	**21**
Time in relation to Baseline	**Day 1**	**Weeks 4, 12, 20, 28, 40, 52, 64**	**8, 16, 24**	**Weeks 32, 36, 44, 48, 56, 60, 68 and 72**	**Week 76 (or early termination)**	**2 weeks after treatment discontinuation**
Visit window, days		**± 7 days**		**± 7 days**	**± 7 days**	**± 7 days**
Physical Examination	(X)	X			X	
Vital Signs	(X)	X			X	
Body Weight [j]	(X)	X (Week 52 only)			X	
C-SSRS [k]	(X)	X	X	X	X	
ECG	(X)	X (Weeks 20 and 52 only)			X	
AEs	(X)	X	X	X	X	X [l]
Pregnancy Test [m]	(X)	X			X	
Clinical Safety Laboratory Test [n p]	(X)	X	X[q]		X	

	Baseline [a]	Open-label treatment [b]				Safety Follow Up
Visit name	**Baseline [c]**	**In-person visits [c]**	**In-person visits**	**Remote visits (telephone calls)**	**End of trial [d] (in person)**	**Safety Follow Up [e] (telephone call)**
Visit number	**1**	**2, 4, 6, 8, 11, 14 and 17**	**3, 5, 7,**	**9, 10, 12, 13, 15, 16, 18 and 19**	**20**	**21**
Time in relation to Baseline	**Day 1**	**Weeks 4, 12, 20, 28, 40, 52, 64**	**8, 16, 24**	**Weeks 32, 36, 44, 48, 56, 60, 68 and 72**	**Week 76 (or early termination)**	**2 weeks after treatment discontinuation**
Visit window, days		**± 7 days**		**± 7 days**	**± 7 days**	**± 7 days**
HEALTH-RELATED QUALITY OF LIFE						
EQ-5D-5L	(X)	X			X	
BIOLOGICAL SAMPLE COLLECTION						
BIOREPOSITORY						
Blood collection	(X)	X (Weeks 20 and 52 only)			X	
Urine collection	(X)	X (Weeks 20 and 52 only)			X	
PHARMACOKINETICS						
Blood sampling (arimoclomol) [o]		X (Weeks 20 and 52 only)			X	
INVESTIGATIONAL MEDICINAL PRODUCT						
Dispensing of IMP	X	X				
Drug Accountability		X			X	

Footnotes:

a. Baseline visit will be conducted on the same date as the End of Trial Visit (Visit 21) of the ORARIALS-01. Assessments marked as (X) will be data collected in the ORARIALS-01 trial (either as part of the Screening Visit or End of Trial Visit) and duplicated into the clinical database of ORARIALS-02. Items marked X are to be conducted specifically at the Baseline visit for ORARIALS-02.

b. 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.

c. At Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 36, 44, 52 and 64 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) may assess the subject by conducting a home visit (if permitted by local regulations). All other visits will be conducted remotely by telephone.
d. The End of Trial Visit (Visit 20) is applicable for all subjects participating in ORARIALS-02. Subjects discontinuing treatment prior to Week 76 should continue in the trial up to Week 76 according to the visit schedule. 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.
e. The Safety Follow Up Visit (Visit 21) must be conducted 2 weeks after the last IMP administration for all subjects.
f. Demographics include age, sex, race and ethnicity
g. General medical history, as well as the history of any diagnostic testing such as electromyography and nerve conduction studies; imaging; muscle biopsy; and antibodies.
h. The diary consists of logs to record: IMP compliance, mode of administration, concomitant medication, and ventilation support. The time of the dose prior to Weeks 20, 52 and 76 (visits involving pharmacokinetics blood sampling) should be recorded in the subject diary and transcribed to the eCRF.
i. The ALSFRS-R will be performed over the telephone for remote visits. If the scale is administered over the telephone and the subject is unable to respond because of significant bulbar impairment the caregiver should relay the questions and responses.
j. Body weight will only be collected when feasible.
k. The C-SSRS assessment will use the 'Since the last visit' version.
l. Only stop dates for ongoing AEs and new SAEs will be collected.
m. Women of child-bearing potential only. A urine pregnancy test will be obtained at all required visits.
n. Clinical safety laboratory tests include haematology, chemistry (including Cystatin C), and urinalysis.
o. At Week 20, PK samples will be collected pre-dose and at 0.5 hours post-dose. At Week 52 and Week 76 PK samples will be collected pre-dose and at 1.5 hours post-dose. PK samples will not be collected if the subject has an early termination visit.
p. 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.
q. Cystatin C will not be required for these visits.
r. Must occur prior to any trial related procedure; may be acquired prior to Visit 1 (Baseline).

Abbreviations: AE = adverse event; ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale-Revised; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; IMP = investigational medicinal product; PAV = permanent assisted ventilation; PK =pharmacokinetics; SAE = serious adverse event; SVC = slow vital capacity; t.i.d. = three times a day.

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 (US) 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 the European Union (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, 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 100 mg 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 in more than 20 years. Edaravone is thought to act as a free-radical scavenger which prevents oxidative stress damage to neurones. Itis 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 the 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 superoxide 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) deoxyribonucleic acid (DNA) binding protein 43 (TDP-43) in cytoplasmic inclusions in affected areas of the central nervous system (CNS) (8). 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 (8), and is involved in regulation of RNA splicing and modulation of microRNA biogenesis (9). TDP-43 plays an important role in neuronal plasticity by regulating protein synthesis in dendrites (10), and mutated and misfolded forms are prone to toxic fibrillization in stress granules (9). 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 (11). 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 (12). 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 13).

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 Nonclinical Experience

In valosin-containing protein transgenic mice, which have prominent TDP-43 pathology in motor neurons and motor neuron loss similar to the pathology associated with human ALS, arimoclomol citrate treatment at exposures corresponding to 1200 mg/day in humans was associated with upregulation of heat shock protein-70 in neurons (demonstrating target engagement), correction of TDP-43 pathology, and preservation of large motor neurons in the spinal cord, indicating a treatment effect on the hallmark pathology of ALS (unpublished data).

Nonclinical safety studies support chronic dosing of arimoclomol citrate 1200 mg/day (2 × 200 mg three times a day [t.i.d.]). A package of nonclinical studies has been performed to evaluate the safety of arimoclomol. See the current version of the Investigator's Brochure (IB) for further information (17).

2.3.2 Clinical Experience

Clinical experience with arimoclomol in ALS originates from seven Phase 1 trials in healthy subjects and 2 Phase 2a trials (trial AALS-01 [14] and trial AALS-01 OL [15]) in patients with ALS. Moreover, one investigator-led Phase 2 trial has been conducted in ALS patients with pathogenic SOD1 mutations (16).

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, 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 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 investigational medicinal product (IMP) and Orphazyme considered the causality to be possibly related. See the current version of the IB for further information (17).

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 (14).

A total of 62 subjects with ALS received arimoclomol citrate 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 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.

In the open-label extension (OLE) to this trial (15), 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 citrate 300 mg/day (100 mg t.i.d.) for up to 6 months. Arimoclomol citrate 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 OLE 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 (VC), body weight or body mass index.

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 (16). The patients randomised to arimoclomol citrate 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) (27). 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.

For further information on experience with arimoclomol, see the current edition of the IB (17).

2.4 Trial Rationale

2.4.1 Justification for Trial Design

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 to the recommendations of the FDA draft guidance document for industry (18) and the European Medicines Agency (EMA) guideline on clinical investigation of medicinal products for the treatment of ALS (19).

This trial will evaluate the safety and efficacy of long-term treatment of 1200 mg/day arimoclomol citrate (400 mg t.i.d.) in those subjects who have completed the double-blind ORARIALS-01 trial (i.e., the subject has met the survival endpoint of either tracheostomy or permanent assisted ventilation (PAV) or the subject as completed 76 weeks of randomised treatment). The clinical safety assessments included in the present trial (safety assessment type, frequency of assessment, schedule of assessment from first exposure) have been selected considering that there is the possibility for subjects to be transitioning from placebo in ORARIALS-01 to first exposure to arimoclomol.

2.4.2 Justification for Selected Dose

The dose of arimoclomol citrate selected for ORARIALS-01 is 1200 mg/day (400 mg t.i.d.). Since the present trial is designed as an open-label extension the same dose will be applicable to this trial.

Subjects who have dose de-escalated to 600mg/day (200 mg t.i.d.) in the ORARIALS-01 and are transitioning into this extension protocol should remain on the deescalated dose throughout the present trial.

Dose de-escalation will not be utilised in the present trial.

2.4.3 Justification for Endpoints

The proposed primary endpoint in the present trial is the safety of long-term arimoclomol use for up to 76 weeks (and for up to 152 weeks for patients previously treated with arimoclomol and completing ORARIALS-01). AEs as well as changes in vital signs, CSSRS, and clinical safety laboratory tests will be evaluated.

The secondary endpoints evaluate the efficacy of long-term arimoclomol use for up to 76 weeks:

2.4.3.1 Permanently Assisted Ventilation- and Tracheostomy-free Survival:

In accordance with the completed SOD1-ALS Phase 2 trial (16) this endpoint is defined as 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.

- For subjects that have completed the 76 weeks randomized treatment period in the ORARIALS-01 trial, all of the survival endpoints; PAV, tracheostomy or death may be recorded as the survival outcome which will be used as the endpoint for the secondary objective of survival.

- For subjects who meet one of the surrogate survival endpoints (tracheostomy or PAV) during the ORARIALS-02 trial, the subject may continue in the trial and time to event for death will also be recorded (as applicable).

