Statistical Analysis Plan

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 400 mg Three Times a Day (t.i.d.) in Subjects with Amyotrophic Lateral Sclerosis (ALS) who have Completed the ORARIALS-01 Trial

Protocol Number: ORARIALS-02

Protocol Version: 6.0/08-JUN-2020

SAP Version 1.0

SAP Issue Date: *30-AUG-2021*

SAP Author: [redacted], MS

Clinicaltrials.gov ID: NCT03836716

Table of Contents

1 INTRODUCTION

This document details the planned statistical analyses for Orphazyme A/S, protocol "ORARIALS-02" study titled "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".

ORARIALS-02 study was terminated by the sponsor on 11-May-2021. Although, there is a version 7 of the protocol (dated 25JAN2021), it had not been officially implemented before termination of the study. The protocol enforced at the time was version 6 (dated 08-JUN-2020). Hence, the study description in this document is based on the content of the protocol version 6.

This is a multicentre, non-randomized, open-label, uncontrolled trial to evaluate the safety and efficacy of long-term treatment with 744 mg/day arimoclomol (248 mg t.i.d.) over a 76 week treatment period, consisting of a combination of in-person visits and remote visits (telephone calls). It is an open-label extension (OLE) for subjects that participated in the ORARIALS-01 study that was designed to assess the efficacy and safety of arimoclomol compared to placebo amongst patients with Amyotrophic Lateral Sclerosis (ALS). Protocol version 6 presents strengths of arimoclomol by weight of citrate salt. However, strengths of arimoclomol are presented throughout this document by base weight (e.g., excluding citrate salt).

Due to the termination of this study, abbreviated analyses will be conducted. Objectives and endpoints have changed. For details regarding change from protocol please see Section 7.

2 STUDY OBJECTIVES

2.1 Primary objective

To assess the long-term safety of arimoclomol treatment of ALS.

2.2 Secondary objectives

"To evaluate the long-term efficacy of arimoclomol treatment of ALS, using disease progression and progression of respiratory dysfunction."

2.3 Exploratory Objectives

To evaluate the effect of arimoclomol on health-related quality of life.

3 ENDPOINTS

3.1 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
- Columbia-Suicide Severity Rating Scale (C-SSRS) over a treatment period of 76 weeks

3.2 Secondary Endpoints

- Change from baseline during 76 weeks in the ALS Functional Rating Scale - Revised (ALSFRS-R)
- Change from baseline during 76 weeks in percent (%) predicted slow vital capacity (PPSVC)

3.3 Exploratory Endpoints

- Change from baseline in EQ-5D-5L VAS score over a treatment period of 76 weeks
- Number (Percent) of patient's responses to EQ-5D-5L dimensions[*] over a treatment period of 76 weeks

4 SAMPLE SIZE

A maximum of 231 subjects might be eligible to be enrolled in this trial, however it is estimated that approximately 60% (i.e. 144 subjects) will be available from ORARIALS-01 for the OLE. As this trial is an OLE restricted to subjects participating in the previous trial, no additional calculation for sample size was performed.

5 RANDOMIZATION

There is no randomization in this trial as it is an OLE wherein all subjects receive active therapy with the same investigational medicinal product (IMP).

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final Clinical Study Report may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Population

6.1.1 Enrolled Population

The Enrolled Population will include all patients who give informed consent to participate in the OLE trial.

6.1.2 Safety Analysis Population

The safety population will include all enrolled patients that receive at least one dose of arimoclomol in the OLE trial. This will be the primary population used for all safety and efficacy displays unless otherwise specified.

6.2 Observation Periods

Patients and the data to be used in an analysis will be selected in a two-step manner.

Firstly, patients will be selected based on the specified analysis populations.

Secondly, data points from the selected patients from the first step will be selected based on the specified observation period.

Information collected with onset date outside the observation period will be excluded from the corresponding analysis.

Two observation periods are defined

6.2.1 In-trial

This observation period represents the time period where patients are considered to be enrolled in the trial and as such under systematic follow-up. The in-trial period starts at baseline visit (which per protocol is conducted on the same date as the end of trial visit of ORARIALS-01). End of the in-trial period will be defined as the end date of the below

1. Patient recorded as dead (prior to withdrawing from study): end date is the date of death

2. Patients withdrawing without being registered as dead: end date is the maximum of withdraw date and all visit dates where assessments took place[§]

[§]: *The protocol stipulates that for withdrawn patients, if allowed by patients or caregiver, follow-up regarding PAV/tracheostomy/death is allowed. With regard to the definition of the in-trial period, as a time period wherein patients are "under observation", the time from date of trial withdrawal to "post withdrawal follow-up PAV/tracheostomy/death" is not relevant for say AEs, safety lab etc." Hence, this post withdraw follow-up will not be included when defining in-trial period.*

6.2.2 On-Treatment

This observation period represents the time period where patients are considered treated with IMP. The on-treatment period is a subset of the in-trial period and starts at the date of first administration of IMP. The protocol allows for patients to temporarily be taken off IMP by the decision of their investigator and later reinstated on IMP. As per the protocol such *drug holidays* ≤ 28 days are allowed.

6.2.2.1 Safety

In order to report safety assessments during IMP interruptions in a consistent manner relative to assessments after final termination of IMP, a patient is considered to be on-treatment at any time point up to 14 days since the latest preceding administration of IMP or the end-date for the in-trial period, whichever comes first. This means that a safety assessment occurring 15 days (or later) within a (temporary) IMP interruption period will not be considered to occur on-treatment.

