



# Safety and efficacy of arimoclomol for inclusion body myositis: a multicentre, randomised, double-blind, placebo-controlled trial



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## Summary

**Background** Inclusion body myositis is the most common progressive muscle wasting disease in people older than 50 years, with no effective drug treatment. Arimoclomol is an oral co-inducer of the cellular heat shock response that was safe and well-tolerated in a pilot study of inclusion body myositis, reduced key pathological markers of inclusion body myositis in two in-vitro models representing degenerative and inflammatory components of this disease, and improved disease pathology and muscle function in mutant valosin-containing protein mice. In the current study, we aimed to assess the safety, tolerability, and efficacy of arimoclomol in people with inclusion body myositis.

**Methods** This multicentre, randomised, double-blind, placebo-controlled study enrolled adults in specialist neuromuscular centres in the USA (11 centres) and UK (one centre). Eligible participants had a diagnosis of inclusion body myositis fulfilling the European Neuromuscular Centre research diagnostic criteria 2011. Participants were randomised (1:1) to receive either oral arimoclomol 400 mg or matching placebo three times daily (1200 mg/day) for 20 months. The randomisation sequence was computer generated centrally using a permuted block algorithm with randomisation numbers masked to participants and trial staff, including those assessing outcomes. The primary endpoint was the change from baseline to month 20 in the Inclusion Body Myositis Functional Rating Scale (IBMFRS) total score, assessed in all randomly assigned participants, except for those who were randomised in error and did not receive any study medication, and those who did not meet inclusion criteria. Safety analyses included all randomly assigned participants who received at least one dose of study medication. This trial is registered with ClinicalTrials.gov, number NCT02753530, and is completed.

**Findings** Between Aug 16, 2017 and May 22, 2019, 152 participants with inclusion body myositis were randomly assigned to arimoclomol (n=74) or placebo (n=78). One participant was randomised in error (to arimoclomol) but not treated, and another (assigned to placebo) did not meet inclusion criteria. 150 participants (114 [76%] male and 36 [24%] female) were included in the efficacy analyses, 73 in the arimoclomol group and 77 in the placebo group. 126 completed the trial on treatment (56 [77%] and 70 [90%], respectively) and the most common reason for treatment discontinuation was adverse events. At month 20, mean IBMFRS change from baseline was not statistically significantly different between arimoclomol and placebo (−3.26, 95% CI −4.15 to −2.36 in the arimoclomol group vs −2.26, −3.11 to −1.41 in the placebo group; mean difference −0.99 [95% CI −2.23 to 0.24]; p=0.12). Adverse events leading to discontinuation occurred in 13 (18%) of 73 participants in the arimoclomol group and four (5%) of 78 participants in the placebo group. Serious adverse events occurred in 11 (15%) participants in the arimoclomol group and 18 (23%) in the placebo group. Elevated transaminases three times or more of the upper limit of normal occurred in five (7%) participants in the arimoclomol group and one (1%) in the placebo group. Tubulointerstitial nephritis was observed in one (1%) participant in the arimoclomol group and none in the placebo group.

**Interpretation** Arimoclomol did not improve efficacy outcomes, relative to placebo, but had an acceptable safety profile in individuals with inclusion body myositis. This is one of the largest trials done in people with inclusion body myositis, providing data on disease progression that might be used for subsequent clinical trial design.

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## Introduction

Inclusion body myositis is the most common progressive, debilitating muscle wasting disease in people older than 50 years. It typically presents with insidious, asymmetric

weakness that predominantly affects the quadriceps, finger flexors, or both.<sup>1-4</sup> Dysphagia can be a presenting feature and frequently occurs during the disease course. The epidemiology varies between and within countries,

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## Research in context

### Evidence before this study

We searched PubMed for randomised, double-blind, placebo-controlled trials published in English since database inception up to Feb 28, 2023, using the following search terms: "Inclusion Body Myositis" AND "treatment" AND "randomised controlled trial". Open-label trials and trials using a historical control group were excluded. We found 11 eligible studies that investigated the following drugs as treatments for inclusion body myositis: intravenous immunoglobulin (three trials), bimagrumab (two trials), sirolimus (one trial), methotrexate (one trial), interferon beta-1a (two trials), oxandrolone (one trial), and arimoclomol (1 trial; the pilot safety and tolerability study that informed the current study). The time of assessment of the primary outcome varied across trials from 8 weeks to 52 weeks and the primary outcome (if specified) also varied widely: safety and tolerability, thigh muscle volume by MRI, quantitative muscle testing of knee extension or multiple muscle groups (using various methods and devices), manual muscle testing, and 6-min walking distance. No trials found a significant benefit and no specific drug treatment for inclusion body myositis is currently supported by evidence.

### Added value of this study

This is one of the largest randomised, double-blind, placebo-controlled trials in participants with inclusion body myositis or any idiopathic inflammatory myopathy. Our findings show that oral arimoclomol at 400 mg three times a day did not improve efficacy outcomes relative to placebo, but had an acceptable safety profile, in individuals with inclusion body myositis.

### Implications of all the available evidence

Inclusion body myositis remains a disease without an approved drug treatment. This trial provides data on disease progression over 20 months that can be used for subsequent standardisation of outcome assessment and clinical trial design in inclusion body myositis, and to inform future drug development strategies in this disease and related diseases. Although disrupted protein dyshomeostasis in people with inclusion body myositis remains a pathway of interest, alternative approaches might be required. The following two other large clinical trials in patients with inclusion body myositis have been initiated: one using sirolimus (NCT04789070) and the other using an anti-KLRG1 antibody (ABC008; NCT05721573). These trials have overall similar designs to ours and share the same primary outcome measure but are targeting different pathways.

with an estimated overall prevalence of 46 per 1 million (increasing to 139 per 1 million for people older than 50 years).<sup>5</sup> The pathogenesis is complex and remains poorly understood, but is thought to consist of an interplay between inflammatory and degenerative pathways.<sup>6,7</sup> The degenerative theory of inclusion body myositis hypothesises that the disease is driven by ageing of muscle fibres associated with accumulation and aggregation of misfolded, ubiquitinated, multiple-protein aggregates in genetically susceptible individuals.<sup>8</sup> Accumulation of these protein aggregates within muscle fibres is thought to trigger an inflammatory or immune response as a secondary consequence of muscle degeneration.<sup>9</sup>

Arimoclomol is a hydroxylamine derivative that acts as a co-inducer of the natural cellular heat shock response.<sup>10</sup> This response enhances expression of heat shock proteins, including molecular chaperones that promote natural folding of new proteins and refolding of damaged or mutated proteins.<sup>11</sup> Activation of the heat shock response might be beneficial in diseases characterised by toxic protein aggregates, such as inclusion body myositis. Concentrations of the heat shock protein HSP70 are increased in muscle biopsy samples from individuals with inclusion body myositis.<sup>12</sup> Arimoclomol can co-induce molecular chaperone genes in cell lines and in isolated cells or tissues, meaning that it further elevates chaperone protein concentrations that are already increased by physiological or metabolic stresses.<sup>13</sup> It elevates the concentrations of these proteins by prolonging activation of the transcription factor HSF-1.<sup>10,14</sup> Arimoclomol might

inhibit protein misfolding and aggregation in inclusion body myositis by helping muscle fibres to upregulate inducible heat shock proteins,<sup>13</sup> and therefore might slow or prevent muscle degeneration in this otherwise relentlessly progressive, debilitating disease.

