Design and Rationale for a Randomized, Double-blind, Placebo-controlled Phase 2/3 Trial of Oral Arimoclomol in Inclusion Body Myositis

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ABSTRACT

Introduction/Aims: Inclusion body myositis (IBM) is the most common progressive, debilitating muscle disease in people over the age of 50 years, for whom there is no effective treatment. Here, we present the design and rationale for one of the largest clinical studies conducted in IBM to date, to evaluate the efficacy, safety, and tolerability of arimoclomol, a novel, oral amplifier of the cellular heat shock response.

Methods: This is a randomized, double-blind, placebo-controlled, parallel group trial conducted at 11 centers in the US and one center in the UK. Eligible patients had a diagnosis of IBM fulfilling European Neuromuscular Centre 2011 criteria, with onset of weakness at > 45 years of age. Enrolled participants were randomized 1:1 to receive either oral arimoclomol citrate 1,200 mg/day or matching placebo for up to 20 months. The primary endpoint is the change from baseline to Month 20 in the IBM functional rating scale (IBMFRS) total score. The secondary efficacy endpoints include evaluations of participants' functional abilities, strength, and physical health-related quality of life (HRQoL). A sub-study was planned to characterize muscle changes using MRI in a subset of participants.

Discussion: This study will generate important clinical data on a novel therapeutic strategy for patients with IBM, a population with no current treatment options.

Key words: heat shock response; IBMFRS; inclusion body myositis; MRI, muscle atrophy.

Introduction

Sporadic inclusion body myositis (IBM) is the most common progressive, debilitating muscle disease in people over the age of 50 years. IBM typically presents with insidious, asymmetric weakness that predominantly affects the quadriceps and/or finger flexors.[1] The epidemiology of IBM varies between and within countries, with an estimated overall prevalence of 46 per million (increasing to 139 per million for people above the age of 50 years).[2] The pathogenesis of IBM is complex and remains poorly understood but is thought to consist of an interplay between inflammatory and degenerative pathways.[3] The degenerative theory of IBM hypothesizes that the disease is driven by aging of the muscle fiber associated with accumulation and aggregation of misfolded, ubiquitinated, multiple-protein aggregates in a genetically susceptible individual.[4] Accumulation of these protein aggregates within muscle fibers is considered likely to trigger an inflammatory/immune response as a secondary consequence of muscle degeneration.[5]

Arimoclomol is a hydroxylamine derivative that acts as a co-inducer of the natural cellular 'heat shock response.'[6] The heat shock response enhances expression of heat shock proteins (HSPs), including 'molecular chaperones,' so called because they promote natural folding of new proteins and refolding of damaged or mutated proteins.[7] Activation of the heat shock response may be beneficial in diseases characterized by toxic protein aggregates, such as IBM. In fact, levels of HSP70 have been shown to be increased in IBM muscle biopsies.[8] Arimoclomol has been shown to co-induce molecular chaperone genes in cell lines and in isolated cells/tissues, meaning that it further elevates chaperone protein levels that are already increased by physiological or metabolic stresses.[9] It accomplishes this by prolonging activation of the transcription factor heat shock factor-1 (HSF-1).[6,10] Arimoclomol may inhibit the process of protein misfolding and aggregation in IBM by helping muscle fibers to up-regulate inducible HSPs.[9] As a result, arimoclomol may slow or prevent muscle degeneration in this otherwise relentlessly progressive, debilitating disease.