- For subjects having met one of the surrogate survival end-points during the ORARIALS-01 trial, time to event for death will be recorded however the subjects will not contribute to the secondary objective of survival.

2.4.3.2 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 (20,21,22,23) The functional decline averages about 1 point per month in untreated patients (24).

2.4.3.3 Decline of Respiratory Function, as Quantified by Change from Baseline on the Slow Vital Capacity as Percentage of Predicted:

Vital capacity has been most thoroughly studied and has been shown to decline by about 3% per month throughout much of the disease course (25). 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 (26) 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 VC can be impacted by treatments. The slow vital capacity (SVC) is a valid and robust measurement of the pulmonary function and is highly correlated with survival.

2.4.4 Benefit-Risk 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 (AALS-001-OL) 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.

2.5 Ethical Considerations

Subjects will only be enrolled in this trial if they provide written informed consent. This trial is open to subjects that have completed the 76 weeks randomised treatment period or who met one of the surrogate survival end-points (tracheostomy or PAV) in the ORARIALS-01 trial.

The open label design was chosen as it was considered most ethical to allow active therapy for all patients. Although the results of ORARIALS-01 will not be known at the start of the open label trial, the open label approach is in line with the Declaration of Helsinki, stating that "sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial."

No paediatric patients or other vulnerable subject's or women who are pregnant, breastfeeding, or trying to become pregnant will 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 foetuses are exposed to the IMP.

Since ALS is a rapidly progressing neurological condition, and subjects may be up to 36 months from first symptom onset (signs of weakness) due to their involvement in ORARIALS-01 trial, it is possible that some subjects may be incapable of providing informed consent at the point of entry to the present trial (i.e., the trial subject may have significantly declined, including signs of fronto-temporal dementia, to a legal status of an incapacitated adult). Other subjects that are competent at the time of trial entry may also face significant decline.

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. 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. Where permitted, a legal representative will be nominated by the time of the Baseline visit to ensure that this occurs while the subject is competent. Additionally, this individual will give consent to be contacted during the conduct of the trial, should contact with the subject become challenged.

As a further consequence of the progressing condition of the disease, some subjects may be incapable of attending the clinic for the eligibility screening and informed consent acquisition. It is considered unethical to deny subjects fulfilling the eligibility criteria access to arimoclomol solely based on their inability to be transported to the clinic. Therefore, the possibility of having the eligibility screening and informed consent acquisition performed by appropriate trial site staff remotely is allowed (if permitted by local regulations).

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 to ensure subject safety.

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

3 OBJECTIVES AND ENDPOINTS

Table 3-1: Objectives and Endpoints

Objectives	Endpoints
Primary objective	Primary endpoint
To assess the long-term safety of arimoclomol treatment of ALS.	• Incidence and severity of TEAEs over a treatment period of 76 weeks • Mean and change from Baseline (of the present trial) to Week 76 (or end of trial) in clinical safety laboratory tests and vital signs • Incidence of potentially clinically significant abnormalities in clinical safety laboratory tests and vital signs over a treatment period of 76 weeks • C-SSRS over a treatment period of 76 weeks
Secondary objectives	Secondary endpoints
To evaluate the long-term efficacy of arimoclomol treatment of ALS.	• Time to PAV/tracheostomy/death (for subjects entering this trial having completed 76 weeks of randomised treatment in ORARIALS-01) • Change in ALSFRS-R from Baseline (of the present trial) to the end of the trial • Change in SVC from Baseline (of the present trial) to the end of the trial (for subjects who did not meet the survival endpoint in the ORARIALS-01 trial)
Exploratory objectives	Exploratory endpoints
Health-Related Quality of Life	
To evaluate the effect of arimoclomol on health-related quality of life	• EQ-5D-5L over a treatment period of 76 weeks
Pharmacokinetics (will be reported separately from the main Clinical Trial Report)	
To investigate plasma levels of arimoclomol following administration of 1200 mg/day arimoclomol citrate (400 mg t.i.d.)	• Plasma concentrations of arimoclomol at weeks 20, 52 and 76
Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale-Revised; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-5L = Euroqol Five-Dimensional, Five-Level Descriptive System; PAV = permanent assisted ventilation; SVC = slow vital capacity; TEAE = treatment-emergent adverse event; t.i.d. = three times daily	

4 TRIAL DESIGN

4.1 Overall Trial Design

This is a multicentre, non-randomised, open-label, uncontrolled trial to evaluate the safety and efficacy of long-term treatment with 1200 mg/day arimoclomol citrate (400 mg t.i.d.) (Figure 4-1: T).

Subjects diagnosed with ALS according to the revised El Escorial criteria must have completed the double-blinded ORARIALS-01 trial. They will either have met the surrogate survival endpoint (tracheostomy or PAV) or they will have completed the 76 weeks randomised treatment period. The end-of-treatment visit of the double-blinded ORARIALS-01 trial corresponds to the Visit 1 of the OLE trial. All subjects will receive open-label arimoclomol treatment.

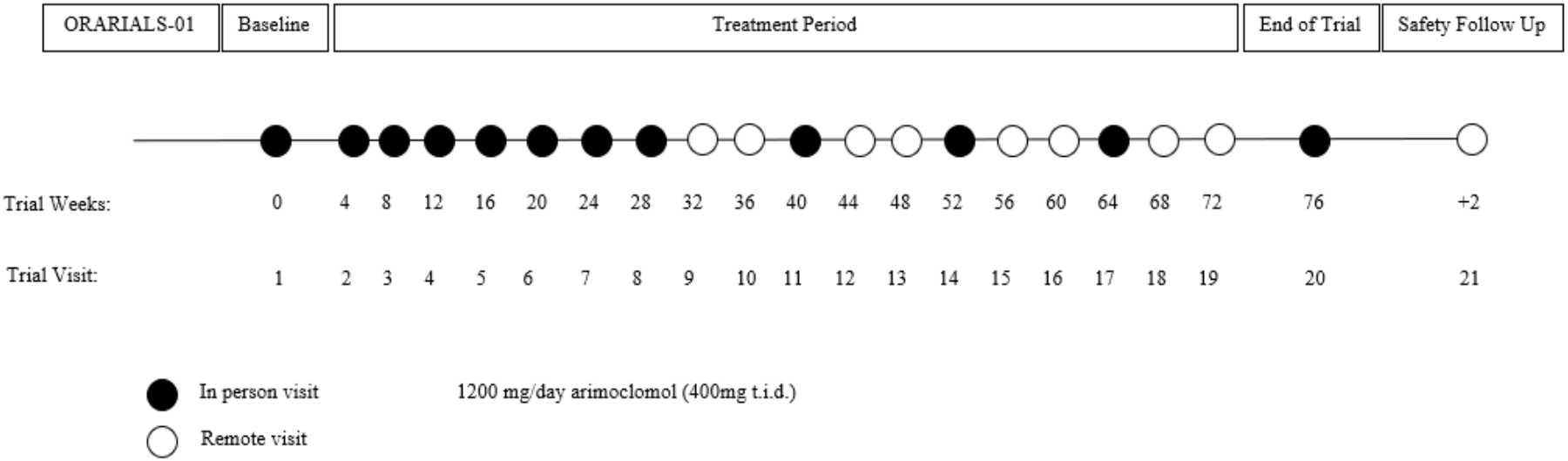
Subjects will attend the investigator site for an in-person visit on a 4-weekly basis for the initial 6 months of treatment (on Day 1, Weeks 4, 8, 12, 16, 20, 24, 28). Following Week 28, in-person visits will be conducted on a 12-weekly basis until Week 76 (i.e., weeks 40, 52, 64 and 76) with remote visits (conducted by telephone) every 4 weeks in the intervening period (Table 1-1). All visits should be scheduled within the visit window of ± 7 days. 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.

In the event that a subject is no longer able to attend the trial site, an in-person visit may be conducted in the subject's home/residency.

Subjects who discontinue treatment will be encouraged to attend all planned visits as per protocol after drug discontinuation. Additionally, these subjects will have a remote visit 2 weeks after the premature IMP discontinuation.

Subjects completing this trial may be offered continued treatment with arimoclomol via an early access program as permitted by local regulation. Early access programs may vary depending on location and include: compassionate use, named patient, expanded access and managed access programs. Continued access to treatment will be contingent on the continued favourable benefit-risk profile of arimoclomol in ALS as assessed by Orphazyme. Access may cease if development of arimoclomol in ALS is terminated, if the marketing application is rejected by a Health Authority or if the product becomes commercially available.

Figure 4-1: Trial Design



Notes:

Remote visits are done via telephone.

If a subject is no longer able to attend the trial site, an in-person visit may be conducted in the subject's home/residency.

The Safety Follow Up Visit will be performed 2 weeks after the last dose of IMP for all subjects. For subjects that discontinue treatment early, the Safety Follow Up Visit may occur during the treatment period.

For subjects withdrawing from the trial, the last in-person visit should be conducted as per the schedule for End of Trial Visit.

4.1 Number of Subjects

The anticipated disposition of subjects is as follows:

Number of subjects planned to be enrolled: theoretically all 231 subjects in ORARIALS-01 may join the trial, however it is estimated that approximately 60% (i.e., 144 subjects) will be available for the OLE trial.

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

4.2 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 10.3 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. Subject is able to comprehend and is willing to provide written informed consent and is capable and willing to comply with trial procedures or in the circumstance that the subject is incompetent, informed consent/assent is provided in accordance with local regulation and/or procedures.

2. Subject has completed the ORARIALS-01 trial (i.e., met one of the surrogate survival endpoints of tracheostomy or PAV or has completed the 76 weeks randomised treatment period).

