Phase II Study of Arimoclomol in IBM FDA-OOPD (Orphan Products Division) R01

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Grant#: R01 FD004809
IND #: 76,773
Submitted: 2015

Grant was: Funded

In the prior issue of the RRNMF journal, we published the history of research and development of arimoclomol in IBM in the last 15 years (1). In this report, we provide the protocol that was ultimately approved for funding by the FDA OOPD and the associated reviewer comments. We had submitted the protocol to the same funding agency twice prior to being funded as of June 01, 2015. There were several constructive reviewer comments that we addressed along the way. Support and advice from the arimoclomol investigative team that met yearly at the annual Muscle Study Group (MSG) meetings helped us tremendously in responding to reviewer's comments and amplified the energy driving this process. This grant was an official MSG project. It was approved by the MSG executive committee. The plan was for it to be managed by the MSG coordinating center (Drs. McDermott, Tawil, and Martens). After this was funded, Orphazyme became more involved as a partner and took over the data management. Dr. McDermott remained on-board as a leader of the statistics team. There were 12 MSG sites in the study: University of Kansas Medical Center; HonorHealth; The University of California, Irvine Medical Center; University College London; Houston Neurocare Pa; The Johns Hopkins University School of Medicine; Brigham and Women's Hospital; University of Rochester Medical Center; The Ohio State University Wexner Medical Center; University of Colorado Denver; University of Virginia Health Sciences Center; University of Utah Health.

As you can imagine, it was really discouraging to be turned down the 1st time and then a 2nd time. However, with drug development and funding, persistence is very important to move clinical research and discovery forward. Having the right team of investigators and support of the MSG Data Coordinating Center were critically important to our success. We hope you enjoy and get inspired by reading about our arduous journey to what ultimately became the Phase 2/3 Study of Arimoclomol in IBM.

Reference

1. Dimachkie, M., Machado, P., Sundgreen, C., Blaettler, T., Statland, J., Heim, A., Herbelin, L., Greensmith, L., Hanna, M., & Barohn, R. J. (2021). The Early History of Arimoclomol for Inclusion Body Myositis. RRNMF Neuromuscular Journal, 2(2). https://doi.org/10.17161/rrnmf.v2i2.15404

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FDA-IND # 76,773
Version date: 10/13/2014

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Abstract

Sporadic inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy presenting after age 50 years. It presents with chronic insidious proximal leg and distal arm asymmetric muscle weakness. Muscle histopathology reveals endomysial inflammatory exudates surrounding and invading non-necrotic muscle fibers often times accompanied by rimmed vacuoles and inclusions. Unlike polymyositis and dermatomyositis, patients with IBM do not improve with therapy; at present there is no effective treatment for IBM. The histopathological features and lack of response to immunotherapies has led many experts in the field to believe that IBM is primarily a degenerative disorder of muscle with secondary inflammation.

We completed a randomized controlled pilot study in 24 IBM subjects, 18 of whom received arimoclomol 100 mg PO TID for four months and 8 were on placebo. Arimoclomol increases heat shock proteins and may prevent protein misfolding. We found arimoclomol to be safe. The IBM functional rating scale (IBMFRS) decline at 1 year was less in the arimoclomol group compared to placebo with the p value approaching significance at 8 months.

We are therefore proposing a twenty months randomized, placebo-controlled Phase II study of arimoclomol in 150 IBM subjects. The primary aim is to assess the efficacy and safety of arimoclomol (200 mg TID). The primary efficacy endpoint is the IBMFRS. Secondary efficacy outcomes will include different measures of strength and function: manual muscle testing (MMT), maximum voluntary isometric contraction (MVICT) of quadriceps, grip and pinch test, modified timed up and go (mTUG), 6 minute walk test with 2 minute distance captured; a general physical function measure: Health Assessment Questionnaire (HAQ- DI); a Health-Related Quality of Life (HRQoL) measure using SF36. Safety laboratory and adverse events will be collected. Our long-term goal is to find an effective treatment for people with IBM.

1. Summary of Specific Aims

The primary objective of the proposed Phase II study is to assess the efficacy of arimoclomol (200 mg TID) as compared with placebo over twenty months of treatment in 150 patients with Inclusion Body Myositis (IBM); 75 randomized to arimoclomol and 75 to placebo.

Specific Aim # 1
To determine if arimoclomol 200 mg TID can slow down the rate of IBM disease progression over 20 months of treatment. The primary outcome measures will be the comparison of the rate of decline in the Inclusion Body Myositis Functional Rating Scale (IBMFRS) [1,2] between control and experimental subjects. Conservatively, we have an 80% power to detect a 40% or greater difference between the 2 groups at 12 months. Although the above sample size justification applies to the 12-month change in IBMFRS score; it will also apply to the 20-month change in IBMFRS score if, as expected, the magnitude of the treatment effect relative to the magnitude of the standard deviation of the change in IBMFRS does not diminish over time.

Specific Aim # 2

The second aim is to determine if secondary endpoint measures are affected by arimoclomol. This includes muscle strength testing (manual muscle testing and maximal voluntary isometric contraction), grip and pinch, 6 minute walk test (with distance at 2 minutes captured), number of falls, modified timed up and go (mTUG), quality of life and self-reported disability. We will also compare the change in these parameters between placebo and arimoclomol at twenty months.

Specific Aim # 3

The third aim is to collect safety and tolerability information on arimoclomol (200 mg TID) for up to twenty months in IBM. We currently have safety data on arimoclomol 100 mg TID for 4 months in IBM subjects. Whereas 200 mg dose was safe in ALS over 1 year (personal communication by Dr. Michael Benatar), we intend to determine if these findings can be extended to a different clinical patient population in IBM for twelve and twenty months.

2. Background and Significance

Clinical Features: IBM is the most common progressive and debilitating muscle disease beginning in persons over age 50 years, with an annual incidence estimated at 1-2:100,000.[3-9] Because biopsies of IBM muscle contain lymphocytic inflammatory cells, IBM was originally grouped with the inflammatory idiopathic myopathies: polymyositis and dermatomyositis. However, pathologic studies during the past 25 years have clearly defined it as a unique pathogenic entity.[10-11] IBM is a progressive, debilitating disease causing both proximal and distal muscle weakness, characteristically most prominent in the quadriceps and finger flexors.[12-15] Over time it can lead to severe disability, including falls due to quadriceps muscle weakness and foot drop, dysphagia, and eventually respiratory muscle weakness.[11, 16-18] IBM seldom affects patients under 40 and is much more common over the age of 50. Men are affected more frequently than women.[19] The natural history of IBM has been followed prospectively in three studies.[20-24] Rose et al. followed 11 subjects for six months, and found an overall four percent decrease of strength from baseline. [21] Data collection from 136 IBM patients from the Paris and Oxford groups was completed either during a clinic visit (52%), or by extraction from previous medical records (48%). After a median duration of 14 years from onset, 75% of patients had significant walking difficulties and 37% used a wheelchair.[24] Patients were treated with immunosuppression agents (prednisone, intravenous immunoglobulins, methotrexate or azathioprine) for a median duration of 41 months were more severely disabled on last assessment. We performed a retrospective chart review of 51 IBM cases from the University of Kansas.[11,25] After a 7.5-year mean disease duration, 56% of our cases required an assistive device, with 20% requiring a wheelchair or motorized scooter (Table 1).[11]

Table 1: Retrospective chart review of IBM from 2000 to 2010 at KUMC

Male:female ratio	1.7:1
Ethnicity (n=51)	49 Caucasian; 2 Hispanics
Mean age at onset (yrs)	61 (45-80)
Symptom onset before age 50 yrs:	12%
Mean time to diagnosis (yrs)	5.1 (1-15)
Mean follow up period (yrs)	2.5 (0.5-8)
CK (IU/L)	609 (59-3000)
Nerve conductions with axon loss neuropathy	32%
Electromyography	60% irritative myopathy 12% non-irritative myopathy 28% mixed neuropathic/ myopathic pattern
Asymmetry	90%
Non-dominant side weaker	85%
Typical phenotype: Weak Finger Flexor (FF) and quadriceps (quads)	39/51 (76%): 13 - Classic phenotype (FF and quads weakest)

	11 - Classic FF, no preferential quads weakness 6 - Classic quads, no preferential FF weakness 9 - FF and quads weak but not weakest
Atypical phenotype	12/51 (24%): 5/12: classic FF with leg weakness sparing quads 4/12: limb-girdle weakness 3/12: other atypical phenotypes (FF arm only, hip flexion/ankle dorsiflexion, facioscapulohumeral)
Muscle pathology	43: inflammation and rimmed vacuoles 8: phenotypic IBM with inflammation but no vacuoles
Mobility Outcome	75%: recurrent falls 56%: assistive device use at mean 7.5 years 20%: wheelchair or scooter
Bulbar dysfunction	51%: dysphagia 55%: facial weakness

There is also myonuclear degeneration early on in IBM because the majority of rimmed vacuoles are lined with nuclear membrane proteins. IBM myonuclei are often abnormally filled with neurofilaments and this may be the earliest detectable pathologic change in IBM.[3]

In IBM, myofibers contain nonnuclear sarcoplasmic Tar DNA binding protein 43 (TDP-43) accumulations together with a reduction of the normal nuclear TDP-43 content. This suggests that TDP-43 has redistributed from nuclei to sarcoplasm in a large percentage of IBM myofibers.[26] The extranuclear accumulation of TDP-43 may be toxic to cells perhaps through altered binding to and splicing of mRNA. Immunohistochemically, TDP-43 and p62 were the most sensitive markers, accumulating in all definite IBM and in 31% and 37%, respectively, of possible IBM cases.[27] Therefore, IBM muscle accumulates multiple toxic protein aggregates suggesting a disorder of protein homeostasis.

The degenerative theory of IBM hypothesizes that IBM is a degenerative muscle disease occurring in an aged cellular environment, associated with cellular accumulation and aggregation of several proteins, involving abnormal signal transduction and transcription, protein misfolding, inhibition of the cellular protein degradation pathway, and mitochondrial dysfunction.[28] The lymphocytic infiltrate is considered likely to be secondary to muscle fiber degeneration.

A model of pathogenesis in IBM has been proposed (see Figure 1).[29] In this model the aging muscle intracellular environment, combined with environmental factors like oxidative stress, viruses, or other toxins, and in combination with mutations in predisposing genes leads to up-regulation of Aβ precursor protein. This leads to abnormal accumulation of Aβ 40 and 42 fragments. The Aβ 42 fragment in particular has a hydrophilic face and tends to aggregate into cytotoxic oligomers. Increased transcription of Aβ precursor protein leads to up-regulation of other proteins which co-aggregate with Aβ fragments. The effects of these toxic oligomers cause oxidative stress in the cell, phosphorylation of tau protein, an increase in misfolded proteins, and inhibition of the proteosome protein degradation pathway. This creates a positive feedback cascade. The cell increases its levels

of heat shock proteins to help counteract this increase in misfolded proteins, in particular HSP70, but cannot keep up with increasing levels of toxic protein products. This upregulation of Aβ precursor protein can also lead to mitochondrial defects, further exacerbating the cycle. In support of this theory, cultured muscle fibers with overexpressing Aβ precursor proteins display similar pathology to that seen in human IBM muscle biopsies. Accumulation of these misfolded proteins eventually leads to the characteristic Aβ amyloid inclusions and paired helical fibers containing phosphorylated tau seen in IBM muscle biopsy specimens. [28,30-32]

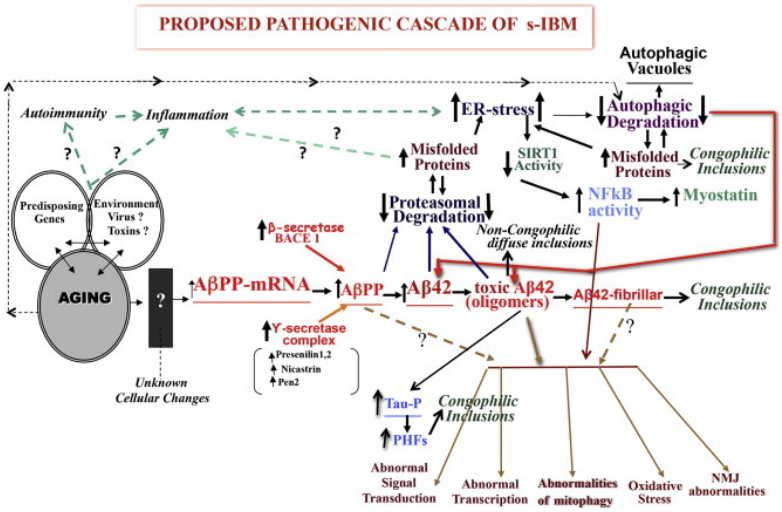

Figure 1. Proposed pathogenic cascade of sIBM [29]

Six of 7 IBM patients showed increased PIB levels in at least 1 gastrocnemius muscle, and the median PIB of the gastrocnemius muscles was significantly higher in IBM patients than in non-IBM subjects. [33] In two patients, muscle biopsies available from the gastrocnemius muscle with increased PIB uptake showed several fibers with dense amyloid-β and PIB positive inclusions on immunostaining. However, another IBM patient with normal deltoid muscle PIB uptake was amyloid-β positive without any detectable PIB positive inclusions.