A preliminary study was performed in which 24 participants were randomly assigned in a 2:1 ratio to receive either arimoclomol 300 mg/day or matching placebo in a double-blind manner.[9] The data suggested that arimoclomol was safe and well tolerated in IBM.[9] In

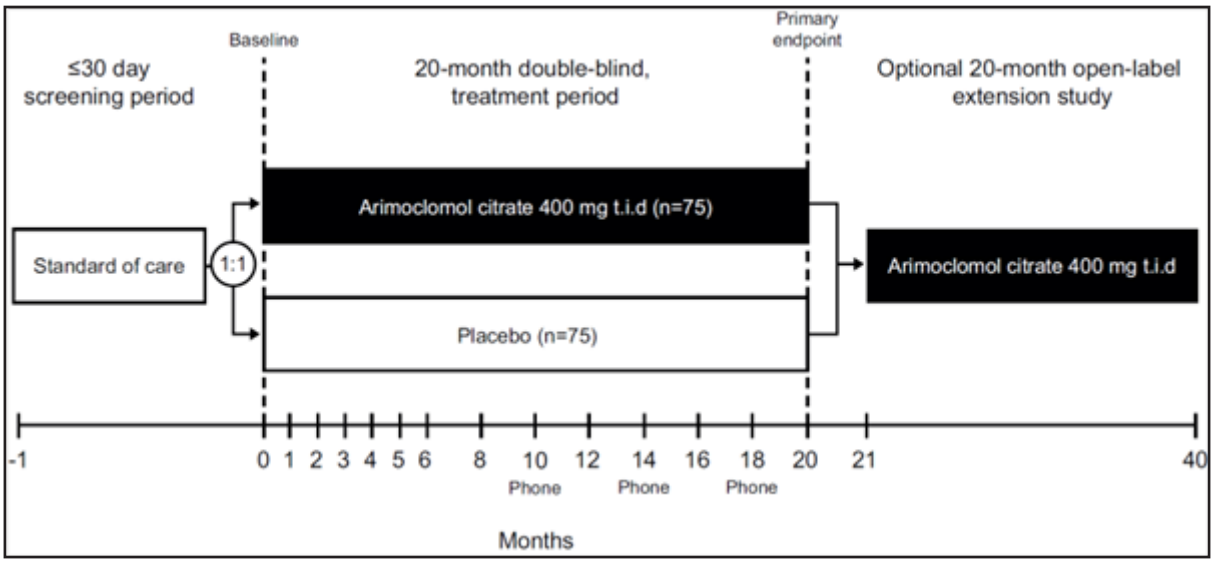

Figure 1: Trial Design

parallel, arimoclomol reduced key pathologic markers of IBM in two robust rat myoblast *in vitro* models representing the degenerative and inflammatory components of IBM.[9] Arimoclomol also improved disease pathology and muscle function in mutant valosin-containing protein (VCP) mice, which develop IBM-like muscle histopathologic features.[9]

Based on these data, the lead investigator group (primary investigator [PI]: M.M.D., and co-PIs: R.J.B., P.M.M., and M.G.H.) from the Neuromuscular Study Group (NMSG, musclestudygroup.org) secured funding from the United States Food and Drug Administration Office of Orphan Products Development in 2015 for a larger-scale clinical trial of arimoclomol in patients with IBM. With funding secured, the commercial developer of arimoclomol, Orphazyme A/S, expressed interest in increasing their collaborative role and this trial became a joint industry-academia co-funded study. This collaborative partnership with Orphazyme A/S has been fundamental not only for providing the experimental drug but also for assuming the operational trial conduct and ensuring compliance with International Council for Harmonization (ICH) guidelines.[11] This strong partnership drove regulatory interactions and processes and allowed for the initiation of add-on studies to investigate pharmacokinetics, perform further validation studies of clinical endpoints, assess muscle magnetic resonance imaging (MRI) outcomes, and provide for an open-label extension trial.

The resulting study is a randomized, double-blind, placebo-controlled trial of arimoclomol in patients with IBM. With planned enrollment of 150 patients and follow-up duration of up to 20 months, it represents one of the largest and longest studies ever conducted in an IBM population. We recently published the study results.[12] Here, we provide a summary of the rationale for the study and overview of its design.

Methods

The objectives of this study are to evaluate the efficacy, safety, and tolerability of arimoclomol citrate 1,200 mg/day (400 mg three times daily [t.i.d.]; equivalent to 744 mg/day arimoclomol free base) compared with placebo in participants with IBM over 20 months. An exploratory sub-study was planned to characterize muscle changes using MRI in a subset of participants from the main study.