In a pilot study, 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.<sup>13</sup> The results suggested that arimoclomol was safe and well-tolerated in individuals with inclusion body myositis. Arimoclomol also reduced key pathological markers of the disease in two robust rat myoblast in vitro models of the degenerative and inflammatory components of inclusion body myositis. Furthermore, arimoclomol improved disease pathology and muscle function in mice with mutant valosin-containing protein, which develop inclusion body myositis-like muscle histopathological features.<sup>13</sup>

We present the results of a randomised, double-blind, placebo-controlled trial of arimoclomol 400 mg three times daily in participants with inclusion body myositis. The aims of the trial were to evaluate the safety, efficacy, and tolerability of arimoclomol compared with placebo in participants with inclusion body myositis over 20 months.

## Methods

### Study design and participants

This study was a randomised, double-blind, placebo-controlled trial conducted at 11 US specialist neuromuscular centres and one UK specialist neuromuscular

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centre. Eligible participants had a diagnosis of inclusion body myositis fulfilling the European Neuromuscular Centre research diagnostic criteria 2011,<sup>15</sup> with onset of weakness at older than 45 years. 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 ft (6 m) with or without an assistive device. Participants were excluded if they were taking more than 7.5 mg/day of prednisolone or equivalent, or taking intravenous immunoglobulin or other immunosuppressants or immunomodulators, within the previous 3 months. Up to 4 weeks of systemic prednisolone more than 7.5 mg/day or equivalent was allowed during the study for conditions not related to inclusion body myositis (eg, asthma). A full summary of eligibility criteria is provided in the appendix pp 1–2.

See Online for appendix

Governance of study conduct and scientific direction was provided by a scientific steering committee comprising the authors MMD (Chair), PMM, MGH, RJB, and MPM, and a representative of the study funder, Orphazyme (CS). The study protocol was approved by the relevant institutional review board or research ethics committee, using a single institutional review board review via the SMART institutional review board platform for the 11 US centres, and the Health Research Authority approval process for the UK centre. The trial was conducted in accordance with the protocol, the principles of the Declaration of Helsinki, the International Conference on Harmonization Guideline on Good Clinical Practice, and all applicable laws and regulations including local laws and guidance. An independent data monitoring committee assessed study drug safety and tolerability at regular intervals (approximately 1 year after the first patient first visit and every 6 months thereafter, and a close-out meeting was held after study completion). Written informed consent was provided by all participants before the first study activity or assessment; the signature of an impartial witness was permitted for those with impaired manual dexterity.

### Randomisation and masking

Eligible participants were randomly assigned (1:1) to receive either oral arimoclochol 400 mg three times a day or placebo (matched in texture, appearance, solubility, smell, and flavour). Randomisation was computer generated using a permuted block algorithm to randomly allocate study drug to randomisation numbers, these numbers were then assigned sequentially via a telephone-based system as participants entered the trial. Appropriately numbered study medication bottles were distributed to centres in advance of randomisation and were dispensed to participants at the baseline visit. Randomisation was stratified by study centre. All study participants, the funders (the US Food and Drug Administration [FDA] Office of Orphan Products Development grant and Orphazyme), medical monitor,

investigators, site personnel, and people doing assessments were masked to treatment assignment.

### Procedures

The trial dosage, arimoclochol 1200 mg/day (400 mg three times a day), was selected following scientific advisory meetings with the FDA and was based on the following information: first, oral arimoclochol 100 mg three times a day was well tolerated in the pilot study;<sup>13</sup> second, oral arimoclochol 200 mg three times a day was well tolerated for 1 year in people with familial amyotrophic lateral sclerosis, and safety data held by Orphazyme supported the use of oral arimoclochol 400 mg three times a day over 28 days; third, preclinical (animal) data held by Orphazyme supported a maximum tolerated dose of oral arimoclochol 1800 mg in humans.

Study treatment consisted of two 200 mg arimoclochol capsules administered orally three times a day (total daily dosage of 1200 mg/day), or matching placebo, for up to 20 months (appendix p 12). Study drug dosing could be interrupted for up to 4 weeks if a participant had an intolerable adverse event. If the same adverse event persisted on rechallenge with the full dose, the dose could be reduced by half (ie, one 200 mg capsule three times a day) for the remainder of the study, or the treatment was permanently discontinued if this lower dose was not tolerated. The study drug could be administered in multiple ways to accommodate increasing dysphagia associated with disease progression: capsules could either be swallowed whole or opened and the granules dispersed in 10–30 mL of liquid or soft food. Once dispersed in water, the capsule contents could also be administered via a feeding tube.

Scheduled study visits, including safety assessments, were performed over the course of 20 months (appendix p 12). All data were captured in an electronic data capture system with source data verification; sex at birth was determined by participant self-report. As the study progressed, in-person visits to study centres became less frequent, but during the trial additional in-person safety visits were implemented (via protocol amendment) to monitor liver function. In response to COVID-19 pandemic restrictions, the protocol was amended after study initiation to allow additional phone visits (beyond those prospectively planned for months 10, 14, and 18, and the month 21 safety follow-up after the end of treatment), home nursing visits for safety laboratory blood draws, and delivery of study medication to participants unable to attend the clinic. All protocol amendments during the conduct of the trial are summarised in the appendix p 3.

### Outcomes

The primary endpoint was the change from baseline to month 20 in the Inclusion Body Myositis Functional Rating Scale (IBMFRS) total score and was centrally assessed. Initially derived from the Amyotrophic Lateral

For more on the protocol see  
<https://classic.clinicaltrials.gov/ct2/show/NCT02753530>

Sclerosis Functional Rating Scale, the IBMFRS is administered by a trained clinician or evaluator to determine participants' assessment of their capability and independence.<sup>16</sup> It includes ten items relevant to inclusion body myositis function, each graded on a Likert scale from zero (being unable to perform) to four (normal): 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 ten items yields a value between zero and 40, with a higher score representing less functional limitation.<sup>16,17</sup>

Secondary endpoints intended to provide confirmation of results for the primary endpoint were evaluations of participants' functional abilities and strength, arranged in the following predefined hierarchy: changes from baseline to month 20 in hand grip strength using the Jamar device (Patterson Medical, Chicago, IL, USA; strongest hand), modified Timed Up and Go (mTUG), Manual Muscle Testing total score (24 muscles), 6-min walk test (6MWT) distance, and physical component score of the Short-Form 36 health survey (SF-36).<sup>18</sup>

Other secondary endpoints included changes from baseline to month 20 in knee extensor strength (strongest knee at baseline) using the MicroFET hand-held dynamometer (Hoggan Health Industries, Salt Lake City, UT, USA), Health Assessment Questionnaire-Disability Index (HAQ-DI; using the alternative version that does not incorporate the use of aid devices or personal help; the standard version of the HAQ-DI was used as a supportive measure), 2-min walk test (2MWT) distance, and 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), and accumulated number of falls and near-falls were also collected as secondary endpoints. Other secondary endpoints were changes from baseline to month 12 in IBMFRS total score, hand grip strength, mTUG, MMT total score, 6MWT, and physical component score of the SF-36, as well as PGIS, PGIC, CGIS, and CGIC at month 12. Evaluators underwent periodic training throughout the study to maintain proficiency in study assessments. The timepoints of all secondary endpoint assessments are listed in the study protocol.

