PROTOCOL

PRODUCT NAME:	Arimoclomol
PROTOCOL NUMBER:	IBM-OLE
IND NUMBER:	076773
EUDRACT NUMBER:	2019-000749-11
DEVELOPMENT PHASE:	Phase 3b
PROTOCOL TITLE:	An open-label, non-randomized trial to investigate the efficacy and safety of early versus delayed start of arimoclomol in patients with sporadic inclusion body myositis who have completed the IBM4809 trial
PROTOCOL DATE:	Version 5.0, 18-Jan-2021
INTERNATIONAL COORDINATING INVESTIGATOR:	[redacted], MD, Professor of Neurology, University of Kansas Medical Center (KUMC) University of Kansas Medical Center Research Institute, Inc. 3901 Rainbow Boulevard, Mailstop 2012 Kansas City, KS 66160, US
SPONSORED BY:	Orphazyme A/S Ole Maaløes Vej 3 DK2200 Copenhagen N Denmark [redacted]
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive, Suite 150 Durham, NC 27709 US

Clinicaltrials.gov ID: NCT04049097

This trial will be performed in compliance with ICH Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents.

The amendments contained in this version of the Clinical Trial Protocol are intended to be implemented immediately by all investigators as either an Urgent Safety Measure as defined by the EU clinical trials directive or as permitted in other regions. This may mean that the implementation of the amendment is prior to approval by competent authority or IRB/IEC.

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: IBM-OLE (version 5.0)

PROTOCOL TITLE: An open-label, non-randomized trial to investigate the efficacy and safety of early versus delayed start of arimoclomol in patients with sporadic inclusion body myositis who have completed the IBM4809 trial

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the trial.

SIGNATURE **DATE:**

[redacted] MD
International Coordinating Investigator
Professor of Neurology, University of Kansas Medical Center (KUMC)

[redacted] MD
International Coordinating Co-Investigator
Professor in Clinical Neurology
University College of London

[redacted] 19 JAN 2021
Medical Director
Orphazyme A/S

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SIGNATURE	**DATE:**
[redacted], MD International Coordinating Investigator Professor of Neurology, University of Kansas Medical Center (KUMC)	
[redacted]	19th January 2021
[redacted], MD International Coordinating Co-Investigator Professor in Clinical Neurology University College of London	
[redacted], MD Medical Director Orphazyme A/S	

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I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the trial.

SIGNATURE	**DATE:**
[redacted]	January 18, 2021
[redacted], MD International Coordinating Investigator Professor of Neurology, University of Kansas Medical Center (KUMC)	
[redacted], MD International Coordinating Co-Investigator Professor in Clinical Neurology University College of London	
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2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	Arimoclomol
PROTOCOL NUMBER	IBM-OLE
EUDRACT NUMBER	2019-000749-11
DEVELOPMENT PHASE	Phase 3b
PROTOCOL TITLE	An open-label, non-randomized trial to investigate the efficacy and safety of early versus delayed start of arimoclomol in patients with sporadic inclusion body myositis who have completed the IBM4809 trial
INDICATION	sporadic inclusion body myositis
OBJECTIVES	Primary: • To determine the efficacy (based on the Inclusion Body Myositis Functional Rating Scale [IBMFRS]) of early* versus delayed start of arimoclomol treatment of IBM up to Month 20 in the open-label extension (OLE) trial. Secondary: • To determine the safety and tolerability of long-term treatment of IBM with arimoclomol up to Month 40 in the OLE trial. • To determine the efficacy (on secondary efficacy endpoints) of early* versus delayed start of arimoclomol treatment of IBM up to Month 20 in the OLE trial. • To determine the efficacy (on secondary efficacy endpoints) of early* versus delayed start of arimoclomol treatment of IBM up to Month 40 in the OLE trial. Exploratory: • [redacted] • To explore population pharmacokinetics (popPK) and popPK/PD. • To determine the efficacy (on secondary efficacy endpoints) of early** versus delayed start of arimoclomol treatment over periods of 20 months duration. * Including 20 months arimoclomol treatment and 20 months placebo treatment from trial IBM4809 for the early and delayed start group, respectively. ** Including (only) 20 months arimoclomol treatment from trial IBM4809 for the early start group.
RATIONALE	The IBM4809 trial was a double-blind, placebo-controlled trial designed to determine the efficacy of 1200 mg/day arimoclomol citrate (400 mg t.i.d.) for 20 months, compared to placebo, in patients with IBM. In the present extension trial, patients completing trial IBM4809 will be invited to receive open-label arimoclomol at the same daily dosage for a further 40 months; those patients who received arimoclomol in the IBM4809 trial will be considered the early start group; patients who received placebo in the IBM4809 trial

	will be considered the delayed treatment group. This design allows the comparison of efficacy and safety of arimoclomol between the two groups. The additional 20 months treatment period will permit the evaluation of efficacy and safety over a long-term period (40 months) in a greater number of subjects, while affording continued access to arimoclomol in the absence of approved effective treatments for IBM.
TRIAL DESIGN	This Phase 3b, multicenter, nonrandomized, open-label, uncontrolled clinical extension trial is designed to compare the efficacy and safety of early versus delayed start of arimoclomol in the treatment of IBM. Up to 150 male and female patients who have completed the IBM4809 trial will be available for this trial. Patients must currently be on treatment with the investigational medicinal product (IMP) from the blinded IBM4809 trial (arimoclomol or placebo) and will enroll in this trial at Visit 14/Month 20 of the blinded IBM4809 trial. Patients who completed the IBM4809 study at a reduced dose of 600 mg/day arimoclomol citrate will continue to receive their reduced dose in this open-label extension (OLE) study. All other patients will receive 1200 mg/day arimoclomol citrate (400 mg t.i.d.). The duration of treatment in this trial is expected to be 40 months. The trial is split into two treatment periods, with a more comprehensive data collection in the first treatment period (Month 0 – 20) compared to the second treatment period (Month 21 – 40). The treatment regime will remain the same throughout the two treatment periods. Treatment period 1: Patients will be seen in the clinic at baseline and months 1, 5 and 9, 15 and 20. Visits will be conducted by telephone at month 2, 3, 4, 6, 12 and 18. For the telephone visits at month 2, 3, 4 and 6 a clinical safety laboratory assessment is also required. Efficacy will be assessed by the IBMFRS total score, 6-Minute Walk Test, Modified Timed Up and Go (mTUG), Maximal Voluntary Isometric Contraction Testing (MVICT) of the quadriceps muscle, hand grip strength testing, 36-Item Short Form Health Survey (SF-36), and falls and near falls. [redacted]. Sparse PK samples will be collected for popPK analysis and explorative popPK/PD modeling (reported separately). Additional blood will be drawn for biobanking for future potential tests. Safety will be assessed by evaluating adverse events (AEs), clinical laboratory test results, vital sign measurements, 12-lead electrocardiograms (ECGs), physical examination findings, and the Columbia Suicide Severity Rating Scale (C-SSRS). Treatment period 2: Patients will be seen in the clinic at months 23, 29, 35 and 40. Visits will be conducted by telephone at month 26, 32 and 38. Efficacy will be assessed by the in-clinic IBMFRS total score and hand grip strength testing. Safety will be assessed by evaluating AEs, clinical laboratory test results and C-SSRS. All AEs observed by the trial personnel or reported by the patient during the trial (from the time of visit 1(screening) in IBM-OLE) will be collected. If a patient discontinues treatment (or the trial is terminated) an early termination (ET) visit will be performed as soon as possible after discontinuation, with a follow-up ET phone assessment 2 weeks later. Depending on the timing of discontinuation (before or after Month 20) the assessments performed at the ET visit differs according to the relevant visit schedule (Treatment period 1 and Treatment period 2).

PLANNED NUMBER OF PATIENTS	Up to 150 patients who have completed the IBM4809 trial will be available for this trial.
TRIAL ENTRY CRITERIA	Inclusion criteria: 1. Patient is able to comprehend and is willing to provide written informed consent and is capable and willing to comply with trial procedures. 2. Patient has completed the IBM4809 trial on treatment with IMP. Exclusion criteria: 1. Known or suspected allergy or intolerance to arimoclomol or its constituents. 2. Exposure to any other investigational treatment within 30 days or <5 half-lives of the baseline visit or taking part or planning to take part in another interventional trial. 3. Significant protocol deviation in the blinded IBM4809 trial based on the investigator's judgement in discussion with the medical monitor. 4. 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 up to 3 months after last dose. Premenopausal women must have a negative pregnancy test prior to dosing with trial medication. Acceptable methods of birth control are: • 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 patient's usual menstrual cycle period) before arimoclomol administration. • Total abstinence from sexual intercourse since the last menses before arimoclomol 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 patient. Periodic abstinence [calendar, symptothermal, post-ovulation] methods, are not acceptable methods of contraception). • Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS). 5. Any concurrent condition that in the investigator's opinion will significantly interfere with assessment of safety or efficacy. 6. Inability to comply with the protocol-specified procedures/evaluations and scheduled visits as per the investigator.
TEST PRODUCT	Name: Arimoclomol citrate will be provided in the form of size "0", white hard capsules of 200 mg for oral administration. Dose, route, frequency: Patients who completed the IBM4809 study at a reduced dose of arimoclomol will continue to receive their reduced dose of 600 mg/day arimoclomol citrate (200 mg t.i.d.) in this OLE study. All other patients will receive 1200 mg/day arimoclomol citrate (400 mg t.i.d.) orally.
CONTROL PRODUCT(S)	Not applicable.