3. Subject completed ORARIALS-01 while on treatment, where on treatment is defined as having taken the last dose of IMP within 2 weeks of the End of Trial visit (whether at week 76 or prior)

5.3 Exclusion Criteria

1. Known or suspected allergy or intolerance to the IMP (arimoclomol or constituents).

2. Exposure to any other investigational treatment, advanced therapy medicinal product (ATMP) or use of any other prohibited concomitant medications (see Section 6.8)

3. Women who are lactating or pregnant, or men or women unwilling to use a highly effective method of birth control if not surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy for women; vasectomy for men) for female participants until 4 weeks after last dose and for male participants until 3 months after last dose. Pre-menopausal women must have a negative pregnancy test prior to dosing with trial medication. Acceptable methods of birth control are:

    a. Hormonal methods associated with inhibition of ovulation such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before IMP administration.

    b. Total abstinence from sexual intercourse since the last menses before IMP administration. (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence methods [calendar, symptothermal, post-ovulation methods] are not acceptable methods of contraception).

    c. Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).

4. Any of the following medically significant conditions:

    a. Clinically significant renal or hepatic disease OR clinical laboratory assessment (results ≥ 3 times the upper limit of normal [ULN] for aspartate aminotransferase and/or alanine aminotransferase, bilirubin ≥ 2 times the ULN, or creatinine ≥ 1.5 times the ULN).

    b. Any new condition or worsening of existing condition which, in the opinion of the investigator would put the subject at undue risk.

5. Any serious adverse event or moderate/severe adverse event from the ORARIALS-01 trial which is ongoing at the time of transitioning to ORARIALS-02 and assessed as probably related to IMP.

5.4 Subject Enrolment Procedure

Trial participation begins once written informed consent is obtained (see Appendix 10.2.2 for details on the informed consent process) and the subject has met the eligibility criteria for joining the ORARIALS-02 trial. A subject will retain the identification (ID) number (subject ID assigned during ORARIALS-01) and the Baseline evaluations to assess eligibility criteria may begin. The subject ID will be used to identify the subject throughout trial participation, if applicable. A master log of all consented subjects will be maintained at the trial site.

The end-of-trial visit in ORARIALS-01 will constitute the Baseline visit in ORARIALS-02.

5.5 Discontinuation

A subject may withdraw from the 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

Medical reasons for permanent discontinuation of IMP are given in Section 6.4.

If a subject discontinues treatment they 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 final dose of IMP.

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 electronic case report form (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.

Subjects meeting the surrogate endpoint of PAV or tracheostomy in the present trial may continue on treatment.

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 will be asked to provide (optional) consent via the informed consent 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 interactive response technology (IRT) and provided to the subject (by direct to patient shipment, as required). Subjects will coordinate the next scheduled visit according to visit schedule (Table 1-1).

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 7.1.8)
- 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 Product

Arimoclomol is considered the IMP. It is formulated into size "0", white hard capsules for oral administration either in whole or sprinkled and dispensed in liquid or food stuff will be manufactured and supplied by Orphazyme, Denmark.

Each trial site will be supplied with sufficient IMP for the trial on an on-going basis as controlled via an 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.

The description of IMP is provided in Table 6-1 and the quantification of ingredients in Table 6-2.

Table 6-1: Description of Investigational Medicinal Product

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

Table 6-2: Quantities of Ingredients in Trial Product

Ingredient	Function	Grade	Content (mg/capsule)
OR 003 (BRX-345) arimoclomol citrate[1]	Active	-	200.0
Microcrystalline Cellulose PH102	Filler	Ph. Eur./USP-NF	178.1
Magnesium stearate	Lubricant	Ph. Eur./USP-NF	1.9
HPMC capsule shells (Size 0, white)	Coni-Snap sprinkle capsules®	Ph. Eur./USP-NF	-

Abbreviations: HPMC = hydroxypropyl methylcellulose; Ph. Eur. = European Pharmacopeia; USP-NF = United States Pharmacopeia-National Formulary

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

6.2 Administration of Investigational Medicinal Product

Arimoclomol citrate 2 x 200 mg 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 on or prior to 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 (see Section 6.2); if needed, additional instruction should be provided, including provision of a further copy of the PIL.

For subjects who received the reduced dose of 600 mg/day (200 mg t.i.d.) in ORARIALS-01, the same dose should be administered to the subject in this present trial.

6.3 Treatment Assignment

6.3.1 Randomisation

There is no randomisation in this trial as it is an OLE where all subjects will receive active therapy of the same IMP-. Subjects will take 1200 mg/day arimoclomol citrate (400 mg t.i.d.) throughout the trial regardless of the IMP to which the subject was randomised to in

ORARIALS-01. Subject that received a deescalated dose in ORARIALS-01 will continue on this reduced dose of 600 mg (200 mg t.i.d.) in the present trial.

6.3.2 Blinding

This is an open-label trial; there is no blinding required in this trial since only a single IMP is administered to all eligible subjects.

6.3.3 Emergency Unblinding of Individual Subject Treatment

Emergency unblinding provisions are not required for this trial as all subjects will receive open-label IMP.

6.4 IMP Discontinuation

6.4.1 Permanent Discontinuation of IMP

In case of a safety concern or unacceptable intolerability, the IMP must be permanently discontinued. In case of pregnancy or intention to become pregnant the trial product must be discontinued. 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) (34), 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 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.

6.4.2 Temporary Halt of IMP

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 treatment.

A temporary halt of IMP treatment can be implemented only once for intolerable AEs within a given organ/body system. If the subject experiences a different intolerable AE within a different organ/body system, a further temporary halt can be initiated 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 of 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 7.4.9.2.

The missed doses must be recorded in the eCRF.

An end-of-treatment visit should not be conducted when a temporary halt of IMP is initiated.

6.5 Treatment Logistics and Accountability

6.5.1 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) in addition to the bulk batch number.

The labelling of IMPs will be in accordance with Annex 13 (28), local regulations and trial requirements. Label text will be translated into local languages, as required.

6.5.2 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 the interactive response technology (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. In certain circumstances, excursions between 2°C-30°C may be permitted by the Orphazyme Clinical Trial Supply Coordinator based on certificates of analysis and stability statements.

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

6.5.3 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 × 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. The use of such service will receive all required permissions prior to being implemented.

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 with the service provider, which requires sponsor approval. The IMP should be dispensed per the schedule of procedures (Table 1-1), 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 through the chain of custody. The service should be used for reverse logistics to ensure that used and unused IMP 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.

6.5.4 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 IMP at the trial site and for maintaining adequate control of the IMPs and for documenting all transactions with them.

The IRT will allocate IMP bottle codes from the site level inventory to a subject at each 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 in-person 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.

6.5.5 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.

6.6 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.

6.7 Concomitant Medication

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

All concomitant medications that are ongoing at the time of transitioning from the ORARIALS-01 trial to the present trial will be duplicated into the eCRF of ORARIALS-02.

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 6.8. 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, multidrug and toxin extrusion (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 of 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 (35).

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 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 corrected QT (QTc) interval in a dose-dependent matter (less than moxifloxacin); hence, concomitant therapy with medications that prolong the QT interval and are metabolized by CYP2D6 should be used with caution.

Animal studies have indicated a possible pharmacodynamic interaction between arimoclomol and furosemide resulting in increased urinary volume and increased urinary creatinine, potassium, sodium, phosphorus and calcium (additive effect) at high doses. Consequently, concomitant treatment with furosemide should be used with caution.

The following concomitant medications related to ALS treatment are permitted if used during participation in the ORARIALS-01 trial:

- Stable dose of riluzole (50 mg twice daily).
- Stable dose of edaravone.

- Other medication or treatments that are deemed necessary to provide adequate supportive care.

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

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

6.8 Prohibited Medication and Procedures

The following medications are prohibited during the trial from the Baseline visit until the end of the trial:

- Commencement of treatment with edaravone
- Commencement of riluzole treatment. Adjustment of riluzole dose, including temporary halt due to tolerability may be permitted at the investigator's discretion.
- Other investigational treatments or ATMP.

Diaphragmatic pacemakers are not permitted for the duration of the trial.

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

6.9 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.

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 assessments 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.

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, ECG, physical examination, 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 any Baseline tests must be dated and signed to confirm subject's eligibility prior to the dispensing of IMP. 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 7.4.4.

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, 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.

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 operational rater training plans) will be delivered to qualified site staff. Certification on designated scales and management of rater training will be provided by the Clinical Assessment Technologies group of Worldwide Clinical Trials following the adequate completion of the training program.

For scales in which 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 1-1). IMP will be dispensed to the subject by the site, hospital pharmacy or equivalent. Subjects will be instructed in the handling and administration of IMP prior to or at the Baseline visit (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 1-1). The investigator or delegate should instruct the subjects on how to complete the diary and provide ongoing instruction as necessitated by data quality. The diaries dispensed to subjects should be collected at the specified visits (see Table 1-1) and data used to complete the eCRF.

7.1.4.3 *Patient-Reported Outcomes*

Site staff who have undergone training will instruct subjects on the completion of questionnaires, measurements and assessments as described in Section 7.1.3.

7.1.5 Sequence of Assessments

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

Sequence of scale assessments:

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

7.1.7 Transitioning of Subjects from ORARIALS-01 to ORARIALS-02

The end of trial visit (Visit 21) of ORARIALS-01 will be performed for all subjects completing the ORARIALS-01 trial (i.e., met one of the surrogate survival endpoints of tracheostomy or

PAV or has completed the 76 weeks randomised treatment period). For subjects withdrawn from the trial prematurely, the investigator should conduct the last in-person visit as per the end of trial visit.