The safety and tolerability assessments included adverse events, haematology, clinical chemistry, vital signs, and Columbia Suicide Severity Rating Scale. 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. Severity of adverse events was graded using the following scale:

mild (awareness of symptoms or signs, but easily tolerated and does not interfere with the patient's usual function), moderate (interferes to some extent with the patient's usual function causing enough discomfort to interfere with usual activity), and severe (interferes significantly with the patient's usual function causing incapacity to work or to do usual activities).

### Statistical analysis

We planned to enrol 150 participants (75 per group). In the pilot trial of arimoclomol in inclusion body myositis,<sup>13</sup> the SD of the 12-month change in IBMFRS total score was 2.9 and the mean change was  $-3.5$  in the placebo group and  $-2.1$  in the arimoclomol group. A sample size of 68 participants per group (136 total) would provide 80% power to detect a treatment group difference in mean response of 1.4 points, using a two-sample *t* test and a 5% significance level (two-tailed). Given the absence of information on the minimal clinically important group difference on the IBMFRS total score, this effect size was selected as a balance between clinical meaningfulness (projected 40% slowing of functional decline) and recruitment feasibility. To account for an anticipated 10% dropout rate, the sample size was inflated to 75 participants per group (150 total). Although this calculation strictly applied only to a trial with 12-month follow-up, it would also apply to this trial if the magnitude of the treatment effect relative to the magnitude of the SD of the change in IBMFRS total score did not diminish over time.

Analyses of all efficacy endpoints included all randomly assigned participants, except for those who were randomised in error and did not receive any study medication and those who did not meet inclusion criteria (full analysis set). The decision to exclude randomised participants from the statistical analyses was incorporated in the final version of the statistical analysis plan (March 2, 2021) in advance of database lock and unblinding (March 4, 2021). The study protocol termed this analysis set the intent-to-treat population, even though the analyses did not strictly adhere to the intention-to-treat principle due to the exclusion of some randomised participants from the analyses. Analyses of all safety data included all randomly assigned participants who received at least one dose of study medication (safety analysis set). In the safety analyses only events that occurred or assessments that were done while the participant was taking study medication (or within 14 days of stopping study medication) were included.

The primary estimand was the treatment group difference in mean change from baseline in the IBMFRS total score at month 20, regardless of exposure and adherence to randomised treatment or changes in background therapy. The primary efficacy endpoint was analysed using the restricted maximum likelihood-based approach of mixed model for repeated measurements,<sup>19</sup> 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.

Subgroup analyses were done for the primary outcome variable by adding the appropriate main effect (subgroup-defining baseline variable) and interaction terms to the primary analysis model. The subgroups were country, IBMFRS total score (less than or greater than the median of 27·5), 6MWT distance (less than or greater than the median of 321·3 m), and CN1A antibody status (positive or negative).

All statistical tests were done using a two-tailed 5% significance level. Statistical analyses were done using SAS (version 9.4 or higher). This trial is registered with ClinicalTrials.gov, number NCT02753530.

### Role of the funding source

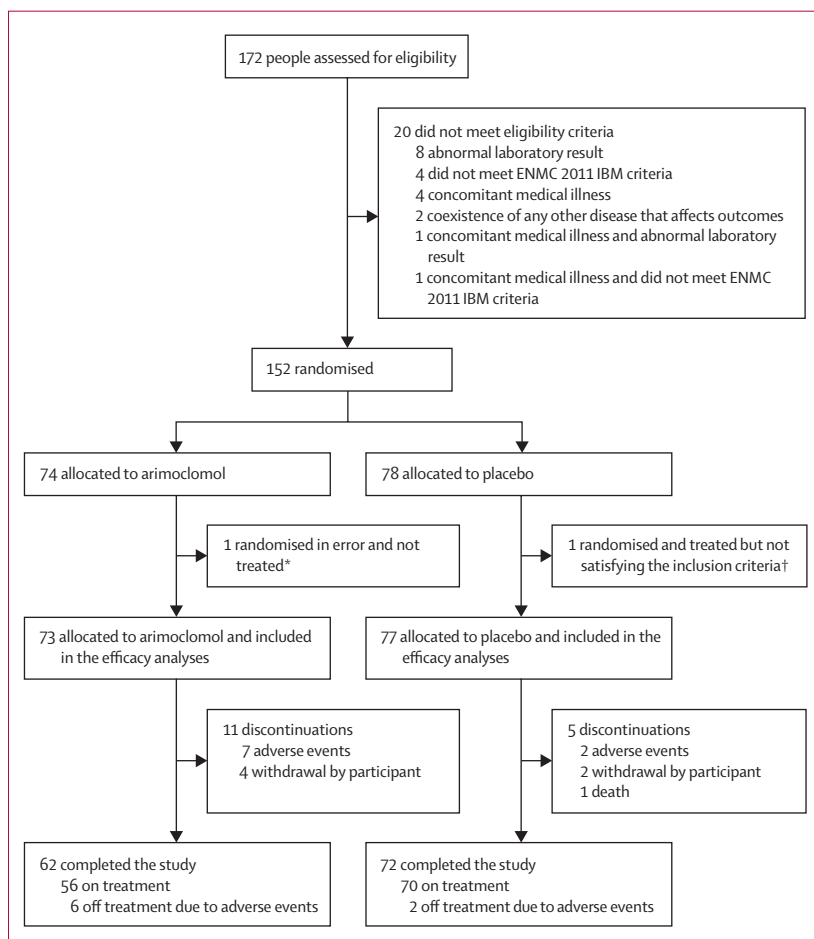
This was an investigator-initiated trial, with funding from the FDA Office of Orphan Products Development grant and Orphazyme. The Orphazyme sponsorship was transferred to Zevra Denmark, formerly known as KemPharm Denmark, after study completion. The pharmaceutical funder had a role in study design, study implementation, data collection, data management, data analysis, data interpretation, and preparation, review, and approval of the report; the academic funder did not have a role in any of these activities.