Protein Misfolding: Many systemic and neurodegenerative disorders, termed 'protein-misfolding disorders' are characterized by the accumulation of intracellular or extracellular protein aggregates [32]. The initiating event in the disease process may be a crucial conformational change that occurs in the disease protein, possibly mediated by physical trauma, oxidative damage, or an infectious agent that leads to protein aggregates. These aggregates, or more likely their intermediate oligomeric precursor forms, can act to catalyze the process of additional aggregation, accelerating the "sequestration" of the normal protein and potentially trapping other important proteins that are prone to aggregation. In most instances these aggregated protein products are found to be cytotoxic, although the exact mechanism of toxicity is unclear.

A highly conserved class of proteins called molecular chaperones has evolved to prevent inappropriate interactions within and between non-native polypeptides, to enhance the efficiency of *de novo* protein folding, and to promote the refolding repair of proteins that have become misfolded as a result of cellular stress [34-36] (see Figure 2). In addition to this protein repair activity, chaperones can mediate targeting to the proteasome system or to lysosomes, resulting in selective degradation of the misfolded protein when the chaperones cannot repair the misfolded proteins. These activities of the molecular chaperones may be sufficient to prevent the normal accumulation of misfolded proteins. Under conditions of cellular stress, chaperone activity is increased, adjusting to the consequent increase in damaged proteins. However, under certain pathological conditions (perhaps due to prolonged exposure during chronic disease), the capacity of this protein quality

control machinery can be exceeded, and misfolded proteins accumulate to dangerous levels.

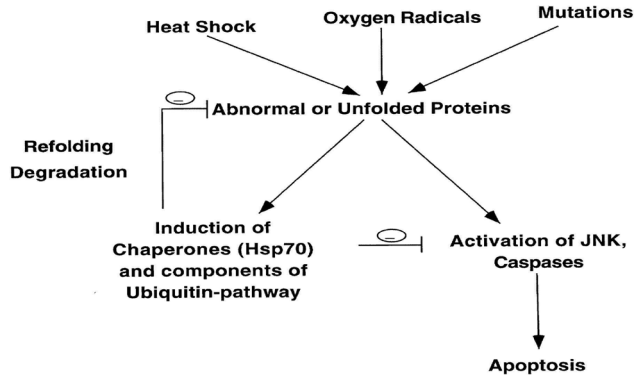

Figure 2. Schematic of the mechanism of action of HSP70 [34]

Arimoclomol: Arimoclomol (/+/-(2R),(Z)-N-[2-hydroxy-3-(piperidin-1-yl)propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate (1:1)) (BRX-345) is an analog of bimoclomol, a hydroxylamine derivative that acts as a co-inducer of "heat shock" or "molecular chaperone" gene expression. This compound has been developed by a small biotechnology company, CytRx and currently owned by Orphazyme. Although the precise molecular mechanism of action of arimoclomol is not known, the compound has been shown to co-induce molecular chaperone genes, meaning that it further elevates the chaperone protein levels already induced by physical or metabolic stresses in cell lines and in isolated cells/tissues (see Figure 3). It apparently accomplishes this by stabilizing the active phosphorylated trimer of the transcription factor, Heat Shock Factor-1 (HSF-1). Recent evidence suggests protein misfolding and aggregation play a key role in pathogenesis in IBM. Indeed HSP70 levels have been shown to be increased in IBM muscle biopsies. Arimoclomol may slow down the process of protein misfolding and aggregation in IBM by helping the muscle fiber to up-regulate inducible heat shock proteins. It may also slow progression of muscle degeneration in this progressively debilitating disease.

Trials assessing immunotherapeutic agents have not demonstrated significant efficacy against IBM. If arimoclomol were found to be beneficial for the treatment of IBM, this would represent the only effective treatment for this otherwise progressive disease. Preliminary studies in healthy volunteers have shown arimoclomol to be relatively safe and well-tolerated. We also present in the next section preclinical and clinical research study data. Linda Greensmith is a neuroscientist at the University College of London (Institute of Neurology) who studies the effects of arimoclomol in cell cultures and in an animal model of IBM. We also present data from our pilot safety study of arimoclomol in humans with IBM. We also describe our research in MR imaging of IBM muscle.

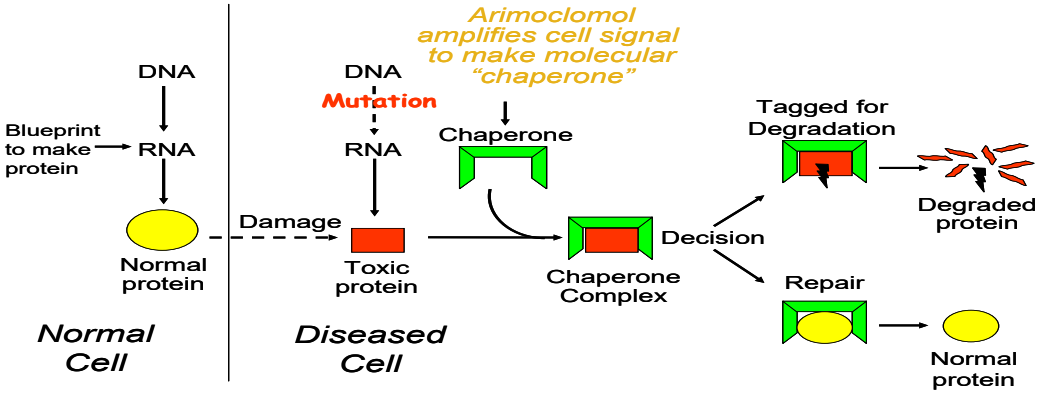

Figure 3. Arimoclomol amplifies cell signal to make molecular chaperones.

3. Preliminary Studies, with Figures

HSP70 is increased 4.5 times above normal in muscle biopsies of patients with IBM and has been shown by immunocytochemistry to co-localize with Aβ amyloid deposits. [30-31] In the SOD1 mouse model of amyotrophic lateral sclerosis, arimoclomol significantly increased levels of HSP70 and HSP90 in the spinal cords of mice and increased survival [37] (see Figure 4). In a manner similar to ALS, HSP70 levels are already upregulated in IBM; however, they may be sequestered in Aβ amyloid aggregates and thus rendered less effective. Increasing the availability of heat shock proteins in IBM may therefore be of therapeutic importance.

Arimoclomol has also been shown to interact with acidic lipids, including cardiolipin, a lipid component specific to the mitochondria. This lipid interaction may play a role in the protection of the mitochondria and prevention of apoptosis. In IBM cell culture models, mitochondria are thought to be affected by Aβ precursor protein and Aβ fragment over-expression. [30] Mitochondrial abnormalities are found in IBM muscle biopsies at a higher frequency than in the normal population. [38-39] Arimoclomol may help stabilize mitochondria in this environment.

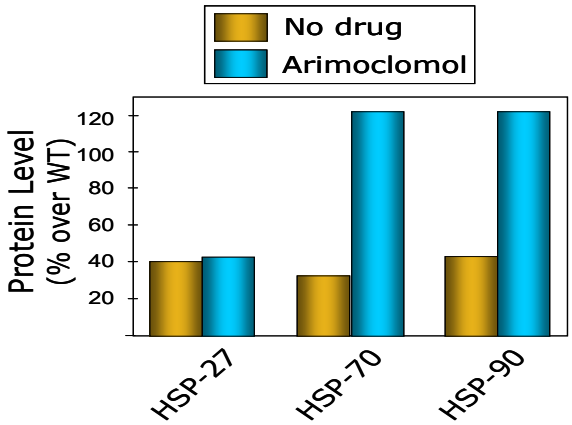

Figure 4. Arimoclomol-induced increase in HSP70 and HSP90 in SOD1 mice [37]

In vitro cell model of IBM:

We have recently developed and characterized an in vitro model in which primary rat muscle cells in vitro were transfected with β-APP in order to model the protein mishandling features of the disease. Over-expression of human β-APP in primary rat muscle cells recapitulated several of the key pathological characteristics of IBM, including the formation of intracellular inclusion bodies which were immunoreactive for β-APP and ubiquitin as well as AB-42, TDP-43, p-Tau, caspase-3 Hsp70 and p62. In addition, β-APP transfection resulted in activation of the NFkB cascade, as demonstrated by nuclear translocation of the p65 subunit, as well as ER stress.

Using this model, we examined the effects of treatment with arimoclomol on these IBM-like pathological characteristics by assessing the following outcome measures: i) cell survival; ii) formation of inclusion bodies; iii) HSP expression; iv) TDP-43 translocation from the nucleus to the cytoplasm; v) NFkB activation; iv) ER Stress.

Following treatment with arimoclomol, there was a significant increase cell survival, an increase in Hsp70 expression and a significant reduction in the formation of ubiquitinated inclusions in β-APP transfected myotubes. In addition, in untreated β-APP transfected cultures, cytoplasmic mis-localisation of TDP-53 was observed in 52.2% of myotubes by 4 DIV, and this was dramatically

reduced to only 2.4% of myotubes in arimoclomol-treated cultures (P<0.0001). Furthermore, the proportion of β-APP transfected myotubes in which the NFkB cascade was activated was also reduced by treatment with arimoclomol, so that the proportion of myotubes demonstrating p65 nuclear staining was reduced from 43% in untreated cultures to 23% in arimoclomol-treated cultures (p<0.05). Finally, examination of ER calcium handling and markers of ER stress revealed that β-APP transfection resulted in a significant reduction in ER [Ca^{2+}] (an indicator of ER stress), compared to empty vector treated controls (190nM compared to 280nM; p<0.05), a deficit that was completely prevented by arimoclomol (ER [Ca^{2+}] 290nM). This dramatic and beneficial effect of arimoclomol on ER stress was reflected in a reduction in the expression of th e ER stress markers CHOP and BiP in arimoclomol-treated β-APP transfected myotubes, compared to untreated cultures. [40-42]

Together these results indicate that arimoclomol ameliorates several key pathological features of IBM-like pathology, at least in an in vitro model of the disease (see Figure 5).