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, Phase 2/3 trial conducted at 11 centers in the U.S. and one center in the U.K. (**Figure 1**; ClinicalTrials.gov no. NCT02753530). The MRI sub-study is being conducted at one center in the U.S. (University of Kansas Medical Center) and one in the U.K. (University College London), using the UCL Queen Square quantitative muscle MRI protocol.[13] Eligible participants were randomized 1:1 to receive either oral arimoclomol citrate 400 mg t.i.d. or matching placebo for up to 20 months. Randomization was computer generated using a permuted block algorithm to randomly allocate study drug to randomization numbers. Study medication bottle numbers to be dispensed at the baseline visit were distributed to centers in advance of randomization. Randomization was stratified by study center.

In response to the COVID-19 pandemic restrictions, the study protocol was amended after study initiation to allow additional phone visits (beyond those prospectively planned), home health nursing visits for safety laboratory blood-draws, and delivery of study medication to participants unable to attend the clinic. On completion of follow-up in this study, qualified participants will be offered the opportunity to enter a separate 20-month, single-arm, open-label extension study (IBM-OLE study; ClinicalTrials.gov no. NCT04049097).

Governance of study conduct and scientific direction is provided by a Scientific Steering Committee comprising the authors M.M.D. (Chair), M.G.H., P.M.M., R.J.B., and M.P.M. (MSG Biostatistician), and a representative of the study sponsor, Orphazyme A/S. The study protocol was approved by the relevant Institutional Review Board (IRB)/Research Ethics Committee, utilizing a single IRB review via the SMART IRB platform for the 11 US centers,[14] and the Health Research Authority approval process for the U.K. center. The trial is being conducted in accordance with the protocol, the principles of the Declaration of Helsinki, the ICH Good Clinical Practice guidelines, and all applicable laws and regulations, including local laws and guidance. An independent Data Monitoring Committee was established to assess study drug safety and tolerability at regular intervals. Informed consent was provided by all participants prior to any study procedure; the signature of an impartial witness was permitted for those with impaired manual dexterity. Consent for blood samples to be stored in the Biobank for future use was voluntary. Separate informed consent was also provided by participants included in the optional MRI sub-study.

Participants

A full summary of inclusion and exclusion criteria is provided in **Table 1**. Eligible participants had a diagnosis of clinicopathologically defined IBM, clinically defined IBM, or probable IBM as defined by the European Neuromuscular Centre IBM research diagnostic criteria 2011,[15] with onset of weakness at >45 years of age. Participants were also required to demonstrate the ability to rise from a chair without support from another person or device and to walk at least 20 feet / 6 meters with or without an assistive device. Patients were excluded if they were taking >7.5 mg/day prednisolone or equivalent, taking intravenous immunoglobulin (IVIg), or other immunosuppressants, within the last 3 months. A short course (up to 4 weeks) of systemic prednisolone >7.5 mg/day or equivalent was allowed during the study for conditions not related to IBM (e.g., asthma). Topical, nasal, and ocular corticosteroids were permitted unless they were being widely applied or the severity of the underlying condition made them unsuitable in the investigator's opinion. Local steroid injections were allowed.