### Results

Between Aug 16, 2017 and May 22, 2019, 172 individuals with inclusion body myositis were screened, of whom 152 were randomly assigned to arimoclochol 1200 mg/day (74 participants) or placebo (78 participants). One participant was randomly assigned to arimoclochol in error but was not treated and did not have any follow-up evaluations and therefore was excluded from all analyses; another participant who did not meet inclusion criteria was randomly assigned to placebo and treated and therefore included in the safety analyses (n=151, 73 in the arimoclochol group and 78 in the placebo group) but not in the efficacy analyses (n=150, 73 in the arimoclochol group and 77 in the placebo group; figure 1).

Of the 151 participants who were treated, 134 (62 [85%] of 73 participants in the arimoclochol group and 72 [92%] of 78 in the placebo group) completed the trial, and 126 completed the trial on treatment (56 [77%] and 70 [90%]). The most common reason for treatment discontinuation was an adverse event (13 [18%] and four [5%]).

There were more male participants (114 [76%]) than female participants (36 [24%]). Mean age was 67·2 years (SD 8·1), and 87 (58%) participants were older than



**Figure 1: Trial profile**

The efficacy analysis (n=150) included 73 participants in the arimoclochol group and 77 in the placebo group. The safety analysis (n=151) included 73 participants in the arimoclochol group and 78 in the placebo group. ENMC=European Neuromuscular Centre. IBM=inclusion body myositis. \*Participant excluded from both the safety and efficacy analyses. †Participant excluded from the efficacy analyses but included in the safety analyses.

65 years (table 1). Mean IBMFRS total score was 26.9 (4.7) in the arimoclomol group and 27.9 (4.4) in the placebo group, reflecting overall moderate disability. The distribution of enrolling centre by treatment group is provided in appendix p 4.

For the primary efficacy endpoint, both groups showed a reduction from baseline in IBMFRS total score (indicating more functional limitations than at baseline) at month 20 ( $-3.26$ , 95% CI  $-4.15$  to  $-2.36$  in the arimoclomol group vs  $-2.26$ ,  $-3.11$  to  $-1.41$  in the placebo group), and a statistically significant treatment effect was not detected (arimoclomol–placebo difference in adjusted group means of  $-0.99$  [95% CI  $-2.23$  to  $0.24$ ],  $p=0.12$ ; table 2, figure 2). The amount of missing data was slightly greater in the arimoclomol group than in the placebo group (appendix p 5) but 1411 (94%) of 1500 of the scheduled IBMFRS total scores were obtained overall.

As the primary endpoint was not statistically significant, the secondary endpoints could not be analysed according to planned testing hierarchy with a confirmatory interpretation. All of the secondary endpoints worsened during the trial for participants in both the arimoclomol and placebo groups (table 2, figure 2; appendix p 6). Subgroup analyses of the primary endpoint revealed mean changes that consistently favoured the placebo group regardless of subgroup, with some variation in terms of the observed magnitudes of the treatment effects (appendix p 7).

The median incidence rates of falls (3.0 [IQR 1.2–6.7] falls per year in the arimoclomol group vs 3.1 [1.2–6.7] in the placebo group) and near-falls (0.6 [0–3.7] vs 0.6 [0–4.9]) were similar between groups. Data for PGIC are summarised descriptively in appendix p 8. The CGIS and CGIC measures were introduced after study initiation through a protocol amendment and were assessed at month 20 for only 12 participants; therefore, these data are not presented.

During the on-treatment period, the 151 participants were observed for 219.7 participant-years and 142 participants (94%) had at least one adverse event. A higher proportion of participants treated with arimoclomol had at least one adverse event than those treated with placebo (72 [99%] of 73 participants in the arimoclomol group vs 70 [90%] of 78 participants in the placebo group; table 3). The total number of adverse events (593 events in the arimoclomol group vs 450 events in the placebo group) and the rate of adverse events over time (5.99 events per year vs 3.73 events per year) were also higher in participants treated with arimoclomol than with placebo. There was a higher incidence of mild adverse events in the arimoclomol group than the placebo group, whereas moderate and severe adverse events occurred in similar proportions in the two groups (table 3). Overall, mild adverse events (681 events in total) and moderate adverse events (334 events) were more common than severe adverse events (28 events).

	Arimoclomol (N=73)	Placebo (N=77)
Age, years	67.0 (8.2)	67.4 (8.1)
>65 years	41 (56%)	46 (60%)
Sex		
Male	53 (73%)	61 (79%)
Female	20 (27%)	16 (21%)
Race		
Asian	2 (3%)	1 (1%)
Black or African American	1 (1%)	0
White	69 (95%)	74 (96%)
Other	1 (1%)	1 (1%)
Mixed	0	1 (1%)
Country		
UK	17 (23%)	17 (22%)
USA	56 (77%)	60 (78%)
Age at diagnosis, years	63.4 (8.7)	63.5 (7.9)
Duration of weakness, months	101.4 (60.6)	95.4 (55.1)
Inclusion body myositis diagnostic category		
Clinically defined	39 (53%)	41 (53%)
Clinicopathologically defined	23 (32%)	26 (34%)
Probable	11 (15%)	10 (13%)
Height, cm	175.0 (8.7)	175.6 (9.3)
Weight, kg	83.3 (16.3)	81.9 (15.9)
BMI, kg/m <sup>2</sup>	27.2 (4.1)	26.4 (4.2)
CN1A antibody positive	39 (53%)	39 (51%)
IBMFRS total score	26.9 (4.7)	27.9 (4.4)
Hand grip strength, kg	10.0 (6.0–16.0)	11.0 (8.0–17.0)
mTUG, m/s	0.43 (0.32–0.59)	0.46 (0.36–0.62)
MMT total score	7.6 (1.1)	7.8 (0.9)
6MWT, m	314.3 (104.1)	335.4 (96.0)
SF-36 PCS	36.0 (8.9)	38.4 (6.9)
Knee extensor strength, kg	9.1 (4.4–15.9)	10.8 (5.9–19.6)
HAQ-DI total score	1.25 (0.88–1.75)	1.00 (0.63–1.38)
2MWT, m	107.8 (33.2)	114.6 (34.1)
SF-36 MCS	55.6 (8.4)	57.8 (7.5)

Data are n (%), mean (SD), or median (IQR) for the full analysis set. Sex and race were determined by patient self-report. Results for hand grip and knee extensor strength are for the stronger limb, as identified at baseline. 2MWT=2-min walk test. 6MWT=6-min walk test. HAQ-DI=Health Assessment Questionnaire Disability Index. IBMFRS=Inclusion Body Myositis Functional Rating Scale. MMT=Manual Muscle Testing. mTUG=modified Timed Up and Go. SF-36 MCS=Short Form-36 Health Survey mental component score. SF-36 PCS=Short Form-36 Health Survey physical component score.