The definition implies that the on-treatment time for a given patient potentially may be composed by several periods separated by interruption intervals.

6.2.2.2 Efficacy

The on-treatment period used for efficacy evaluation ends at the first time point where a patient has not administered IMP for consecutive 15 days or more, or at or the end-date for the in-trial period, whichever comes first. This definition is intended to reflect an effect that can be attributed as close as possible to a continuous treatment regimen (i.e. without interruptions that potentially can weaken the effect following an interruption).

6.3 Imported Data from Orarials-01

Per protocol, the baseline visit for this study is the end of trial visit (Visit 21) of the ORARIALS-01. The electronic case report database was designed to import data from Orarials-01 database (e.g. medical history at screening , assessments collected from Visit 21) of the orarials-01. Once imported into the 02 database, a site is able to change the data.

6.4 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.4.1 Age

Age at time of informed consent for the OLE trial will be used to represent age of subject in the study.

6.4.2 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

6.4.3 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of investigational Medicinal Product (IMP). Per protocol, the baseline visit for this study is the end of trial visit (Visit 21) of the ORARIALS-01.

6.4.4 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of investigational medicinal product (IMP).

- date of event – date of first dose of IMP + 1, for events on or after first dose
- date of event – date of first dose of IMP, for events before first dose.

6.4.5 Conventions for Missing and Partial Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

6.4.5.1 Missing / Partial Start / Stop Date of Adverse Events (AE) and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes as follows

Partial or missing stop date will be imputed as follows:

If the stop date is completely missing and the event has resolved or the patient has stopped taking the concomitant medication, the stop date will be imputed as the date of the patient's last clinic visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the patient's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the patient's last clinic visit in which case the date of patient's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of IMP or the event/concomitant medication is ongoing, the start date will be imputed as the date of the first dose of IMP.
- If the stop date occurs before the start of IMP, the start date of the event/concomitant medication will be imputed as the patient's screening date or the stop date of the event/concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of IMP or the event/concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as "01-Jan" of the same year or the date of the first dose of IMP whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of IMP, the start date of the event/concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of IMP or the event/concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of IMP in which case the date of first dose of IMP will be used.

- If the stop date occurs before the start of IMP, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing it will only be imputed in the case where the start date of the concomitant medication/event corresponds to the date of the first dose of IMP. The time will be imputed as the time as the first dose of IMP+ 1 min. In all other cases the time will not be imputed.

6.4.5.2 Missing Last Dates of Study Drug Dosing

If the date of last dose of study drug is completely missing, then for analysis purposes, last dose date will be imputed as the earliest date among the following dates:

- Date patient would run out of study drug assuming full compliance from the date of the study drug was last dispensed taking into account dose (e.g., was patient de-escalated to 372 mg/day)
- Date of early withdraw or
- Date of death

Similarly, if only the month and year of last dose was recorded, then for analysis purposes, day of last dose will be imputed as the earliest day among the above dates and last day of the month of the recorded last dose.

6.4.5.3 Missing Diagnosis Dates

If the month and year are present but the day is missing, the diagnosis date will be set to first day of the relevant month. If only the year is recorded the diagnosis date will be set as "01-Jan" for that year.

6.4.6 Exposure to Study Drug

Exposure to IMP will be calculated as follows from the date of last dosing minus the first day of dosing + 1. The exposure calculation will not take into account breaks in therapy.

6.4.6.1 Compliance

Per protocol, subjects rolling over from the original study (Orarials-01) who were on a reduced dose of 372 mg/day (124 mg t.i.d.) should maintain the same dose in the Orarials-02. All other subjects will be on 744 mg/day (248 mg t.i.d.).

Overall treatment compliance will be determined as follows

Compliance = 100 x (capsules taken/capsules expected to be taken)

where,

capsules taken = number of capsules expected to be taken* – number of missed capsules (regardless of reason including investigator instituted temporary halt).

*Number of capsules expected to be taken should take into account prescribed dose.

6.4.7 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.4.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

The following outcomes are C-SSRS categories and have binary responses (yes / no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent
Category 6	Preparatory Acts or Behavior
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non fatal)
Category 10	Completed Suicide

C-SSRS "Since last visit" version is used in this study.

Suicidal Ideation – A "yes" answer at any time during treatment to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS.

Suicidal Behavior – A "yes" answer at any time during treatment to any one of the 5 suicidal behavior questions (categories 6-10) on the C-SSRS.

Suicidal Ideation or Suicidal Behavior- A "yes" answer at any time during treatment to any of suicidal ideation/behavior questions (categories 1-10) on the C-SSRS.

There will be no imputation of missing data for C-SSRS.

6.4.9 Visit Windowing

The summary and analysis of the study endpoints by visit is conditioned on each patient contributing no more than one observation per visit. As some parameters may have assessments occurring very close in time and thus may be attributable to the same planned visit, an algorithm whereby maximally 1 (one) is being selected for summary analysis is detailed below.

There are two observation periods (in-trial and on-treatment). When doing in-trial windowing, all visits that occur in the in-trial period are included in the process whereas for on-treatment windowing only visits at or before date of last dose+14 (for the latter identify the assessments that meet these criteria before windowing; refer to on-treatment period definition). It should be noted that the last eligible assessment (e.g. end of study (EOS)) should flagged as eligible for analysis. It may be that if last assessment falls into a window with another assessment, that the last assessment would be assigned to the next visit window (see below for rules).