Table 1: Participant eligibility criteria

Inclusion criteria	Exclusion criteria
1. Meet any of the European Neuromuscular Centre IBM research diagnostic criteria 2011 categories for IBM.[15]	**1.** History of any of the following: • Chronic infection, particularly HIV or hepatitis B or C • Cancer other than basal cell cancer <5 years prior • Other chronic serious medical illnesses
2. Demonstrate the ability to rise from a chair without support from another person or device.	**2.** Presence of any of the following on routine blood screening: • White blood cells <3,000/µL • Platelets <100,000/µL • Hematocrit <30% • Blood urea nitrogen >30 mg/dL • Creatinine >1.5 times the ULN • Serum albumin <3 g/dL with symptomatic liver disease
3. Able to walk ≥20 feet / 6 meters with or without an assistive device. Once arisen from the chair, the participant may use any walking device (i.e., walker/frame, cane, crutches, or braces). They cannot be supported by another person and cannot use furniture or a wall for support.	**3.** History of most recent creatine kinase >15 times the ULN without any other explanation besides IBM.
4. Age at onset of weakness >45 years.	**4.** History of non-compliance with other therapies.
5. Body weight ≥40 kg.	**5.** Use of testosterone except for physiologic replacement doses in case of androgen deficiency. The participant must have documented proof of the androgen deficiency.
6. Able to give informed consent.	**6.** Coexistence of any other disease that would be likely to affect outcome measures.
	7. Drug or alcohol abuse within the past 3 months. The participant has recent history (within 6 months before the screening visit) of chronic alcohol or drug abuse that may compromise the participant's safety or ability to participate in study activities. Cannabis for IBM symptoms is allowed (where legal).
	8. Participation in a recent drug study ≤30 days prior to the screening visit or use of a biologic agent <6 months prior to the screening visit.
	9. Women who are lactating or pregnant, or sexually active female participants of childbearing potential who intend to become pregnant or are 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 childbearing potential who are 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).
	10. Participants taking >7.5 mg prednisolone or equivalent, or participants on IVIg or other immunosuppressants within the last 3 months. 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.
	11. Clinically significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥3 times the ULN for alanine aminotransferase combined with bilirubin ≥2 times the ULN; symptomatic liver disease with serum albumin <3 g/dL; or creatinine ≥1.5 times the ULN). Laboratory tests may be repeated once at the screening visit. Reasons to repeat laboratory tests may include suspension of the medication causing the laboratory abnormality, any other suspected cause no longer existing, or ruling out laboratory error.

HIV, human immunodeficiency virus; IBM, inclusion body myositis; IVIg, intravenous immunoglobulin; MRI, magnetic resonance imaging; ULN, upper limit of normal.

Participant criteria for the MRI sub-study were the ability to give informed consent, the ability to have a baseline MRI performed prior to or within 4 weeks of starting treatment, and the absence of an issue that would prevent MRI (such as a heart pacemaker or other metallic implant, or uncontrollable claustrophobia). The investigator was responsible for evaluating each participant for potential MRI contraindications prior to each MRI.

Study treatment and dosing

Study treatment consists of two 200 mg arimoclomol citrate capsules administered orally t.i.d. (total daily dosage of 1,200 mg/day), or matching placebo, for up to 20 months. Study drug dosing can be interrupted for up to 4 weeks if a participant experiences an intolerable adverse event (AE). If the same AE persists on rechallenge with the full dosage, the dosage can be reduced by half (i.e., one 200 mg capsule t.i.d.) for the remainder of the study, or the treatment is permanently discontinued if this lower dosage is not tolerated.

We selected the arimoclomol citrate dosage of 1,200 mg/day for this study based on FDA guidance for a dosage approaching the maximum tolerated dose. Phase 1 studies showed that arimcolomol was tolerated at dosages up to 1,800 mg/day for 5 days and well tolerated at a dosage of 1,200 mg/day over 28 days (data on file).

Arimoclomol and matching placebo can be administered in multiple ways to accommodate increasing dysphagia associated with disease progression. Capsules can either be swallowed whole or opened and dispersed in 10–30 mL of liquid or soft food. Once dispersed in water, the capsule contents can also be administered via a feeding tube.