TREATMENT REGIMENS	The contents of the hard capsules can be dispersed in 10 to 30 mL (i.e., 1 to 2 tablespoons) of water, milk, or juice; or sprinkled on foods such as apple sauce or yogurt to promote dose compliance. In an aqueous dispersed state, the capsule content can be administered through a gastric tube. The tube should be flushed with 5 mL of water. If a patient experiences an intolerable AE, dosing may be interrupted, and supportive therapy may be administered as required. An interruption of up to 4 weeks (calculated from the first day of interruption) prior to resuming arimoclomol is permitted. The interruption of the dose should be as short as possible. If the patient experiences the same intolerable AE after re-challenge with the full dose of arimoclomol, arimoclomol must be discontinued permanently. Re-challenge with IMP in cases of increased transaminases should only be done in accordance with section 0 of the protocol.
COORDINATING INVESTIGATOR	[redacted], MD, Professor of Neurology University of Kansas Medical Center (KUMC)
PLANNED TRIAL SITES	Approximately 11 trial sites in the United States and 1 trial site in the United Kingdom.
CRITERIA FOR EVALUATION	• Primary efficacy endpoint: o Change in the IBMFRS total score from IBM4809 baseline to Month 20 in the OLE trial. • Secondary efficacy endpoints: o Change in 6-Minute Walk Test Distance from IBM4809 baseline to Month 20 in the OLE trial. o Change in Modified Timed Up and Go (mTUG) from IBM4809 baseline to Month 20 in the OLE trial. o Change in MVICT of the quadriceps muscle from IBM4809 baseline to Month 20 in the OLE trial. o Change in hand grip strength from IBM4809 baseline to Month 20 in the OLE trial o Change in SF-36 from IBM4809 baseline to Month 20 in the OLE trial. o Number of Falls from IBM4809 baseline to Month 20 in the OLE trial. o Number of Near Falls from IBM4809 baseline to Month 20 in the OLE trial. o Change in the IBMFRS total score from IBM4809 baseline to Month 40 in the OLE trial. o Change in hand grip strength from IBM4809 baseline to Month 40 in the OLE trial. • Exploratory endpoints: o Population pharmacokinetics (popPK) and popPK/PD (reported separately) o Change from baseline* over 20 months of arimoclomol treatment in IBMFRS total score in arimoclomol naïve patients o Change from baseline* over 20 months of arimoclomol treatment in 6-Minute Walk Test Distance in arimoclomol naïve patients o Change from baseline* over 20 months of arimoclomol treatment in Modified Timed Up and Go (mTUG) in arimoclomol naïve patients o Change from baseline* over 20 months of arimoclomol treatment in MVICT of the quadriceps muscle in arimoclomol naïve patients

	○ Change from baseline* over 20 months of arimoclomol treatment in hand grip strength in arimoclomol naïve patients ○ Change from baseline* over 20 months of arimoclomol treatment in SF-36 in arimoclomol naïve patients • Safety endpoints: ○ Safety parameters (AEs, SAEs, clinical safety laboratory values, vital signs, C SSRS to month 40 * Baseline is defined at the visit at which the subject receives first administration of arimoclomol (corresponding to Month 0 in IBM4809 baseline and Month 0 in the OLE trial for patients randomized to arimoclomol and placebo in IBM4809, respectively).
STATISTICAL METHODS	Analyses will compare efficacy and safety findings between those patients who received arimoclomol (early start group) in the IBM4809 trial and those who received placebo (delayed start group). Summaries will also present data for the overall group. Analysis Populations: Safety Population: All patients who receive at least 1 dose or partial dose of arimoclomol in the extension trial. Safety analyses will be performed on the Safety Population. Modified Intent-to-treat (mITT) Population: All patients receiving at least 1 dose or partial dose of arimoclomol in the extension trial, with a baseline value and at least 1 post-baseline value for IBMFRS. Efficacy analyses will be performed on the mITT Population. Patient Characteristics and Disposition: The distributions of demographic and clinical characteristics will be described for the early start and delayed start groups as well as the overall cohort using standard summary statistics. Efficacy Analysis: Differences in change from IBM4809 baseline to Month 20 in the OLE trial in IBMFRS between patients randomized to arimoclomol (early start) and placebo (delayed start) in IBM4809 will be determined using a modified 2-treatment period/delayed randomization analysis (to be detailed in the statistical analysis plan). Additional efficacy variables will be explored through descriptive statistics at each scheduled visit of the current trial. For statistical analyses 95% confidence intervals will be provided for changes from baseline. PopPK and popPK/PD Analyses: All plasma arimoclomol concentration and dosing data will be merged with the PK sampling dates and times and used to create the population PK input file for use in a popPK modelling analysis. In addition, the potential relationship between systemic exposure of arimoclomol and efficacy/safety measures may be explored using appropriate pharmacokinetic/pharmacodynamic models. The population PK and popPK/PD analysis plan will be described in a separate protocol and the results reported separately. Safety Analyses: Safety analysis (AEs, clinical safety laboratory values, vital signs, C-SSRS) will be descriptive, based on the Safety Population. TEAEs will be summarized by incidence, severity and causality. Continuous safety variables (vital signs, clinical safety laboratory test results) will be presented using descriptive statistics. For analyses of changes from baseline for laboratory values and vital signs parameters, baseline values from the blinded IBM4809 trial or from the current trial may be considered.

	The C-SSRS will be summarized. Compliance data will be summarized by treatment group, overall and by visit.
SAMPLE SIZE DETERMINATION	As this trial is an open-label extension planning to include patients from the previous trial (IBM4809), no calculation for sample size was performed.
TRIAL AND TREATMENT DURATION	The overall OLE trial duration from the enrollment of the first patient to the completion of the last patient is expected to be approximately 5 years. The maximum participation period for an individual subject is 41 months.

2.2. Schedule of Events

Table 2-1: Schedule of Events

Treatment period 1 (Month 0-20)

Visit #	**1**	**2**	**3 (ph one visit)**	**4 (ph one visit)**	**5 (ph one visit)**	**5a**	**6 (ph one visit)**	**7**	**8 (ph one visit)**	**9**	**10 (ph one visit)**	**11 / ET[a]**
Month	**0[b]**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**20**
Consent	X											
Eligibility	X											
Demographics	X											
Medical History	X[b]											
Vital signs, including weight	X[b]	X				X		X		X		X
Physical Examination	X[b]	X				X		X		X		X
Electrocardiogram	X[b]							X				X
Clinical Safety Lab Tests	X	X	X	X	X	X	X	X		X		X
Urine Pregnancy Test	X[b]	X				X		X		X		X
Dispensing of Medication	X	X				X		X		X		X
First dose of open-label arimoclomol	X											
Return of Medication		X				X		X		X		X
C-SSRS	X[b]	X	X	X	X	X	X	X	X	X	X	X
MVICT of the quadriceps muscle	X[b]							X				X
SF-36	X[b]							X				X
Falls diary	X[b]	X				X		X		X		X
Hand Grip Strength	X[b]							X				X
IBMFRS	X[b]	X				X		X		X		X
6MWT	X[b]					X		X		X		X
mTUG	X[b]					X		X		X		X
[redacted]	[redacted]								[redacted]			[redacted]
Biobank Samples	X[b]							X				X
PopPK Samples								X				X
Concomitant Medications	X[b,d]	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X[b,d]	X	X	X	X	X	X	X	X	X	X	X

Treatment period 2 (Month 21-40)

Visit #	**12**	**13 (phone visit)**	**14**	**15 (phone visit)**	**16**	**17 (phone visit)**	**18 / ET[f]**	**19 (Safety follow up)**
Month	**23**	**26**	**29**	**32**	**35**	**38**	**40**	**ET+2 wks**
Vital signs, including weight	X		X		X		X	
Clinical Safety Lab Tests	X		X		X		X	
Urine Pregnancy Test	X		X		X		X	
Dispensing of Medication	X	X	X	X	X	X		
Return of Medication	X		X		X		X	
C-SSRS	X	X	X	X	X	X	X	
IBMFRS	X		X		X		X	
Hand Grip Strength	X		X		X		X	
Concomitant Medications	X	X	X	X	X	X	X	X[e]
Adverse Events	X	X	X	X	X	X	X	X[e]

Abbreviations: 6MWT = 6-Minute Walk Test; C-SSRS = Columbia Suicide Severity Rating Scale; ET = early termination; IBMFRS = Inclusion Body Myositis Functional Rating Scale; [redacted]; mTUG = Modified Timed Up and Go; MVICT = Maximal Voluntary Isometric Contraction Testing; PopPK = population pharmacokinetics; SF-36 = 36-Item Short Form Health Survey

Note: Visit windows for all visits are ± 7 days relative to Visit 1.

a If a patient discontinues during treatment period 1 (or the trial is terminated) before Visit 11/Month 20, an ET visit for treatment period 1 (month 20) will be performed as soon as possible after discontinuation, with a safety follow up phone visit 2 weeks later.

b Data from the completion visit of IBM4809 will be transferred to Visit 1 of IBM-OLE if required in the OLE trial, but not collected, except for safety labs, which require samples for both studies. If this extension trial has not yet been initiated at the site, screen the patient per Section 10.2.1.

c [redacted]

d Ongoing AEs and concomitant medications from IBM4809 should be recorded in the IBM-OLE eCRF.

e Assess and record SAEs occurring since the last evaluation and collect stop dates for already ongoing AEs.

f If a patient discontinues during treatment period 2 (or the trial is terminated) between Visit 11/Month 20 and Visit 18/Month 40, an ET visit for treatment period 2 (month 40) will be performed as soon as possible after discontinuation, with a safety follow up phone visit 2 weeks later.