For purposes of by-visit analysis, the following endpoints assessed (Vital signs, Clinical safety laboratory test, ECG, EQ-5D-5L, SVC, C-SSRS, ALSFRS-R assessments), will be assigned to analysis visits based on the below time windows as appropriate.

For efficacy endpoints, only scheduled visits will be assigned to the defined windows (below). For efficacy endpoints, only in-trial windowing will be done.

For all safety endpoints, all scheduled and unscheduled visits with observations will be assigned to the defined windows (below). Only on-treatment windowing will be done for safety endpoints. If more than one measurement falls into a visit window, the measurement collected closest to the scheduled date will be used in the analysis. In case where measurements were collected an equal number of days before and after the scheduled day of the visit window then the later of the two measurements will be used for analysis. The exception is the EOS assessment, if this assessment

falls into a window with another assessment and based on rules wouldn't be flagged as eligible then EOS takes precedence and will be assigned to the next window visit and mark for analysis.

Assessments not marked "as eligible" for analysis will not be used in any analysis (descriptive or inferential) using visits as a means for organizing data and results.

All collected data will be listed and eligibility will be flagged.

Visit Windows

			Time Window (Days)									
Scheduled			Assessments collected at in-clinic visit (except at weeks 8, 16, 24)		Assessments collected at Week 20, 52 and 76 post-baseline (only)		ALSFRS-R and CSSRS		Clinical Safety Labs		Weight	
Visit	Month	Day										
1*	Baseline	1	Assigned as collected (if applicable)									
2*	Week 4	28	2	56			2	42	2	42		
3r,*v3	Week 8	56					43	70	43	70		
4*	Week 12	84	57	112			71	98	71	98		
5r,*v3	Week 16	112					99	126	99	126		
6*	Week 20	140	113	168	2	252	127	154	127	154		
7r,*v3	Week 24	168					155	182	155	182		
8*	Week 28	196	169	238			183	210	183	238		
9r	Week 32	224					211	238				
10r	Week 36	252					239	266				
11c	Week 40	280	239	322			267	294	239	322		
12r	Week 44	308					295	322				
13r	Week 48	336					323	350				
14*	Week 52	364	323	406	253	448	351	378	323	406	2	448
15r	Week 56	392					379	406				
16r	Week 60	420					407	434				
17*	Week 64	448	407	490			435	462	407	490		
18r	Week 68	476					463	490				
19r	Week 72	504					491	518				
20*	Week 76	532	491	EOP[a]	449	EOP[a]	519	EOP[a]	491	EOP[a]	449	EOP[a]

* In-clinic/person visit: In the event a patient is no longer able to attend the site, site staff will conduct a home visit and/or by telephone call. It should be noted for home visits, certain questionnaires are collected via phone. Only a subset of clinical assessments will be conducted; those should also be included in the above windowing scheme.
[r]Remote Visits
[v3]In-person visits per protocol amendment v3
[a]EOP=end date (day) of in-trial period

"Any time, Post-Baseline" visit is derived and should be based on all post-baseline assessments (scheduled/unscheduled) [applies to safety endpoints where applicable].

6.4.10 Protocol deviation Categories

Worldwide PD Categories will be mapped to Sponsor defined categories for presentation purposes (see Appendix X).

6.5 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS version 9.4 or higher[1].

Continuous (quantitative) variable summaries will include the number of patients (n) with non-missing values, mean, standard deviation (SD), median, minimum, maximum, quartile 1 and quartile 3.

Categorical (qualitative) variable summaries will include the number of patients (n) with non-missing values, frequency and percentage of patients who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of patients in the trial population for the treatment groups, unless otherwise specified. The denominator for by-visit displays will be the number of patients in the relevant trial population with non-missing data at each visit.

Percentages will be based on the number of non-missing observations or the patient population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Section 6.4.9 describes rules for deciding which visits/assessments are eligible for (which) analysis. Please note that all data will appear in lists and for analysis non-eligible datapoints will be highlighted in the lists.

Treatment group labels will be displayed as follows: »Arimoclomol 744 mg «.

6.5.1 Decimal Places

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data.

Decimal places for derived data will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer for example day, month, year, number of days and total scores (for rating scales) will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data, dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

P-values will be quoted to 3 decimal places. P-values < 0.001 will be presented as p<0.001.

6.6 Subject Disposition

Patient disposition will be summarized as follows:

- The number of patients in each analysis population (enrolled, Safety) will be tabulated by treatment group.
- Number (percent) of patients in the Safety Population within country and site will be tabulated by treatment group.
- The number of patients in the safety population who completed, withdrew early and reasons for withdrawal, who met survival endpoint (PAV/Tracheostomy/death), for those who withdrew early without meeting a survival event, if they consented to be contacted post-withdraw to determine if they met a survival event by Week 76 and if they did will be tabulated by treatment group.

- The number of patients that discontinued IMP prematurely and primary reason for withdrawal will be tabulated by treatment group.

6.7 Protocol Deviations

Number (percent) of patients with Major Deviations will be presented by treatment group. Important Deviations are defined as deviations classified as critical or major.

Listing of protocol deviations will be presented.

6.8 Demographics and baseline characteristics

Demographic data and baseline characteristics will be summarized for the Safety Population. Standard continuous or categorical variable summaries will be presented where appropriate. Demographic data (e.g., age in years at Informed Consent, gender, race, as well as weight in kg, body mass index (BMI) in kg/m^2) will be summarized.

6.9 Medical History

Medical history will be listed only.