Study procedures and outcomes

All study objectives and endpoints are summarized in **Table 2**. The primary endpoint is the change from baseline to Month 20 in the IBM functional rating scale (IBMFRS) total score. Initially derived from the amyotrophic lateral sclerosis functional rating scale, the IBMFRS is a quickly administered (10-minute) rating scale used to determine participants' assessment of their capability and independence.[16] It includes 10 items, graded on a Likert scale from 0 (being unable to perform) to 4 (normal) (**Appendix 2**). These include one item for swallowing, three items for upper limb function (handwriting; cutting food and handling utensils; and fine motor tasks), three items for activities of daily living (dressing; hygiene; and turning in bed and adjusting covers) and three items for leg function (changing position from sitting to standing; walking; and climbing stairs). The sum of the 10 items yields a value between 0 and 40, with a higher score representing less functional limitation. The IBMFRS has been shown to correlate well with strength measures derived from maximum voluntary isometric contraction testing (MVICT), manual muscle testing (MMT), and handgrip dynamometry, while being a more sensitive gauge of participant functional change than these measures.[16] The IBMFRS has also been shown to correlate well with HRQoL as assessed by the 36-item Short Form Health Survey (SF-36).[16]

Key secondary endpoints include evaluations of participants' functional abilities and strength as listed in Table 2. Evaluators are undergoing periodic training throughout the study to maintain proficiency in study assessments.

Study procedures and assessments were performed over the course of 16 visits, as outlined in **Table 3**. The study was prospectively designed so that in-person visits become less frequent over time, with use of phone calls for visits at Months 10, 14, 18, and 21 to reduce the burden of participation.

Table 2: Study objectives and endpoints

Objectives	Endpoints
Primary objective	***Primary endpoint***
To evaluate the efficacy of arimoclomol citrate at a daily dose of 1,200 mg (400 mg t.i.d.) compared with placebo in the treatment of sporadic IBM at 20 months.	Change from baseline to Month 20 in the IBMFRS total score
	Secondary efficacy endpoints include changes from baseline to Months 12 and 20 in the following measures: • IBMFRS total score (Month 12) • Hand grip strength using the Jamar device • Modified Timed Up and Go (mTUG) • Manual Muscle Testing total score (24 muscles) • 6-min walk test (6MWT) distance • Physical component score of the Short-Form 36 health survey (SF-36) • Knee extensor strength (strongest knee at baseline) • Health Assessment Questionnaire-Disability Index (HAQ-DI) • 2-min walk test (2MWT) distance • Mental component score of the SF-36 • Patient Global Impression of Severity (PGIS) • Patient Global Impression of Change (PGIC) • Clinician Global Impression of Severity (CGIS) • Clinician Global Impression of Change (CGIC) • Accumulated number of falls and near-falls
Safety objective	***Safety endpoints***
To evaluate the safety and tolerability of 1,200 mg/day arimoclomol citrate (400 mg three times daily) compared to placebo in the treatment of sporadic IBM over 20 months.	Safety was assessed at scheduled visits and by recording adverse events and serious adverse events throughout the study. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.
MRI sub-study objective	***Primary MRI sub-study endpoint***
To characterize muscle changes using MRI in a subset of participants	Change from baseline to Month 20 in the MRI whole fat fraction of the thigh
	Secondary MRI sub-study endpoints
	Secondary endpoints will be the change from baseline to Month 12 in whole fat fraction of the thigh, and the changes from baseline to Months 12 and 20 in magnetization transfer ratio (MTR), cross-sectional area (CSA), remaining muscle area (RMA), and muscle volume of the thigh. Changes from Month 12 to Month 20 in each of these endpoints will also be explored.

FET, Force Evaluation and Testing; MRI, magnetic resonance imaging; SF-36, 36-Item Short-Form Health Survey; t.i.d., three times daily.