The end of trial visit (Visit 21) of ORARIALS-01 and Baseline visit (Visit 1) of ORARIALS-01 must be conducted on the same day.

Assessments which are made as part of ORARIALS-01 Screening Visit (Visit 1) or End of Trial Visit (Visit 21) will not be repeated for this trial and will be duplicated into the clinical database of ORARIALS-02.

7.1.8 Subject Assessment When Unable to Travel to the Trial Site

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), a sub-set of clinical assessments as listed below in Table 7-1: will be conducted, in accordance with Table 1-1, 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 arranged by the contract research organisation (CRO), as applicable.

Table 7-1: Clinical Assessments for when an in-person visit is conducted at the subject's home/residency

Day 1 (Baseline)	
Telephone call	**In-Person at Subject's home/residency**
Conducted by investigator and rater	Conducted by trial site staff or via contract nursing services
• Informed Consent • Inclusion/Exclusion Criteria • AEs & concomitant medication (from ORARIALS-01) [b] • ALSFRS-R (from ORARIALS-01) • C-SSRS (from ORARIALS-01)	• AEs & concomitant medication (from ORARIALS-01) [b] • SVC (from ORARIALS-01) • Vital signs (from ORARIALS-01) • Clinical safety laboratory sampling (from ORARIALS-01) • Pregnancy test (urine) (from ORARIALS-01) • Collection of subject diary (from ORARIALS-01), provision of new diary (for ORARIALS-02) • Confirmation of DtP IMP shipment (as applicable)
Weeks: 8, 16, 24	
Telephone call	**In-Person at Subject's home/residency**
Conducted by investigator and rater	Conducted by trial site staff or via contract nursing services
• AEs & concomitant medication • ALSFRS-R • C-SSRS	• AEs & concomitant medication [a] • Clinical safety laboratory sampling
All other weeks	
Telephone call	**In-Person at Subject's home/residency**
Conducted by investigator and rater	Conducted by trial site staff or via contract nursing services
• AEs & concomitant medication • ALSFRS-R • C-SSRS	• AEs & concomitant medication [a] • SVC • Vital signs • Clinical safety laboratory sampling • Pregnancy test (urine) • Collection of subject diary, provision of new diary • Confirmation of DtP IMP shipment (as applicable)

a) Information about potential AEs noticed during a home visit must be provided to the investigator within 24 hours.

b) At the Visit 1 (Baseline), AEs and concomitant medication must be assessed by an Investigator as part of the eligibility review. Any AEs noted by the home nurse must be reported to the Investigator immediately to assist with their eligibility review.

Abbreviations: AE = adverse events; ALSFRS-R = ALS Functional Rating Scale-Revised; C-SSRS = Columbia-Suicide Severity Rating Scale; DtP = direct to patient; IMP = investigational medicinal product; SVC = slow vital capacity

7.2 Baseline Characteristics

Demographic data (i.e., age, sex, race [according to local regulation], and ethnic origin [according to local regulation]), medical history, and ALS characteristics will be recorded as part of the ORARIALS-01 trial and will be duplicated into the database for ORARIALS-02 trial.

The respiratory rate (breaths per minute) will be determined by manual visualisation and count as scheduled in Table 1-1.

7.3 Efficacy Assessments

7.3.1 Survival (permanent assisted ventilation/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.

The following principles are applicable to survival reporting in this present trial:

- For subjects that have completed the 76 weeks randomized treatment period in the ORARIALS-01 trial, all of the survival endpoints; PAV, tracheostomy or death may be recorded as the survival outcome which will be used as the endpoint for the secondary objective of survival

- For subjects who meet one of the surrogate survival endpoints (tracheostomy or PAV) during the ORARIALS-02 trial, the subject may continue in the trial and time to event for death will also be recorded (as applicable).

- For subjects having met one of the surrogate survival end-points during the ORARIALS-01 trial, time to event for death will be recorded however the subjects will not contribute to the secondary objective of survival.

7.3.2 ALS Functional Rating Scale – Revised

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 1-1.

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 subject 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

Slow vital capacity 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 1-1. SVC analysis will include SVC, predicted SVC and percentage 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 (29). Data will be subject to centralised analysis by spirometry experts.

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 EuroQoL Five-Dimensional, Five-Level Descriptive System

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

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 Safety Assessments

7.4.1 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 1-1 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 Baseline 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 7.4.6).

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 subject's home/residency.

7.4.2 Vital Signs

Vital signs (resting blood pressure, pulse, and body temperature) must be assessed as scheduled in Table 1-1. 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.

Any clinically significant changes observed during the trial are to be recorded as AEs (see Section 7.4.6).

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 centralised contract nursing service may instead perform this assessment at an in-person visit at the subject's home/residency.

7.4.3 Body Weight

The body weight will be measured as scheduled in Table 1-1, and only when feasible. 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 visits, this assessment will not be performed.

7.4.4 Electrocardiogram – 12-lead

12-lead ECGs will be performed as scheduled in Table 1-1 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 Baseline 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. In this situation, the Investigator should review AEs and vital signs with particular attention to clinical signs related to conduction disorders to allow for appropriate follow-up, and to ensure that the subject is safe to continue trial participation.

7.4.5 Columbia-Suicide Severity Rating Scale

The C-SSRS is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation through a series of simple, plain-language questions (30). The questionnaire will be administered as an interview by the investigator or a qualified delegate according to the schedule of procedures (Table 1-1). All results from the questionnaire must be transcribed into the eCRF.

The 'since last visit' version will be used throughout the trial.

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 over the telephone.

7.4.6 Adverse Events

7.4.6.1 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. (2).

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 AE meets the definition of an SAE, a conservative viewpoint must be taken, and the AE must be reported as an SAE.

7.4.6.2 *Collection of Adverse Events*

AEs will be collected from the completion of the ORARIALS-01 trial until the end of trial visit. Any SAEs reported to the investigator after the end of trial shall be reported if they are considered at least possibly related to arimoclomol.

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

Adverse events (including pre-treatment AEs) must be recorded in the eCRF. The investigator must provide information on the AE, 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 AE is not related to the IMP, an alternative aetiology must be recorded, if available.

If the AE 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 7.4.6.6).

If individual AEs 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. 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.

All AEs that are ongoing at the time of transitioning from the ORARIALS-01 trial to the present trial will be duplicated into the eCRF of ORARIALS-02.

7.4.6.3 Disease Progression

Disease progression can be considered as a worsening of a subject'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).

7.4.6.4 Death

All deaths that occur during the AE reporting period must be reported.

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.

7.4.6.5 Follow-Up for Final Outcome of Adverse Events

The investigator should follow up for final outcome on all AEs until resolution or the end-of-treatment 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.

7.4.6.6 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 (see contact details above) 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.

7.4.6.7 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 Form and Pregnancy Follow Up Form must be faxed or scanned and e-mailed to the Safety vendor. Please refer to the SAE Reporting Contact Details document.

7.4.6.8 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.

7.4.6.9 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*." (31).

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.

7.4.7 Pregnancy Test

A urine pregnancy test (human chorionic gonadotropin [hCG]) must be performed at the trial site at Baseline prior to dispensing OLE IMP to female subjects of child-bearing potential. The test must be repeated during the trial as scheduled in Table 1-1. In addition, urine pregnancy tests

must be performed at home for females of child-bearing 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 6.4.1) and the pregnancy report must be expedited in accordance with Section 7.4.6.7.

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 centralised contract nursing service may instead perform this assessment at an in-person visit at the subject's home/residency.

7.4.8 Clinical Safety Laboratory Assessments

7.4.8.1 Central laboratory

The clinical safety laboratory parameters (chemistry and haematology) analysed by a central laboratory are presented in Table 7-2. Urine samples will be tested at the trial site and the result recorded in the eCRF (urinalysis and pregnancy test).

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 1-1). Clinical safety laboratory tests may be repeated between the end-of-trial visit in ORARIALS-01 and the Baseline visit. 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 is noted at the end-of-trial visit in the ORARIALS-01 trial and 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 enrolled into the trial (respecting exclusion criterion 4). 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 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 centralised contract nursing service may instead perform this assessment at an in-person visit at the subject's home/residency.

Table 7-2: Clinical Safety Laboratory Parameters

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

[a] Females of child-bearing potential only
[b] Not required at visit 3, 5 and 7.

7.4.8.2 Local laboratory

Local safety laboratory assessments may also occur in case of close monitoring for increased transaminases (see Section 7.4.9.2).

7.4.9 Follow-up for specific laboratory abnormalities

7.4.9.1 Increased serum creatinine

Serum creatinine values > 2-3-fold compared to the subject's baseline value (of the present trial) should be further investigated for signs of kidney injury. Estimation of the subject's glomerular filtration rate 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.

7.4.9.2 Increased transaminases

Transaminases (ASAT, ALAT) > 3 x ULN must be further investigated in line with the FDA Guidance on Drug-Induced Liver Injury (34).

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 6.4).

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 6.4.

7.5 Biological Sample Assessments

7.5.1 Pharmacokinetics Assessments

The plasma samples will be analysed for arimoclomol using a bioanalytical method validated in accordance with the US FDA Guidance for Industry (32) and EMA Guideline on bioanalytical method validation (33). 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 (32).

The bioanalysis will be performed by Covance (see Appendix 10.2.16.3) 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.

Blood Samples

Blood samples will be taken for bioanalysis of concentrations of arimoclomol in plasma at Week 20, 52 and 76 (see Table 1-1).

At Week 20 a blood sample will be drawn pre-dose and at 0.5 hours post-dose. At weeks 52 and 76, 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 weeks 20, 52 and 76 site visits.