6.10 Prior and Concomitant Medications

Prior medications are defined as all medications starting before the date of first dose of IMP. Concomitant medications are defined as medications taken on or after the date of first dose of IMP. Prior and concomitant medications will be coded using B3 WHO Drug Global - Sep 2018 A tabulation will be produced for concomitant medications presented by treatment group for Safety population. Concomitant medications will be summarized using Anatomic Therapeutic Chemical (ATC) Level 2.

All medication data will be listed.

6.11 Exposure to Study IMP

Extent of exposure (number of days of exposure to IMP) will be presented by treatment group for the Safety Population.

The number (percent) of patients that fall into the following “number of interruptions” categories (0, 1, 2, >3 interruptions) and duration of longest interruption of IMP will be summarized by treatment group for Safety Population.

6.12 Treatment Compliance

Overall compliance will be presented by treatment group and overall for the Safety population descriptively (n, mean, standard deviation, median, minimum and maximum) and number (percent) of patients in the following compliance categories (<50%, 50 to <80%, 80 to 100%, >100%).

6.13 Efficacy Analyses

Due to the termination of this study, only certain efficacy and GHO endpoints will be summarized.

6.13.1 Secondary Endpoints and analyses

6.13.1.1 ALSFRS-R

The ALSFRS-R is a short ordinal rating scale used to determine patients' patientive 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', 'climbing stairs', 'dyspnea', 'orthopnea' and 'respiratory insufficiency'). Each activity/item is rated on a 5-point scale (from 0 to 4), giving a maximum ALSFRS-R score of 48 (sum of all 12 items). The higher the score the better functioning.

Absolute and change from baseline in ALSFRS-R will be summarized by visit for the in-trial period by treatment group.

6.13.1.2 % predicted SVC

SVC measures the volume that can be exhaled from a full inhalation after exhaling to a maximum as slowly as possible. SVC is collected at in-clinic and at home visits. Several attempts at the SVC are conducted and the highest SVC result from the acceptable attempts is considered the best attempt/result and used for analysis. The spirometer used in-clinic for assessments is different from the one that will be used for an at home visit. Additionally, in-clinic visit spirometry results were subject to centralized over-read analysis whereas the home visit results were not. PPSVC will be derived as follows for SVC assessments:

PPSVC = (SVC ÷ predicted SVC (PSVC)) * 100

where PSVC is derived per European Community of Coal and Steel (ECCS) reference equations:

- If male: PSVC = 0.061 x height – 0.028 x age – 4.65
- If female: 0.0466 x height – 0.024 x age – 3.28, where [height units (cm); age units (year)]

The quality of the spirometry results could impact interpretation of the results. Hence, data of "unacceptable" quality will be excluded from analysis. For in-clinic assessments, if a spirometry assessment is assigned a best test review (BTR) grade of unacceptable, then this means the data does not meet ATS criteria for data quality and hence will be excluded from analysis. Although, spirometry results from home visits are not overread and an BTR grade isn't assigned, the spirometric device will provide "error codes" for the attempts that are used to determine the best measurement. These "error codes" represent specific issues with the measurement (e.g. error code Q means No stable baseline) which may lead to excluding the best attempt from analysis. This will depend on the error code(s) provided by the device (e.g., any attempt with error code of Q, an assessment with combination of O (no plateau) or (expiration of less than 6 sec) with error code N (no repeatability)).

Absolute and change from baseline in PPSVC will be summarized by visit for the in-trial period by treatment group.

6.13.2 Exploratory Endpoints

- Change from baseline in EQ-5D-5L VAS score over a treatment period of 76 weeks
- Number (Percent) of patient's responses to EQ-5D-5L dimensions[*] over a treatment period of 76 weeks

6.13.3 Multiplicity

Not applicable. No inferential analyses are plan.

6.14 Safety Analyses

Unless otherwise stated, safety summaries are based on the on-treatment period, however, all data will be listed in the appropriate listings.

6.14.1 Adverse Events

A »*pre-treatment AE*« is defined as any AE that has an onset prior to the first dose of IMP. This may include AEs with an onset date in original study, ORARIALS-01 (imported data). This data will be listed.

A »*treatment emergent adverse event*« (TEAE) is defined as

- Any AE that has an onset on or after the date of first dose of IMP or
- Any pre-existing AE that has worsened in severity after the first dose of IMP.

A treatment-related AE is defined as an AE that is being assessed as probably or possibly related to the IMP. If an AE has missing relationship it is assumed to be related to the IMP and assigned as “probably related” to the IMP for analysis purposes.

Maximum severity will be assumed for an AE with missing severity.

An on-treatment period TEAE is defined as

- Any TEAE that has an onset in the on-treatment period as defined for safety (see section 6.2.2.1).

An in-trial period TEAE is defined as

- Any TEAE that has an onset during the in-trial period (see Section 6.2.1)

Maximum severity will be assumed for an AE with missing severity.