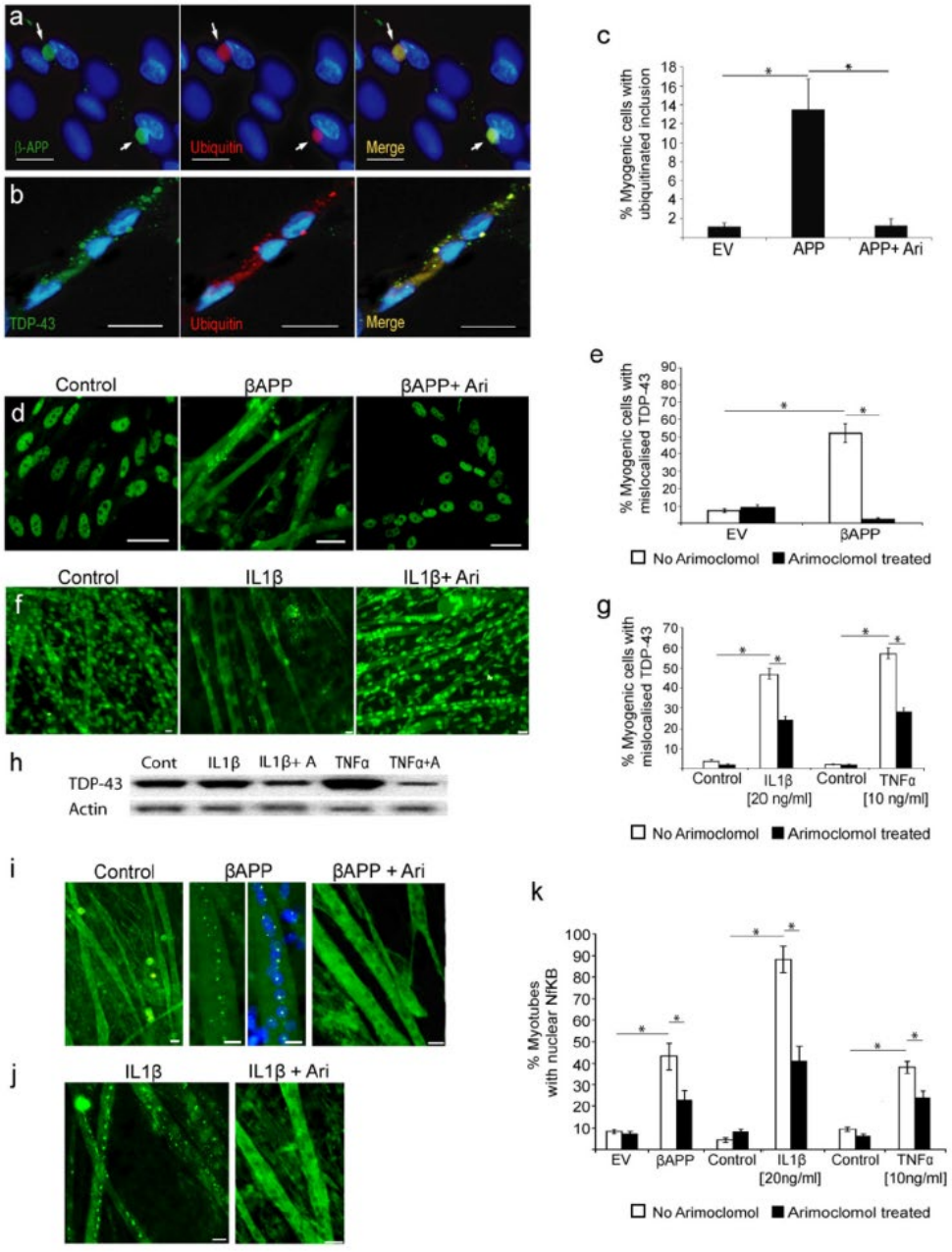

Figure 5. *Over-expression of β-APP and exposure to inflammatory mediators induces IBMlike pathology in cultured myocytes which is ameliorated by treatment with Arimoclomol.* Formation of cytoplasmic inclusion bodies in myocytes immunoreactive for (a) β-APP and ubiquitin and (b) TDP-43. The bar chart (c) shows the percentage of myocytes containing ubiquitinated inclusion bodies. (d) Expression of TDP-43 (green) following β-APP transfection and Arimoclomol treatment and (e) quantification of the number of cells with cytoplasmic mislocalisation of TDP-43. (f) TDP-43 expression (green) following exposure to inflammatory mediators and Arimoclomol treatment and (g) quantification of TDP-43 mislocalisation in inflammatory mediator exposed cultures. (h) Western blot analysis of TDP-43 expression in myocyte cultures exposed to inflammatory mediators in the presence and absence of Arimoclomol. (i) Images show the expression of NFkB subunit p65 (green) in β-APP transfected cultures (DAPI labelled nuclei in blue) and (j) cultures exposed to inflammatory mediators, in the presence and absence of Arimoclomol. (k) The bar chart shows the percentage of cells with nuclear NFkB subunit p65 under all culture conditions investigated. Error bars= S.E.M; Scale bars: a, b =10μm, d, i and j =20μm

In vivo model of IBM

We have recently completed an efficacy trial of Arimoclomol in a mouse model which recapitulates several key features of IBM.[43] Patients with an A232E mutation in valosin-containing protein (VCP), a protein involved in numerous cellular functions including protein degradation, present with a condition called Inclusion body myopathy with Pagets' disease and Frontotemporal Dementia (IBMPFD). Transgenic mice over-expressing the same human mutation in VCP display a muscle pathology that closely resembles that of IBM, including muscle weakness and histopathological signs of IBM such as rimmed vacuoles and TDP-43 and ubiquitin-positive pathology. We treated mutant VCP (mVCP) mice treated with Arimoclomol (120mg/kg per day, orally, in drinking water) from the start of symptom onset at 4 months until 14 months of age, a late stage of disease. Transgenic mice over-expressing wild-type human VCP (wt-VCP) were used as controls, and 10 male mice per group were studied. Muscle strength was assessed longitudinally by performing grip-strength measurements fortnightly from the start of treatment (see Fig.6a). In addition, muscle force was also established using isometric muscle force measurements performed on terminally anaesthetized mice at 14 months of age (Fig. 6b,c). In control wt-VCP mice, there was no significant reduction in grip strength relative to body weight between 4 (6.44g +/- 0.49 SEM) and 14 months of age (5.91g +/- 0.62 SEM). In contrast, in mVCP mice, there was a 44.1% reduction in grip strength during the same period (from 7.19g +/- 0.39g SEM to 4.02g +/- 0.3g SEM). However, in mVCP mice treated with Arimoclomol, there was no significant reduction in grip strength over time; with only a mild reduction from 6.24g +/- 0.42g SEM to 5.18g +/- 0.34g SEM by 14 months. These longitudinal readouts of muscle strength were reflected in the maximal tetanic force measurements obtained from extensor digitorum longus (EDL) muscles of mice examined at 14 months of age. In mVCP mice, EDL muscles generated significantly less force (16.59g +/- 1.86g SEM) than EDL muscles in wt-VCP controls (24.18g +/- 1.94g SEM). However, in Arimoclomol treated mVCP mice, there was no significant difference in the force output of EDL muscles (22.47g+/- 1.84g SEM) compared to controls. These results show that treatment with Arimoclomol prevents the loss in muscle force that occurs as disease progresses in mVCP mice.

Histological assessment of the hindlimb muscles of mVCP mice showed remarkable pathological changes which correspond with characteristic IBM features seen in patient muscle biopsies (Fig 6d,e). Tibialis anterior (TA) muscles of mVCP mice showed clear signs of degenerating and atrophied fibres of irregular sizes, infiltration of inflammatory cells, presence of vacuoles and proteinaceous aggregates. Furthermore, an increase in the number of centralized nuclei was observed which is regarded as a feature of regenerating muscle fibres. Examination of muscle from Arimoclomol treated mVCP mice however showed a greatly reduced level of degenerating and atrophied fibres (Fig. 6f). Quantification of the number fibres containing centralized nuclei showed that Arimoclomol treated mVCP mice had significantly more fibres with centralised nuclei (35.28% +/- 4.51% SEM) compared to untreated mVCP

mice (18.67% +/- 3.43% SEM) or wt-VCP mice (3.09% +/- 3.39% SEM), suggesting a greater extent of regeneration in the muscle of Arimoclomol treated mice.

Since Arimoclomol is known to be a co-inducer of the HSR, we also examined whether the beneficial effects of Arimoclomol on the muscle pathology in mVCP mice was reflected in a change in expression of Hsp70. As can be seen in Fig. 6h, Western blot analysis of muscle from mVCP mice treated with Arimoclomol showed a two-fold increase in the expression of HSP70 compared to that of untreated mVCP mice.

The results of this *in vivo* efficacy study in a mouse that models key aspects of IBM confirm that treatment with Arimoclomol prevents the decline in muscle strength and improves the histopathological characteristics of IBM, most likely as a result of an upregulation in Hsps.

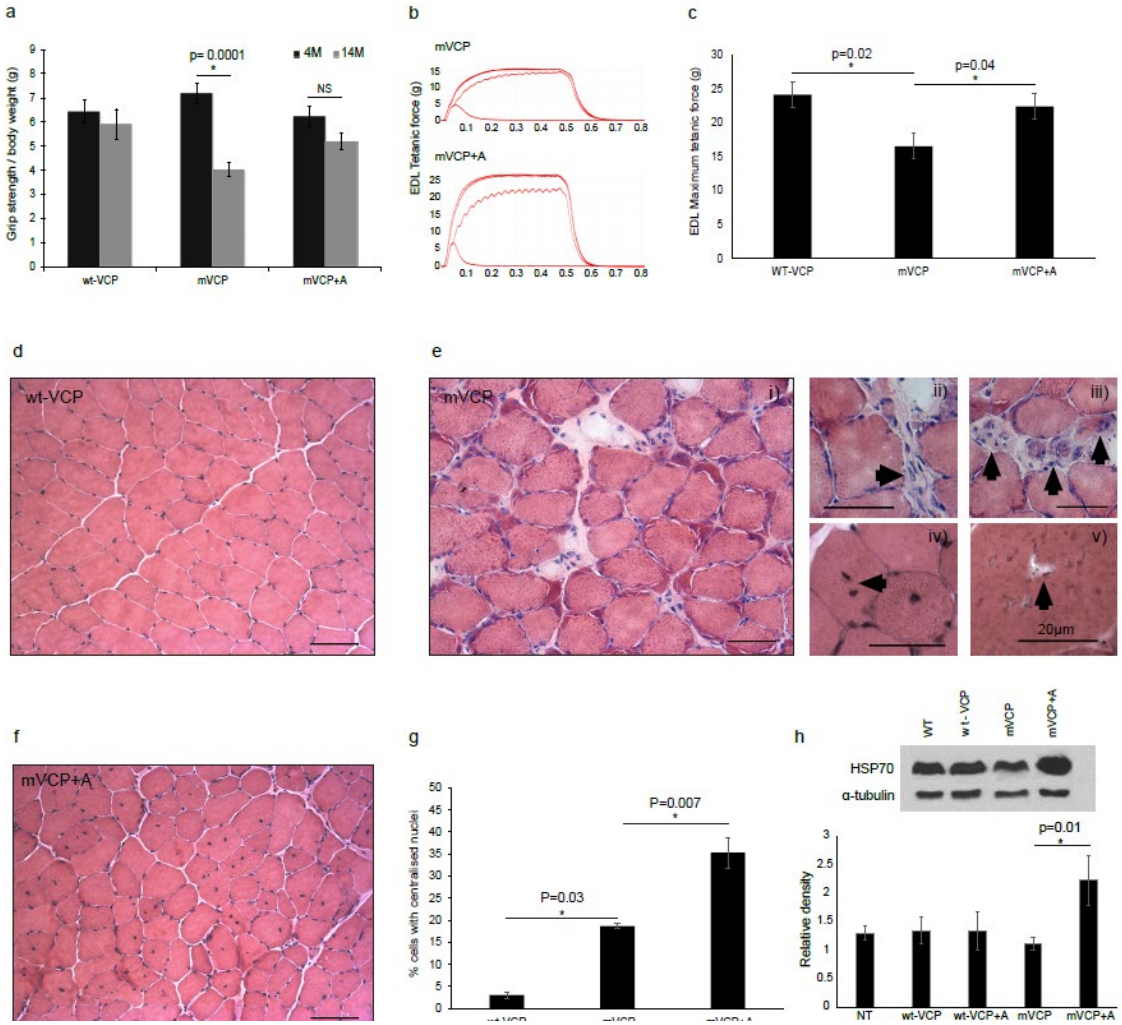

Figure 6. *Treatment with Arimoclomol prevents the loss in muscle force and appearance of IBM-like pathology in mutant VCP mice.* a) Longitudinal analysis of grip strength shows that there is a significant decline in grip strength in mVCP mice between 4 and 14 months of age which is prevented in mice treated with Arimoclomol. b) Typical traces of maximum tetanic force of EDL muscles in anaesthetized mVCP and Arimoclomol treated mVCP mice are shown. C) The bar chart shows that treatment with Arimoclomol prevents the loss in EDL force that occurs in mVCP mice by 14 months of age. Histopathological (H&E) analysis of TA muscles reveals the presence of key IBM-like pathological characteristics in mVCP mice. Compared to wt-VCP mice (d) TA muscles from mVCP mice (ei-v) show atrophied and degenerating fibres, inflammatory cell infiltration, centralized nuclei and the presence of rimmed vacuoles. In contrast, TA muscles from mVCP mice treated with