**Table 1: Baseline characteristics**

A higher proportion of participants treated with arimoclomol than participants treated with placebo had adverse events that were considered related to study medication (61 [84%] in the arimoclomol group vs 38 [49%] in the placebo group), and at a higher rate (2.61 events per year vs 0.72 events per year). Serious adverse events occurred in lower numbers in the

	Arimoclomol (N=73)	Placebo (N=77)	Difference (arimoclomol-placebo)
<b>Primary endpoint</b>			
IBMFRS total score	-3.26 (-4.15 to -2.36)	-2.26 (-3.11 to -1.41)	-0.99 (-2.23 to 0.24; p=0.12)
<b>Confirmatory secondary endpoints, in the predefined hierarchy</b>			
Hand grip strength, kg	-3.71 (-5.05 to -2.37)	-2.60 (-3.82 to -1.38)	-1.11 (-2.93 to 0.70)
mTUG, m/s	-0.12 (-0.18 to -0.06)	-0.11 (-0.16 to -0.06)	-0.01 (-0.09 to 0.07)
MMT total score	-0.53 (-0.75 to -0.32)	-0.56 (-0.76 to -0.37)	0.03 (-0.26 to 0.32)
6MWT, m	-36.37 (-54.35 to -18.39)	-34.58 (-50.90 to -18.27)	-1.79 (-26.09 to 22.51)
SF-36 PCS	-1.39 (-2.96 to 0.17)	-2.88 (-4.36 to -1.40)	1.49 (-0.69 to 3.66)
<b>Other secondary endpoints</b>			
Knee extensor strength, kg	-5.62 (-7.02 to -4.22)	-4.13 (-5.40 to -2.86)	-1.49 (-3.38 to 0.40)
HAQ-DI total score	0.36 (0.24 to 0.47)	0.32 (0.21 to 0.43)	0.04 (-0.12 to 0.20)
2MWT, m	-10.53 (-16.75 to -4.30)	-9.72 (-15.29 to -4.15)	-0.81 (-9.17 to 7.56)
SF-36 MCS	-3.41 (-5.38 to -1.43)	-0.95 (-2.81 to 0.92)	-2.46 (-5.20 to 0.27)
PGIS*	3.15 (2.98 to 3.33)	2.99 (2.83 to 3.16)	0.16 (-0.08 to 0.40)

Data are for the full analysis set and are adjusted group means and associated 95% CIs derived from the primary statistical model. Results for hand grip and knee extensor strength are for the stronger limb, as identified at baseline. Results for the alternative HAQ-DI are shown (similar results were obtained for the standard HAQ-DI, not shown). Data were available for only 12 participants for the CGIS and CGIC and are not presented. 2MWT=2-min walk test. 6MWT=6-min walk test. HAQ-DI=Health Assessment Questionnaire Disability Index. IBMFRS=Inclusion Body Myositis Functional Rating Scale. MMT=Manual Muscle Testing. mTUG=modified Timed Up and Go. PCS=Short Form-36 Health Survey physical component score. PGIS=Patient Global Impression of Severity. SF-36 MCS=Short Form-36 Health Survey mental component score. \*PGIS is reported as the adjusted group mean at month 20 rather than the change from baseline; a 0 to 5 scale was used, with 0 being none, 1 being very mild, 2 being mild, 3 being moderate, 4 being severe, and 5 being very severe.

**Table 2: Changes from baseline to month 20 in primary and secondary endpoints**

arimoclomol group than in the placebo group (11 [15%] participants had 18 serious adverse events in the arimoclomol group and 18 [23%] participants had 28 serious adverse events in the placebo group). The only serious adverse events reported more than once or by more than one participant were syncope (two participants in the arimoclomol group) and falls (one participant in each group); all other serious adverse events were single occurrences in one participant each.

A higher proportion of participants in the arimoclomol group than in the placebo group had adverse events that led to treatment discontinuation (13 [18%] in the arimoclomol group vs four [5%] in the placebo group). Decreased appetite led to treatment discontinuation in three participants in the arimoclomol group. Increased alanine aminotransferase (ALT), increased aspartate transaminase (AST), decreased weight, and syncope each led to treatment discontinuation in two participants in the arimoclomol group. The remaining adverse events leading to treatment discontinuation were each reported in one participant (appendix p 9).

One participant (arimoclomol group) died during the trial due to cholangiocarcinoma and metastases to the liver that were considered not related to arimoclomol. One participant (placebo group) died from unknown cause while sleeping; the death was considered not related to study medication by the investigator or sponsor (the participant was off treatment and therefore is not included in table 3).

On-treatment adverse events reported in greater than 5% of participants regardless of relatedness to treatment in either treatment group are presented in table 4. The following system organ classes were more frequently affected by adverse events in the arimoclomol group than in the placebo group (at least a 10 percentage point difference): gastrointestinal disorders, investigations, nervous system disorders, skin and subcutaneous tissue disorders, and general disorders.

ALT or AST three or more times the upper limit of normal were reported more frequently in the arimoclomol group than in the placebo group (five [7%] participants in the arimoclomol group vs one [1%] participant in the placebo group), with most abnormal values reported in month 2 and leading to study drug discontinuation in four of five participants in the arimoclomol group. Eight (11%) participants in the arimoclomol group and three (4%) in the placebo group had an increase in creatinine of more than 1.5 times their baseline value. One participant in the arimoclomol group had an increase in creatinine of two times their baseline value; the participant was diagnosed with tubulointerstitial nephritis and renal tubular necrosis considered related to the study medication and study drug was discontinued.