The following tables will be presented for AEs:

- Overall incidence and the number of TEAEs (on-treatment and in-trial period), Serious TEAE (SAEs; on-treatment and in-trial period), on-treatment period treatment related TEAEs, on-treatment period treatment related SAEs, on-treatment period TEAEs leading to IMP withdrawal, and on-treatment period TEAEs leading to IMP interruption.
- TEAE by system organ class and preferred term, incidence and number of events
- Treatment related TEAE by system organ class and preferred term, incidence and number of events
- Serious TEAE by system organ class and preferred term, incidence and number of events
- Treatment related Serious TEAE by system organ class and preferred term, incidence and number of events

- TEAE by system organ class, preferred term and maximum severity, incidence
- TEAE by system organ class, preferred term and relationship, incidence
- TEAEs leading to IMP withdrawal by system organ class and preferred term, incidence and number of events
- TEAEs leading to IMP Interruption by system organ class and preferred term, incidence and number of events
- Liver-Related Investigations, Signs and Symptoms (SMQ) , incidence and number of events
- Drug Related Hepatic Disorders, Severe Events only (SMQ), incidence and number of events

- In-trial period
  - TEAE by system organ class and preferred term, incidence and number of events
  - Serious TEAE by system organ class and preferred term, incidence and number of events
- Listing of (all) AEs
- Listing of Serious AEs

Overall incidence of deaths and a listing of all deaths will be presented. Deaths are AEs with reported outcome of Fatal or a reported death due to disease progression (latter would not be captured as an AE).

6.14.2 Laboratory Data

Individual lab parameters will be summarized descriptively by treatment and visit. Descriptive statistics will be presented for each hematology and serum chemistry parameter. In addition to the summaries detailed previously, geometric mean and associated CV[§] of the ratio-to-baseline and observed value of each lab parameter for post-baseline will be output.

[§]: The geometric mean is calculated as the exponentiated mean of the log-transformed parameter where parameter is either observed value or ratio to baseline. The associated CV is calculated as $100\sqrt{\exp(\sigma^2} - 1$ where σ^2 is the variance of the log transformed parameter of interest.

Each measurement (continuous data) will be classed as below (low), within (normal), or above (high) normal range, based on ranges supplied by the laboratory used. Number (%) of patients that fall out-side and within range will be reported by visit.

Listings of patients with parameter results considered to be clinically significantly abnormal by investigator will be presented. The listings will list all lab parameter results where at least one value is considered clinically significantly abnormal.

Furthermore,

- a list of all (in-trial) AEs in patients with ALAT or ASAT ≥ 3 × ULN (in-trial).
- a list of all (in-trial) AEs in patients fulfilling criteria {ALAT ≥ 3 × ULN *and* eosinophilia[*] > 5%} *or* {ASAT ≥ 3 × ULN *and* eosinophilia > 5%} (in-trial).

[*]: SDTM.LB$LBTEST=”Eosinophils/Leukocytes”

All clinical safety lab parameters captured for this study with defined PCS values (Appendix 2) will be summarized descriptively by visit and overall, respectively.

Liver Parameter Categories of Potentially Clinical Significance[*]

- ALAT (Alanine Aminotransferase) or ASAT (Aspartate Aminotransferase) ≥ 3 × ULN
- ALAT or ASAT ≥ 5 × ULN
- ALAT or ASAT ≥ 8 × ULN
- ALAT or ASAT ≥ 20 × ULN
- Total Bilirubin ≥ 2 × ULN
- ALP ≥ 2 × ULN
- ALP ≥ 3 × ULN
- (ALAT or ASAT ≥ 3 × ULN) & Total Bilirubin ≥ 2 × ULN & ALP ≤ 1.5 × ULN
- ALAT ≥ 3 × ULN
- ALAT ≥ 5 × ULN
- ALAT ≥ 8 × ULN
- ALAT ≥ 20 × ULN
- ALAT ≥ 3 × ULN & Total Bilirubin ≥ 2 × ULN & ALP ≤ 1.5 × ULN
- ASAT ≥ 3 × ULN
- ASAT ≥ 5 × ULN

- ASAT ≥ 8 × ULN
- ASAT ≥ 20 × ULN
- ASAT ≥ 3 × ULN & Total Bilirubin ≥ 2 × ULN & ALP ≤ 1.5 × ULN

[*]: The single-parameter categories, like e.g. "ALAT ≥ 3 × ULN" is simply a categorization of the individual recorded value (AVAL in CDISC terminology). For "by visits" summaries, the data will be "in-windowed" records, whereas for "overall" summaries also "not in-windowed" records are eligible for summary.

For multi-parameters categories like e.g. "ALAT or ASAT ≥ 3.0 × ULN & Total Bilirubin ≥ 2 × ULN & ALP ≤ 1.5 × ULN", because of windowing being parameter specific, it is important that parameters get compared/merged *not* by visits (after relocation/windowing) but based on the original sample dates (in CDISC terminology either "VISITNUM" or "ADT").

The above categorical parameters are to be presented in one table for "by visit" and one table for "overall" summaries, respectively.

Furthermore, the following categorical summaries will be summarized descriptively overall:

- ALAT or ASAT ≥ 5 × ULN for more than 14 days[§]
- (ALAT or ASAT ≥ 3 × ULN) & (Total Bilirubin ≥ 2 × ULN)
- (ALAT or ASAT ≥ 3 × ULN) and with ongoing eosinophilia > 5% (in SDTM.LB$LBTEST = "Eosinophils/Leukocytes")

[§]: either or both "ALAT ≥ 5 × ULN for 14 days" and/or "ASAT ≥ 5 × ULN for 14 days".

The above categorical parameters are to be presented in one table for "overall" summary.

The following creatinine related categorical summaries will be summarized both by visit and overall, respectively:

(Creatinine) Categories of Potentially Clinical Significance

- Post baseline value ≥ 1.5 × baseline value
- Post-baseline value ≥ 2 × baseline value
- Post-baseline value ≥ 3 × baseline value

The above categorical creatinine parameters are to be presented in one table for "by visit" and one table for "overall" summaries, respectively.