Arimoclomol shows few if any of these pathological changes (f). Quantification of the number of fibres with centralized nuclei (g) shows that there is a significant increase in the number of fibres with centralized nuclei in Arimoclomol-treated mVCP TA muscles which is indicative of active regeneration. H) Western blot analysis shows that here is a significant increase in the expression of Hsp70 in TA muscles of mVCP mice treated with Arimoclomol, compared to either untreated mVCP or wt-VCP mice. [43]

Non-clinical Safety Studies:

The acute effects of arimoclomol at doses of 100-400 mg/kg have been determined in mice, rats, guinea pigs, and dogs. Long-term toxicity studies have been performed to evaluate the safety of arimoclomol at doses up to 1500 mg/kg/day in rats and up to 210 mg/kg/day in beagle dogs. In preclinical safety studies, the no-observed-adverse-effect level (NOAEL) was 375 mg/kg in rats (28-day toxicity study), 200 mg/kg/day in rats (180-day toxicity study), 70 mg/kg in dogs (28-day toxicity study), and 50 mg/kg in dogs (90-day toxicity study). Short- and long-term animal studies suggest that no observed adverse effects of arimoclomol are observed below doses of 50 mg/kg/day, or at least 8-10 times higher than that proposed for humans in this study. Twelve-month toxicity studies in rodents were completed, and this data has been filed with the FDA by CytRx (the previous owner of the drug). The drug is now owned by Orphazyme. Arimoclomol has been shown to produce damage to chromosomes in hamster cells. Chromosomal damage is known in humans to be the cause of some genetic diseases such as cancer. However, the relationship between effects observed in cells and those in humans is not completely understood.

In a toxicity study performed in rats, sudden and unexplained deaths occurred in animals receiving arimoclomol alone, riluzole alone, and arimoclomol in combination with riluzole. The currently available data indicate that arimoclomol alone is lethal in rats at 1800 mg/kg, but not 900 mg/kg, and that lethality is notably increased when arimoclomol is administered in combination with riluzole. All of the animals which survived the 800 mg/kg dosing were found to have had cataract formation.

Human Safety Profile*:*

Arimoclomol has been tested in two double-blind, placebo-controlled human safety studies in normal subjects. It has been found safe and well-tolerated when administered to 12 healthy male volunteers in single ascending oral dosages up to 800 mg. There were no serious adverse events or deaths reported during the study. Two subjects reported mild sleepiness (approx. 2-2.5 hours duration) after administration of the 400 mg dose. The duration of these events was 2.25 and 5.50 hours, and they were stated by the investigators as “possibly related” to the study treatment. However, after unblinding, it was noted that one of these patients was treated with placebo at that dose level. Following these events both patients continued the study and took the capsules of higher dose levels without any adverse event. No changes in any safety parameters (such as laboratory parameters, vital signs, or electrocardiogram (EKGs) were reported during the study. The pharmacokinetics of arimoclomol after single-ascending oral doses was also assessed. Arimoclomol was absorbed rapidly with Tmax values ranging between 0.5 and 1.1 hours. Mean $t_{½}$ values ranged between 2.5 and 6.2 hours. There was a good dose-proportional increase in AUC and Cmax values.

Arimoclomol was also found safe and well-tolerated when multiple oral doses of 50 mg t.i.d. and 100 mg t.i.d. were administered to a total of 18 healthy young male subjects divided into two groups. Subjects of group A received 50 mg arimoclomol as a single dose on the morning of day one; then 50 mg arimoclomol t.i.d. on days two through nine; and a single 50 mg dose on the morning of day 10. Subjects of group B were treated with 100 mg arimoclomol in a similar regimen. Randomization was stratified by dose and was in the ratio of three placebos to six active treatments. There were no

serious adverse events or deaths reported during the study. Arimoclomol was generally well-tolerated by the study subjects. Fourteen subjects reported 31 adverse events. Seven events were reported by the subjects receiving placebo; 11 adverse events were reported by subjects receiving the 150 mg per day BRX-345 (arimoclomol) treatment; and 20 adverse events were reported on the 300 mg per day BRX-345 treatment. The intensity of these events was rated as mild to moderate. There was no evidence of clinically significant drug effects on vital signs or EKG assessments. There were no statistically significant changes in laboratory parameters. One subject had elevated eosinophils at screening and on day 11 in the 150 mg per day arimoclomol group, and another subject assigned to placebo had elevated eosinophils at day five. Overall, serum creatinine elevation was not found to be statistically significant. However, modest increases were observed in a number of volunteers. The increases were within the clinically accepted normal range and resolved after completion of the dosing regimen. Sleepiness is also a possible drug-related side effect. Maximal tolerated doses were not reached in these studies.

To assess its safety, tolerability, and pharmacokinetics in ALS, eighty-four participants received arimoclomol at one of three oral doses (25, 50, or 100 mg three times daily) or placebo. Participants who completed 12 weeks of treatment could enroll in a 6-month open-label study. Arimoclomol at doses up to 300 mg/day was well tolerated and safe. Serum pharmacokinetic profiles support dosing of three times per day. Arimoclomol at dosages up to 300 mg/day is well tolerated and safe in amyotrophic lateral sclerosis.[44]

A FDA OPD funded clinical trial using Arimoclomol at a dosage of 200mg three times per day is currently recruiting patients (http://clinicaltrials.gov/ct2/show/study/NCT00706147). The purpose of this study will be to demonstrate the safety, tolerability, and efficacy of arimoclomol in subjects with SOD1 positive familial Amyotrophic Lateral Sclerosis (ALS). The primary study objective is to demonstrate the efficacy of Arimoclomol, at a dosage of 200 mg three times per day, as compared with placebo, over 12 months of treatment in people with rapidly progressive familial ALS who harbor a mutation in the superoxide dismutase-1 (SOD1) gene. The primary hypothesis is that Arimoclomol will reduce by at least 30% the rate of progression of disease as measured by changes in the revised ALS functional rating scale (ALSFRS-R). In this study of arimoclomol by Dr. Benatar, PI at the University of Miami, the drug is well tolerated at the 200 mg TID dose (personal communication).

24 patient safety study in arimoclomol in IBM:

The University College of London (UCL) and University of Kansas Medical Center (KUMC) groups have been leaders in collaborating across the Atlantic in investigating the role of arimoclomol in IBM. Over the last decade, the UCL group, led by Michael Hanna, and the KUMC group, led by Richard Barohn, has had a keen interest in the study of the biologic effects of arimoclomol in IBM in vitro and in-vivo. To that extent Linda Greensmith's extensive preclinical laboratory research in IBM is described above in this section. Despite absence of adequate funding, both groups have been tremendously interested in arimoclomol, an interest which converged ultimately to the design, initiation and completion of the 24-patient pilot study by pooling internal resources.

The IBMFRS is a quickly administered (10-minute) ordinal rating scale (ratings 0-40) used to determine patients' assessment of their capability and independence in 10 functional activities. The scale was developed by the MSG investigators and was utilized in the beta-interferon-IBM trials [21-22]. All 10 activities are relevant in IBM. The advantages of the IBMFRS are that the categories are relevant to IBM, it is a sensitive and reliable tool for assessing activities of daily living function in patients with IBM, and it is quickly administered. In the beta-interferon trial, the IBMFRS correlated well with MVICT, MMT, SF-36, and the ALS-FRS [45].

The Inclusion Body Myositis Functional Rating Scale (IBMFRS) was derived from the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) which is another patient-derived subjective scale currently accepted as the primary endpoint measure for nearly all ALS clinical trials for the last 15 years. The IBMFRS has been validated in its use with IBM patients as it correlated well with objective strength measures (Maximum Voluntary Isometric Contraction and Manual Muscle Testing) and quality of life as assessed by the SF-36 [1]. Last year, we presented analysis of prospective IBMFRS data collected over several years in 127 IBM cases from the UK and USA [46].

1. SWALLOWING 4 Normal 3 Early eating problems – occasional choking 2 Dietary consistency changes 1 Frequent choking 0 Needs tube feeding **2. HANDWRITING (*with dominant hand prior to IBM onset)*** 4 Normal 3 Slow or sloppy; all words are legible 2 Not all words are legible 1 Able to grip pen but unable to write 0 Unable to grip pen **3. CUTTING FOOD AND HANDLING UTENSILS** 4 Normal 3. Somewhat slow and clumsy, but no help needed 2 Can cut most foods, although clumsy & slow; some help needed 1 Food must be cut by someone but can still feed slowly 0 Needs to be fed	**4. FINE MOTOR TASKS *(opening doors, using keys, picking up small objects)*** 4 Independent 3 Slow or clumsy in completing task 2 Independent but requires modified techniques or assistive devices 1 Frequently requires assistance from caregiver 0 Unable **5. DRESSING** 4 Normal 3 Independent but with increased effort or decreased efficiency 2 Independent but requires assistive devices or modified techniques (Velcro snaps, shirts without buttons, etc.) 1 Requires assistance from caregiver for some clothing items 0 Total dependence **6. HYGIENE *(Bathing and toileting)*** 4 Normal 3 Independent but with increased effort or decreased activity 2 Independent but requires use of assistive devices (shower chair, raised toilet seat, etc.) 1 Requires occasional assistance from caregiver 0 Completely dependent	**7. TURNING IN BED & ADJUSTING COVERS** 4 Normal 3 Somewhat slow & clumsy but no help needed 2 Can turn alone or adjust sheets but with great difficulty 1 Can initiate but not turn or adjust sheets alone **8. SIT TO STAND** 4 Independent (without use of arms) 3 Performs with substitute motions (leaning forward, rocking) but without use of arms) 2 Requires use of arms 1 Requires assistance from device/person 0 Unable to stand **9. WALKING** 4 Normal 3 Slow or mild unsteadiness 2 Intermittent use of assistive device (AFO, cane, walker) 1 Dependent on assistive device 0 Wheelchair dependent **10. CLIMBING STAIRS** 4 normal 3 Slow with hesitation or increased effort; uses handrail intermittently 2 Dependent on handrail 1 Dependent on handrail and additional support (cane or person) 0 Cannot climb stairs

The IBMFRS scale demonstrated good fit and reliability of items and is therefore ready for use as a Patient-Reported Outcomes Measures (PROM)..Furthermore, over the last 4-5 years, research has focused on subjects' functional ability or at least their perceived functional ability over strength with PROM.

Based on Rasch analysis, the IBMFRS is of good fit and reliability of items and is therefore ready for use as a PROM. Participants were of higher ability than the difficulty level of the scale. Based on this and the above supporting facts, we firmly believe that the IBMFRS is valid and will reliably capture IBM PROM.