Table 3: Schedule of study procedures

Visit #	1	2	3	4	5	6	6a	7	8	9	10	11	12	13	14	15
Month	-1 (Sc)	0 (Base)	1	2	3	4	5	6	8	10	12	14	16	18	20 ‡	21
Consent	X															
Eligibility	X															
Medical History	X															
IBM History	X															
Vital signs, including weight	X	X	X	X		X			X		X		X		X	
Physical Exam	X		X	X	X	X	X	X	X		X		X		X	
Safety Labs**	X		X	X	X	X	X	X	X		X		X		X	
Urine Preg***		X	X	X		X			X		X		X		X	
Blood for CN1A Ab levels	X										X				X	
Blood for biobanking	X					X			X		X				X	
POP PK			X						X							
ECG	X										X				X	
Randomization****	X															
Dispensing of Medication		X	X			X			X		X		X			
Return of Medication			X			X			X		X		X		X	
PGIS/PGIC		X				X			X		X		X		X	
C-SSRS	X		X	X	X	X	X	X	X		X		X		X	
Muscle Testing (MMT, MVICT)		X				X			X		X		X		X	
6 min walk test		X				X			X		X		X		X	
SF-36		X				X			X		X		X		X	
HAQ-DI		X				X			X		X		X		X	
Falls diary		X	X	X		X			X		X		X		X	
Grip		X				X			X		X		X		X	
IBMFRS		X	X	X	X	X		X	X	X	X	X	X	X	X	
mTUG		X				X			X		X		X		X	
CGIS/CGIC		X				X			X		X		X		X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X*

Phone visits are shaded gray.
Note: Visit windows for all visits are ± 7 days relative to baseline.
* = Only stop dates for ongoing AEs and new SAEs
** = Full Safety Labs
*** = Urine pregnancy prior to dispensing study medication
**** = Randomization procedure
‡ = Upon completion of this study, qualified patients may provide informed consent and enter an open label extension study at the Month 20 visit. Assessments recorded at this visit will also constitute the first assessments of such open-label extension study.

Sample size calculations

The standard deviation of the change from baseline to Month 12 in the IBMFRS total score was estimated to be 2.9 based on data from the preliminary trial of arimoclomol.[9] Assuming a 12-month IBMFRS total score change of −3.5 in the placebo group, similar to what was observed in the preliminary arimoclomol trial, a total of 136 participants (68 per treatment group) would provide 80% power to detect a treatment group difference in mean response of 1.4 points at Month 12 (representing a 40% slowing of the rate of decline) using a two-sample t-test and a 5% significance level (two-tailed). To account for an anticipated 10% dropout rate, the planned sample size was inflated to 150 participants (75 per group).

This calculation was performed in the absence of preliminary data on changes in the IBMFRS total score over a 20-month period, so it strictly applies only to a trial with 12-month follow-up. However, it will also apply to this trial with a 20-month follow-up if, as expected, the magnitude of the treatment effect relative to the standard deviation of the change in IBMFRS total score does not diminish over time.

Statistical methods

The primary efficacy endpoint was analysed using the restricted maximum likelihood-based approach of mixed model for repeated measurements, implemented using PROC MIXED in SAS. This approach included all observed follow-up data from visits originally intended to take place in person (months 1, 2, 3, 4, 6, 8, 12, 16, and 20), even if the visits were done remotely owing to the COVID-19 pandemic. It also accommodated missing data under the missing-at-random assumption. The statistical model included terms for treatment group, visit, centre, baseline IBMFRS total score, the interaction between treatment group and visit, and the interaction between baseline IBMFRS total score and visit. An unstructured covariance matrix was used to model dependence of the IBMFRS measurements within the same participant. The Satterthwaite approximation was used to estimate the denominator degrees of freedom. This model was used to estimate the adjusted group mean changes from baseline at each timepoint, as well as the treatment group difference in adjusted group means at month 20 along with its associated 95% CI and p value. For participants with no post-baseline observations, the baseline value was carried forward to month 1 to permit inclusion of those participants in the analysis.

All secondary efficacy endpoints were analysed in a similar way to the primary endpoint; a sequential hierarchical testing procedure was used for the primary and confirmatory secondary endpoints, using the hierarchy specified previously in the Outcomes section, to control the overall type I error probability at 5%. The confirmatory testing stopped at the first endpoint not meeting statistical significance.

Discussion

Given the severe disability and QoL impairment associated with advanced IBM, there is a substantial unmet need for effective treatment capable of altering the disease course.[17] Arimoclomol amplifies the cellular heat shock response to promote natural folding of new proteins, and refolding or degradation of damaged proteins associated with the degenerative component of the disease. This large-scale, controlled study was planned to provide a rigorous assessment of the efficacy and safety of that strategy in IBM.