6.14.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath / min)
- Body temperature (degrees Celsius)
- Body weight (kg)

In addition, the Number (%) of patients that have potentially clinically significant vital sign values overall and by visit will be presented:

Vital Sign Parameters Potentially Clinically Significant Values

Parameters	Unit	Reference Range	PCS LOW	PCS HIGH
Pulse rate	Beats/min	60-100	< 50 and decrease of ≥ 15	>120 and increase of ≥ 15
Diastolic Blood Pressure	mmHg	60-90	≤ 50 and decrease of ≥ 15	> 105 and increase of ≥ 15
Systolic Blood Pressure	mmHg	100-140	≤ 90 and decrease of ≥ 20	> 180 and increase of ≥ 20
Weight	Kg		decrease of ≥ 7%	increase of ≥ 7%

6.14.4 Electrocardiogram Data

Summary tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS) by visit and any time, post-baseline will be presented.

6.14.5 C-SSRS

Number (percent) of patients with Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior without Suicidal Intent Based on the C-SSRS will be summarized for baseline and any Time, Post-baseline separately.

7 CHANGES TO PLANNED PROTOCOL ANALYSIS

Due to termination of the study,

- Objective 2 was changed (highlighted text removed)
  To evaluate the long-term efficacy of arimoclomol treatment of ALS, using intervention-free survival, disease progression and progression of respiratory dysfunction

- Objective 3 had the following objective removed:

  To investigate plasma levels of arimoclomol following administration of 744 mg/day (to be described in a separate PK analysis plan and report).

- Trial analysis sets - Change in Analysis sets.

  Protocol specified that "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." However, now efficacy analyses will be performed on the safety population which consists of all enrolled subjects receiving at least one dose of arimoclomol in the OLE trial.

- Time to PAV/Tracheostomy/Death was removed as an efficacy endpoint.

8 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA

9 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1	Patient Disposition, Analysis Populations Enrolled Population In-trial period	IP	
14.1.1.2	Patient Disposition, Early Withdrawals Safety Population In-trial Period	IP	
14.1.1.3	Patient Disposition, Premature Discontinuation of IMP Safety Population In-trial Period	IP	
14.1.1.4	Patient Disposition, Safety population by Country and site Safety Population In-trial Period	IP	
14.1.1.5	Patient Disposition, Major Protocol Deviations Safety Population In-trial Period	IP	
14.1.2	**Demographics**		
14.1.2	Demographics Safety Population In-trial Period	IP	
14.1.3	**Baseline Characteristics**		
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.2	**Secondary Efficacy Endpoints**		
14.2.2.1	ALSFRS-R, Descriptive Summary by Visit Safety Population In-trial Period	IP	
14.2.2.2	% Predicted SVC, Descriptive Summary by Visit Safety Population In-trial Period	IP	
14.2.3	**Exploratory Endpoints**		