Our pilot study consisted of a randomized placebo-controlled safety study of arimoclomol 100 mg PO TID administered for 4 months (the maximum time allowed by the FDA-IND office at the time), with an 8 month follow up period.[43] Twenty-four IBM subjects received arimoclomol or placebo with a 2/1 ratio. We obtained monthly safety data, strength and functional measures at the 2 participating sites: the UCL-Institute of Neurology-Neuromuscular Centre and the KUMC-Neurology Department-Neuromuscular Section. We enrolled 17 men and 7 women with a mean age of 69 years (53-81) and a diagnosis of definite (10) or probable (14) IBM. There were 8 treatment-possibly-related adverse events in the placebo group and 14 in the arimoclomol group, the most common adverse event being gastrointestinal (see below under *Expected Adverse Events* section). There was one Serious Adverse Event but none of the adverse events led to drug discontinuation. We detected a trend of slower decline in the manual muscle testing (MMT) sum score in the arimoclomol group (figure 7), but no differences were seen on the maximal isometric voluntary contraction or dual-energy X-ray absorptiometry. Though baseline IBMFRS values were lower by 0.9 points at randomization in the placebo group, the p value for that difference at baseline was not significant (0.375) and the yearly IBMFRS decline in the placebo group was 3.5 points (SD=3.3) and 2.1 (SD=2.7) in the treatment group (p=0.538). We identified at 8 months a trend for slower decline in the mean IBMFRS as compared to placebo (figure 8) (p=0.055) and in the average MMT score (p=0.147). [47] Our preliminary data indicates that arimoclomol is safe and well-tolerated in IBM. The IBMFRS is a useful primary outcome measure for future IBM research studies. Given the observed IBMFRS and MMT trends, we feel that further investigation of arimoclomol in a larger IBM patient population is warranted. While we used a dose of 100 mg TID in our pilot study, we are going to use the 200 mg TID dose in the proposed phase II safety and efficacy study. Our reasoning is that the higher dose is being used in the SOD1 positive familial ALS study and is well tolerated. We may be seeing an effect on the IBMFRS and the dose was 100 TID. Therefore, it seems reasonable to use the higher dose for our next IBM study.

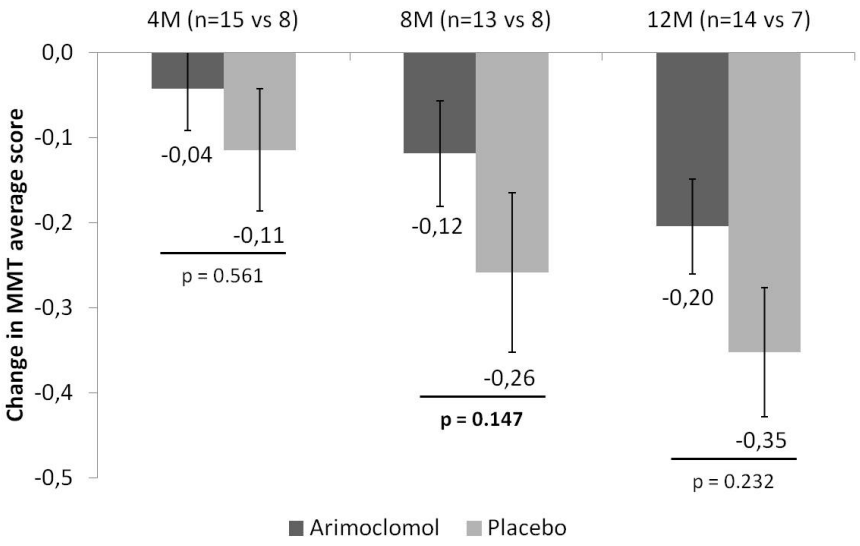

Figure 7. Bar charts showing change from baseline to endpoint (mean ± SEM) in mean MMT score

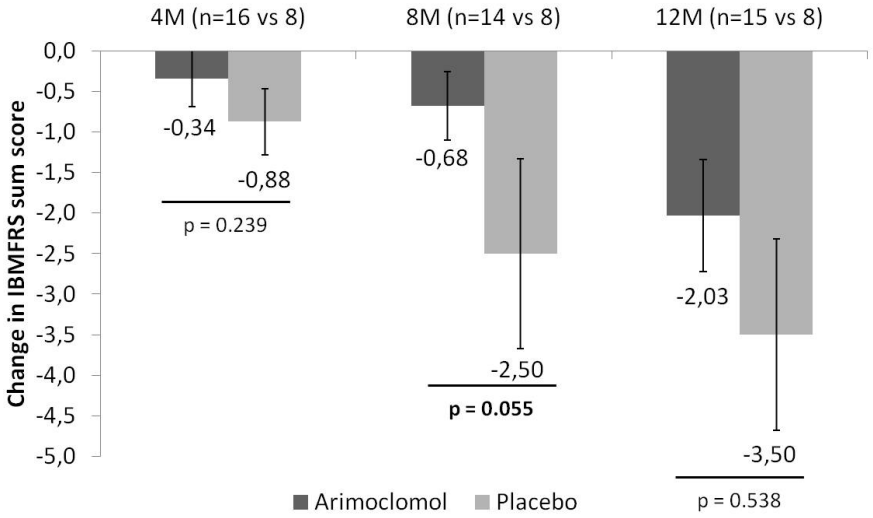

Figure 8. Bar charts showing change from baseline to endpoint (mean ± SEM) in IBMFRS score

Investigators Experience:
Dr. Mazen Dimachkie is Professor of Neurology at the KUMC and Director of the Neuromuscular Section in the Neurology Department at the University of Kansas Medical Center (KUMC). As Director of Neuromuscular Research, he has overseen the conduct of 60 clinical studies. He has had long-standing experience working with IBM patients and being engaged with the local myositis support group for IBM and IIM. He is a member of the International Myositis Assessment & Clinical Studies Group Scientific Committee (IMACS). In that capacity, he is the PI on IMACS Project 2, identifying myositis phenotypes that predict treatment response in the IIM. Dr. Dimachkie has participated in all aspects relating to the conduct of arimoclomol in IBM pilot study. He is the lead author on several publications in IBM [10-13,19,25] and actively participated in other recent IBM studies, both pharma-sponsored and investigator initiated. He is involved in a variety of federally-funded neuromuscular research projects as well Pharma-sponsored studies, nationally and internationally.

Professor Hanna is Director of the UCL institute of Neurology, Director of the MRC Centre for translational research in MRC Centre for Neuromuscular Diseases, chairman of the British Myology Society and co-chair of the North American Muscle Study Group. Professor Hanna has participated in all aspects relating to the conduct of arimoclomol in IBM pilot study, has co-lead two recent international workshops in IBM [48-49] and has brought together one of the world's largest consortia of internationally recognized IBM experts (spanning Europe, USA, Canada and Australia) providing a previously unparalleled IBM DNA bank for genetic studies. In addition Professor Hanna has led the establishment of the UK-wide prospective cohort of IBM patients linked 8 UK centres - "IBM-net". Professor Hanna and the MRC Centre for translational research have existing partnerships with the major patient organizations linked to IBM namely the myositis support group where Professor Hanna is an advisor helped plan annual patient meetings and the Muscular Dystrophy Campaign that also support IBM patient groups. Professor Hanna is actively engaged with the cross party parliamentary group for neuromuscular diseases including IBM and has given evidence in parliament about the impact of neuromuscular diseases including IBM and has worked with this group and the commissioners to develop standards of care for patients- this work is ongoing. Professor Hanna has

been an author of over 175 peer reviewed full publications and has received over 10 million pounds in peer reviewed external grant funding over the last 6 years.

Dr. Pedro Machado works at the MRC Centre for Neuromuscular Diseases, London, UK, and has extensive experience in diagnosing and managing patients with muscle diseases, including IBM. Together with Professor Michael Hanna, Dr Machado has participated in all aspects relating to the conduct of arimoclomol in IBM pilot study and is on the Steering Committee of the International IBM Consortium Genetic Study. Dr Machado is actively engaged in all major IBM research projects conducted at the MRC Centre for Neuromuscular Diseases, namely the UK-wide prospective cohort of IBM patients, MRI studies in IBM and an ongoing exercise trial in IBM. Dr Machado has also had training in clinical epidemiology and statistics and has published several articles related to outcome assessment in musculoskeletal diseases. He is a member of the Muscle Study Group.

Dr. Richard Barohn has had considerable experience working with patients with IBM. Dr. Barohn helped establish the diagnostic criteria for IBM. [7] He is the co-chair of the Muscle Study Group, a multi-center cooperative of neuromuscular specialists committed to pooling their resources to study neuromuscular disorders. He has been an investigator on many treatment trials in IBM. [5-7,22-23,50-51]

Natural History Study in IBM: The natural history of IBM was investigated prospectively by following 11 subjects for six months. [21] Prospective measurements of muscle strength, muscle mass, and lean body mass were performed. Overall a four percent decrease in strength was seen over the six-month period compared to baseline. One-third of the patients stabilized or improved in muscle strength. In our pilot study and using the IBMFRS as the endpoint measure, all but one placebo recipient experienced a decline at 12 month when compared to screen visit. The single exception was a subject in whom the IBMFRS remained stable at 12 month. In the largest study to date reviewing progression of 136 sporadic IBM patients from two European centers, all cases progressed despite therapy.[24]

Beta-Interferon 1A in IBM: This was a double-blind, placebo-controlled trial of Beta-Interferon 1A (30 micrograms) in IBM performed by the MSG. [22] Although this was a phase 1 trial, efficacy was evaluated by looking at changes in strength, functional scores, and SF36. Six muscle groups were tested with maximal voluntary isometric contraction testing (MVICT) on each side (biceps, triceps, quadriceps, hamstrings, ankle flexors, and hand grip), and a composite MVICT score was derived by averaging the standardized (normalized) scores. Strength was also measured by manual muscle testing (MMT) in 34 muscle groups. All testing procedures were done at baseline and repeated on weeks four, 12, and 24. No significant differences between treatment groups were noted in any of these scores.

High-dose Beta-Interferon 1A in IBM: This was a double-blind, placebo-controlled trial of Beta-Interferon 1A (60 micrograms) in IBM performed by the MSG, utilizing similar outcome measures as in our earlier study. [23] No significant differences between treatment groups were noted in any of these scores.

Muscle Study Group: The principal investigator and the co-investigators are members of the Muscle Study Group and have extensive experience in treatment trials in a variety of neuromuscular diseases including IBM, myasthenia gravis, amyotrophic lateral sclerosis, muscular dystrophies, inflammatory myopathies, and peripheral neuropathies. In addition to the two key sites, we recruited 10 sites from the Muscle Study Group to conduct this study. All centers to be chosen have experience in recruiting and enrolling patients into clinical trials. In addition, all of the centers are accustomed to working together as a group in clinical trials.

4. Methods, Expected Results, Data Analysis, Interpretations, and Significance

Study Design

This is a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of arimoclomol in subjects with IBM. One hundred and fifty subjects will be randomized to one of two groups: placebo (75 patients) or arimoclomol (75 patients) 200 mg TID. Participants will receive study medication for twenty months. Subjects will be seen at screening, day 0 (Baseline) and months 1, 4, 8, 12, 16 and 20. They will be contacted by phone at months 2, 3, 6, 10, 14, and 18. There will be a follow-up phone call 30 days post treatment.

Study Eligibility

Inclusion Criteria

Study subjects must meet all of the following criteria:

1. Meet any of the European Neuromuscular Centre Inclusion Body Myositis research diagnostic criteria 2011 categories for IBM. [52] (see appendix A)
2. Able to ambulate with or without assistive device
3. Age at onset > 45years
4. Women of childbearing age must have a negative pregnancy test prior to dosing with study medication.
5. Able to give informed consent.

Exclusion Criteria

1. The presence of any of the following excludes subject participation in the study: chronic infection; cancer other than basal cell cancer less than five years prior; or other chronic serious medical illnesses.
2. Presence of any of the following on routine blood screening: WBC<3000; Platelets < 100,000; hematocrit < 30%; BUN > 30 mg %; creatinine > 1.5 mg%; symptomatic liver disease with serum albumin < 3 G/DL.
3. History of non-compliance with other therapies.
4. Coexistence of other neuromuscular disease.
5. Drug or alcohol abuse within past three months.
6. Participation in a recent drug study in the last 30 days prior to screen visit.
7. Women who are lactating or unwilling to use adequate method of birth control who are not surgically sterile. Adequate birth control includes use of intrauterine device, abstinence, or oral contraceptives or a double barrier method, e.g. condom plus diaphragm.