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
BBB	blood-brain barrier
BMI	body mass index
CRA	clinical research associate
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ET	Early termination
GCP	Good Clinical Practice
GD	Gaucher's disease
HSP	heat shock protein
IB	investigator brochure
IBM	inclusion body myositis
IBMFRS	Inclusion Body Myositis Functional Rating Scale
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
INR	International Normalised Ratio
IRB	institutional review board
ITT	intent-to-treat
IVIg	intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
mTUG	Modified Timed Up and Go
MVICT	Maximal Voluntary Isometric Contraction Testing
NASH	Non-Alcoholic Steatohepatitis

ABBREVIATION	EXPLANATION
NPC	Niemann-Pick Type C
OLE	open-label extension
PK	pharmacokinetics
Pop-PK	population pharmacokinetics
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	36-Item Short Form Health Survey
t.i.d.	3 times a day (ter in die)
TMF	trial master file
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

5. INTRODUCTION

5.1. Background and Rationale

In the US, the prevalence of sporadic inclusion body myositis (IBM) is unknown, but is conservatively estimated to be 24 cases per million and the upper prevalence estimate is 45 per million (Callan et al., 2017). Because biopsies of IBM muscle contain lymphocytic inflammatory cells and show up-regulation of major histocompatibility complex class I molecules (MHC-I), IBM was originally grouped with the idiopathic inflammatory myopathies: polymyositis and dermatomyositis. However, pathologic trials during the past 25 years have clearly defined it as a unique pathogenic entity. Sporadic inclusion body myositis causes both proximal and distal muscle weakness, characteristically most prominent in the quadriceps and finger flexors. Over time it can lead to severe disability, including falls due to quadriceps muscle weakness and foot drop, dysphagia, and eventually respiratory muscle weakness. Sporadic inclusion body myositis seldom affects patients under 40 and is much more common over the age of 50. Men are affected more frequently than women. Causes of death in patients with IBM are often ascribed to dysphagia, weakness of respiratory muscles, malnutrition, cachexia, aspiration, respiratory infection, or even respiratory failure (Price et al., 2016). There are no effective treatments for IBM. Therefore, there is a significant unmet need for these patients. Patients are often given steroids or intravenous immunoglobulin treatment, but the evidence for these treatments is lacking. Supportive measures include physical therapy and mild to moderate intensity exercise, and the use of devices and aids to mobility including motorized wheelchairs.

Arimoclomol is an orally available small molecule that readily crosses the blood-brain barrier (BBB) to stimulate an increased production of heat shock proteins (HSPs), in particular HSP70, which are natural defenses against protein misfolding under cellular stress. Arimoclomol may therefore be used to treat conditions that involve misfolded proteins, including lysosomal storage diseases such as Niemann-Pick Type C (NPC) and Gaucher's disease (GD), and protein aggregation disorders such as amyotrophic lateral sclerosis (ALS) and IBM. Arimoclomol is being developed for the indications NPC, GD, ALS, and IBM. Clinical trials have been or are currently conducted in healthy subjects, patients with NPC, GD, ALS, and IBM. Arimoclomol has also been evaluated in investigator-led trials in patients with ALS and IBM.

5.2. Clinical Experience

A total of 14 clinical trials with arimoclomol relevant for the indications NPC, GD, ALS, and IBM have been completed or are ongoing. These include 8 Phase 1 trials in healthy subjects for evaluation of a single dose, multiple doses, food effects, absorption, distribution, metabolism and elimination, as well as renal safety. In the Phase 1 trials, 112 healthy subjects were exposed to arimoclomol and 24 received placebo. Daily doses in healthy subjects ranged from 50 to 1800 mg. In NPC, 1 trial is ongoing: a Phase 2/3 trial to evaluate the efficacy and safety of arimoclomol compared to placebo (trial CT-ORZY-NPC-002), including 50 patients treated with arimoclomol (300 mg/day) or placebo. In ALS, a Phase 2 trial (trial AALS-001) has been conducted assessing safety and tolerability and pharmacokinetics (PK) in serum and cerebrospinal fluid. In an extension to this trial (trial AALS 001-OL), the safety and exploratory efficacy of longer term (6 months) open-label arimoclomol treatment was evaluated. In trial AALS-001, 62 patients with ALS received arimoclomol (75 to 300 mg/day) and 22 patients received placebo. In trial AALS-001-OL, 69 patients received arimoclomol (300 mg/day). Results from these trials suggest that arimoclomol crosses the BBB. The ALS functional rating scale-revised (ALSFRS-R) progression

rates in the 6-month open-label part of the trial showed slowing of functional loss compared to a historical control group. Arimoclomol was safe and well-tolerated in these trials. In addition, an investigator-initiated trial in rapidly progressive SOD1-ALS has been conducted where 17 patients received arimoclomol (300 to 600 mg/day) and 19 patients received placebo (trial 20100758). An investigator-initiated clinical trial with arimoclomol in which 16 patients with inclusion body myositis (IBM) received arimoclomol (300 mg/day) and 8 received placebo has been completed (trial 10656).

5.3. Summary of Potential Risks and Benefits

Trials assessing immunotherapeutic agents have not demonstrated significant efficacy against IBM. In experimental cellular and animal models, arimoclomol ameliorates key degenerative and inflammatory features of IBM pathology. In a randomized, placebo-controlled safety and tolerability trial, arimoclomol (300 mg/day) was found to be safe and well tolerated in patients with IBM. There was a trend in favor of arimoclomol in secondary endpoints of muscle function and functional IBM scales (Ahmed et al., 2016). If arimoclomol was found to be beneficial for the treatment of IBM, this would represent the only effective treatment for this otherwise progressive disease.

Data from the completed trials indicate that arimoclomol may lead to a drug-related increase in serum creatinine and a decrease in mean creatinine clearance. There was no change in glomerular filtration rate and serum cystatin C, suggesting an inhibitory effect of arimoclomol on tubular secretion of creatinine. The increase in serum creatinine may be explained by an interaction of arimoclomol with the organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion (MATE) transporters. One elderly patient with IBM experienced severe tubulointerstitial nephritis with acute tubular injury and acute tubular necrosis approximately 1 month after initiation of arimoclomol. Although the patient had autoimmune disease (Sjogren's syndrome) and was treated with omeprazole, both of which may have contributed to the event, it cannot be ruled out that the event was caused by treatment with arimoclomol. A summary of the pharmaceutical properties and known potential risks of arimoclomol is provided in the current version of the investigator's brochure (IB). The investigator must become familiar with all sections of the arimoclomol IB before the start of the trial.

6. OBJECTIVES AND PURPOSE

6.1. Objectives

6.1.1 Primary Objective

The primary objective is to determine the efficacy (based on the Inclusion Body Myositis Functional Rating Scale [IBMFRS]) of early* versus delayed start of arimoclomol treatment of IBM up to Month 20 in the OLE trial.

6.1.2 Secondary Objectives

Secondary objectives include the following:

- To determine the safety and tolerability of long-term treatment of IBM with arimoclomol up to Month 40 in the OLE trial.
- To determine the efficacy (on secondary efficacy endpoints) of early* versus delayed start of arimoclomol treatment of IBM up to Month 20 in the OLE trial.
- To determine the efficacy (on secondary efficacy endpoints) of early* versus delayed start of arimoclomol treatment of IBM up to Month 40 in the OLE trial.

6.1.3 Exploratory Objectives

Exploratory objectives include the following:

- [redacted].
- To explore population pharmacokinetics (popPK) and popPK/PD.
- To determine the efficacy (on secondary efficacy endpoints) of early** versus delayed start of arimoclomol treatment over periods of 20 months duration.

* Including 20 months arimoclomol treatment and 20 months placebo treatment from trial IBM4809 for the early and delayed start group, respectively.

** Including (only) 20 months arimoclomol treatment from trial IBM4809 for the early start group.

7. TRIAL DESIGN

7.1. Overall Trial Design and Plan

This Phase 3b, multicenter, nonrandomized, open-labelled, uncontrolled clinical extension trial is designed to compare the efficacy and safety of early versus delayed start of arimoclomol in the treatment of IBM and to explore long-term safety and tolerability of arimoclomol. Up to 150 male and female patients who have completed the IBM4809 trial will be available for this trial. Patients must currently be on treatment with the investigational medicinal product (IMP) from the blinded IBM4809 trial (arimoclomol or placebo) and will enroll in this trial at Visit 14/Month 20 of the blinded IBM4809 trial.

Patients who completed the IBM4809 study at a reduced dose of arimoclomol will continue to receive their reduced dose of 600 mg/day arimoclomol citrate (200 mg t.i.d.) in this open-label extension (OLE) study. All other patients will receive 1200 mg/day arimoclomol citrate (400 mg t.i.d.).

The OLE trial is a 40 months open-labelled extension of the blinded IBM4809 trial. Combined with the IBM4809 data from treatment period 1 the patients in the active group of IBM4809 will provide long-term (up to 60 months) efficacy, safety and tolerability data. For the placebo group in IBM4809 the OLE trial will provide additional safety and tolerability data over 40 months and information about the impact of delayed treatment initiation on efficacy.

The OLE trial consist of 2 treatment period. The only difference between the 2 treatment periods is the assessments performed and the visit schedule. Both treatment periods are described below.

Treatment period 1 (Month 0 – 20)

Patients will be seen in the clinic at baseline and month 1, 5 and 9, 15 and 20. Visits will be conducted by telephone at month 2, 3, 4, 6, 12 and 18. For the telephone visits at month 2, 3, 4 and 6 a clinical safety laboratory assessment is also required.

Efficacy will be assessed by the IBMFRS total score, 6-Minute Walk Test, Modified Timed Up and Go (mTUG), Maximal Voluntary Isometric Contraction Testing (MVICT) of the quadriceps muscle, hand grip strength testing, 36-Item Short Form Health Survey (SF-36), and falls and near falls. [redacted]

Sparse PK samples will be collected for popPK analysis and explorative popPK/PD modeling. Additional blood will be drawn for biobanking for future potential tests.

Safety and tolerability will be assessed by evaluating adverse events (AEs), clinical laboratory test results, vital sign measurements, 12-lead electrocardiograms (ECGs), physical examination findings, and the Columbia Suicide Severity Rating Scale (C-SSRS).

All AEs observed by the trial personnel or reported by the patient during the trial will be documented.

Analyses will compare efficacy and safety findings between those patients who received arimoclomol (early start group) in the IBM4809 trial and those who received placebo (delayed start group).

Treatment period 2 (Month 21-40)

Patients will be seen in the clinic at month 23, 29, 35 and 40. Visits will be conducted by telephone at month 26, 32 and 38.

Efficacy will be assessed by the IBMFRS total score and hand grip strength testing.

Safety and tolerability will be assessed by evaluating AEs, clinical laboratory test results, vital sign measurements and C-SSRS.

Treatment period 2 will provide efficacy and safety data for up to an additional 20 months.

For the early start group, treatment period 2 provides data from a period which represents the 41st to 60th month of active treatment across both clinical trials. For the delayed start group, treatment period 2 provides data from a period which represents the 21st to 40th month of active treatment across both clinical trials.