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.2.3.1	EQ-5D-5L, Categorical Summary of Dimensions by Visit Safety Population In-trial Period	IP	
14.2.3.2	EQ-5D-5L, Descriptive Summary of VAS Score by Visit Safety Population In-trial Period	IP	
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1	Adverse Events, Overall Summary of Adverse Events Safety Population In-trial Period	IP	
14.3.1.2	Adverse Events, TEAEs by Primary System Organ Class and Preferred Term Safety Population On-treatment Period	IP	
14.3.1.3	Adverse Events, Treatment Related TEAEs by Primary System Organ Class and Preferred Term Safety Population On-treatment Period	IP	
14.3.1.4	Adverse Events, Serious TEAEs by Primary System Organ Class and Preferred Term Safety Population On-treatment Period	IP	
14.3.1.5	Adverse Events, Treatment Related Serious TEAEs by Primary System Organ Class and Preferred Term Safety Population On-treatment Period	IP	
14.3.1.6	Adverse Events, TEAEs Leading to IMP Withdrawal by Primary System Organ Class and Preferred Term Safety Population On-treatment Period	IP	
14.3.1.7	Adverse Events, TEAEs Leading to IMP Interruption by Primary System Organ Class and Preferred Term Safety Population On-treatment Period	IP	
14.3.1.8	Adverse Events, TEAEs by Primary System Organ Class, Preferred Term and Severity Safety Population On-treatment Period	IP	
14.3.1.9	Adverse Events, TEAEs by Primary System Organ Class, Preferred Term and Relationship Safety Population On-treatment Period	IP	
14.3.1.10	Adverse Events, TEAEs by Primary System Organ Class and Preferred Term Safety Population In-trial Period	IP	
14.3.1.11	Adverse Events, Serious TEAEs by Primary System Organ Class and Preferred Term Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	In-trial Period		
14.3.1.12	Adverse Events, TEAEs - Liver-Related Investigations, Signs and Symptoms (SMQ) Safety Population On-treatment Period	IP	
14.3.1.13	Adverse Events, TEAEs - Drug Related Hepatic Disorders, Severe Events only (SMQ) Safety Population On-treatment Period	IP	
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1	Deaths, Listing – Safety Analysis Population	IP	
14.3.2.2	SAE Listing – Safety Analysis Population	IP	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1	Hematology, Descriptive Summary of Parameters by Visit-Safety Population-On-treatment Period	IP	
14.3.4.2	Hematology, Categorical Summary of Potentially Clinically Significant Values at Any Time, Post-Baseline-Safety Population-On-treatment Period	IP	
14.3.4.3	Hematology, Categorical Summary of Potentially Clinically Significant Values at by Visit-Safety Population-On-treatment Period	IP	
14.3.4.4	Hematology, Categorical Summary of In/Out of Normal Range Values by Visit Safety Population On-treatment Period	IP	
14.3.4.5	Chemistry, Descriptive Summary of Parameters by Visit-Safety Population-On-treatment Period	IP	
14.3.4.6	Chemistry, Categorical Summary of Potentially Clinically Significant Values at Any Time, Post-Baseline-Safety Population-On-treatment Period	IP	
14.3.4.7	Chemistry, Categorical Summary of Potentially Clinically Significant Values at by Visit-Safety Population-On-treatment Period	IP	
14.3.4.8	Chemistry, Categorical Summary of In/Out of Normal Range Values at by Visit-Safety Population-On-treatment Period	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.4.9	Lab Parameters, Categorical Summary of Potentially Clinically Significant Categories by Post-Baseline Visit-Safety Population-On-treatment Period	IP	
14.3.4.10	Lab Parameters, Categorical Summary of Potentially Clinically Significant Categories by at Any Time, Post-Baseline-Safety Population-On-treatment Period	IP	
14.3.4.11	All Adverse Events in patients with ALAT or ASAT ≥ 3x ULN during the in-trial period, Listing Safety Population In-trial Period	IP	
14.3.4.12	All Adverse Events in patients with ALAT or ASAT ≥ 3x ULN in combination with eosinophils > 5% during the in-trial period, Listing Safety Population In-trial Period	IP	
14.3.4.13	Lab parameters, listing of patients with ALAT or ASAT ≥ 3x ULN in combination with eosinophils > 5%, Listing Safety Population In-trial Period	IP	
14.3.4.14	Hematology Lab Parameter Results where at least one value is Abnormal Clinically Significant, Listing Safety Population In-trial Period	IP	
14.3.4.15	Chemistry Lab Parameter Results where at least one value is Abnormal Clinically Significant, Listing-Safety Population-In-trial Period	IP	
14.3.4.16	Hematology Lab Parameter Results where at least one value is Potentially Clinically Significant, Listing-Safety Population-In-trial Period	IP	
14.3.4.17	Chemistry Lab Parameter Results where at least one value is Potentially Clinically Significant, Listing-Safety Population-In-trial Period	IP	
14.3.5	**Extent of Exposure, Dosage Information, And Compliance**		
14.3.5.1	Extent of Exposure Safety Population In-trial Period	IP	
14.3.5.2	Investigational Medicinal Product Interruptions	IP	
14.3.5.3	Overall Treatment Compliance		
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1	Vital Signs, Descriptive Summary of Parameters by Visit	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	Safety Population On-treatment Period		
14.3.6.2.1	Vital Signs, Categorical Summary of Potentially Clinically Significant Categories by Post-Baseline Visit Safety Population On-treatment Period	IP	
14.3.6.2.2	Weight, Categorical Summary of Potentially Clinically Significant Categories by Post-Baseline Visit Safety Population On-treatment Period	IP	
14.3.7	**Other Safety**		
14.3.7.1	ECG, Categorical Summary of Overall Interpretation of findings by Visit Safety Population On-treatment Period	IP	
14.3.7.2	C-SSRS, Number and Percentage of patients with Suicidal ideation, Suicidal Behavior and Self-Injurious Behavior without Suicidal Intent at baseline Safety Population On-treatment Period	IP	
14.3.7.3	C-SSRS, Number and Percentage of patients with Suicidal ideation, Suicidal Behavior and Self-Injurious Behavior without Suicidal Intent at Any Time Post-Baseline Safety Population On-treatment Period	IP	
14.3.8	**Concomitant Medication**		
14.3.8.1	Concomitant Medications -Safety Population In-trial Period	IP	
14.4	**PK Tables**		
14.5	**PD Tables**		
14.6	**Other Data**		

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.2.1.1	ALSFRS-R Total Score by Visit Safety Population In-trial Period	IP	
14.2.1.2	% Predicted SVC by Visit Safety Population In-trial Period	IP	
14.2.1.3	Hematology, Mean by Visit – Safety population On-treatment period	IP	
14.2.1.4	Chemistry, Mean by Visit – Safety population On-treatment period	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition and Reasons for Discontinuation from Study- Safety Population-In-trial Period	IP	
16.2.1.2	Early Discontinuation From Study Drug Safety Population-In-trial Period	IP	
16.2.1.3	Analysis Population Enrolled Population In-trial Period	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations-Safety Population-In-trial Period	IP	
16.2.2.2	Site-Level Subject Related Protocol Deviations Safety Population-In-trial Period	IP	
16.2.3	**Subjects Excluded from The Efficacy Analyses**		
16.2.4	**Demographic Data**		
16.2.4.1	Demographic Data Safety Population In-trial period	IP	
16.2.4.2	Medical History Safety Population In-trial period	IP	
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.5.1	Prior/Concomitant Medication-ITT Population-In-trial Period	IP	
16.1.5.2	Investigation Medicinal Product Administration: Missed Doses, Extra Doses and/or Temporary IMP interruptions-ITT Population	IP	
16.1.5.3	Investigation Medicinal Product Administration: Overall Compliance and Extent of exposure-ITT Population	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	ALSFRS-R total Score - Safety Population-In-trial Period	IP	
16.2.6.2	SVC Safety Population In-trial period	IP	
16.2.6.3	EQ-5D-5L-Safety Population In-trial Period		
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Events Safety population in-trial Period	IP	
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Hematology Safety population-in-trial Period	IP	
16.2.8.2	Chemistry Safety population-in-trial Period	IP	
16.2.8.3	Vital Signs Safety population-in-trial Period	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8.4	ECG Findings Safety population-in-trial Period	IP	
16.2.8.5	C-SSRS Safety population-in-trial Period	IP	

10 APPENDICES

10.1 Appendix 1

Mapping WorldWide protocol deviation categories to Orphazyme defined categories

Orphazyme Category	WW categories
INCLUSION / EXCLUSION CRITERIA	Eligibility Criteria
WITHDRAWAL CRITERIA	Other: Withdrawal
IMP COMPLIANCE	Investigational Product
DISALLOWED CONCOMITANT MEDICATION	Prohibited Medications
OTHER	Informed Consent Other: Subject Trial ID Card Study Procedures Safety Other: Miscellaneous

10.2 Appendix 2

Laboratory Test	**CDISC**	**Unit**	**PCS LOW**	**PCS HIGH**
Haematology / Coagulation				
B-haemoglobin	HGB	g/dL	≤ 9.5 (women); ≤ 11.5 (men)	≥ 16.5 (women); ≥ 18.5 (men)
B-erythrocytes (red cell count)	RBC	X 10E12/L	≤ 3.5 (women); ≤ 3.8 (men)	≥ 6.0 (women); ≥ 7.0 (men)
B-haematocrit (packed cell volume)	HCT	V/V	≤ 0.32 (women); ≤ 0.37 (men)	≥ 0.50 (women); ≥ 0.55 (men)
B-total leucocyte (white cell count)	WBC	X 10E9/L	≤ 2.8	≥ 16
B-neutrophils/leucocytes	NEUTLE	%	≤ 20	≥ 85
B-eosinophils/leucocytes	EOSLE	%	-	≥ 10
B-basophils/leucocytes	BASOLE	%	-	≥ 10
B-lymphocytes/leucocytes	LYMLE	%	≤ 10	≥ 75

Laboratory Test	CDISC	Unit	PCS LOW	PCS HIGH
B-monocytes/leucocytes	MONOLE	%	-	≥ 15
B-thrombocytes (platelet count)	PLAT	X 10E9/L	≤ 75	≥ 600
P-INR (prothrombin ratio)	INR	Ratio	-	≥ 2.0
B-prothrombin time	PT	Sec	-	≥ 18
Liver				
S-aspartate aminotransferase	AST	IU/L	-	≥ 3 x ULN
S-alanine aminotransferase	ALT	IU/L	-	≥ 3 x ULN
S-bilirubin	BILI	µmol/L	-	≥ 34
S-bilirubin, direct	BILDIR	µmol/L	-	≥ 12
S-bilirubin, indirect	BILIND	µmol/L	-	≥ 22
S-alkaline phosphatase	ALP	IU/L	-	≥ 3 x ULN
S-gamma glutamyl transferase	GGT	IU/L	-	≥ 200
S-alpha-glutathione S-transferase (alpha-GST)	GSTAL	µg/L	-	≥ 20
Kidney				
S-creatinine	CREAT	µmol/L	-	≥ 1.5 x ULN
B-urea nitrogen (BUN)	BUN	mmol/L	-	≥ 11
Electrolytes				
S-sodium (natrium)	SODIUM	mmol/L	≤ 125	≥ 155
S-potassium (kalium)	K	mmol/L	≤ 3.0	≥ 6.0
S-calcium	CA	mmol/L	≤ 1.8	≥ 3.0
S-chloride	CL	mmol/L	≤ 90	≥ 117

Laboratory Test	CDISC	Unit	PCS LOW	PCS HIGH
S-magnesium	MG	mmol/L	≤ 0.6	≥ 1.3
S-phosphate (phosphorus, (inorganic))	PHOS	mmol/L	≤ 0.65	≥ 1.95
S-bicarbonate	BICARB	mmol/L	≤ 12	≥ 38
Endocrine / Metabolic				
B-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.4	≥ 9.4
B-glucose, fasting	GLUC	mmol/L	≤ 3.0	≥ 6.0
S-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.9	≥ 11.1
S-glucose, fasting	GLUC	mmol/L	≤ 3.5	≥ 7.0
B-glycosylated haemoglobin, fasting	HBA1C	%	-	≥ 6.5
S-prolactin	PROLCTN	mIU/L	-	≥ 1350
S-protein (total)	PROT	g/L	≤ 45	≥ 95
S-albumin	ALB	g/L	≤ 27	-
Lipids				
S-cholesterol total, non-fasting/unknown	CHOL	mmol/L	-	≥ 7.8
S-cholesterol total, fasting	CHOL	mmol/L	-	≥ 6.2
S-triglycerides, non-fasting/unknown	TRIG	mmol/L	-	≥ 5.65
S-triglycerides, fasting	TRIG	mmol/L	-	≥ 4.2
S-LDL cholesterol, non-fasting/unknown	LDL	mmol/L	-	≥ 5.3
S-LDL cholesterol, fasting	LDL	mmol/L	-	≥ 4.9

Laboratory Test	CDISC	Unit	PCS LOW	PCS HIGH
S-HDL cholesterol, non-fasting/unknown	HDL	mmol/L	≤ 0.8	-
S-HDL cholesterol, fasting	HDL	mmol/L	≤ 0.9	-
Cardiac / Skeletal / Muscle				
S-creatinine kinase (total)	CK	IU/L	-	≥ 400 (women); ≥ 750 (men)
S-lactate dehydrogenase (total)	LDH	IU/L	-	≥ 750
Infection				
S-C-reactive protein	CRP	mg/L		≥ 25
Urine				
Urinary pH	PH		≤ 4	≥ 9