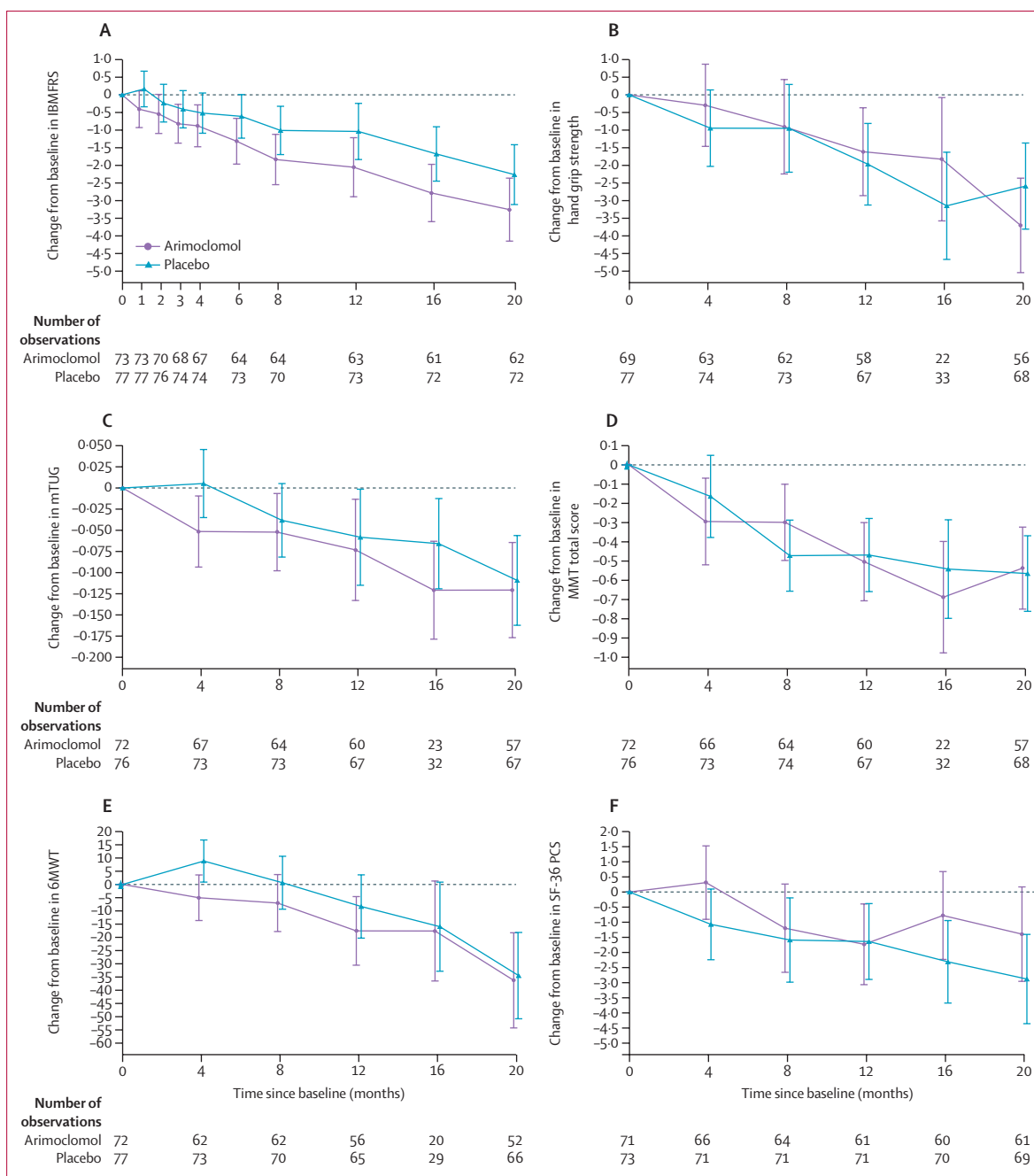
Results from vital signs, physical examinations, and electrocardiograms showed no differences between treatment groups. No worsening in suicidal ideation or behaviour was reported. Compliance, as measured by pill counting, was high, with mean compliance of 93.0% (SD 12.7) in the arimoclomol group and 94.7% (12.0) in the placebo group.

The list of protocol deviations by treatment group (in the safety analysis set) is presented in appendix pp 10–11. The majority of deviations were classified as not important. The majority of the important deviations were informed consent deviations due primarily to delays in asking the participant to renew their consent after protocol amendments.

## Discussion

Our findings show that oral arimoclomol at a dosage of 400 mg three times a day (1200 mg/day) had no beneficial effect relative to placebo on the IBMFRS total score after 20 months of treatment. The upper boundary of the 95% CI for the effect of arimoclomol relative to placebo was 0.24, which would not be considered clinically meaningful. No beneficial effects of treatment were apparent on any of the secondary outcome variables. Participants assigned to arimoclomol had fewer serious adverse events than placebo, and most adverse events were mild.

Given the severe disability and quality-of-life impairment associated with advanced inclusion body myositis, there is a substantial unmet need for effective treatment capable of altering the disease course. This trial followed repeated clinical studies showing no benefit of investigational therapies for inclusion body myositis.



**Figure 2: Adjusted group mean changes from baseline by visit**

Adjusted group means and associated 95% CIs derived from the primary statistical model for IBMFRS total score (A), hand grip strength (B), mTUG (C), MMT total score (D), 6MWT distance (E), and SF-36 PCS (F). Error bars represent 95% CIs. 6MWT=6-min walk test. IBMFRS=Inclusion Body Myositis Functional Rating Scale. MMT=Manual Muscle Testing. mTUG=modified Timed Up and Go. SF-36 MCS=Short Form-36 Health Survey mental component score. SF-36 PCS=Short Form-36 Health Survey physical component score.

Despite the disease pathology having a clear inflammatory component, multiple studies of immunosuppressive agents (including corticosteroids, intravenous immunoglobulin, methotrexate, and azathioprine) have shown no benefit. Similarly, trials of immune system cytokines and cytokine receptor inhibitors in individuals

with inclusion body myositis did not show a clinically meaningful benefit.<sup>7</sup> Consequently, research has turned to other strategies, namely those combating muscle wasting and atrophy, such as modulation of the myostatin pathway. A phase 2b trial with the human monoclonal antibody bimagrumab, an inhibitor of activin



	Arimoclomol (N=73)	Placebo (N=78)
Observation time (participant-years)	99.0	120.7
Adverse events	72 (99%); 593	70 (90%); 450
Mild	68 (93%); 403	62 (79%); 278
Moderate	51 (70%); 175	52 (67%); 159
Severe	9 (12%); 15	11 (14%); 13
Adverse events related to study medication	61 (84%); 258	38 (49%); 87
Serious adverse events	11 (15%); 18	18 (23%); 28
Serious adverse events related to study medication	5 (7%); 6	2 (3%); 2
Adverse events leading to temporary interruption of study medication	11 (15%); 18	13 (17%); 20
Adverse events leading to discontinuation of study medication	13 (18%); 29	4 (5%); 4
Adverse events leading to dose reduction	2 (3%); 3	0; 0
Adverse events with fatal outcome*	1 (1%); 2	0; 0

Severity of adverse events were graded as mild (does not interfere with the patient's usual function), moderate (interferes to some extent with the patient's usual function), or severe (interferes significantly with the patient's usual function). Data are for the safety analysis set and are number of participants who had at least one on-treatment adverse event (%), followed by the total number of occurrences of the adverse event. An on-treatment adverse event was defined as an event that emerged during treatment, having been absent before treatment, or worsened relative to the pre-treatment state. The on-treatment period started on the date of first administration of study medication and ended 14 days from the latest administration of study medication. \*One participant died during the trial due to cholangiocarcinoma and metastases to the liver that were considered not related to arimoclomol; cholangiocarcinoma and metastases to the liver are listed as separate events. One participant assigned to placebo died off treatment and therefore is not included in the table; this patient died on day 425 of unknown cause while sleeping and the death was considered not related to study medication by the investigator or the sponsor (Orphazyme).