Study Procedures

Screening and Informed Consent: During the participant's first study visit, written informed consent will be obtained by the study investigator or his/her designee. Before any study-specific procedures or assessments are done, each participant will be given a consent form that explains the aims, methods, anticipated benefits, and potential hazards of the study. Each participant will be given adequate time to first read the consent form and then to discuss any questions with the investigator. After the participant willingly agrees to take part in the study, the investigator will then review the inclusion/exclusion criteria. A medical history, physical examination will also be completed. Subjects will be given a falls diary to record the number of falls they experience. Vital signs, weight, and

concomitant medications will be recorded. Safety laboratory tests will be performed including complete blood count (CBC) with differential and Chem 12.

Randomization: The site investigator will review all inclusion and exclusion criteria and safety laboratory tests prior to randomization. If the subject passes all screening procedures and is confirmed as eligible, the baseline visit can be scheduled. Randomization for each site will be performed at baseline visit using the RedCap system at the University of Rochester Data Management Center.

Baseline: Baseline evaluations will include vital signs, weight check and urine pregnancy test, concomitant medication review, adverse events, completion of the IBMFRS, MMT, MVICT of quadriceps and grip, mTUG, Grip and Pinch, and 6 minute walk test with 2 minute distance. We will obtain the Health Assessment Questionnaire (HAQ-DI) and SF-36. A new falls diary will be given to subjects. Subjects will receive their study medication after all baseline procedures are performed. The subject will be observed for 1 hour after the initial dosing of the medication. The study medication will be dispensed for the initial one-month period, and the patient will be given instructions regarding dosing schedule and study requirements. If the patients are seen within 2-4 weeks from screening, lab tests will not need to be repeated.

Follow-up Visits: All follow-up visits will be performed at month 1, month 4, month 8, month 12, month 16 and month 20. Phone calls will be made at month 2, month 3, month 6, month 10, month 14, month 18, and 28 days after the month 20 visit. Every month is made up of 28 days. There is a 3 day window from the visit date. At month 1, participants will be assessed with a physical examination, IBMFRS, CBC and Chem 12. At month 4, month 8, month 12, month 16 and month 20, participants will be assessed with a physical exam, IBMFRS, MMT, MVICT of quadriceps and grip, mTUG, Grip and Pinch, and 6 minute walk test with 2 minute distance, CBC and Chem 12, SF-36 and HAQ-DI. A new falls diary will be given out. Concomitant medications, and adverse events, will be assessed at each study time point. Unscheduled visits to evaluate potential adverse events can occur at any time. Phone visits: Subjects will be contacted by phone at months 2, 3, 6, 10, 14, and 18 to capture IBMFRS, adverse events and concomitant medications. There will be a follow-up phone call 30 days post treatment.

Figure 8: Study Visit Schedule

Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Month	-1 (Sc)	0 (Base)	1	2	3	4	6	8	10	12	14	16	18	20	Phone call
Consent/Eligibility	X														
Medical History	X														
Physical Exam	X		X			X		X		X		X		X	
Safety Labs*	X		X			X		X		X		X		X	
Urine Preg**		X													
Dispensing of Medication		X	X			X		X		X		X			
Return of Medication			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	
Grip and pinch		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	
Concomitant Medication	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

* = **Full Safety Labs:** CBC and Chem 12, Serum pregnancy
**= Urine pregnancy prior to dispensing study medication
MMT, Manual Muscle Testing; MVICT, Maximum Voluntary Isometric Contraction Testing, SF-36, Short Form Health Survey 36; HAQ-DI, Health Assessment Questionnaire Disability Index; IBMFRS, Inclusion Body Myositis Functional Rating Scale; mTUG, modified Timed Up and Go Test;.

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

Muscle Strength Testing: We will measure MVICT using the Quantitative Muscle Assessment (QMA) system designed by Computer Source, Atlanta, GA. The system uses an adjustible cuff to attach the patient's arm or leg to an inelastic strap that is connected to force transducer with a load of 0.5 to 1,000 Newtons. Two muscle groups are tested bilaterally (i.e., quadriceps, and hand grip). Each muscle is tested twice while the patient is encouraged by the CE to exert maximal effort. The

maximum force generated by the patient from the two trials is recorded for each muscle group. MVICT has been shown to be reliable and valid in several neuromuscular disorders. We have used MVICT in natural history and treatment trials of various myopathies, including FSHD [53-57], DMD [58-63], and IBM. [21-23] Our CEs have demonstrated excellent intra-rater and inter-rater reliability in regards to MVICT with intraclass correlation coefficients ranging from 0.86-0.99. [64-65] We will measure MMT of 26 muscle groups. [22-23]

Health Assessment Questionnaire (HAQ- DI): This is a self-report functional status (disability) measure based on the five patient-centered dimensions (death, disability, discomfort, drug toxicity and dollar costs). [66-67]

Modified Timed Up and Go (mTUG)*:* We will measure the patient's ability to get up from a chair allowing subjects to use their arms (since most with sIBM cannot perform the task without pushing off), walk 3 meters, turn around and walk back to the chair and sit down. The use of nearby walls, or assistance from a caregiver was not allowed. This test will be performed twice and the fastest time was used in the data analysis. [68-70]

6 minute walk test with 2 minute distance captured: We will assess the distance IBM patients can walk in 6 minutes. [68,71-72] Subjects were instructed to walk down one side of the track and back along the opposite side as quickly and safely as possible for 6 minutes. Subjects were allowed to take break as needed during the walking period, but timing continued during breaks. Time to complete each 50-meter lap and distance walked in meters is recorded after 2 minutes and 6 minutes.

Grip and Pinch: We will measure grip and pinch strength using the Jamar dynamometer and Jamar pinch device.

Falls diary: Each subject will record the number of falls within each four months.

5. **Study medication: Arimoclomol**

Dose and formulation

Arimoclomol will be administered at 200 mg orally TID in this study using the following up titration plan. As Arimoclomol 100 mg orally TID was well tolerated dose in our pilot study, we will initiate subjects on that dose or matching placebo. If this dose level is well tolerated for one week, Arimoclomol dose will be increased to 200 mg orally TID and maintained at that dose for the remainder of the study. Since the main adverse event recorded in our data is related to mild to moderate gastrointestinal tolerability, a drug-related severe gastrointestinal adverse event will lead to drug dose reduction down to the lower initial dose level; if the severe drug-related adverse event persists for more than one week after dose reduction, we might be consider discontinuation of the treatment for this subject. Then, the patient will be followed up as planned per protocol for adverse events recording.

Drug Supply

We have a letter of support from Orphazyme to supply drug and placebo to support this study.

Drug dispensing, labeling and storage

Medication will be shipped to each site. The medications will be stored at room temperature and protected from light.

Compliance and return of study drug

Subjects will receive study medication at clinic visits baseline, month 1, 4, 8,12 and 16. Subjects will use a medication log and will be instructed to return all unused study medication at each clinic visit. Compliance will be assessed by review of the medication log at each visit and by documentation of unused study medication.

Concomitant medications

Concomitant medication use, including over-the-counter supplements, will be documented throughout the study. The entry will include the dose, regimen, route, indication, and dates of use. Antioxidants and vitamins will be allowed.

6. Adverse events and serious adverse events

Adverse Events: An adverse event (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, laboratory or physiologic observations occurring in study participants. The safety of arimoclomol will be evaluated using vital signs and weight, clinical laboratory determinations, physical examination, reporting of AEs, deaths and other serious adverse events (SAEs), and treatment discontinuations due to AEs. Information on adverse effects and on intercurrent events will be determined at each visit by direct questioning of the subjects, clinical examination, and laboratory tests. Tolerability will be determined by the ability to complete the study on the assigned experimental medication. AEs will be assessed using the MedDRA system of coding. The site PI or Co-I will monitor AEs monthly, grade them, and indicate if the AE is related to the study medication (probable, possible, unrelated). Patients will be instructed to call the PI's office (or on-call resident if at night or on the weekend) to report events that occur between study visits.

Expected Adverse Events:

Arimoclomol. Based on the two studies in healthy volunteers, no significant adverse events can be predicted. In the 10-day, multiple-dose study, there was slight serum creatinine elevation noted in some volunteers, although serum creatinine never exceeded the normal range. Other dose-related events noted in experimental animals were slight increases in cholesterol and bilirubin. In either obese or diabetic rats, arimoclomol treatment resulted in a slight reduction in serum glucose and improvement of any abnormalities on glucose tolerance tests. No significant changes in serum glucose are expected in non-diabetic human subjects. Safety laboratory tests will be performed at each visit and monitored for significant changes.

In the twenty-four patient pilot study we conducted, there were no significant differences between treatment groups regarding the rate, type and severity of adverse events (AEs) (Table 2). There were 8 treatment-possibly-related AEs in the placebo group and 14 with Arimoclomol, the most common being gastrointestinal. The 14 AEs in the Arimoclomol group were constipation (*n*=3), hyponatremia (*n*=2), loose stools (*n*=2) and 1 of each of the following: bowel movement problems, gas pains, nausea, cramps, dizziness/tinnitus, hypertension and rheumatoid arthritis flare. In the Arimoclomol group, one serious AE was reported: a study subject requiring overnight hospitalization after the first trial muscle biopsy as a result of persistent high blood pressure. This

patient had known poorly controlled hypertension and the muscle biopsy was identified as a stressful event that raised the patient´s blood pressure. Blood pressure normalized after adjustment of the patient´s antihypertensive medication and kept within normal range throughout the remainder of the trial. Hypertensive episodes were also observed in two placebo patients, under similar circumstances, although these cases did not require hospitalization. Two cases of hyponatremia and one case of high thyroxine levels were observed in the Arimoclomol group, however these changes were transient, asymptomatic and did not require treatment. The episode of hematuria in the Arimoclomol group was also limited and did not require treatment. All infections resolved with standard treatments, with or without antibiotics, and did not require hospitalization. Ocular toxicity and arrhythmia were not observed in any study subjects.