7.2. Rationale and Discussion of Trial Design

The IBM4809 trial is a double-blind, placebo-controlled trial designed to determine the efficacy and safety of 1200 mg/day arimoclomol citrate (400 mg t.i.d.) for 20 months, compared to placebo, in patients with IBM. In the present extension trial, patients completing trial IBM4809 will be invited to receive open-label arimoclomol at the same daily dosage for a further 20 months; those patients who received arimoclomol in the IBM4809 trial will be considered the early start group; patients who received placebo in the IBM4809 trial will be considered the delayed treatment group. The 40 months extension will together with the IBM4809 trial data provide additional information on the safety and tolerability of arimoclomol for a total of 60 months for the patients who were randomized to arimoclomol in the IBM4809 trial.

This extension trial allows for additional comparison of efficacy and safety of arimoclomol between the two groups, while affording continued access to arimoclomol in the absence of approved pharmaceutical treatment for IBM.

7.3. Selection of Doses in the Trial

Patients who completed the IBM4809 study at a reduced dose of 600 mg/day arimoclomol citrate will continue to receive their reduced dose in this OLE study. All other patients in this open-label extension trial will be assigned to receive 1200 mg/day arimoclomol citrate (400 mg t.i.d.).

7.4. Trial Sites

The trial will take place at approximately 11 sites in the US and 1 site in the UK.

7.5. End of Trial Definition

The clinical trial will be considered completed when the last patient's last trial visit has occurred.

8. PATIENT POPULATION

8.1. Selection of Trial Population and Diagnosis

There is no indication from the available data that age, sex, or race can potentially affect the safety or the efficacy of arimoclomol. Thus, male and female patients may be included in the trial.

Patients who do not satisfy all of the eligibility criteria will not be enrolled.

8.2. Trial Entry Criteria

8.2.1 Inclusion Criteria

A patient will be eligible for trial participation if he or she meets all of the following criteria:

1. Patient is able to comprehend and is willing to provide written informed consent and is capable and willing to comply with trial procedures.
2. Patient has completed the IBM4809 trial on treatment with IMP.

8.2.2 Exclusion Criteria

A patient will be excluded from the trial if he or she meets any of the following criteria:

1. Known or suspected allergy or intolerance to arimoclomol or its constituents.
2. Exposure to any other investigational treatment within 30 days or <5 half-lives of the baseline visit or taking part or planning to take part in another interventional trial.
3. Significant protocol deviation in the blinded IBM4809 trial based on the investigator's judgement in discussion with the medical monitor.
4. Women who are lactating or pregnant, or sexually active female subjects of child-bearing potential* intending to become pregnant or unwilling to use a highly effective method of contraception** during the trial through 1 month after the last dose of trial medication. Sexually active males with female partners of child-bearing potential* unwilling to use a condom with or without spermicide in addition to the birth control used by their partners during the trial until 3 months after the last dose of trial medication unless surgically sterile (vasectomy).

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

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

child-bearing potential). The reliability of sexual abstinence needs to be evaluated by the investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

5. Any concurrent condition that in the investigator's opinion will significantly interfere with assessment of safety or efficacy.
6. Inability to comply with the protocol-specified procedures/evaluations and scheduled visits as per the investigator.

8.3. Premature Patient Withdrawal

All patients will be advised that they are free to withdraw from participation in this trial at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep patients in the trial; however, patients must be withdrawn from the trial if they withdraw consent to participate. Investigators must attempt to contact patients who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a patient due to protocol deviations or other reasons.

The investigator also has the right to withdraw patients from the trial at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the patient, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with trial procedures, administrative reasons, or in the investigator's opinion, to protect the patient's best interest.

If a patient is withdrawn before completing the trial, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the trial should be performed at the time of premature discontinuation. Discontinuation of Study Intervention

8.4. Discontinuation of Study Intervention

Discontinuation from arimoclomol means discontinuation from the trial, and a final visit and 2-week follow-up call should be completed as scheduled.

According to the FDA Guidance for Industry on Drug-Induced Liver Injury (DILI) (4), IMP must be permanently discontinued in the case of the following:

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

Re-challenge in case of increased transaminases:

If in the Investigator's judgement, a temporary halt in IMP is instituted because of elevated transaminases, medical monitor should be consulted. A re-challenge must not occur if the patient had the following:

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

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

8.5. Participant Discontinuation/Withdrawal from the Trial

The patient will be advised in the informed consent form (ICF) that they have the right to withdraw from the trial at any time without prejudice and may be withdrawn at the investigator's or sponsor's discretion at any time. In addition, early withdrawal may occur for any of the following reasons:

- Patient request
- Investigator decides that it is in the patient's interest
- A serious adverse event (SAE) that is probably or definitely related to arimoclomol
- Significant protocol violation
- Pregnancy
- Commencing systemic treatment with prednisolone >7.5 mg or equivalent (except if short course [up to 4 weeks] administration not related to IBM e.g., due to an asthma attack), intravenous immunoglobulin (IVIg), or other immunosuppressants
- Commencing other experimental or prohibited treatments

9. TREATMENTS

9.1. Identification of Investigational Medicinal Product

Arimoclomol citrate will be provided in the form of size "0", white hard capsules of 200 mg for oral administration.

9.1.1 Rescue Medication

Currently there are no rescue medications, treatments, or procedures to treat IBM.

9.2. Selection of Timing of Dose for Each Patient

Patients who completed the IBM4809 study at a reduced dose of 600 mg/day arimoclomol citrate will continue to receive their reduced dose in this OLE study. For all other patients, including all patients who were randomized to placebo in the IBM4809 study, the dose will be 1200 mg/day (400 mg t.i.d).

The contents of the hard capsules can be dispersed in 10 to 30 mL (i.e., 1 to 2 tablespoons) of water, milk, or juice; or sprinkled on foods such as apple sauce or yogurt to promote dose compliance.

In an aqueous dispersed state, the capsule content can be administered through a gastric tube. The tube should be flushed with 5 mL of water.

9.3. Dose Adjustment Criteria

If a patient experiences an intolerable AE, dosing may be interrupted (not reduced) and supportive therapy may be administered as required. An interruption of up to 4 weeks (calculated from the first day of interruption) prior to resuming arimoclomol is permitted. The interruption of the dose should be as short as possible. If the patient experiences the same intolerable AE after re-challenge with the full dose of arimoclomol, arimoclomol must be discontinued permanently.

9.3.1 Stopping Rules

According to the FDA Guidance for Industry on Drug-Induced Liver Injury (DILI) (4), IMP must be permanently discontinued under circumstances related to elevated transaminases (see Section 0). IMP must also be discontinued for subjects with elevated transaminases where close observation (repeated laboratory tests) is not possible, see Section 0.

9.4. Treatment Compliance

Patients will use a medication log and will be instructed to return all unused arimoclomol at each clinic visit. Compliance will be assessed by review of the medication log at each visit and by documentation of unused arimoclomol. A patient who is not adherent (taking less than 80% of assigned capsules) will be counseled at each visit on the importance of taking arimoclomol as instructed.

9.5. Method of Assigning Patients to Treatment Groups

In this open-label, single-treatment trial, all patients will receive the same treatment.

9.6. Blinding and Unblinding Treatment Assignment

During the OLE trial, patients must remain blinded as to their treatment assignment in IBM4809.

9.7. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

9.7.1 Permitted Therapies

There may be soreness from the strength and functional tests that the patients must undergo. They may take normal prophylactic medications or undergo treatments or procedures to ease the soreness. Other concomitant medications are also allowed except as prohibited below.

9.7.2 Prohibited Therapies

Arimoclomol is an in vitro inhibitor of the OCT2, MATE-1, and MATE-2K transporters and consequently may inhibit the elimination of cationic drugs that are significantly eliminated by tubular secretion. In addition, arimoclomol is an in vitro substrate of the MATE-1 and MATE-2K transporters. Arimoclomol undergoes renal tubular secretion and concomitant treatment with drugs that are MATE1 or MATE-2K inhibitors may therefore lead to increased exposure of arimoclomol. Consequently, the concomitant use 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.

Based on in vitro studies, drug interactions related to cytochrome P450 (CYP) enzymes are not expected. Even though CYP2D6 inhibition was observed in vitro, the mechanistic static model predicts that it will not be clinically relevant. Consequently, concomitant use of drugs that are CYP2D6 substrate is not considered to be of concern.

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

The following medications are prohibited during the trial:

- Use of testosterone except for physiologic replacement doses in case of androgen deficiency. Participants must have documented proof of the androgen deficiency
- Cannabis except for treatment of IBM symptoms (where legal)
- Prednisone, IVIg, or other immunosuppressants. A short course (up to 4 weeks) of systemic treatment with prednisolone >7.5 mg or equivalent is allowed for conditions not related to IBM (e.g., due to an asthma attack). Topical, nasal, and ocular corticosteroids are allowed unless they are being widely applied or the severity of the underlying condition makes them unsuitable in the investigator's opinion. Local steroid injections are allowed

- Participation in other interventional trials, treatment with other investigational medicinal products or advanced therapeutic medical products (stem cells, gene therapy etc.), or treatment with investigational devices is not allowed.

If a new precautionary or prohibited medication, treatment, or procedure is identified during the trial, all patients will be notified immediately and Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs) will be notified as soon as possible.

9.7.3 Restrictions

No other restrictions are specified.

9.8. Treatment After End of Trial

Subjects completing this trial may be offered to continue arimoclomol treatment via Early Access Programs as per applicable local regulations until arimoclomol is commercially available. Early Access Programs may vary depending on location and include Compassionate Use, Named Patient, Expanded Access, and Managed Access Programs.

9.9. Dispensing and Storage

The study drug (arimoclomol) supplied by Orphazyme A/S is to be used exclusively in the clinical trial according to the instructions of this protocol. The investigator is responsible for dispensing the study drug according to the dosage scheme and for ensuring its proper storage.

The investigator must confirm the receipt of the study drug with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Orphazyme A/S and/or Premier Research. Until the study drug is dispensed to the patients, it must be stored in a securely locked area that is not generally accessible. Based on the available stability data, the study drug capsules are recommended to be stored at USP controlled room temperature, i.e., at 15º to 25ºC (59º to 77ºF) with excursions permitted between 2º and 30ºC (36º to 86ºF).