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.

7.5.2 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 testing of disease-specific biomarkers. The location of the biorepository is detailed in Appendix 10.2.16.3.

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.

Samples will be collected in accordance the schedule of procedures (see Table 1-1). Residual blood and urine from clinical safety laboratory sampling will also be submitted to the biorepository.

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).

7.5.3 Estimate of Total Blood Volume Collected

Blood samples will be drawn for analysis of safety (chemistry, haematology, pregnancy test). 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 drawn on a single occasion will not exceed 30 mL.

7.5.4 Destruction of Biological Material

All biological material will be retained until the results have been reported. The material will subsequently be destroyed by the responsible laboratory.

7.6 Home Visit / Contract Nursing Service

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

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

A maximum of 231 subjects are planned to be enrolled. However, it is estimated that approximately 60% (i.e., 144 subjects) will be available for the OLE from ORARIALS-01. As this trial is an OLE planning to include subjects from the previous trial, no calculation for sample size was performed.

8.2 Trial Analysis Sets

Safety analyses will be performed on the safety population which consists of subjects receiving at least one dose of arimoclomol in the OLE trial.

Efficacy analyses will be performed on subjects receiving at least one dose of IMP in the in the OLE trial, with a Baseline (of the present trial) and at least one post-baseline value of ALSFRS-R and SVC if applicable.

8.3 Statistical Analysis

8.3.1 Disposition of Subjects

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

8.3.2 Demographics and Other Baseline Characteristics

Continuous demographic and baseline parameters will be summarised 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 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 overall and by trial visit.

8.3.4 Analysis of Efficacy

As secondary objectives of the trial, efficacy variables will be explored through descriptive statistics at each scheduled visit of the current trial. Formal statistical testing is not planned, and alpha adjustments not needed. When applicable, 95% confidence intervals (CIs) will be provided for absolute and percent changes from Baseline (of the present trial).

8.3.5 Analysis of Safety

8.3.5.1 Adverse Events

AEs will be coded by system organ class and preferred term from the current version of Medical Dictionary for Regulatory Activities. 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.

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

8.3.5.2 Other Safety Parameters

Safety analysis (AEs, laboratory, and vital signs) will be descriptive, based on the safety population. The safety analysis will focus on the TEAEs period defined as the time from the first dose of the current trial to the last dose of arimoclomol + 2 weeks.

For analyses of changes from Baseline for laboratory and vital signs parameters, Baseline of the present trial will be used.

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

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

8.3.6 Exploratory Analysis

8.3.6.1 Health-related Quality of Life

The EQ-5D-5L will be summarised at each visit using descriptive statistics.

8.3.6.2 Pharmacokinetics

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

8.3.7 General Principles

Summary statistics will be done by various sub-groups and overall. Sub-groups will include the randomized treatment group from the ORARIALS-01, subjects on edaravone, and other entry criteria sub-groups.

No formal hypothesis testing will be done. When applicable, unless otherwise stated, all significance tests will be two-sided using the 5% significance level. All 95 % 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. 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 prior to enrolment of the first subject under this protocol.

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

Missing data will not be imputed. All summaries will be based on observed data.

9 REFERENCE LIST

1. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. World Medical Association. Oct 2013.

2. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1), Step 4. 10 Jun 1996.

3. Rothstein, JD. "Excitotoxicity Hypothesis." *Neurology* 1996;47 (Issue 4, Supplement 2):19S–26S. doi:10.1212/WNL.47.4_Suppl_2.19S.

4. Crul T, Toth N, Piotto S, et al. Hydroximic Acid Derivatives: Pleiotropic HSP Co-Inducers Restoring Homeostasis and Robustness. *Current Pharmaceutical Design* 2013;19 (3): 309–46. http://www.ncbi.nlm.nih.gov/pubmed/22920902.

5. Subhankar P and Mahanta S. Association of Heat-Shock Proteins in Various Neurodegenerative Disorders: Is It a Master Key to Open the Therapeutic Door? *Molecular and Cellular Biochemistry* 2014a;386 (1–2): 45–61. doi:10.1007/s11010-013-1844-y.

6. Kalmar B, Lu C, and Greensmith L. The Role of Heat Shock Proteins in Amyotrophic Lateral Sclerosis: The Therapeutic Potential of Arimoclomol. *Pharmacology & Therapeutics* 2014;141 (1). Elsevier Inc.: 40–54. doi:10.1016/j.pharmthera.2013.08.003.

7. Kalmar B, Novoselov S, Gray A, et al. Late Stage Treatment with Arimoclomol Delays Disease Progression and Prevents Protein Aggregation in the SOD1G93A Mouse Model of ALS. *J Neurochem*. 2008a;107 (2): 339–50. doi:10.1111/j.1471-4159.2008.05595.x.

8. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis. *Science.* 2006'314 (5796): 130–33. doi:10.1126/science.1134108.

9. Taylor JP, Brown RH, and Cleveland DW. Decoding ALS: From Genes to Mechanism. *Nature.* 2016;539 (7628): 197–206. doi:10.1038/nature20413.

10. Scotter EL, Chen HJ, and Shaw CE. TDP-43 Proteinopathy and ALS: Insights into Disease Mechanisms and Therapeutic Targets. *Neurotherapeutics* 2015;12 (2): 352–63. doi:10.1007/s13311-015-0338-x.

11. Ahmed M, Machado PM, Miller A, et al. Targeting Protein Homeostasis in Sporadic Inclusion Body Myositis. *Science Translational Medicine.* 2016; 8 (331): 331ra41. doi:10.1126/scitranslmed.aad4583.

12. Chen HJ, Mitchell JC, Novoselov S, et al. The Heat Shock Response Plays an Important Role in TDP-43 Clearance: Evidence for Dysfunction in Amyotrophic Lateral Sclerosis. *Brain*. 2016;aww028. doi:10.1093/brain/aww028.

13. Kalmar B, and Greensmith L. Cellular Chaperones As Therapeutic Targets in ALS to Restore Protein Homeostasis and Improve Cellular Function. *Frontiers in Molecular Neuroscience.* 2017;10 (September): 1–10. doi:10.3389/fnmol.2017.00251.

14. Cudkowicz ME, Shefner JM, Simpson E, et al. Arimoclomol at Dosages up to 300 Mg/day Is Well Tolerated and Safe in Amyotrophic Lateral Sclerosis. *Muscle & Nerve* 2008;38 (1): 837–44. doi:10.1002/mus.21059.

15. Open label extension of AALS-001, 6 months; Clinical Trial Report; AALS-001 OL, Available on request.

16. Benatar M, Wuu J, Andersen PM, et al. Randomized, Double-Blind, Placebo-controlled Trial of Arimoclomol in Rapidly Progressive SOD1 ALS. *Neurology*. 2018;Jan. doi: 10.1212/WNL.0000000000004960.

17. Investigator's Brochure. Arimoclomol. Niemann-Pick Disease Type C, Gaucher's Disease, Amyotrophic Lateral Sclerosis, Sporadic Inclusion Body Myositis. Edition 3.0. 13 September 2019.

18. United States Food and Drug Administration (US FDA). Guidance for Industry: Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment. Draft Guidance. February 2018.

19. Committee for Medicinal Product for Human Use (CHMP) Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS). 19 November 2015 EMA/531686/2015, Corr.1 1

20. Kaufmann P, Levy G, Montes J, et al. Excellent Inter-rater, Intra-rater, and Telephone-administered Reliability of the ALSFRS-R in a Multicenter Clinical Trial." *Amyotrophic Lateral Sclerosis* 2007;8 (1): 42–46. doi:10.1080/17482960600888156.

21. Maier A, Holm T, Wicks P, et al. Online Assessment of ALS Functional Rating Scale Compares Well to in-Clinic Evaluation: A Prospective Trial. *Amyotrophic Lateral Sclerosis* 2012;13 (2): 210–16. doi:10.3109/17482968.2011.633268.

22. Leigh PN, Swash M, Iwasaki Y, et al. Amyotrophic Lateral Sclerosis: A Consensus Viewpoint on Designing and Implementing a Clinical Trial. *Amyotrophic Lateral Sclerosis* 2004;5 (2): 84–98. doi:10.1080/14660820410020187.

23. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: A Revised ALS Functional Rating Scale That Incorporates Assessments of Respiratory Function. *J Neuro Sci* 1999;169 (1–2):13-21. doi:10.1016/S0022-510X(99)00210-5.

24. Castrillo-Viguera C, Grasso DL, Simpson E, et al. Amyotrophic Lateral Sclerosis Clinical Significance in the Change of Decline in ALSFRS-R Clinical Significance in the Change of Decline in ALSFRS-R. *Amyotrophic Lateral Sclerosis* 2010;11 (June 2009): 1–2. doi:10.3109/17482960903093710.

25. Traynor BJ, Zhang H, Shefner JM, Schoenfeld D, and Cudkowicz ME. Functional Outcome Measures as Clinical Trial Endpoints in ALS. *Neurology* 2004;63: 1933–35. doi:10.1212/01.WNL.0000144345.49510.4E.

26. Meininger V, Bensimon G, Bradley WG, et al. Efficacy and Safety of Xaliproden in Amyotrophic Lateral Sclerosis: Results of Two Phase III Trials. *Amyotrophic Lateral Sclerosis* 2004;5 (2):107-17. doi:10.1080/14660820410019602.

27. Hankinson JL, Crapo RO, and Jensen RL. Spirometric Reference Values for the 6-S FVC Maneuver. *Chest* 2003;124 (5): 1805–11. doi:10.1378/chest.124.5.1805.