**Table 3: On-treatment adverse events**

type 2 receptor signalling that blocks the action of myostatin (an endogenous negative regulator of muscle growth), did not show statistically significant improvement relative to placebo in the primary endpoint of change from baseline to week 52 in 6MWT, or in multiple secondary endpoints.<sup>20,21</sup>

With arimoclomol, we assessed the alternative strategy of augmenting the heat shock response, which is hypothesised to improve protein degradation pathways and consequently reduce cell stress. However, this drug also did not show clinical efficacy in individuals with inclusion body myositis with the chosen dose. Other ways of targeting dysregulated protein dyshomeostasis, or drugs (or a combination of drugs) targeting more than one pathway (eg, degeneration, inflammation, mitochondrial changes, and muscle atrophy), might be required to treat inclusion body myositis. Data from a xenograft model of inclusion body myositis support the view that inclusion body myositis should be considered within the spectrum of neurodegenerative diseases that show TDP-43

	Arimoclomol (N=73)	Placebo (N=78)
Injury, poisoning, and procedural complications	38 (52%); 80	48 (62%); 112
Contusion	9 (12%); 16	13 (17%); 20
Fall	8 (11%); 10	7 (9%); 9
Laceration	6 (8%); 6	8 (10%); 8
Ligament sprain	7 (10%); 8	5 (6%); 9
Skin abrasion	5 (7%); 8	7 (9%); 14
Foot fracture	4 (5%); 4	6 (8%); 7
Joint injury	2 (3%); 5	7 (9%); 9
Limb injury	2 (3%); 2	4 (5%); 5
Rib fracture	0; 0	4 (5%); 5
Infections and infestations	37 (51%); 72	41 (53%); 64
Nasopharyngitis	10 (14%); 12	13 (17%); 15
Upper respiratory tract infection	6 (8%); 7	11 (14%); 12
Sinusitis	4 (5%); 4	6 (8%); 6
Bronchitis	2 (3%); 3	5 (6%); 5
Influenza	4 (5%); 5	2 (3%); 2
Gastrointestinal disorders	40 (55%); 73	31 (40%); 42
Constipation	14 (19%); 15	9 (12%); 9
Diarrhoea	12 (16%); 13	9 (12%); 12
Nausea	9 (12%); 12	1 (1%); 1
Dry mouth	7 (10%); 7	1 (1%); 1
Abdominal pain upper	5 (7%); 6	1 (1%); 1
Musculoskeletal and connective tissue disorders	33 (45%); 63	31 (40%); 64
Arthralgia	15 (21%); 17	15 (19%); 17
Back pain	9 (12%); 9	8 (10%); 14
Pain in extremity	8 (11%); 11	6 (8%); 6
Musculoskeletal pain	6 (8%); 6	7 (9%); 7
Joint swelling	5 (7%); 5	2 (3%); 2
Muscle spasms	4 (5%); 4	2 (3%); 4
Investigations	30 (41%); 62	21 (27%); 30
Blood creatinine increased	9 (12%); 9	1 (1%); 1
Weight decreased	7 (10%); 7	3 (4%); 3
Alanine aminotransferase increased	6 (8%); 6	3 (4%); 4
Nervous system disorders	31 (42%); 57	16 (21%); 20
Headache	7 (10%); 12	4 (5%); 4
Dizziness	8 (11%); 9	0; 0
Hypoaesthesia	6 (8%); 6	1 (1%); 1
Paraesthesia	4 (5%); 5	0; 0
Skin and subcutaneous tissue disorders	31 (42%); 52	14 (18%); 18
Rash	14 (19%); 16	4 (5%); 7
Erythema	6 (8%); 8	0; 0
General disorders and administration site conditions	20 (27%); 32	13 (17%); 17
Fatigue	8 (11%); 8	3 (4%); 4
Oedema peripheral	6 (8%); 8	2 (3%); 2

(Table 4 continues on next page)

	Arimoclomol (N=73)	Placebo (N=78)
(Continued from previous page)		
Metabolism and nutrition disorders	13 (18%); 15	11 (14%); 13
Decreased appetite	5 (7%); 5	0; 0
Gout	0; 0	5 (6%); 5
Alcohol intolerance	4 (5%); 4	0; 0
Respiratory, thoracic, and mediastinal disorders	12 (16%); 17	9 (12%); 13
Cough	5 (7%); 5	4 (5%); 5
Vascular disorders	12 (16%); 12	6 (8%); 6
Hypertension	5 (7%); 5	1 (1%); 1

Data are for the safety analysis set and are number of participants who had at least one on-treatment adverse event (%), followed by the total number of occurrences of the adverse event. All adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1. An on-treatment adverse event was defined as an event that emerged during treatment, having been absent before treatment, or worsened relative to the pre-treatment state. At each level of summarisation (system organ class and preferred term), participants who had more than one adverse event were only counted once. System organ classes and preferred terms are sorted in descending order of frequency of total on-treatment adverse events. The on-treatment period started on the date of first administration of study medication and ended 14 days from the latest administration of study medication.

**Table 4: On-treatment adverse events reported in more than 5% of participants in either treatment group by system organ class and preferred term**

proteinopathy, along with amyotrophic lateral sclerosis and frontotemporal dementia, and suggest that drugs targeting degenerative pathways should continue to be investigated in inclusion body myositis.<sup>22</sup> Better understanding of its complex pathophysiology will be crucial to therapeutic success in this disease.

The unmet treatment need in inclusion body myositis, therefore, remains after this trial. Other therapeutic strategies are currently being explored. Following some encouraging secondary endpoint results from a phase 2b trial of sirolimus,<sup>23</sup> a multinational study has now been launched (NCT04789070); sirolimus inhibits the mTOR pathway, which plays a role in protein turnover, autophagy, and IL-2 immune mechanisms. Depletion of KLRG1<sup>+</sup> T cells is also being pursued as a treatment strategy in inclusion body myositis. KLRG1 is a marker of highly differentiated effector CD8<sup>+</sup> cytotoxic T cells, which are present in muscle tissue of people with inclusion body myositis,<sup>24</sup> and phase 1 (NCT04659031)<sup>25</sup> and phase 2/3 (NCT05721573) studies of ABC008 (a humanised monoclonal antibody against KLRG1) in participants with inclusion body myositis are ongoing.

We selected the IBMFRS total score as primary trial endpoint, as opposed to the 6MWT, which was used in the phase 2b bimagrumab trial.<sup>20</sup> The 6MWT might not be an optimal primary outcome measure for inclusion body myositis, given that performance on the test depends on multiple factors other than leg muscle function, including cardiopulmonary function, fatigue,

skeletal pain, motivation, and general physical fitness.<sup>26</sup> The IBMFRS, used in this study, is a broader assessment of ten distinct functional activities relevant to the overall effect of inclusion body myositis on participants' lives.<sup>16,27</sup> Therefore, we thought it to be a more valid, sensitive, and reliable tool than the 6MWT for assessing clinical benefit in inclusion body myositis. The IBMFRS total score correlates well with measures of muscle strength and health-related quality of life in individuals with inclusion body myositis.<sup>16,17</sup> The FDA regulatory division accepted the IBMFRS total score as a clinically relevant primary endpoint for this study in 2016 as part of our Type C meeting correspondence.<sup>28</sup> However, modifications to the scale could be considered, as suggested after Rasch analysis,<sup>27</sup> although these modifications still need to be validated.