The key to the storage area is to be kept by the investigator or designee responsible for the study drug. The storage area will be accessible only to those persons authorized by the investigator to dispense the study drug.

9.10. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the study drug, including the date, quantity, batch or code number, and identification of patients (patient number) who received the study drug. The investigator will not supply the study drug to any person except those named as sub-investigators on the Form FDA 1572, designated trial personnel, and patients in this trial. The investigator will not dispense the study drug from any trial sites other than those listed on the Form FDA 1572. The study drug may not be relabeled or reassigned for use by other patients. Any study drug not dispensed; lost, stolen, spilled, or unusable; or received in a damaged container must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Patients will receive trial medication at visits at baseline and at Months 1, 5, 9, 15, 20, 23, 26, 29, 32, 35 and 38. Patients will use a medication log and will be instructed to return all unused trial medication at each clinic visit.

Upon completion of the trial, the study drug (partly used, unused, and empty bottles) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.11. Labeling and Packaging

Labeling and packaging of the study drug will be performed according to the IMPD.

9.11.1 Labeling

Each bottle will have a label affixed that meets the applicable regulatory requirements in the countries where the trial is to be conducted.

Save all empty packaging or packaging containing unused capsules for final disposition by the sponsor or contract pharmacy.

9.11.2 Packaging

The study drug will be packaged in high density polyethylene (HDPE) bottles, each containing 84 capsules, and closed with a child-resistant screw cap.

10. TRIAL PROCEDURES

Patients must provide written informed consent before any trial-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the trial, refer to the schedule of events (Section 2.2). Throughout the trial, every reasonable effort should be made by trial personnel to follow the timing of assessments and procedures in the schedule of events for each patient. If a patient misses a trial visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Trial Duration

10.1.1 Overall Trial Schedule

The overall open-label extension trial duration from the enrollment of the first patient to the completion of the last patient is expected to be approximately 5 years. The maximum participation period for an individual subject adhering to the planned visit schedule is 41 months, including the planned safety follow-up visit two weeks after the scheduled ET visit at Month 40.

10.2. Trial Periods and Visits

See Section 10.3 for details on conducting the study assessments listed below.

10.2.1 Baseline

Patients must currently be on treatment with the IMP from the blinded IBM4809 trial (arimoclomol or placebo). The following procedures performed at Visit 14/Month 20 of the blinded IBM4809 trial will serve as the baseline evaluations for this trial:

1. Measure vital signs, including weight.
2. Perform a physical examination.
3. Perform a 12-lead ECG.
4. Perform a urine pregnancy test for female patients of childbearing potential.
5. Record concomitant medications and concomitant therapies.
6. Assess and record AEs occurring since the last evaluation.
7. Complete the IBMFRS, MVICT of quadriceps muscle, mTUG, hand grip strength testing, 6-minute walk test, and SF-36.
8. Complete the C-SSRS (“since last visit” assessment).
9. Collect and review the falls diary.

(NOTE: If this extension trial has not yet been initiated at a patient’s clinical site or if the patient are not able to perform in-clinic visits due to COVID-19 when the patient completes Visit 14, that patient may enroll in this trial up to 12 weeks after Visit 14/Month 20 of the blinded IBM4809 trial. Such patients will need to undergo the full set of baseline assessments, and the investigator must confirm eligibility. This possibility will only be available if the patient is able to perform visit 14 in the IBM4809 trial before 01-Feb-2021).

The following procedures will be performed at baseline for this OLE trial:

1. Obtain written informed consent (and/or assent if applicable).
2. Record demographics.
3. Record medical history.
4. Assess inclusion/exclusion criteria.
5. Collect blood for safety laboratory tests and biobanking.
6. When all baseline procedures are completed and the site investigator confirms that the patient is eligible, enroll the patient.
7. Administer the first dose of open-label arimoclomol and observe for 1 hour after dosing.
8. Dispense arimoclomol for the initial 1-month period and give the patient instructions regarding dosing schedule and trial requirements.
9. Give the patient a new falls diary.

10.2.2 Treatment Periods:

Treatment period 1: The treatment period begins at the baseline visit and continues until the ET visit at month 20.

Treatment period 2: The treatment period begins after completing treatment period 1 and until the ET visit at month 40.

For a detailed overview of the 2 treatment periods, see Section 2.2.

10.2.2.1 Clinic Visits

Treatment period 1: (Months 1, 5, 9, 15, and 20)

The following procedures will be performed at the clinic visits:

1. Measure vital signs, including weight.
2. Perform a physical examination.
3. Perform a 12-lead ECG (Months 9 and 20 only).
4. Collect blood for clinical safety laboratory tests (all visits) and for biobanking (Months 9 and 20 only; pre-dose).
5. Collect blood for PK, at Months 9 and 20 only, at the following timepoints:
    - Month 9: pre-dose and 0.5 hours (+ 60 min) post-dose
    - Month 20: pre-dose and 1.5 hours (+ 60 min) post-dose
6. Perform a urine pregnancy test for female patients of childbearing potential.
7. Record concomitant medications and concomitant therapies.
8. Assess and record AEs occurring since the last evaluation.

9. Complete the IBMFRS.
10. Complete the 6-minute walk test, and mTUG (Months5, 9, 15, and 20 only).
11. Complete the MVICT of quadriceps muscle, hand grip strength testing, and SF-36 (all at Months 9 and 20 only).
12. Complete the C-SSRS ("since last visit" assessment).
13. Collect and review the falls diary.
14. Collect empty arimoclomol packaging and unused arimoclomol, and (at all but final visit) dispense additional arimoclomol.

Treatment period 2: (Months 23, 29, 35 and 40)

The following procedures will be performed at the clinic visits:

1. Measure vital signs, including weight.
2. Collect blood for clinical safety laboratory tests (all visits)
3. Perform a urine pregnancy test for female patients of childbearing potential.
4. Collect empty arimoclomol packaging and unused arimoclomol, and (at all but final visit) dispense additional arimoclomol.
5. Complete the C-SSRS ("since last visit" assessment).
6. Complete the IBMFRS.
7. Complete the hand grip strength testing
8. Record concomitant medications and concomitant therapies.
9. Assess and record AEs occurring since the last evaluation.

10.2.2.2 Telephone Visits

Treatment period 1: (Months 2, 3, 4, 6, 12, and 18)

The following procedures will be performed at the telephone visits:

1. Record concomitant medications and concomitant therapies.
2. Assess and record AEs occurring since the last evaluation.
3. Complete the C-SSRS ("since last visit" assessment).
4. Ensure the patient has sufficient arimoclomol and arrange for additional arimoclomol supplies if needed.
5. Clinical Safety Laboratory assessments must be obtained at month 2, 3, 4 and 6 (preferably using Home Health Care or alternatively Local Laboratory)

Treatment period 2: (Months 26, 32 and 38)

The following procedures will be performed at the telephone visits:

1. Complete the C-SSRS ("since last visit" assessment).
2. Record concomitant medications and concomitant therapies.
3. Assess and record AEs occurring since the last evaluation.

10.2.2.3 Early Termination Visit and Telephone Visit for Patients Who Discontinue Prematurely

Treatment period 1:

If a patient discontinues treatment (or the trial is terminated) before Visit 11/Month 20, an ET visit (see visit 11 in visit schedule) will be performed as soon as possible after discontinuation, and a follow-up phone assessment will be done 2 weeks later (see visit 19 in visit schedule for treatment period 2) .

The following procedures will be performed at the ET visit:

1. Measure vital signs, including weight.
2. Perform a physical examination.
3. Perform a 12-lead ECG.
4. Collect blood for clinical safety laboratory tests, biobanking, and PK.
5. Perform a urine pregnancy test for female patients of childbearing potential.
6. Record concomitant medications and concomitant therapies.
7. Assess and record AEs occurring since the last evaluation.
8. Complete the IBMFRS, 6-minute walk test, and mTUG.
9. Complete the MVICT of quadriceps muscle, hand grip strength testing, and SF-36.
10. Complete the C-SSRS ("since last visit" assessment).
11. Collect and review the falls diary.
12. Collect empty arimoclomol packaging and unused arimoclomol.

The following procedures will be performed at the ET phone visit:

1. Record concomitant medications and concomitant therapies.
2. Assess and record SAEs occurring since the last evaluation and collect stop dates for already ongoing AEs.

Treatment period 2:

If a patient discontinues treatment (or the trial is terminated) after Visit 11/Month 20 and before visit 18/month 40, an ET visit (see visit 18 in visit schedule) will be performed as soon as possible

after discontinuation, and a follow-up phone assessment will be done 2 weeks later (see visit 19 in visit schedule for treatment period 2).

The following procedures will be performed at the ET visit:

1. Measure vital signs, including weight.
2. Collect blood for clinical safety laboratory tests (all visits)
3. Perform a urine pregnancy test for female patients of childbearing potential.
4. Collect empty arimoclomol packaging and unused arimoclomol.
5. Complete the C-SSRS ("since last visit" assessment).
6. Complete the IBMFRS.
7. Complete the hand grip strength testing
8. Record concomitant medications and concomitant therapies.
9. Assess and record AEs occurring since the last evaluation.

10.3. Assessments

Trial assessments will be performed at the time points listed in the Schedule of Events (Section 2.2).

10.3.1 Efficacy Variables

10.3.1.1 IBM Functional Rating Scale

The IBMFRS is a quickly administered (10 minutes) ordinal rating scale used to determine patients' assessment of their capability and independence. It includes 10 measures (swallowing, handwriting, cutting food and handling utensils, fine motor tasks, dressing, hygiene, turning in bed and adjusting covers, changing position from sitting to standing, walking, and climbing stairs), graded on a Likert scale from 0 (being unable to perform) to 4 (normal). The sum of the 10 items gives a value between 0 and 40, with a higher score representing less functional limitation. The IBMFRS is provided in Appendix 1.

10.3.1.2 6-Minute Walk Test with 2-Minute Distance Captured

Patients will be instructed to walk down one side of the track and back along the opposite side as quickly and safely as possible for 6 minutes. Patients will be allowed to take breaks as needed during the walking period, but timing will continue during breaks. The distance walked in meters will be recorded after 2 minutes and 6 minutes. Use of assistive devices during the test will be recorded.