28. European Union. The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Manufacture of Investigational Products - Brussels. 3 Feb 2010.

29. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Series ‘‘ATS/ERS Task Force: Standardisation of Lung Function Testing’’ edited by V. Brusasco, R. Crapo and G. Viegi Mumber 2 in this Series. *Eur Respir J.* 2005;26:319–338. doi: 10.1183/09031936.05.00034805

30. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA’s Pediatric Suicidal Risk Analysis of Antidepressants. *Am J Psychiatry*. 2007; 164(7):1035-1043.

31. European Parliament and Council of the European Union. Directive 2001/20/EC of 4 April 2001 On the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use [2001], article 10.

32. United States Food and Drug Administration (US FDA). Guidance for Industry: Bioanalytical Method Validation. May 2001.

33. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP). Guideline on Bioanalytical Method Validation. EMEA/CHMP/EWP/192217/2009. 21 July 2011.

34. FDA Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009

35. Addendum version 1.0 to Investigator's Brochure v3.0 dated 13-Sep-2019. Arimoclomol. Niemann-Pick disease type C, Gaucher's disease, amyotrophic lateral sclerosis, sporadic inclusion body myositis. Release date 04-Jun-2020.

10 APPENDICES

10.1 Protocol Summary

Title	Arimoclomol in ALS – Open-Label Extension Trial Open-label, Non-randomised Extension Trial to Assess the Long-Term Safety and Efficacy of 1200 mg/day Arimoclomol citrate 400 mg Three Times a Day (t.i.d.) in Subjects with Amyotrophic Lateral Sclerosis (ALS) who have Completed the ORARIALS-01 Trial
ICI	[redacted], MD, PhD
Phase	3b
Indication	ALS
Design	This is a multicentre, non-randomised, open-label, uncontrolled, trial to evaluate the safety and efficacy of long-term treatment of 1200 mg/day arimoclomol citrate (400 mg t.i.d.). Subjects diagnosed with ALS according to the revised EL Escorial criteria must have completed the double-blind ORARIALS-01 trial. They will either have met the survival endpoint (tracheostomy or PAV) or they will have completed the 76 weeks randomised treatment period. The end-of-treatment visit of the double-blinded ORARIALS-01 trial corresponds to the Visit 1 of the OLE trial. All subjects will receive open-label arimoclomol treatment. **Treatment Period** Subjects will attend the investigator site for an in-person visit on a 4-weekly basis for the initial 6 months of treatment (on Day 1, Weeks 4, 8, 12, 16, 20, 24, 28). Following Week 28, in-person visits will be conducted on a 12-weekly basis until Week 76 (i.e., weeks 40, 52, 64 and 76). Throughout the treatment period subjects will also have remote visits (conducted by telephone) every 4 weeks (Table 1-1). All visits should be scheduled within the visit window of ± 7 days. 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.

	In the event that a subject is no longer able to attend the trial site, an in-person visit may be conducted in the subject's home/residency. **Safety Follow Up** Subjects who discontinue treatment will be encouraged to attend all planned visits as per protocol after drug discontinuation. Additionally, these subjects will have a remote (telephone) visit 2 weeks after the premature IMP discontinuation. **End of Trial** All subjects will attend an end of trial visit.
IMP	Two arimoclomol capsules of 200 mg t.i.d. (1200 mg/day) will be taken orally.
Primary objective	To assess the long-term safety of arimoclomol treatment of ALS.
Primary endpoints	• Incidence and severity of TEAEs over a treatment period of 76 weeks • Mean and change from Baseline (of the present trial) to Week 76 (or end of trial) in clinical safety laboratory tests and vital signs • Incidence of potentially clinically significant abnormalities in clinical safety laboratory tests and vital signs over a treatment period of 76 weeks • C-SSRS over a treatment period of 76 weeks
Secondary objective	To evaluate the long-term efficacy of arimoclomol treatment of ALS.
Secondary endpoints	• Time to PAV/tracheostomy/death (for subjects entering this trial having completed 76 weeks of randomised treatment in ORARIALS-01) • Change in ALSFRS-R from Baseline (of the present trial) to the end of the trial • Change in SVC from Baseline (of the present trial) to the end of the trial (for subjects who did not meet the survival endpoint in the ORARIALS-01 trial)
Exploratory objectives	**Health-related quality of life**

	• To evaluate the effect of arimoclomol on health-related quality of life. **Population pharmacokinetics** • To investigate plasma levels of arimoclomol following administration of 1200 mg/day arimoclomol citrate (400 mg t.i.d.)
Exploratory endpoints	**Health-related quality of life** • EQ-5D-5L over a treatment period of 76 weeks **Population pharmacokinetics** • Plasma concentrations of arimoclomol at weeks 20, 52 and 76
Sample size	Theoretically all 231 subjects from ORARIALS-01 trial may join the ORARIALS-02 trial, however it is estimated that approximately 60% (i.e., 144 subjects) will be available for ORARIALS-02. Within the total number of subjects to participate in ORARIALS-02, up to 18 subjects could be on a stable dose of edaravone if they had been using edaravone in ORARIALS-01.
Statistical methods	**Primary Analysis** AEs will be coded by system organ class and preferred term from the current version of Medical Dictionary for Regulatory Activities. 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. All AEs, severe AEs, SAEs, and AEs causing premature treatment discontinuation will be listed by subject. Analysis for other safety parameters (AEs, laboratory, and vital signs) will be descriptive, based on the safety population. The safety analysis will focus on the TEAEs period defined as the time from the first dose of the current trial to the last dose of arimoclomol + 2 weeks. For analyses of changes from Baseline for laboratory and vital signs parameters, Baseline of the present trial will be used.

	The incidence of potentially clinically significant abnormal values for vital signs and safety laboratory values will be summarised. The C-SSRS will be summarised at each visit and overall using descriptive statistics. **Secondary analysis** As secondary objectives of the trial, efficacy variables will be explored through descriptive statistics at each scheduled visit of the current trial. Formal statistical testing is not planned, and alpha adjustments not needed. When applicable, 95% confidence intervals (CIs) will be provided for absolute and percent changes from Baseline.
Eligibility criteria	**Inclusion Criteria** 1. Subject is able to comprehend and is willing to provide written informed consent and is capable and willing to comply with trial procedures or in the circumstance that the subject is incompetent, informed consent/assent is provided in accordance with local regulation and/or procedures. 2. Subject has completed the ORARIALS-01 trial (i.e., met one of the surrogate survival endpoints of tracheostomy or PAV or has completed the 76 weeks randomised treatment period). 3. Subject completed ORARIALS-01 while on treatment, where on treatment is defined as having taken the last dose of IMP within 2 weeks of the End of Trial visit (whether at week 76 or prior). **Exclusion Criteria** 1. Known or suspected allergy or intolerance to the IMP (arimoclomol or constituents). 2. Exposure to any other investigational treatment, advanced therapy medicinal product (ATMP) or use of any other prohibited concomitant medications (see Section 6.8) 3. Women who are lactating or pregnant, or men or women unwilling to use a highly effective method of birth control if not surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy for women; vasectomy for men) for female participants until 4 weeks after last dose and for male participants until 3 months

	after last dose. Pre-menopausal women must have a negative pregnancy test prior to dosing with trial medication. Acceptable methods of birth control are: a. Hormonal methods associated with inhibition of ovulation such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before IMP administration. b. Total abstinence from sexual intercourse since the last menses before IMP administration. (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence methods [calendar, symptothermal, post-ovulation methods] are not acceptable methods of contraception). c. IUD or IUS. 4. Any of the following medically significant conditions: a. Clinically significant renal or hepatic disease OR clinical laboratory assessment (results ≥ 3 times the upper limit of normal [ULN] for aspartate aminotransferase and/or alanine aminotransferase, bilirubin ≥ 2 times the ULN, or creatinine ≥ 1.5 times the ULN). b. Any new condition or worsening of existing condition which, in the opinion of the investigator would put the subject at undue risk. 5. Any serious adverse event or moderate/severe adverse event from the ORARIALS-01 trial which is ongoing at the time of transitioning to ORARIALS-02 and assessed as probably related to IMP.
Anticipated trial period	First Subject First Visit: approximately April 2019 Last Subject First Visit: approximately December 2022 Last Subject Last Visit: approximately July 2024
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 International Ethical Guidelines.
- Current version of applicable ICH 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 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, and subjects may be up to 36 months from first symptom onset (signs of weakness) due to their involvement in ORARIALS-01 trial, it is possible that some subjects may be incapable of providing informed consent at the point of entry to the present trial the ability of a trial subject to confirm ongoing or provide new consent may be diminished (i.e., the trial subject may have significantly declined, including signs of fronto-temporal dementia, to a legal status of an incapacitated adult). Other subjects that are competent at the time of trial entry may also face significant decline.

Since there is the possibility of needing to re consent 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. Where permitted, a legal representative will be nominated by the time of the Baseline visit to ensure that this occurs while the subject is competent. 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).

For subjects unable to attend a clinic visit, informed consent may be done remotely (if permitted by local regulations).

10.2.3 Subject Card

At or prior to the Baseline visit, 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 ID code list and a subject enrolment log.

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*

If an abnormal finding (vital signs, physical examination, laboratory tests, ECG) at visit (including the Baseline visit) it is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with Section 7.4.6. 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 7.4.6.

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 schedule of subject visit attendance as well as 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.