Our study has limitations. Rate of deterioration in the IBMFRS total score was lower than expected in the placebo group, which might reflect differences between this and other study populations, influenced by factors such as the trial environment (and participants' expectations regarding drug efficacy) and the heterogeneity of the condition. Indeed, people with inclusion body myositis have very different rates of disease progression and trajectories over time at the individual level, with these rates and trajectories being influenced by factors such as age, sex, clinical manifestations (eg, dysphagia), and disease duration.<sup>17,29,30</sup> Also, the projected mean decline in the placebo group was based on a relatively small preliminary study.<sup>13</sup> The use of a single dose could also be considered a limitation. The selection of the dose was based on scientific advisory meetings with the FDA and preclinical (animal) and clinical data. However, the chosen dose had not been used in individuals with inclusion body myositis before. Although multi-arm or dose titration study designs could have been considered, they posed feasibility concerns: the required increased sample size in a multi-arm trial for the purpose of submitting a new drug application to regulatory agencies; the delay in the development pathway by opting for an early phase, exploratory dose-ranging study that would have informed future studies; and the challenges of designing a titration study in a slowly progressive disease such as inclusion body myositis. For a titration study, a longer follow-up duration would probably be necessary due to the hypothesised mechanism of slowing disease progression in the long term rather than providing an early symptomatic effect. Finally, average disease duration in our study was around 8 years, and a different trial outcome might have been observed if only participants with early-stage disease had been recruited.

Arimoclomol had an acceptable safety profile in our study. In general, the observed elevations of ALT and AST were reversible upon cessation of arimoclomol or during continued treatment, and there were no concurrent increases in total bilirubin, alkaline phosphatase, or eosinophil concentrations. The mild

elevations in creatinine are consistent with data from previous clinical trials that have shown that arimoclomol might lead to an increase in blood creatinine via inhibition of the OCT2, MATE-1, and MATE-2 transporters, resulting in inhibited tubular secretion of creatinine. The case of tubulointerstitial nephritis was unexpected; this event is typically a result of a drug hypersensitivity reaction and was therefore considered unrelated to the inhibition of the OCT2, MATE-1, and MATE-2 transporters.

In conclusion, treatment with arimoclomol did not improve the IBMFRS total score or other measures of physical function, strength, mobility, disease severity, and health-related quality of life. This is one of the largest randomised controlled trials done in people with myositis and it provides data on disease progression over 20 months that can be used for subsequent design of clinical trials for people with inclusion body myositis.

#### **Arimoclomol in Inclusion Body Myositis Investigator Team of the Neuromuscular Study Group**

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#### **Contributors**

All authors contributed to the conception and design of the study. The first draft of the manuscript was written by PMM. AR performed the statistical analyses, which were independently verified by MPM. PMM, MPM, TB, CS, AR, RJB, MGH, and MMD accessed and verified the data, and all authors were permitted access to all the data in the study. PMM, MPM, RJB, MGH, and MMD were responsible for the decision to submit the manuscript. All authors critically reviewed and commented on each draft of the manuscript, and approved the final manuscript for submission.

#### **Declaration of interests**

PMM has received consulting fees and funding support from Orphazyme, paid to his academic institution (University College London) for the oversight and conduct of this study, and has also received honoraria from Abbvie, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer, Roche, and UCB. MPM has received research funding from the US National Institutes of Health (NIH), the US Food and Drug Administration, Cure SMA, and PTC Therapeutics; received consulting fees from NeuroDerm and Fulcrum Therapeutics; and served on data and safety monitoring boards for NIH, Eli Lilly and Company, Catabasis Pharmaceuticals, Vaccinex, Neurocrine

Biosciences, Voyager Therapeutics, Prilenia Therapeutics Development, ReveraGen BioPharma, and NS Pharma. TB, CS, AR, TDC, KB, ANJ, and KP are previous employees of Orphazyme. MF has received consulting fees from UCB, Argenx, Alexion, and CSL Behring; and research support paid to her institution (Ohio State University) from UCB, Argenx, Alexion, Fulcrum, Avidity, Pharnext, Janssen, and Roche. TEL has served as a consultant for Aavogen, Abata Therapeutics, Abcuro, Acceleron, DrenBio, EMD Serano, Kezar Life Sciences, Ono Pharma, Orphazyme, Regenacy, Sarepta, and Takeda; DSMB was Chair of the data and safety monitoring board for a Pharnext-sponsored clinical trial; and received research support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the NIH (R01 AR076390), the Muscular Dystrophy Association (MDA630399), Horizon Therapeutics, and The Peter and Carmen Lucia Buck Foundation. TM has served as an advisor to Alexion (AstraZeneca), Amicus, AnnJi, Argenx, Arvinas, Ask-Bio, Audentes (now Astellas Gene Therapy), Horizon Therapeutics, Maze Therapeutics, Momenta (now Janssen), Sanofi, Sarepta, Spark Therapeutics, UCB/Ra Pharmaceuticals, and Modis/Zogenix (now UCB); has served on the speaker's bureau for Sanofi-Genzyme, Alexion, and Argenx; has served on the medical advisory board for the Myositis Association, Neuromuscular Disease Foundation, Myasthenia Gravis Foundation of California, and Myasthenia Gravis Foundation of America; has received research funding from the Myositis Association, the Muscular Dystrophy Association, NIH, and from the following commercial sponsors: Alexion, Amicus, AnnJi, Argenx, Audentes/Astellas Gene Therapy, Bristol Myers Squibb, Cartesian Therapeutics, Grifols, ML-Bio, Momenta, Ra Pharmaceuticals, Sanofi, Spark Therapeutics, UCB, and Valerion; and he serves on the data safety monitoring boards for Acceleron, Avexis, Sarepta, and NIH. RJB has received funding from the FDA Office Orphan Products Development grant for his role in this study. MGH receives research funding from the Medical Research Council UK and has previously acted as a consultant for Novartis and Orphazyme. MMD is a consultant for Orphazyme and received funding support, paid to his academic institution (University of Kansas Medical Center, Research Institute), from Orphazyme for the oversight and conduct of this study. He also serves or recently served as a consultant for Abcuro, Amamentis, ArgenX, Astellas, Catalyst, Cello, Covance/Labcorp, CSL-Behring, EcoR1, Janssen, Kezar, MDA, Medlink, Momenta, NuFactor, Octapharma, Priovant, RaPharma/UCB, Roivant Sciences, Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, Abata/Third Rock, UCB Biopharma and received research grants or contracts or educational grants from Alexion, Alnylam Pharmaceuticals, Amicus, Biomarin, Bristol Myers Squibb, Catalyst, Corbus, CSL-Behring, FDA Office of Orphan Products Development, GlaxoSmithKline, Genentech, Grifols, Kezar, Mitsubishi Tanabe Pharma, Muscular Dystrophy Association, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, The Myositis Association, Ra Pharma/UCB, Viromed/Healixmith, and The Myositis Association. All other authors declare no competing interests.

#### **Data sharing**

Data sharing requests can be submitted after 1 year following publication of the main study results, to the corresponding authors, who will provide a data access request form. Data sharing requests will be considered by the Trial Steering Committee on a case-by-case basis, and data will be shared if the request is considered reasonable, of scientific interest, and legally and ethically possible.

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