Table 2 Summary of all adverse events over the course of 1 year.*

MedDRA System Organ Class	Arimoclomol (16 patients)	Placebo (8 patients)
Blood and lymphatic system disorders	-	-
Cardiac disorders	Palpitations (*n*=1)	
Congenital, familial and genetic disorders	-	-
Ear and labyrinth disorders	Dizziness/tinnitus (*n*=2)	
Endocrine disorders	-	-
Eye disorders	Conjunctivitis (*n*=1), eye pain (*n*=1)	Dry eyes (*n*=1)
Gastrointestinal disorders	Constipation (*n*=4), throat irritation (*n*=4), loose stools (*n*=2), nausea (*n*=2), dry mouth (*n*=2), bowel movement problems (*n*=1), epigastralgia (*n*=1), gas pain (*n*=1), pyrosis (*n*=1), vomiting (*n*=1), geographic tongue (*n*=1)	Constipation (*n*=4), loose stools (*n*=4), painful parotids (*n*=2)
General disorders and administration site conditions	Weight loss (*n*=1), dizziness (*n*=1), loss of consciousness (*n*=1)	Fatigue (*n*=1)
Hepatobiliary disorders	-	-
Immune system disorders	-	-
Infections and infestations	Sinus infection (*n*=2), upper respiratory tract infection (*n*=7), lower respiratory tract infection (*n*=2), erysipelas (*n*=1), tooth infection (*n*=1)	Tooth infection (*n*=4), upper respiratory tract infection (*n*=3), cellulitis (*n*=1), leg ulcer infection (*n*=1)
Injury, poisoning and procedural complications	Fall/contusion (*n*=23), post-biopsy pain (*n*=3), post-biopsy fatigue (*n*=1)	Fall/contusion (*n*=9), post-biopsy pain (*n*=1), pruritus in biopsy scar (*n*=1), finger cut (*n*=1)
Investigations	Hyponatremia (*n*=2), high thyroxine levels (*n*=1)	Spinal stenosis (*n*=1), herniated disk (*n*=1)
Metabolism and nutrition disorders	-	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain (*n*=10), cramps (*n*=1), rheumatoid arthritis flare (*n*=1), heat and soreness of proximal lower limbs (*n*=1)	Musculoskeletal pain (*n*=2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	-	-
Nervous system disorders	Headache (*n*=7), worsening of restless leg syndrome (*n*=1),	Headache (*n*=3), paresthesia (*n*=1), stroke (*n*=1)

	paresthesia (*n*=1)	
Pregnancy, puerperium and perinatal conditions	-	-
Psychiatric disorders	-	-
Renal and urinary disorders	Hematuria (*n*=1)	-
Reproductive system and breast disorders	-	Decreased libido (*n*=1)
Respiratory, thoracic and mediastinal disorders	Cough (*n*=2)	Cough (*n*=1)
Skin and subcutaneous tissue disorders	Rash (*n*=2), rosacea (*n*=1), insect bite with erythema (*n*=1), cold sores (*n*=1)	Rash (*n*=1)
Social circumstances		
Surgical and medical procedures	Tooth extraction (*n*=1), sinus surgery (*n*=1), solar lentigines removal (*n*=1)	Tooth extraction (*n*=1)
Vascular disorders	Hypertension (*n*=3), edema (*n*=2)	Hypertension (*n*=3), edema (*n*=3)
Average number of adverse events (AEs) per patient	**AEs = 6.8/patient**	**AEs = 6.5/patient**

Recording adverse events

Definition - adverse events are clinical abnormalities (illness, signs, or symptoms) that begin or worsen during the course of the study whether or not the abnormality is believed by the investigator to be related to the study medication, and for the purposes of this study, are not thought to be directly related to the expected course of IBM itself.

Recording - the investigator will monitor each patient closely and record all adverse events on the adverse event page of the case report form.

Severity - adverse events should be graded for severity:

Mild: causing no limitation of usual activities
Moderate: causing some limitation of usual activities
Severe: causing inability to carry out usual activities

The investigator will indicate his/her opinion as to the relationship of the event to the study drug. If the investigator believes that the adverse event is not related to the study medication, he should indicate what he believes to be the probable cause of the adverse event.

Causality will be defined by the following:

Not Related:
Exposure to drug has not occurred
OR
The administration of study medication and the occurrence of the AE are not reasonably related in time
OR
The AE is considered likely to be related to an etiology other than the use of study medication

Possibly Related:

The administration of study medication and the occurrence of the AE are reasonably related in time AND
The AE could be explained equally well by factors or causes other than exposure to study medication

Probably Related:
The administration of study medication and the occurrence of the AE are reasonably related in time AND
The AE is more likely explained by exposure to study medication than by other factors or causes.

All AEs are considered unexpected except if listed in the investigator brochure. Otherwise they are considered related

Serious adverse events

Definition: Serious adverse events are life threatening, fatal, result in hospitalization or prolonged hospitalization, permanent disability, congenital anomaly, cancer, or overdose, or are any event that the investigator believes is very unusual or potentially serious.

Report: Any serious adverse event will be reported immediately (within 24 hours). All serious adverse events will be recorded on the standard adverse events page of the case report form, and a serious adverse event form will be completed. The coordinating center will be notified within 24 hours.

Follow-up of Adverse Events: The site investigator is responsible for appropriate medical management and laboratory tests for adverse events until the event is resolved. The management and resolution of each adverse event should be recorded on the adverse event page of the case report form.

Serious adverse events and adverse events will be entered into the computerized research informatics system at the University of Rochester. The study coordinator and investigator from each site are responsible for accuracy and completeness of all events. Mazen Dimachkie, MD, and Michael Hanna, MD will be notified by email of all serious adverse events.

Serious adverse events will be reported to the Human Subjects Committees at the University of Kansas Medical Center. All sites will receive notification as well. The FDA Orphan Products Division will be notified as needed.

7. Statistical Considerations

The MSG Biostatistics Center will randomize patients to the treatment assignments. The randomization will be stratified by center and will include blocking to facilitate approximate balance in the number of subjects assigned to each treatment group within each center. The programmer will provide (by mail) the appropriate treatment assignments to each site.

In accordance with the intention-to-treat principle, all randomized participants will be included in the statistical analysis according to the treatment group to which they were originally assigned. All randomized subjects will be considered able to be evaluated for the primary and secondary outcome measures. Every effort will be made to retain subjects in this trial, to promote adherence to the study protocol, and to collect all data at every visit. If a subject cannot tolerate or refuses to continue taking study medication, we will continue to follow and evaluate that subject if he/she is willing. If a subject withdraws from the trial, attempts will be made to bring the subject in for a final evaluation.

Compliance with trial procedures, subject disposition, and reasons for subject withdrawal will be carefully tracked throughout the study.

Subject identity will be protected by unique study identification variable. This code will be used for all data faxed from the other sites. The information will be kept in a key-locked office.

Study sample size calculation:

The primary outcome variable is the change from baseline to Month 20 in the IBMFRS. In the arimoclomol pilot study, the standard deviation of the 12-month change in IBMFRS was 2.9. The mean change in the placebo group was -3.5 and the mean change in the arimoclomol group was -2.1. A sample size of 68 subjects per group (136 total) will 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). To account for an anticipated 10% drop-out rate, the sample size will be inflated to 75 subjects per group (150 total).

Analysis of Efficacy Outcomes

The primary statistical analysis will involve the use of a repeated measures analysis of covariance model for the IBMFRS (i.e., the so-called “mixed model repeated measures”, or MMRM, analysis strategy) [73], with terms for treatment group (arimoclomol, placebo), center, baseline IBMFRS score, month (treated as a categorical variable), and interaction terms for baseline IBMFRS and time and treatment group and time. The covariance matrix for the within-subject observations will be modeled using an unstructured pattern. Ninety-five percent confidence intervals for treatment effects (differences in adjusted group means) at each visit will be computed using this model, with the Month 20 time point being of primary interest. A test for significance of the treatment effect at Month 20 will likewise be performed with this model using a significance level of 5% (two-tailed). Similar analyses will be performed for the secondary outcome variables for efficacy including strength outcomes (MVICT and MMT scores, grip strength, pinch strength), HAQ-DI , modified timed up and go, and distance walked in 6 minutes.

The underlying assumptions of the repeated measures analysis of covariance models will be thoroughly checked (normality, linearity, etc.) and remedial measures (e.g., transformations) will be taken if serious violations of these assumptions are detected. These are not anticipated to be violated for the IBMFRS in this study.

The primary analyses will be performed according to the intention-to-treat principle and will include all available data from all randomized subjects. The repeated measures analysis of covariance model to be used for the primary analyses uses maximum likelihood to estimate the parameters of interest (treatment effects) using available data from all subjects. This direct likelihood method accommodates missing data in a valid manner under the missing at random assumption [73]. Other strategies for dealing with missing data such as pattern-mixture models [74] will be attempted as well; these models will be used to perform sensitivity analyses since they rely on assumptions about the missing data mechanism that are difficult to verify. It is hoped that the overall conclusions regarding the effect of arimoclomol will not depend greatly on the analysis strategy used, particularly if subject withdrawal is minimized.

Analysis of Safety Outcomes

Adverse events (AEs) will be summarized by treatment group, maximum severity, and perceived relationship to study medication. For each adverse event (MedDRA preferred term), the treatment groups will be compared regarding the occurrence of at least one event using Fisher's exact test. The comparisons will be repeated excluding all mild symptoms. Similar analyses will be performed after grouping adverse events by MedDRA system organ class. Individual adverse events will be listed, with particular attention paid to serious adverse events, including death.

Analyses of tolerability outcomes (e.g., ability to complete the trial on the assigned dosage of study medication; ability to complete the trial) will be performed using Fisher's exact tests.

Continuous measures of safety (vital signs, laboratory test results) will be performed using models similar to those used for the primary outcome variable for efficacy (MMRM).

Compliance data will be summarized by treatment group, overall and by visit.

8. ***Data management and case report forms***

Data will be collected on paper case report forms (CRFs). The compiled information from these forms will be remotely entered by study site personnel into a Redcap database at the University of Rochester. A web-based database system designed specifically for this clinical trial will be used. A data manager will be responsible for the database. All corrections to the CRFs will be initialed and dated by the study coordinator, clinical evaluator, or investigator. Subject folders will contain copies of CRFs, laboratory data, patient histories, physical examinations, and any adverse experience reports. These will be filed in a dedicated filing cabinet at each center organized by patient code number. Drug dispensing logs will be kept to record the total amount of medication received from and returned to the site. Completed informed consent forms from each subject will be available in the subject's file and verified for proper documentation.

Reporting obligations

The site investigators will be responsible for insuring that all blank data spaces on each CRF are filled in. The statistician, along with the coordinating center, will notify each investigator of any missing data. All completed CRFs are to be reviewed by the site investigator. Changes/additions to data entered on original case report forms must be made with a single line drawn through the error, so as to leave the error still legible. The correction will be entered in black ink, with the date and the initial of the person making the correction. All data entry for a visit will be completed by site personnel within 5 business days of the visit date. If all expected CRFs are not entered within 5 days of the end of the allowable window for the visit the data system will generate an email reminder to the site.

9. Stopping Guidelines

Premature discontinuation, protocol violation, loss to follow-up

All attempts will be made to enhance patient compliance. Early withdrawal may occur for any of the following reasons:

- Patient requests;
- Investigator decides that it is in the patient's interest
- Serious adverse event that is probably related to study medication
- Significant protocol violation occurs
- Breaking of the blind

If the patient withdraws early, termination evaluations will be completed and the patient will be encouraged to continue with scheduled visits. If a patient is unable to return to the center, a phone call will be made to the patient. In the event of a loss to follow-up, information about the patient will be sought from the family or family physician.

Study discontinuation

The DSMB can recommend to the sponsor / study PI that the study to be terminated at any time . Reasons for terminating the study may include the following:

- Incidence or severity of AEs indicates a potential health hazard to study subjects
- Study enrollment is unsatisfactory
- Data recording is inaccurate or incomplete.

Code break procedures

Each site will receive documentation to break the randomization code if needed. The site investigators will not have access to the randomization codes. An individual at each site (who is not involved in this study) will be identified to receive the unblinding codes. This person at the study site will get sealed envelopes that can be opened only in the case of a dire medical emergency requiring knowledge of treatment assignment. It should be emphasized that this step should only be taken if absolutely necessary, that we anticipate that most of these situations can be handled simply by suspending study medication, and that code breaks will occur very rarely in this trial.

Mazen Dimachkie, MD or Michael Hanna, MD will be notified prior to unblinding if at all possible to make absolutely sure that the situation cannot be handled any other way (e.g., by simply suspending study medication. If this is not possible, then one of the above listed investigators must be notified at the first possible moment.

For most emergencies that would cause a subject to be discontinued from the study, cessation of the study drug is usually sufficient. In most cases, the identity of the study drug would not change the course of the subject's emergency treatment. In the rare instance where establishing the identity of the study drug is vital for safe emergency treatment of the subject, the investigator after communicating with the safety monitor will have the authority to ask the research pharmacy to un-blind the code for that subject only. If the safety monitor is unavailable, the investigator may proceed with unblinding if it is in the best interest of the subject.

A data and safety monitoring board (DSMB) will be established for this study as well as an independent medical monitor. If the AE rate leading to discontinuation of the study is >25%, the medical monitor will immediately draw these events to the attention of the DSMB. In other words, if more than 38 participants have an adverse event considered by the PI to be probably related to the study medication and that leads the local PI to discontinue the medication in that subject, then the DSMB would recommend to the overall study PI that the study be temporarily halted. The DSMB will then determine if it is safe for the study to proceed. AEs SAEs and completion of data entry will be assessed by the DSMB.