This ultimately negative trial occurred against a backdrop of repeated failure for investigational IBM therapies in previous clinical studies.[12] Despite a clear inflammatory component of disease pathology, multiple studies of immunosuppressive agents (including corticosteroids, IVIg, methotrexate, and azathioprine) have shown no beneficial effect.[3] Similarly, trials of immune system cytokines and cytokine receptor inhibitors in IBM have failed to show clinically meaningful benefit.[3] The failure of targeting inflammation was one of the main arguments in favour of a predominantly degenerative mechanism of IBM disease.

Consequently, research has turned to other strategies, namely those combating muscle wasting and atrophy, such as modulation of the myostatin pathway. The human monoclonal antibody bimagrumab is an inhibitor of activin type 2 receptor signalling that blocks the action of activin and myostatin and significantly improves lean muscle mass in patients with IBM.[18] However, the RESILIENT study of 251 IBM participants showed that improvements in muscle mass with bimagrumab (3 or 10 mg/kg dosages) failed to translate into a significant improvement relative to placebo in the primary endpoint of change from baseline to Week 52 in 6MWT distance, as well as in multiple other secondary endpoints (isometric quadriceps muscle strength, hand grip and pinch strength, number of falls, swallowing efficiency, and short physical performance battery).[18,19]

It has been noted that the 6MWT may not be an optimal primary outcome measure for IBM, given that performance on the test is dependent on multiple factors other than leg muscle function, including cardiopulmonary function, fatigue, skeletal pain, motivation and general physical fitness.[20] The IBMFRS, used in this study, is a broader assessment of 10 distinct functional activities relevant to the overall impact of IBM on participants' lives.[16,21] Therefore, it may be a more sensitive and reliable tool than the 6MWT for assessing clinical benefit in IBM. The IBMFRS has also been shown to correlate well with measures of muscle strength and HRQoL in IBM.[16] The FDA regulatory division accepted the IBMFRS as a clinically relevant primary endpoint for this study in 2016 as part of our Type C meeting correspondence.[11] Our study's key secondary efficacy endpoints will provide evaluations of participants' specific functional abilities, strength, and HRQoL. The selected outcome measures are generally accepted based

on the known impact of IBM on muscle strength, function, and HRQoL over time. Finally, we recently investigated the IBMFRS and demonstrated its content validity, inter-rater and intra-rater reliability, and equivalence between in-person and phone administration.[22]

An exploratory sub-study was planned to assess the value of quantitative MRI assessments as outcome measures in IBM.[13,23] This is to characterize muscle changes using a subset of patients participating in the main study, the primary endpoint being the change from baseline to Month 20 in thigh muscle MRI fat fraction. MRI can non-invasively monitor muscle properties in IBM with high responsiveness and has shown validity by correlation with conventional functional measures.[13,24] These data suggest that MRI biomarkers might be valuable in clinical trials, particularly for treatments in the mid stages of clinical development (e.g., proof-of-concept studies). The characterization of muscle changes using MRI in this sub-study will provide insight into the pathophysiology of IBM and the influence of arimoclomol relative to placebo on these changes.

This study is noteworthy as an example of a successful collaboration between industry and academia and serves as a useful model for future trials.[11] The collaboration, including a Scientific Steering Committee comprising members of the MSG and Orphazyme A/S, harnessed our complementary strengths to overcome numerous challenges in conducting an international study in a rare disease. The cost and complexity of clinical research can be a significant barrier and both partners worked together to secure adequate funding from commercial and academic sources. A clear program of research defined at the outset provided decision-making clarity. However, central to our success to date has been a partnership based on respect and trust with regular and honest communication in a collegial atmosphere. Industry-academia collaborations conducted in this way can be mutually beneficial in achieving our ultimate shared goal of bringing new medicines to the clinic, particularly in rare disease.