10.3.1.3 Modified Timed Up and Go (mTUG)

The mTUG measures the patient's ability to get up from a chair (allowing patients to use their arms), walk 3 meters, turn around, walk back to the chair, and sit down. The use of nearby walls or assistance from a caregiver is not allowed. This test will be performed twice and both results will be recorded.

10.3.1.4 Quadriceps Muscle Strength Testing

Maximal voluntary isometric contraction testing (MVICT) of the patient's quadriceps muscle will be performed using the MicroFET hand myometer. This is a hand-held device that allows the examiner to push against a muscle while the patient resists. The patient will be encouraged by the clinical evaluator (CE) to exert maximal effort. Each test will be performed twice on each side and both sets of results will be recorded. The CE should strive to perform each test consistently between the 2 trials (see the Clinical Evaluator's Manual).

10.3.1.5 Hand Grip Strength Testing

Hand grip strength will be assessed using a Jamar Dynamometer. The test will be performed twice on each hand and both sets of results will be recorded (see the Clinical Evaluator's Manual).

10.3.1.6 SF-36

The 36-Item Short Form Health Survey is a 36-item, patient-reported survey of health status.

10.3.1.7 Number of Falls and Near Falls

Falls are common for patients with IBM. Patients will record the number of falls and near falls in a falls diary.

10.3.2 PK and Biobanking

10.3.2.1 Population Pharmacokinetics (PopPK)

Arimoclomol plasma concentrations will be assayed. Approximately 1 mL of blood will be drawn for each sample. Samples of blood will be drawn as specified in the laboratory manual at Month 9 (Visit 7) pre-dose and 0.5 hours (+ 60 min) post-dose, and at Month 20 (Visit 11) pre-dose and 1.5 hours (+ 60 min) post-dose. A total of 4 samples per patient will be drawn; 2 samples at Month 9 and 2 samples at Month 20. Patients will be asked to confirm the mode of administration (as per Section 9.2) of the last dose taken at home before the PopPK blood draw.

10.3.2.2 Biobanking

Blood will be drawn for biobanking for future potential tests. Blood samples of approximately 9 mL per time point will be obtained, stored, and shipped as detailed in the Central Laboratory Manual.

10.3.3 Safety Variables

Safety assessments will include the evaluation of adverse events (AEs), clinical safety laboratory test results, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, and the C-SSRS, depending on the treatment period (see Table 2-1).

10.3.3.1 Clinical Safety Laboratory Assessments

10.3.3.1.1 Clinical Safety Laboratory Tests to be Performed

Samples for the following clinical safety laboratory tests will be collected at the time points specified in the schedule of events (Section 2.2).

Hematology:	hemoglobin; hematocrit; mean corpuscular volume (MCV); red blood cells (RBC/erythrocytes); white blood cells (WBC/leukocytes); and differential count (basophils, eosinophils, lymphocytes, monocytes, neutrophils [% and absolute count], and platelets)
Serum Chemistry:	albumin; alkaline phosphatase; alanine aminotransferase (ALT/SGPT); aspartate aminotransferase (AST/SGOT); bilirubin (total); calcium; chloride; cholesterol; creatine kinase; creatinine; gamma-glutamyl transferase (GGT); glucose (random); iron; lactate dehydrogenase (LDH); phosphate; potassium; protein total; sodium; triglycerides; BUN; uric acid
Other:	cystatin C
Urine pregnancy test:	for women of childbearing potential only

Blood samples for safety testing will be sent to a central laboratory for analysis. Urine pregnancy tests will be conducted at the trial sites.

If the subject cannot attend the trial site for close observation in relation to elevated transaminases, the analyses may be conducted at a local laboratory. For guidance on follow-up of specific laboratory abnormalities, see section 10.3.3.1.2**.**

10.3.3.1.2 Follow-up for specific laboratory abnormalities

10.3.3.1.2.1 Increased serum creatinine

Serum creatinine values > 2-3-fold compared to the patient's baseline value should be further investigated for signs of kidney injury. Estimation of the patient's GFR based on BUN, creatinine, and cystatin C should be performed. In addition, follow-up should be done according to local hospital guideline. 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.

10.3.3.1.2.2 Increased transaminases

Transaminases (AST, ALT) > 3 x ULN must be further investigated in line with the FDA Guidance on Drug-Induced Liver Injury (4).

Upon first observation of transaminases (AST, ALT) > 3 x ULN, a repeat test must be performed within 48-72 hours (ALT, AST, 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 ALT, AST, 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. The values should be monitored until the values have stabilised or the baseline level of the patient has been reestablished.
- 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 discontinued (see section 0)

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 CRF including the appropriate reference ranges.

10.3.3.1.3 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all trial personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of patient samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the trial laboratory manual. The investigator is responsible

for ensuring that all trial samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

10.3.3.1.4 Evaluation of Clinical Safety Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this trial will be provided by the responsible laboratory and submitted to Orphazyme A/S prior to the beginning of the trial. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical relevance in the appropriate CRF/eCRF.

All clinical laboratory values that in the investigator's opinion show clinically relevant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.

All measurements described in this section are recognized standard methods.

10.3.3.2 Clinical Examinations

10.3.3.2.1 Vital Signs

Vital signs, including weight, heart rate, respiratory rate, and sitting blood pressure will be measured after the patient has been in a sitting position for 5 minutes. Temperature will also be measured. Any clinical significant abnormality must be reported as an AE.

10.3.3.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the patient has been lying down for at least 5 minutes. All ECG recordings will be identified with the patient number, date, and time of the recording. The ECG interpretation will be recorded in the patient's eCRF. Any clinically significant abnormality must be reported as an AE.

10.3.3.2.3 Physical Examination

A general physical examination must be performed by a physician; in countries where accepted, this task can be delegated when documented on a delegation log. Any clinically significant abnormality must be reported as an AE.

10.3.3.2.4 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be administered to the patient by trial personnel using the "since last visit" version of the scale at all visits, including telephone visits.

10.3.3.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a pre-existing condition is considered an AE.

11.1.2 Unexpected Adverse Events

An unexpected adverse event is one for which the nature or severity is not consistent with the applicable product information (e.g., current version of the arimoclomol IB). Orphazyme will assess expectedness for any SAEs reported in the trial.

For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected.)

11.1.3 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.
- results in persistent or significant disability/incapacity

- is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE. However, a newly diagnosed pregnancy in a patient that has received study drug is not considered an SAE unless it is suspected that the study drug(s) interacted with a contraceptive method and led to the pregnancy.
- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.4 Treatment-Emergent Adverse Events

An AE is defined as treatment-emergent if the first onset or worsening is after the first administration of arimoclomol in the current trial.

11.2. Collection of Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the patient will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

AEs will be collected from the Visit 1 and 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.

All AEs will be followed to resolution or the last visit, whichever comes first. SAEs will be followed up until a final outcome has been established. For SAEs which have stabilised and for which the patient 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.

Information to be collected includes event description, duration, clinician's assessment of severity, causality, seriousness, concomitant therapy given (or other action taken), action taken with respect to arimoclomol, and outcome. All AEs occurring while in study must be documented appropriately regardless of relationship.

All new AEs or worsening of any ongoing events from the completion of IBM4809 will be recorded on the AE pages of the CRF (ongoing AEs from IBM4809 should also be recorded on AE page of the CRF).

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 11.4).

11.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing])
Severe	Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable]).

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.3.

11.2.2 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to arimoclomol. The categories for classifying the investigator's opinion of the relationship are as follows:

Probably Related	AEs that are temporally linked and for which the trial product is more likely to be the explanation than other causes, which may improve when not using trial product
Possibly Related	AEs that could equally well be explained by trial product or other causes, which are usually temporally linked and may improve when not using trial product but do not reappear when using trial product
Not Related	AEs that can be clearly explained by extraneous causes and 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 arimoclomol if it is at least possibly related.

11.3. Treatment of Adverse Events

Adverse events that occur during the trial will be treated, if necessary, by established standard of care. If such treatment constitutes a deviation from the protocol, the patient's participation in the trial should be evaluated. The decision about whether the patient may continue in the trial will be made by the sponsor after consultation with the investigator and/or medical monitor and documented in the eCRF.

If a patient experiences AEs that are not tolerable, the investigator must decide whether to stop the patient's involvement in the study and/or treat the patient.

11.4. Reporting of Serious Adverse Events

The Investigator must report (by fax or email) all SAEs to the safety vendor within 24 hours of awareness of an SAE by completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and CRF, and sending the SAE form to the safety vendor by one of the following methods:

Trial Contact for Reporting Serious Adverse Events

Please refer to the SAE Reporting Contact Details document.

If, for any reason, it is not possible to complete all sections of the SAE form within 24 hours, transmission of the form must not be delayed, and the outstanding information should be sent on a follow-up SAE form.

Information on SAEs will be recorded on a SAE form. Blank copies are included in the trial Investigator's file.

The SAE form must be completed as fully as possible with information relevant to the SAE(s) being reported. All fields should be populated or marked accordingly if no information is available.

Follow-up SAE Reports

For all SAEs where important or relevant information is missing, active follow-up should be undertaken. The follow-up information must be presented on an SAE form marked as follow-up.

Follow-up information should also be provided within 24 hours of the investigator becoming aware of it.

It is necessary only to provide the new information, together with the following minimal information (initial report, adverse event, date of occurrence, patient identification (ID), trial ID, study drug name [arimoclomol], and site number); this will allow the follow-up information to be linked to the initial SAE report, with the SAE form signed by an Investigator.

Specific information may be requested by the safety vendor using a data clarification form.

Investigators or other site personnel should only send relevant or requested anonymized supporting documentation (e.g. ECG, laboratory results, autopsy report) to the safety vendor.

Follow-up reports (as many as required) should be completed and submitted following the same procedure above.

Reporting to Competent Authorities and IRBs/IEC

The investigator is responsible for reporting SAEs to the institutional review board (IRB)/ independent ethics committee (IEC) 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.

Orphazyme is responsible for reporting all SAEs that are assessed as causally related to the IMP by either the investigator or Orphazyme, and that 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 IRBs/IECs that require unblinded reporting.