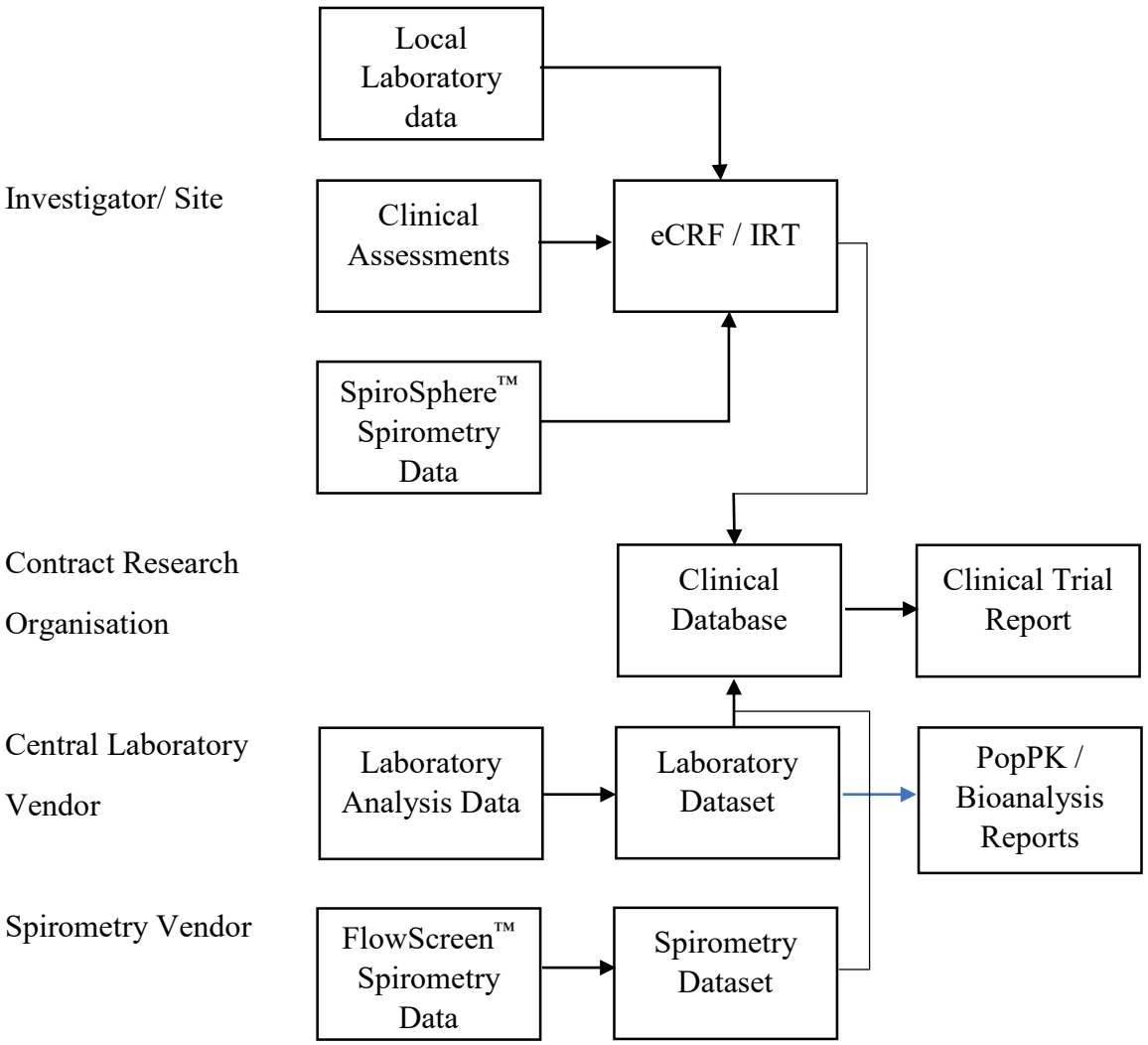
10.2.6.8 *Data Handling*

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 Figure 10-1.

Figure 10-1: 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 Trial and Site Disclosure

10.2.10.1 *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.
- No inclusion of subjects by the investigator.
- Discontinuation of further IMP development.

10.2.10.2 *Completion of Trial*

Only subjects that have completed the ORARIALS-01 trial (i.e., met one of the surrogate survival endpoints of tracheostomy or PAV or has completed the 76 weeks randomised treatment period) may enroll into the present trial.

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.

10.2.11 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.

10.2.12 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]@med.miami.edu

10.2.13 National Coordinating Investigator

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

10.2.14 Investigators

The list of investigators is maintained outside of the protocol.

10.2.15 Sponsor

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

Biostatistician (consultant representative of Sponsor)
[redacted], PhD, Statistician, President ProSoft Clinical, Phone: [redacted], email: [redacted]@prosoftclinical.com

Data Manager
[redacted], Senior Data Manager, Orphazyme A/S, Copenhagen, Phone: [redacted], email: [redacted]@orphazyme.com

Clinical Safety
[redacted], Clinical Safety Operations Manager, Orphazyme A/S, Copenhagen, Phone: [redacted], email: [redacted]@orphazyme.com

Clinical Trial Supply
[redacted], Senior Clinical Trial Supply Coordinator, Orphazyme A/S, Copenhagen, Phone [redacted], email: [redacted]@orphazyme.com

Clinical Trial Manager
[redacted], Senior Clinical Trial Manager, Orphazyme A/S, Copenhagen, Phone: [redacted], email: [redacted]@orphazyme.com

10.2.16 Service Providers

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

10.2.16.1 *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.

10.2.16.2 *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 DtP distribution and logistics as agreed in a contract.

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

10.2.16.3 *Contract laboratory services*

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

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

10.3 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. The specific sections of the protocol are referenced requiring change for a given country are noted in following sections.

10.3.1 Canada

7.4.6.6 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.

10.2.6.9 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 ICF.

10.3.2 France

10.3.2.1 Inclusion Criteria 5

An additional inclusion criterion for subjects recruited in France is mandatory under this protocol. Criterion number five as described below is required to ensure compliance with this additional national requirement.

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

10.3.2.2 Neurological Examination

As part of the Safety assessments per Table 1-1, a neurological examination should also be conducted by a neurologist in all subjects who have in clinic visit at Visits 6, 14 and 20 (Weeks 20, 52 and 76, respectively).

A neurological examination including general, cranial nerves, reflexes, motor system, coordination/cerebellar function and sensation will be carried out and only for subjects who are able to attend the trial site (see Table 10-1 for the parameters of the neurological examination).

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 7.4.6). 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.

Table 10-1 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

10.3.2.3 Temporary Halt of IMP

The below text will replace the text in Section 6.4.2 Temporary Halt of IMP:

A temporary halt of IMP treatment can be implemented only once for intolerable AEs within a given organ/body system. If the subject experiences a different intolerable AE within a different organ/body system, the IMP should be discontinued permanently.

10.3.2.4 ECG Assessments

For subjects in France, the ECG examinations should be conducted in all subjects for visits at Day 1, Weeks 20, 52 and 76 regardless of whether the visit is conducted at the trial site or in the subject's home. Section 7.4.4 statement regarding "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" will therefore not be applicable.

Day 1 coincides with the End of Trial / Week 76 visit of the ORARIALS-01 trial and therefore, results will be transferred over from the ORARIALS-01 database.

10.4 Coronavirus (COVID) operational changes

The document *ORARIALS-02 (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.

(COVID-19) Addendum 1.0 to Clinical Trial Protocol v5.0 dated 28-Feb-2020

Open-label, Non-randomised Extension Trial to Assess the Long-Term Safety and Efficacy of 1200 mg/day Arimoclomol 400 mg Three Times a Day (t.i.d.) in Subjects with Amyotrophic Lateral Sclerosis (ALS) who have Completed the ORARIALS-01 Trial

Sponsor: Orphazyme A/S, Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark
Coordinating investigator: [redacted], MD PhD
Protocol number: ORARIALS-02
EudraCT No.: 2019-000374-39
Trial product name: Arimoclomol Capsules
Date of Addendum: 24-Mar-2020

Clinicaltrials.gov ID: NCT03836716

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).

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.

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Justification for Addendum

The international outbreak of a novel respiratory disease named Coronavirus Disease 2019 (COVID-19) is currently an ongoing threat to our global health. Characterized as a respiratory virus, those infected present symptoms that underlie mild respiratory tract syndrome, severe pneumonia, and organ failure, which in several cases have led to fatality. The unprecedented transmission of the disease has meant that the World Health Organization have identified this outbreak as a pandemic.

As a result of the scale and severity of COVID-19, governments have intervened to curtail the spread of the virus. Such mitigation strategies include, travel bans, quarantine of persons who have been exposed to the disease, isolation of infected persons, closure of public and private sectors, and a general limitation on the movement/mobilization of individuals to reduce social interaction and thus contamination.

In line with the newly imposed restrictions, changes in clinical trial logistics/operations or logistics within a hospital may also be required to enforce similar measures to safeguard individuals at risk of severe disease and try to contain the spread of the virus. Namely, this will concern situations where subjects may be unable to attend scheduled clinic visits to undergo protocol assessments, and where deliveries of clinical trial supplies to subjects may not be permitted.

This 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 their currently approved Clinical Trial Protocol.

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 changes introduced in this Addendum qualify for classification as a Non-Substantial Amendment, and is applicable globally.

Modification to the Clinical Trial Protocol due to COVID-19

The following changes shall be made to the respective sections of the Clinical Trial Protocol version 5.0. In countries where version 5.0 is not yet fully in effect, the same principles will apply based on the site's currently approved version.