In conclusion, this study was planned to generate important data on the efficacy, safety, and tolerability of arimoclomol for people with IBM, a group with no treatment options to change disease trajectory at present. The trial outcome for this novel therapeutic strategy may also have implications for our understanding of IBM pathophysiology.

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of conflicts of interest

P.M.M. has received consulting fees and funding support from Orphazyme A/S, paid to his academic institution (University College London), for the oversight and conduct of this study.

R.J.B. has received funding from the FDA Office Orphan Products Development grant for his role in this study.

M.P.M. has no relevant conflicts of interest to declare.

C.S. and T.B. are employees of Orphazyme A/S.

M.G.H. receives research funding from the Medical Research Council UK and has previously acted a consultant for Novartis and for Orphazyme A/S.

M.M.D. is a consultant for Orphazyme A/S and received funding support, paid to his academic institution (University of Kansas Medical Center, Research Institute), from Orphazyme A/S for the oversight and conduct of this study.

Abbreviations

AE: Adverse event
Base: Baseline
CGI-C/CGI-S: Clinical Global Impression of Change/ Severity
cN1A Ab: Cytosolic 5′-nucleotidase 1A antibody
C-SSRS: Columbia Suicide Severity Rating Scale
FDA: Federal Drug Association
FET: Force Evaluation and Testing
HAQ-DI: Health Assessment Questionnaire – Disability Index;
HIV: Human immunodeficiency virus
HRQoL: Health-related quality of life
HSF-1: Heat shock factor-1
HSPs: Heat shock proteins
IBM: Inclusion body myositis
IBMFRS: Inclusion body myositis functional rating scale
ICH: International Council for Harmonization guidelines
IRB: Institutional Review Board
IVIg: Intravenous immunoglobulin
MMT: Manual muscle testing

MRI: Magnetic resonance imaging
MSG: Muscle Study Group
mTUG: Modified Timed Up and Go test
MVICT: Maximum voluntary isometric contraction testing
6MWT: Six-minute walk test
OLE: Open label extension
PGI-C/PGI-S: Patient Global Impression of Change/Severity
Pop PK: Population pharmacokinetics
QoL: Quality of life
SAE: Serious adverse event
Sc: Screening
SF-36: 36-item Short Form Health Survey
t.i.d: Three times daily
UCL: University College London
UK: United Kingdom
ULN: Upper limit of normal
US: United States of America

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Appendix 1. Arimoclomol in IBM Investigators of the Muscle Study Group

Investigator name	**Investigator center**
Anthony A. Amato	Brigham & Women's Hospital, Boston, MA, USA
Richard J. Barohn	University of Missouri, Columbia, MO, USA
Emma Ciafaloni	University of Rochester Medical Center, Rochester, NY, USA
Mazen M. Dimachkie	University of Kansas Medical Center, Department of Neurology, Kansas City, KS, USA
Miriam Freimer	The Ohio State Wexner Medical Center, Columbus, OH, USA
Summer B. Gibson	University of Utah School of Medicine, Salt Lake City, UT, USA
Michael G. Hanna	University College London, Queen Square Institute of Neurology, London, UK
Sarah M. Jones	University of Virginia, Charlottesville, VA, USA
Todd D. Levine	HonorHealth, Phoenix, AZ, USA
Thomas E. Lloyd	Johns Hopkins University, Baltimore, MD, USA
Pedro M. Machado	University College London, Queen Square Institute of Neurology, London, UK
Tahseen Mozaffar	University of California, Irvine, Orange, CA, USA
Aziz I. Shaibani	Nerve & Muscle Center of Texas, Houston, TX, USA
Matthew Wicklund	University of Colorado – Denver, Denver, CO, USA

Appendix 2. IBM Functional Rating Scale [15]

Item	Score
1. Swallowing	4 - Normal 3 - Early eating problems – occasional choking 2 - Dietary Consistency changes 1 - Frequent choking 0 - Needs tube feeding
2. Handwriting (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 and 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 and adjusting covers	4 - Normal 3 - Somewhat slow and 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 (ankle foot orthosis, 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