11.5. Pregnancy

Should a pregnancy occur in a female patient or the partner of a male patient, it must be reported promptly, within 24 hours of the site first becoming aware of the pregnancy, by entering the pregnancy as a non-serious AE in the CRF and completing, signing, and dating the pregnancy report form. The pregnancy report form should be sent to the safety vendor using the contact details in Section 11.4. A pregnant patient should discontinue trial treatment.

All pregnancies must be followed up until delivery or termination of the pregnancy and final outcome must be reported on the Pregnancy Follow-Up Form within 24 hours of first knowledge and sent to the safety vendor using the contact details in Section 11.4.

12. STATISTICS

12.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a P value of ≤ 0.05 will be considered statistically significant.

For analyses involving trial site, if the number of patients per site is small, sites may be pooled for analysis or omitted from statistical models. The final determination will be made prior to database lock.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will typically include the number of patients, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of patients in each category.

Analyses will compare efficacy and safety findings between those patients who received arimoclomol and placebo, respectively, in the IBM4809 trial, reflecting the original randomisation. This facilitates an analysis of the effect of early versus delayed treatment start of arimoclomol. Summaries will also present data for the overall group.

12.1.1 Analysis Populations

Safety Population: All patients who receive at least 1 dose or partial dose of arimoclomol in the extension trial. Safety analyses will be performed on the Safety Population.

Modified Intent-to-treat (mITT) Population: All patients receiving at least 1 dose or partial dose of arimoclomol in the extension trial, with a baseline value and at least 1 post-baseline value for IBMFRS. Efficacy analyses will be performed on the mITT Population.

Inclusion in the analysis populations will be determined prior to database lock.

12.1.2 Trial Patients and Demographics

12.1.2.1 Disposition and Withdrawals

The numbers of patients enrolled, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by IBM4809 treatment groups. The number of patients in each analysis population will be reported.

12.1.2.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the trial site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working

days of the scheduled protocol-required activity. All deviations must be addressed in trial source documents and reported to Premier Research. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan. Deviations assessed as important will be addressed in the study report.

12.1.2.3 Demographics and Other Baseline Characteristics

The distributions of demographic and clinical characteristics will be described for the early start and delayed start groups as well as the overall cohort using standard summary statistics.

Prior and concomitant medications will be summarized overall and by treatment group, by the number and percentage of patients taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

12.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of each patient's duration of exposure. Descriptive statistics, including the mean, median, SD, minimum, maximum, and quartiles, will be provided overall and by treatment group.

12.1.4 Efficacy Analysis

Efficacy variables will be summarized and analysed using the mITT population.

12.1.4.1 Efficacy Endpoints

- Primary efficacy endpoint:
  - Change in the IBMFRS total score from IBM4809 baseline to Month 20 in the OLE trial.
- Secondary efficacy endpoints:
  - Change in 6-Minute Walk Test Distance from IBM4809 baseline to Month 20 in the OLE trial.
  - Change in Modified Timed Up and Go (mTUG) from IBM4809 baseline to Month 20 in the OLE trial.
  - Change in MVICT of the quadriceps muscle from IBM4809 baseline to Month 20 in the OLE trial.
  - Change in hand grip strength from IBM4809 baseline to Month 20 in the OLE trial
  - Change in SF-36 from IBM4809 baseline to Month 20 in the OLE trial.
  - Number of Falls from IBM4809 baseline to Month 20 in the OLE trial.
  - Number of Near Falls from IBM4809 baseline to Month 20 in the OLE trial.
  - Change in the IBMFRS total score from IBM4809 baseline to Month 40 in the OLE trial.
  - Change in hand grip strength from IBM4809 baseline to Month 40 in the OLE trial.

- Exploratory endpoints:
  - Population pharmacokinetics (popPK) and popPK/PD (reported separately)
  - Change from baseline* over 20 months of arimoclomol treatment in IBMFRS total score in arimoclomol naïve patients
  - Change from baseline* over 20 months of arimoclomol treatment in 6-Minute Walk Test Distance in arimoclomol naïve patients
  - Change from baseline* over 20 months of arimoclomol treatment in Modified Timed Up and Go (mTUG) in arimoclomol naïve patients
  - Change from baseline* over 20 months of arimoclomol treatment in MVICT of the quadriceps muscle in arimoclomol naïve patients
  - Change from baseline* over 20 months of arimoclomol treatment in hand grip strength in arimoclomol naïve patients
  - Change from baseline* over 20 months of arimoclomol treatment in SF-36 in arimoclomol naïve patients
- Safety endpoints:
  - Safety parameters (AEs, SAEs, clinical safety laboratory values, vital signs, C SSRS to month 40

* Baseline is defined at the visit at which the subject receives first administration of arimoclomol (corresponding to IBM4809 baseline and IBMOLE baseline for patients randomized to arimoclomol and placebo in IBM4809, respectively)

12.1.4.2 Efficacy Analysis

Differences in change from IBM4809 baseline to Month 20in the OLE trial in IBMFRS between patients randomized to arimoclomol (early start) and placebo (delayed start) in IBM4809 will be determined using a modified 2-treatment period/delayed randomization analysis (to be detailed in the statistical analysis plan [SAP]).

Additional efficacy variables will be explored through descriptive statistics at each scheduled visit of the current trial. For statistical analyses, 95% confidence intervals will be provided for changes from baseline.

12.1.4.3 Exploratory, Corroborative, Sensitivity, and Other Analyses

Additional exploratory analyses as well as sensitivity analyses for the primary efficacy endpoint will be described in the SAP as appropriate.

12.1.5 PopPK and PopPK/PD Analyses

All plasma arimoclomol concentration and dosing data will be merged with the PK sampling dates and times and used to create the population PK input file for use in a popPK modelling analysis. In addition, the potential relationship between systemic exposure of arimoclomol and efficacy/safety measures may be explored using appropriate pharmacokinetic/pharmacodynamic models. The population PK and popPK/PD analysis plan will be described in a separate protocol and the results reported separately.

12.1.6 Safety and Tolerability Analyses

Safety analysis, based on AEs, SAEs, clinical safety laboratory values, vital signs, and C-SSRS, will be descriptive, based on the Safety Population.

Continuous safety variables (vital signs, laboratory test results) will be presented using descriptive statistics. For analyses of changes from baseline for laboratory values and vital signs parameters, baseline values from the blinded IBM4809 trial or from the current trial may be considered.

The C-SSRS will be summarized.

12.1.6.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0 or higher.

An AE is defined as treatment-emergent if the first onset or worsening is after the first administration of arimoclomol in the current trial.

The number and percentage of patients with AEs will be displayed overall and for each treatment group by system organ class (SOC) and preferred term (PT). Summaries of AEs by severity and relationship to arimoclomol will also be provided. Serious adverse events and AEs resulting in discontinuation of arimoclomol will be summarized separately in a similar manner. Patient listings of AEs, SAEs, and AEs causing discontinuation of arimoclomol will be produced.

12.1.6.2 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values overall and for each treatment group at each time point.

The number of patients with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte overall and by treatment group and by trial visit.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

12.1.6.3 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and respiratory rate (RR.)

The number of patients with vital signs values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each parameter overall and by treatment group and by trial visit. Pre- and post-treatment values may also be presented with an analysis of mean changes from baseline.

12.1.7 Interim Analysis

No interim analyses are planned.

12.2. Sample Size Determination

As this trial is an open-label extension planning to include patients from the previous trial, no calculation for sample size was performed.

13. TRIAL CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and associated personnel before the trial, periodic monitoring visits, and meticulous data management.

13.1. Sponsor and Investigator Responsibilities

13.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the trial in accordance with strict ethical principles (Section 15). The sponsor reserves the right to withdraw a patient from the trial (Section 8.3), to terminate participation of a trial site at any time (Section 13.7), and/or to discontinue the trial (Section 13.6).

Orphazyme A/S agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the trial according to the trial protocol.

13.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the trial in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with ICH GCP and applicable United States (US) Code of Federal Regulations (CFR). The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this trial have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated trial-related responsibilities are adequately qualified and informed about the protocol, the study drug, and their specific duties within the context of the trial. Investigators are responsible for providing Orphazyme A/S with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the trial may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all trial documentation by authorized individuals.

13.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor, and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The trial monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying trial product may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records.

The trial participant's contact information will be securely stored at each clinical site for internal use during the trial. At the end of the trial, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

13.2. Site Initiation

Trial personnel may not screen or enroll patients into the trial until after receiving notification from the sponsor or its designee that the trial can be initiated at the trial site. The trial site will not be authorized for trial initiation until:

1. The trial site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory/GCP documents have been submitted to and approved by the sponsor or its designee.
3. The trial site has a Clinical Trial Agreement in place.
4. Trial site personnel, including the investigator, have participated in a trial initiation meeting.

13.3. Trial Documents

All documentation and material provided by Orphazyme A/S for this trial are to be retained in a secure location and treated as confidential material.

13.3.1 Informed Consent

Consent forms describing in detail the trial intervention, trial procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering trial intervention.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the trial and continues throughout the individual's trial participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research trial to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the trial and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the trial with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the trial. Participants must be informed that participation is voluntary and that they may withdraw from the trial at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the participant undergoes any

trial-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this trial.

13.3.2 Investigator's Regulatory/Good Clinical Practice Documents

The regulatory/GCP documents listed in the trial plan and must be received from the investigator and reviewed and approved by Orphazyme A/S or its designee before the trial site can initiate the trial and before Orphazyme A/S will authorize shipment of study drug to the trial site. Copies of the investigator's regulatory/GCP documents must be retained at the trial site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the arimoclomol IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and study drug accountability records should also be retained as part of the investigator's regulatory/GCP documents. It is the investigator's responsibility to ensure that copies of all required regulatory/GCP documents are organized, current, and available for inspection.

13.3.3 Case Report Forms

By signing the Investigator's Agreement (Section 17.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all patients who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRFs used during the trial to ensure that the trial information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual patient visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the eCRFs is accurate and true.

13.3.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

13.4. Data Quality Control

Orphazyme A/S and its designees will perform quality control checks on this clinical trial.