10. Data and safety monitoring plan

Medical Monitor

An independent neurologist or rheumatologist will serve as the medical monitor. This person will be picked prior to the beginning of the study. The medical monitor will be responsible for independent

review of the safety laboratory tests and adverse events will be responsible for monitoring the real-time reporting of Serious Adverse Events, will review laboratory reports and adverse events monthly, or more frequently as needed. The medical monitor will be blinded to treatment assignment. If the safety monitor has concerns regarding the safety data, they may notify the DSMB. The safety monitor may request additional or clarifying information from the coordinating center of the treating physician. The safety monitor will prepare a report to present to the DSMB prior to their meetings.

Data and Safety Monitoring Board (DSMB)

A DSMB will be established through the University of Kansas Medical Center Office of Compliance. The DSMB will meet every six months by phone to review recruitment, adverse events, and serious adverse events. They will meet with the study statistician prior to the meetings to review the event reports and identify any issues that need to be addressed. The DSMB is comprised of a clinical trialist, two IBM specialists, and a statistician. An IBM specialist will head the DSMB. The members of the DSMB are not located at the University of Kansas Medical Center.

Data and Safety Monitoring Executive Committee (DSM-EC)

Administrative support of DSMB is through the Office of Compliance at the University of Kansas Medical Center. The scope of the DSM-EC is to provide multi-disciplinary, independent oversight of research studies. The DSM-EC will arrange the conference calls and will prepare minutes of the DSMB meetings.

Protocol Adherence

The study PI will work closely with principal investigators at all other sites to ensure adherence of the protocol by the study sites and study data integrity. The principal investigator will be responsible for communicating with all sites to ensure smooth conduct of the study and prompt data submission. The principal investigator will coordinate e-mail and conference call communications and work with the data coordinator to prepare monthly reports from each site indicating the status of the study and problems that might arise. Serious adverse events will be reported immediately to the principal investigator and reviewed promptly by the safety monitor.

Based upon our previous experience in managing multicenter studies of neuromuscular disorders at KUMC, we will again assemble a communications and computing infrastructure and technical staff to ensure the success of this study. We will use strategies for intra- and inter-site communication, data entry, storage, management, and analysis similar to those we have previously used and currently use. We will have several ways to ensure adequate communication between the data center and the individual clinical sites. Telephone, fax, and electronic mail will be the primary modes of inter- and intra-site communication for investigators and study staff. The existing infrastructure at each site includes sophisticated telephone networks, voice messaging systems, fax machines and Ethernet connections to the Internet to support this strategy. All study computers at the data center and each of the clinical sites will be password protected, and kept in locked offices. The evaluators performing the monthly studies will complete a CRF after each visit. The principal investigator/study coordinator will be responsible for dispensing and accounting for all study medication. The principal investigator at each study site is responsible for all aspects of the study at the site. The investigator agrees to cooperate fully with monitors.

Monitoring Plan

The University of Kansas Medical Center Monitoring division will monitor all sites. This will consist of remote monitoring. Sites will send in their source documents as the first subject enters the study and

periodically anytime throughout the study. The University of Kansas Medical Center Monitoring division personnel in collaboration with the MSG Data Coordinating Center will verify accuracy of data entered on RedCap.

Data Storage and Backup

Original paper CRFs will be stored at each of the clinical sites in double locked storage. Electronic data at the data center will be backed up daily. Frequent checks of backup integrity will be conducted. In the event of a loss or corruption of records at any one site, data can be reconstructed.

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Appendix A

European Neuromuscular Centre Inclusion Body Myositis research diagnostic criteria 2011			
Diagnostic sub-group	**Clinico-pathologically defined IBM**	**Clinically defined IBM**	**Probable IBM**
Clinical features			
Duration of weakness > 12 months	X	X	X
Age at onset > 45 years	X	X	X
Creatine kinase ≤ 15x ULN	X	X	X
FF weakness > SA weakness ***AND/OR*** KE weakness ≥ HF weakness	X	-	-
FF weakness > SA weakness ***AND*** KE weakness ≥ HF weakness	-	X	-
FF weakness > SA weakness ***OR*** KE weakness ≥ HF weakness	-	-	X
Pathological features			
Endomysial inflammatory infiltrate	X	≥1, but not all of the 4 pathological features	≥1, but not all of the 4 pathological features
Rimmed vacuoles	X		
Protein accumulation* or 15-18nm filaments	X		
Up-regulation of MHC Class I	-		
*Demonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). FF, Finger flexion; HF, Hip flexion; KE, Knee extension; SA, Shoulder abduction; MHC Class I, Major histocompatibility complex class I; ULN = Upper limit of normal.			

Review Group: FDA Orphan Products Development Ad Hoc Panel Review

Investigator: Mazen Dimachkie
Degree: MD
Position: Professor
Organization: University of Kansas Medical Center
City, State: Kansas City, KS
Requested Start Date: 11/01/2015

Project Title: Phase 2 Study of Arimoclomol for the Treatment of Sporadic Inclusion Body Myositis

Recommendation: Approval **Priority Score: 118**
Special Note: Human Subjects

Project Year	Total Costs Requested
01	$394,501
02	$391,250
03	$399,300
04	$397,836

R01 FD004809-01-A2 Dimachkie, M

RESUME AND SUMMARY OF DISCUSSION:
This resubmission proposes a Phase 2 multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of arimoclomol in 150 adults with inclusion body myositis. The strengths of the proposal include the strong scientific rationale, the study design, expertise of the investigators, and the available resources and environment. Although a weakness remains in that clinical benefit has not been demonstrated with this type of product in other diseases, the concerns raised in previous reviews have been addressed. The reviewers recommended approval of this application with high enthusiasm.

DESCRIPTION (provided by applicant):
Sporadic inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy presenting after age 50 years. It presents with chronic insidious proximal leg and distal arm asymmetric muscle weakness. Muscle histopathology reveals endomysial inflammatory exudates surrounding and invading non-necrotic muscle fibers, oftentimes accompanied by rimmed vacuoles and inclusions. Unlike polymyositis and dermatomyositis, patients with IBM do not improve with therapy; at present there is no effective treatment for IBM. The histopathological features and lack of response to immunotherapies has led many experts in the field to believe that IBM is primarily a degenerative disorder of muscle with secondary inflammation. A randomized controlled pilot study in 24 IBM subjects has been completed. Eighteen subjects received oral arimoclomol 100 mg three times daily (TID) for four months and 8 were on placebo. Arimoclomol increases heatshock proteins and may prevent protein misfolding. The investigators reported that arimoclomol was safe and the IBM functional rating scale (IBMFRS) decline at 1 year was less in the arimoclomol group compared to placebo with the p-value approaching significance. The proposed study is a twenty month, randomized, placebo-controlled Phase 2 study of arimoclomol in 150 IBM subjects. The primary aim is to assess the efficacy and safety of arimoclomol (200 mg TID). The primary efficacy endpoint is the IBMFRS. Secondary efficacy outcomes will include different measures of strength

and function: manual muscle testing (MMT), maximum voluntary isometric contraction (MVICT) of quadriceps and grip, modified timed up and go (mTUG), 6 minute walk test with 2 minute distance captured, grip and pinch test; a general physical function measure: Health Assessment Questionnaire (HAQ- DI); a Health-Related Quality of Life (HRQoL) measure using SF36. Safety laboratory and adverse events will be collected.

CRITIQUE 1:
Strengths:

- The overall significance of the proposal is high, particularly in view of the lack not only of an effective therapy for IBM but its relative lack of study in view of its prevalence and disability. There is also inherent and general scientific value for a treatment trial for IBM in view of the widespread interest in neurologic diseases where protein misfolding and aggregation have been implicated in the pathogenesis. That the previous unsuccessful treatment trials were based on an earlier less accurate view of the disease as primarily inflammatory in nature, also adds to the significance of the proposed trial.
- The study drug arimoclomol has a mechanism of action, that of induction of molecular chaperone expression that is of long standing interest as a treatment for diseases associated with pathogenic proteins. Data is also shown supporting a second mechanism of action, that of reduced sequestration of molecular chaperones in conditions where they are already induced and a benefit in a novel cellular model of IBM created by the investigators involved in the current proposal.
- The investigators also present efficacy data from a murine model of familial IBM with mutations of the valosin containing protein, where a significant level of prevention of loss of grip strength and tetanic force was seen. Prevention of histopathologic changes in these mice was also seen with treatment.
- Preclinical data is summarized from multiple species with a wide range of dosing, supporting safety and tolerance of the drug at the proposed dose. This conclusion is supported by Phase 1 data in normal volunteers and in amyotrophic lateral sclerosis (ALS) patients, where it appears that there is reasonable tolerance of this drug but at this point its efficacy remains uncertain.
- The investigators have also completed a 24 patient pilot study validating the patient scale for IBM. This open label study also supports the rationale for the current proposed study. The change in dose from 100 mg to 200mg TID is also justified. Trends seen in this small study, although not statistically significant, also justify further evaluation in a larger population and with a higher dose.
- The study design is reasonable and the use of the patient report scale, muscle strength and functional activities as outcome measures are well justified considering the limitations of variable and relatively slow rate of progressive worsening in the study population.
- The investigators have addressed the comments of the previous review reasonably well such as: 1) documenting support for supply of drug for the study, 2) justification of the use of the IBMFRS as the primary outcome measure, and 3) cost concerns regarding surrogate laboratory outcome measure-although magnetic resonance imaging (MRI) changes would in particular strengthen the study design, they are not essential to the core study and they will seek other funding to do this in the future, and 4) concerns regarding the adequacy of the sample size and the duration of the study to detect

changes in outcome measurements have been addressed and the study design has been lengthened to 20 months. This raised concern regarding long-term tolerance, but there is supporting evidence from the ALS trial that beyond one year as open label this product continues to have good tolerance.

Weaknesses:

- Arimoclomol is one of many drugs that have extended the lifetime of mice expressing mutant SOD1. However the validity of this model is clearly open to questions since none of these compounds have shown clinical benefit in ALS, with arimoclomol still under study.

The investigative team is highly expert in this population and the appropriate group to execute this study. They have extensive preclinical and clinical experience with both IBM and arimoclomol and are the source of the vast majority of data justifying the study. The Principal Investigator (PI), Dr. Dimachkie, is an experienced neuromuscular specialist. He has participated in many clinical trials of neuromuscular disease, where he has been PI on several of these studies. Dr. Dimachkie has several directly relevant publications to the goals of the study. The Co-Investigator, Dr. Barohn, is a leader in neuromuscular clinical research. The University of Kansas Medical Center has clearly sufficient facilities and patient resources for the goals of the study. The consortium sites will allow for fulfillment of recruitment goals.

In summary, this proposal has been significantly revised and has the potential to be a landmark study for this field.

CRITIQUE 2:
The reviewer agreed with the previous comments and added that this would be a very important trial in IBM not just for developing a possible treatment, but because of the general paucity of trials studying this disease which is one of the more common rare neuromuscular disorders. In addition, the IBMFRS, a validated outcome that this group has validated itself and is based on the revised ALS Functional Rating Scale (ALSFRSR) which has been the primary outcome for ALS clinical trials for the last decade, and a number of secondary efficacy outcomes will be measured. The outcomes are excellent, the investigators are excellent, the scientific rationale is very sound, and they have addressed the concerns of the previous review so approval is recommended.

CRITIQUE 3:
The application is impressive and the two previous reviews are excellent.

CRITIQUE 4:
There are no other concerns.

INVESTIGATORS:
The investigators appear to be well qualified to conduct this study.

RESOURCES AND ENVIRONMENT:
The resources and environment appear adequate to conduct this study.

BUDGET:
The budget appears appropriate and well justified to conduct this study.

MONITORING AND HUMAN SUBJECTS PROTECTION:
The rights and welfare of human subjects and monitoring appear to be adequate.

OPD RECOMMENDATION:
OPD concurs with the recommendations of the review panel.