Section	*Modification*	*Rationale (including risk/benefit justification)*
6.4.2 Temporary Halt of IMP and Dose Modification	**Potential postponement of laboratory testing, Temporary halt of IMP and re-challenge due to missed clinical safety laboratory assessments:** In case a clinical safety laboratory sample cannot be acquired at a planned visit (see Schedule of Procedures), the Sponsor must be informed. An individual subject safety review will be performed by the Investigator. Reviews should include laboratory results and clinical assessments since baseline and reported adverse events. This evaluation must be documented in the subject's medical records and shared with Medical Monitor. The IMP should be halted immediately in any subject where safety concerns have been identified. For subjects with no safety findings, IMP may be continued to be taken, on the condition that a clinical safety laboratory sample will be acquired as soon as possible based on the below timelines: <u>For subjects who have not passed week 28 (visit 8):</u> a clinical safety laboratory assessment must occur within the visit window as per the Clinical Trial Protocol, with the visit windows being extended from -7/+7 days to -14/+14 days. If a clinical safety laboratory sample (central or	There needs to be a differentiation between subjects who have been dosed for less than 6 months, and those that have been dosed for more than 6 months. Subjects who have been on IMP for less than 6 months will require continued review of clinical safety laboratory assessments in a timely manner according to the protocol to ensure an adequate safety profile. The risk to the subjects who have been on IMP for more than 6 months is lower, where most IMP related adverse events is expected to have emerged. Subjects are only allowed to postpone safety laboratory testing if it is considered to have no added risk, set by the criteria of the Addendum. The Investigator should assess if it is in the best interest of the subjects to continue with IMP.

Section	*Modification*	*Rationale (including risk/benefit justification)*
	local) cannot be acquired within the visit window, IMP must be interrupted. <u>For subjects who have passed week 28 (visit 8):</u> the maximum permitted time between two clinical safety laboratory sample is defined by the per protocol visit interval (time between two in-person visits), plus an additional 30 days. Subjects should return to the planned schedule and resume normal blood draws as per the planned Scheduled of Procedures when possible. Subjects in need of close monitoring where appropriate follow-up cannot be performed are required to halt IMP. **IMP re-challenge after a temporary halt:** In subjects where a temporary halt does not exceed 4 weeks, IMP may be re-challenged once laboratory testing is available, and the subject is deemed safe to continue in the trial. For subjects who have halted IMP for greater than 4 weeks, a clinical safety laboratory sample should be acquired at the earliest opportunity. The Sponsor will assess whether the subject can be re-challenged with IMP. If it is deemed appropriate that IMP can be reinitiated, additional subject-specific monitoring may be required (e.g. increased frequency of the clinical safety laboratory samples). Temporary halts due to an adverse event should follow the guidance in the existing Clinical Trial Protocol (section 6.4.2).	

Section	*Modification*	*Rationale (including risk/benefit justification)*
6.5.3 Drug Distribution and Dispensation	**Drug distribution:** IMP shall be shipped to the subjects via the following routes, as permitted per local legislation: 1) Subject to collect directly from the site, as per protocol 2) Direct to subject shipment from site 3) Direct to subject shipment from depot 4) In extenuating circumstances where a site may be blocked (for example, due to quarantine), and no shipment from the depot may be possible, a subject transfer to another open site may be considered. In cases of direct to subject shipment, the shipment of IMP to the subjects will be done in a manner that does not compromise the treatment blinding. 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 through the chain of custody. The service should be used for reverse logistics to ensure that used and unused IMP 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.	The overriding objective of all changes in distribution is to provide the participating patients with the IMP as needed according to the trial protocol to ensure the right, safety and well-being of trial participants as well as the integrity of the clinical trial.

Section	*Modification*	*Rationale (including risk/benefit justification)*
6.5.3 Drug Distribution and Dispensation	**Collection of IMP:** The drug distribution logistics can be found in section 6.5.3 Drug Distribution and Dispensation above. If collecting IMP from the site, arrangements for a nominated person to collect IMP may be implemented with the subject's verbal consent if subjects are self-isolating or in quarantine. This should be documented in the source notes.	The overriding objective of all changes in distribution is to provide the participating patients with the IMP as needed according to the trial protocol to ensure the right, safety and well-being of trial participants as well as the integrity of the clinical trial.
6.5.3 Drug Distribution and Dispensation	**Additional dispensation of 4-month IMP buffer:** Subjects are normally dispensed enough IMP to last until the next clinic visit. An additional dispensation of 4 months' worth of IMP will be shipped to all Subjects. Subjects who are close to End of Trial (EOT) will only have IMP shipped to cover the remaining time in the trial. This should be documented in the accountability log as per the Clinical Trial Protocol. Individual safety assessments will be made to determine whether the subjects can continue on the IMP provided also in this Addendum (see section 6.4.2 Temporary Halt of IMP and Dose Modification).	This change is done with the overall objective to provide subjects with IMP as needed according to the protocol to ensure the right, safety and well-being of the subjects and the integrity of the clinical trial. The additional IMP will be dispensed to ensure that patients have enough IMP in case the site pharmacy closes and direct to patient IMP shipment is not possible. The additional 4-month dispensation of IMP buffer is considered acceptable as the IMP is appropriate for administration and general storage at the trial participant's home. The IMP has a long shelf-life, with the earliest expiration date noted as 31-March-2021 for the current batches. The product has a very strong temperature stability range – the recommended storage temperature is between 15-25°C, but the stability data supports excursions of 0-2°C and 25-40°C for up to 72 hours. This action ensures subjects who can have home visits/local laboratory testing, also have sufficient IMP to allow their continuation in the trial.

Section	*Modification*	*Rationale (including risk/benefit justification)*
		Management of subject safety shall continue as planned, with additional requirements in case a clinical safety laboratory test cannot be drawn for any reason. See Addendum to section 6.4.2 Temporary Halt of IMP and Dose Modification.
7.4.8 Clinical Safety Laboratory Assessments	**Use of home visits and remote visit / local laboratory:** **Use of home visit:** If a subject cannot attend a clinic visit at site, a home visit may be conducted – refer to Table 7-1: Clinical Assessments for when an in-person visit is conducted at the subject's home/residency) for the task split between the site staff and the home nursing vendor. Subjects whom, per the Investigator's opinion, should not come to clinic due to the increased infection risk (e.g. self-isolation) may also utilise the home visit. **Use of local laboratory:** Site staff should continue with the phone assessments, if an in-person visit cannot be conducted. A local local laboratory sample should be requested for continued safety review. Subjects should be instructed to provide their local laboratory results to the site as soon as possible. All local laboratory assessments in lieu of central laboratory tests must be filed as part of the site's source data for update to the eCRF.	To ensure patient safety, this flexibility will allow the continuation of safety assessments, enabling patients to remain in the trial whilst reducing the risk of contamination. In the event where in-clinic visits may enhance the risk of contamination for a given patient, the Investigator can suggest the use of home nursing to acquire safety laboratory samples limiting patient exposure to the virus. In extenuating circumstances where both in-clinic and home visits are not possible, a local laboratory may be used to ensure continued safety review, alongside a remote telephone visit. Alternative methods for safety blood analysis may be utilized in these times to reduce the risk of infection, such as dry blood spot testing. Sponsor will ensure first that these methods must be validated, and data made available for Medical Monitor reviews, prior to approval. The purpose of allowing such methods is to ensure subject safety is maintained so that they can continue on IMP.

Section	*Modification*	*Rationale (including risk/benefit justification)*
	If full clinical safety laboratory assessments cannot be performed, the following should be prioritized: 1) Liver and kidney 2) Haematology Site staff must inform the trial Medical Monitor of the results as soon as it is available. **Use of alternative laboratory methods for safety review:** Alternative methods of safety blood analysis, such as dry blood spot testing, may be applied following Sponsor review and approval. Site staff should continue with the phone assessments, if an in-person visit cannot be conducted.	
10.2.2 Informed consent process	**Informed Consent Process:** The site staff should inform the subject of the changes remotely (for example: telephone, skype) and document this conversation in the source notes. The verbal consent will be supplemented with e-mail confirmation and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants will be back at the regular sites.	A verbal consent is appropriate to reduce the risk of having subjects being exposed to the virus in-clinic. This is to facilitate subject continuation in the trial without having the need to come back to the clinic for minor logistical amendments to the protocol.
10.2.6.5 Trial monitoring	**Remote Monitoring:**	Oversight of the trial must be maintained as per ICH-GCP. In case the CRA can no longer visit the site, remote monitoring will allow

Section	*Modification*	*Rationale (including risk/benefit justification)*
	Remote monitoring refers to verification of the source by the CRA, while not on site. Remote monitoring shall be utilized where possible to allow continuation of trial review to ensure subject safety and compliance with the protocol. Methods for remote monitoring, such as direct access to electronic medical records for the CRA, teleconferencing/videoconferencing or sending on anonymized data via email for verification, should be in accordance with local legislation and ICH-GCP.	continuation of trial review to ensure subject safety and protocol compliance.
10.2.6.6 Protocol compliance	**Missed protocol assessments due to local guidance:** There may be assessments deemed as risk factors for spreading the virus during this time, and local authorities issue guidance on reduced assessments in clinic. Site staff should adhere to the local guidance and note in the source notes that such assessments could not be performed. Rules applied at the hospital should also be applied at the home visits. This should also be captured as a reason in the eCRF.	Local guidance should be adhered.
NA	**Site staff location:** In case a hospital is closed, site staff may conduct telephone assessments from home, if possible. The phone assessments should be conducted as per the Clinical Trial Protocol. Site staff should continue to document all assessments as appropriate in the source notes.	Hospital quarantine may result in site staff being asked to work from home. If permitted, site staff can easily administer certain assessments remotely, as planned, per the Clinical Trial Protocol.