13.4.1 Monitoring Procedures

Orphazyme A/S and/or its designee will conduct site visits to monitor the trial and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and trial site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Orphazyme A/S personnel access. The CRA(s) will maintain current personal

knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures
- storage and accountability of study drug and trial materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRFs are described in the trial plan. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.1), the investigator agrees to meet with the CRA(s) during trial site visits; to ensure that trial staff is available to the CRA(s) as needed; to provide the CRA(s) access to all trial documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Orphazyme A/S or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan (CMP).

13.4.2 Data Management

Orphazyme A/S or designee will be responsible for activities associated with the data management of this trial. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data management plan (DMP) will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Trial site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the trial plan.

13.4.3 Quality Assurance/Audit

This trial will be subject to audit by Orphazyme A/S or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits
- Trial Master File (TMF) audits
- database audits
- document audits (e.g., protocol and/or CSR)

Orphazyme A/S or its designee may conduct additional audits on a selection of trial sites, requiring access to patient notes, trial documentation, and facilities or laboratories used for the trial.

The trial site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Orphazyme A/S immediately.

13.5. Study Leadership

A Scientific Steering Committee will govern the conduct of the study and provide scientific direction. The Steering Committee composition is composed of [redacted] (Chair), [redacted], [redacted], [redacted], [redacted], and an Orphazyme representative. The Steering Committee will meet and act according to the Steering Committee Charter.

13.6. Trial Termination

The trial may be terminated at Orphazyme A/S's discretion at any time and for any reason.

13.6.1 Regular Trial Termination

The end of this trial is defined as the date of the last visit of the last patient (last patient out or last patient last visit) participating in the trial. Within 90 days of the end of the clinical trial, Orphazyme A/S or designee will notify the IECs and regulatory authorities about the regular termination of the trial as required according to national laws and regulations.

13.7. Trial Site Closure

At the end of the trial, all trial sites will be closed. Orphazyme A/S may terminate participation of a trial site at any time. Examples of conditions that may require premature termination of a trial site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate patient enrolment

13.7.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the trial, specifically including, but not limited to, those defined by GCP as essential until:

- At least 5 years after the last marketing authorization for arimoclomol has been approved or the sponsor has discontinued its research with arimoclomol, or
- At least 5 years have elapsed since the formal discontinuation of clinical development of arimoclomol.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

13.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalysed. In addition, identifiable samples can be destroyed at any time at the request of the patient.

De-identified biological samples will be stored as detailed in the Central Laboratory Manual

During the conduct of the trial, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to bio sample storage may not be possible after the trial is completed.

13.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Orphazyme A/S. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agencies having jurisdiction over the conduct of the trial.

13.9. Use of Information and Publication

The study will be registered at www.clinicaltrials.gov. By signing the study protocol, the investigator agrees with the use of results of the trial for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals.

As the trial is a multi-center trial, any publication based on the results obtained at the trial site shall not be made before the first multi-center publication describing the primary results of the OLE has been published. If a publication concerns the analyses of subsets of data from the trial, the publication shall make reference to the relevant multi-center publication(s). Upon completion of the trial, and any prior publication of multi-center data, or when the trial data are adequate (in Orphazyme's discrete and reasonable judgement), the trial site may prepare the data deriving from the trial for publication. The publishing investigator(s) will not make any publication or other public disclosure, whether oral or written, that includes any trial data or describes any work carried out using the study drug unless a draft of such proposed publication or other public disclosure has been provided to UCL ([redacted] and [redacted]), KUMC ([redacted] and [redacted]), other members of the Scientific Steering Committee who will also perform the review for the Muscle Study Group, and to Orphazyme A/S for review at least 45 days prior to any such submission for publication or public disclosure. During such 45-day period, Orphazyme A/S may require that any publication or other public disclosure is delayed for up to 4 months to permit adequate steps to be taken to secure patent or other protection of the subject matter referred to therein and/or to require the deletion of any confidential information that would be disclosed by such publication or public disclosure. After Orphazyme has secured that intellectual property protection of the subject matter and Orphazyme has released the manuscript for publication, the publishing investigator(s) may submit the proposed publication to outside reviewers or publications for review.

In any publication or public disclosure, whether oral or written, that mentions the trial, the publishing investigator(s) will acknowledge Orphazyme A/S.

Orphazyme A/S may use all such publications and public disclosures at its own discretion, including the use for regulatory submissions.

14. FINAL CLINICAL STUDY REPORT

Orphazyme A/S will retain ownership of the data.

The final CSR will be written within 1 year of completion of the clinical part of the trial and submitted to regulatory authorities if appropriate or required. This report will include a summary of the trial results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Declaration of Helsinki and Good Clinical Practice

This trial will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential trial documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the trial is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

See Appendix C for regulation and guidelines.

15.2. Patient Information and Informed Consent and/or Assent

A properly constituted, valid IRB or IEC must review and approve the protocol, the investigator's ICF, and related patient information and recruitment materials before the start of the trial.

It is the responsibility of the investigator to ensure that written informed consent and/or assent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

15.3. Approval by Institutional Review Boards and Independent Ethics Committees

A valid IRB/IEC must review and approve this protocol before trial initiation. Written notification of approval is to be provided by the investigator to the sponsor or designee before shipment of investigational drug supplies and will include the date of the committee's approval and the chairperson's signature.

Until written approval by the IRB/IEC has been received by the investigator, no patient may undergo any procedure not part of routine care for the patient's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by Orphazyme A/S before implementation.

15.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

16. REFERENCES

1. Callan A, Capkun G, Vasanthaprasad V, Freitas R, Needham M. A systematic review and meta-analysis of prevalence trials of sporadic inclusion body myositis. *J Neuromuscul Dis*. 2017;4(2):127-137.
2. Price MA, Barghout V, Benveniste O, et al. Mortality and causes of death in patients with sporadic inclusion body myositis: survey study based on the clinical experience of specialists in Australia, Europe and the USA. *J Neuromuscul Dis*. 2016 Mar 3;3(1):67-75.
3. Ahmed M, Machado PM, Miller A, et al. Targeting protein homeostasis in sporadic inclusion body myositis. *Sci Transl Med*. 2016;8(331):331ra41.
4. FDA Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009

17. ATTACHMENTS

17.1. Investigator's Agreement

PROTOCOL NUMBER:	IBM-OLE (version 5.0)
PROTOCOL TITLE:	An open-label, non-randomized trial to investigate the efficacy and safety of early versus delayed start of arimoclomol in patients with inclusion body myositis who have completed the IBM4809 trial
FINAL PROTOCOL:	18-Jan-2021

The undersigned acknowledges possession of and has read the Investigator's Brochure on arimoclomol and has discussed these data with the trial monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the study drug to selected patients in his/her care, according to the trial protocol.

He or she agrees to use the trial material, arimoclomol, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Orphazyme A/S.

He or she understands that any deviation from the protocol may lead to early termination of the trial.

He or she agrees to report to Orphazyme A/S within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of arimoclomol.

He or she agrees to comply with Orphazyme A/S and regulatory requirements for the monitoring and auditing of this trial.

In addition, he or she agrees that the trial will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the trial.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp):

APPENDICES

A. Trial-Specific Requirements

B. Regulations and Good Clinical Practice Guidelines

C. Address List

A. Trial-Specific Requirements

17.1.1 Coronavirus (COVID) operational changes

The document (COVID-19) Addendum 1.0 dated 06-Aug-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.

APPENDIX 1: IBM FUNCTIONAL RATING SCALE

1. SWALLOWING
- 4 Normal
- 3 Early eating problems – occasional choking
- 2 Dietary consistency changes
- 1 Frequent choking
- 0 Needs tube feeding

2. HANDWRITING **(***with dominant hand prior to IBM onset)*
- 4 Normal
- 3 Slow or sloppy; all words are legible
- 2 Not all words are legible
- 1 Able to grip pen but unable to write
- 0 Unable to grip pen

3. CUTTING FOOD AND HANDLING UTENSILS
- 4 Normal
- 3 Somewhat slow and clumsy, but no help needed
- 2 Can cut most foods, although clumsy & slow; some help needed
- 1 Food must be cut by someone but can still feed slowly
- 0 Needs to be fed

4. FINE MOTOR TASKS ***(opening doors, using keys, picking up small objects)***
- 4 Independent
- 3 Slow or clumsy in completing task
- 2 Independent but requires modified techniques or assistive devices
- 1 Frequently requires assistance from caregiver
- 0 Unable

5. DRESSING
- 4 Normal
- 3 Independent but with increased effort or decreased efficiency
- 2 Independent but requires assistive devices or modified techniques (Velcro snaps, shirts without buttons, etc.)
- 1 Requires assistance from caregiver for some clothing items
- 0 Total dependence

6. HYGIENE ***(Bathing and toileting)***
- 4 Normal
- 3 Independent but with increased effort or decreased activity
- 2 Independent but requires use of assistive devices (shower chair, raised toilet seat, etc.)
- 1 Requires occasional assistance from caregiver
- 0 Completely dependent

7. TURNING IN BED & ADJUSTING COVERS
- 4 Normal
- 3 Somewhat slow & clumsy but no help needed
- 2 Can turn alone or adjust sheets but with great difficulty
- 1 Can initiate but not turn or adjust sheets alone
- 0 Unable or requires total assistance

8. SIT TO STAND
- 4 Independent (without use of arms)
- 3 Performs with substitute motions (leaning forward, rocking) but without use of arms)
- 2 Requires use of arms
- 1 Requires assistance from device/person
- 0 Unable to stand

9. WALKING
- 4 Normal
- 3 Slow or mild unsteadiness
- 2 Intermittent use of assistive device (AFO, cane, walker)
- 1 Dependent on assistive device
- 0 Wheelchair dependent

10. CLIMBING STAIRS
- 4 normal
- 3 Slow with hesitation or increased effort; uses handrail intermittently
- 2 Dependent on handrail
- 1 Dependent on handrail and additional support (cane or person)
- 0 Cannot climb stairs

APPENDIX 2: [redacted] SUB-STUDY

This was an exploratory sub-study and the details are not relevant for the primary or secondary endpoints and therefore not included here.

B. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives (and applicable regulations/guidance's):

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents>

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf