Zilucoplan in immune-mediated necrotizing myopathy: a phase 2, randomised, double-blind, placebo-controlled, multicentre trial

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Abstract (300/300 words)

Background

Immune-mediated necrotizing myopathy (IMNM) is an autoimmune myopathy characterised by proximal muscle weakness, high creatine kinase (CK) values, and autoantibodies recognizing 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) or the signal recognition particle (SRP). There are currently no approved therapies for IMNM and many patients experience active disease despite off-label treatment with intravenous immunoglobulin, glucocorticoids, and immunosuppressants. Detection of complement-activating anti-HMGCR and anti-SRP autoantibodies and the presence of complement deposition on the sarcolemma of non-necrotic myofibers led to the hypothesis that complement activation may be pathogenic in IMNM, therefore zilucoplan, a complement component 5 (C5) inhibitor, could be a potential therapy.

Methods

IMNM01, a phase 2, multicenter, randomised, double-blind, placebo-controlled study (NCT04025632) at 15 sites (four countries) evaluated efficacy, safety, and tolerability of zilucoplan in adult participants with anti-HMGCR or anti-SRP autoantibody-positive IMNM. Participants were randomised 1:1 to receive daily subcutaneous zilucoplan (0·3mg/kg) or placebo for eight weeks; with optional enrolment in the study open-label extension. Primary efficacy endpoint was percent change from baseline to Week 8 in CK levels. Secondary endpoints included safety.

Findings

Between 07 November 2019 and 07 January 2021, 27 participants received zilucoplan (n=12) or placebo (n=15) and completed the 8-week main study. At Week 8 there were no clinically relevant or statistically significant differences, despite target engagement based on mode of action, between treatment arms in mean percent change (standard deviation) of CK levels versus baseline (-9·86% [26·06] versus -20·72% [31·22] in zilucoplan [n=10] and placebo arms [n=14], p=0·46, respectively) and no clinically relevant improvement over time within the treatment arm. There were no unexpected adverse safety or tolerability findings.

Interpretation

C5 inhibition does not appear to be an effective treatment modality for IMNM. Rather than driving myofiber necrosis, complement activation may be secondary to muscle injury.

Funding

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Research in context

Evidence before this study

Most patients with immune-mediated necrotizing myopathy (IMNM) have autoantibodies against 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) or the signal recognition particle (SRP) that can be complement activating, and the titres of these antibodies appear to correlate with the clinical course. In addition, complement levels in IMNM muscle are higher than in other inflammatory myopathies. Passive transfer animal models using patients' sera suggested the pathogenic potential of anti-HMGCR and anti-SRP antibodies, with disease attenuation in the context of complement deficiency and increased disease activity with complement adjunction. No randomised double-blind placebo-controlled multicentre trial had been conducted in IMNM, and no validated outcome measures for such trials had been established.

Added value of this study

Prior evidence suggested that classical pathway activation of complement could have an important role in the pathogenesis of IMNM and therefore created the possibility of terminal complement pathway inhibition as a potential therapeutic target. Our study is the first clinical trial conducted in IMNM, to our knowledge, and paves the way for the efficient design of future trials in this disease. In addition, our study provides important insights into the relevance of C5 activation in IMNM.

Implications of the available evidence

The clear results, while disappointingly negative, provide important novel data on the pathobiology of IMNM, suggesting that complement activation may not be causative and complement deposition on myofibers may be reactive rather than pathogenic.

Introduction

Immune-mediated necrotizing myopathy (IMNM) is a clinical subtype of inflammatory myopathy with distinct clinicopathological characteristics including symmetric proximal muscle weakness, elevated muscle enzyme levels, myofiber necrosis with rare inflammatory infiltrate on muscle biopsy, and autoantibodies recognizing 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) or the signal recognition particle (SRP).(1, 2) Unfortunately, proximal muscle weakness may progress and become disabling despite treatment with intravenous immunoglobulin (IVIg), corticosteroids, and immunosuppressants.(2)

Given that not all patients with IMNM respond adequately to first-line therapies,(2) there is a need for additional treatment modalities. Several observations suggested that autoantibodies may cause muscle damage by activating complement. First, anti-HMGCR and anti-SRP autoantibody levels are associated with disease activity.(3, 4) Second, autoantibody isotypes are complement activating (5) and complement deposits are observed on the sarcolemma of non-necrotic myofibers on muscle biopsy specimens.(6) Furthermore, a passive transfer mouse model showed that anti-HMGCR and anti-SRP autoantibodies cause weakness and myofiber necrosis in the presence of complement. However, C3-deficient animals and those treated prophylactically with complement C5 inhibitors showed an attenuated disease course.(7, 8) Given these findings, we hypothesised that inhibiting the terminal complement pathway could be an effective treatment in IMNM.

Zilucoplan is a 15 amino acid peptide inhibitor of complement component C5. Zilucoplan inhibits the cleavage of C5 into its split products C5a, which is a potent anaphylatoxin, and C5b which together with complement components C6, C7, C8, and C9 forms the membrane attack complex (MAC, also called terminal complement complex or C5b-9). As zilucoplan binds the C5 protein in the region where its split product C5b interacts with C6, it also sterically hinders the formation of MAC, in addition to interfering with the cleavage of C5. Zilucoplan administration achieves complete complement inhibition within 3–6 hours of dose administration,(9) and has shown significant improvement on clinical endpoints in Phase 2 and Phase 3 trials in generalised myasthenia gravis.(10-13)

Patients with IMNM exhibit the greatest elevation of serum creatine kinase (CK) levels seen among all forms of myositis, and serum CK levels correlate well with disease activity.(14) Unlike in myopathies with less prominent tissue destruction, serum CK levels in IMNM are thought to directly reflect the degree of skeletal myocyte necrosis.(15) Therefore, CK is frequently used for routine clinical follow-up and to evaluate response to medication in patients with IMNM, in addition to clinical measures such as standardised muscle strength testing. Specifically, CK levels may increase prior to manifestation or deterioration of clinical weakness, and a decline in CK levels is often the first sign of response after treatment initiation while muscle regeneration and recovery of muscle strength may follow weeks to months later.(3)

To better understand the effect of C5 inhibition on IMNM, we conducted a randomised, double-blind, placebo-controlled, multicentre Phase 2 clinical trial to evaluate the safety, tolerability, and efficacy of subcutaneous (SC) zilucoplan 0·3 mg/kg daily in adult participants with anti-HMGCR or anti-SRP autoantibody-positive IMNM. To our knowledge, this is the first phase 2 clinical trial in participants with IMNM. The dose of zilucoplan 0·3mg/kg was selected for this study based on previously published efficacy, almost complete inhibition of the terminal complement pathway, and favourable safety in the Phase 2 study in participants with generalised myasthenia gravis (gMG).(10) This resulted in rapid, sustained and complete (97%) inhibition of the terminal complement pathway in all gMG participants receiving the 0·3mg/kg dose.

Given the reliable relationship between CK levels, disease activity, treatment response in IMNM, and the faster response and greater higher sensitivity of CK to effective treatment interventions compared with clinical measures, the main objective of this study was to assess the change in CK level after 8 weeks of zilucoplan therapy.

Methods

Study design

This study (IMNM01, NCT04025632) was a multicenter, randomised, double-blind, placebo-controlled study to evaluate the efficacy, tolerability and safety of zilucoplan in participants with IMNM who were positive for anti-HMGCR or anti-SRP autoantibodies.

Study participants were randomised in a 1:1 ratio to receive daily SC 0·3 mg/kg zilucoplan or matching placebo (supplementary figure S1). Randomization was stratified based on autoantibody status (anti-HMGCR+ versus anti-SRP+). The main study included a screening period of up to four weeks and an 8-week treatment period. Participants were evaluated at Baseline, and at Weeks 1, 2, 4, and 8. Participants were required to continue taking their existing standard of care medication for IMNM at the same dose levels throughout the study, including glucocorticoids, immunosuppressants, and IVIg. At the end of the main study, eligible participants had the opportunity to enter the open-label extension of the study.

Updates to the global protocol were made to include provisions for the COVID-19 pandemic, to update the statistical methods used to analysis the study objectives and endpoints and to update the inclusion and exclusion criteria. Specifically, the contraception information inclusion criteria were updated and hypersensitivity to study treatment was added as an exclusion criterion.

The study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki. Independent ethics committees or institutional review boards provided written approval for the study protocol and all amendments.

Further details on the study, including the protocol amendments can be found in the study protocol in the Supplementary Material.

Study participants

Participants aged ≥18 to <75 years with a clinically confirmed diagnosis of IMNM, positive serology for anti-HMGCR or anti-SRP autoantibodies, clinical evidence of weakness (≤ Grade 4 out of 5) on the Medical Research Council (MRC) Scale with manual muscle testing (MMT) in at least one proximal limb muscle group (out of either trapezius, deltoid, biceps brachii, iliopsoas, gluteus medius, gluteus maximus, quadriceps), serum total CK of >1000U/L at screening, and no change in glucocorticoids or other immunosuppressive therapies for at least 30 days prior to baseline, or anticipated to occur during the first eight weeks of the study were eligible for inclusion. Participants who had received rituximab within 90 days prior to baseline, had recently initiated IVIg treatment (first cycle <90 days prior to baseline), or had received plasma exchange within four weeks prior to baseline, were excluded from the study. Other medications were permitted while in the study, pursuant to the exclusion criteria. Participants were expected to remain on stable doses of the permitted standard of care therapy for IMNM throughout the main portion of the study and through the Week 8 visit of the open-label extension; this included glucocorticoids, immunosuppressive drugs, and IVIg. Additional details of the inclusion and exclusion criteria, including eligibility criteria for inclusion in the open-label extension, can be found in the Supplementary Material.

All study participants were required to receive meningococcal vaccination at least two weeks before starting study treatment due to the potential risk of *Neisseria meningitidis* infection, an established risk with complement C5 inhibition or genetic C5 deficiencies.(16, 17). Participants who initiated treatment less than two weeks after receiving a meningococcal vaccine received appropriate antibiotic prophylaxis.

Randomization and blinding

Participants were randomised in a 1:1 ratio to receive daily SC doses of 0·3 mg/kg zilucoplan or a matching placebo using a computerised randomisation algorithm; randomisation was stratified based on autoantibody status (anti-HMGCR+ versus anti-SRP+).

Participants and study staff remained blinded to treatment assignments until after the data from Week 8 of the main study were reviewed, locked, and unblinded. Participants and investigators were blinded to laboratory study results including CK, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) in order to prevent study unblinding.

Procedures

Following in-clinic education and training, all participants self-injected daily SC doses of zilucoplan or placebo, according to randomised treatment allocation, throughout the 8-week study period. Zilucoplan was provided in single-use prefilled syringes for self-injection using weight bracketed dosing, i.e. each of 3 fixed amounts of the drug covered a range of study participants weights (43 to 150kg).

Participants were evaluated at baseline and at Weeks 1, 2, 4, and 8. At the conclusion of the 8-week main study, all participants had the option to receive zilucoplan in the open-label extension provided they met the selection criteria for this part of the study. All participants entering the open-label extension received open-label once-daily SC zilucoplan 0·3mg/kg. Visits during the first eight weeks of the open-label extension were identical to the main study for all participants to ensure appropriate monitoring of those transitioning from placebo to active treatment. The study remained double-blinded until after the data from the main treatment period had been reviewed, locked, and unblinded.

For participants who permanently discontinued treatment with the study drug, and for those who completed the 8-week study but did not enter the open-label extension, a safety follow-up visit was performed at 40 days after the last study dose.

Outcomes

The primary endpoint was the percent change from baseline to Week 8 in CK levels. Pre-specified secondary outcomes included safety and clinical efficacy endpoints. Safety assessments included evaluations of treatment-emergent adverse events (TEAEs), clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations. Efficacy assessments included minimal response based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Response Criteria Scale at Week 8, change from baseline to Week 8 in Triple Timed Up and Go (3TUG) Test (in ambulatory participants only), proximal MMT (trapezius, deltoid, biceps brachii, iliopsoas, gluteus medius, gluteus maximus, and quadriceps bilaterally), Physician Global Activity visual analogue scale (VAS), Patient Global Activity VAS, Health Assessment Questionnaire (HAQ), Myositis Disease Activity Assessment Tool (MDAAT) Extramuscular Disease Activity VAS Score, and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale. Subgroup analyses of the primary and continuous secondary efficacy variables were summarised for the ITT population for the main study based on sex (female, male), age (<55 years, ≥55 years), and stratification factor (anti-HMGCR/anti-SRP groups).

Plasma samples were analysed to confirm inhibition of the terminal complement pathway using an ex vivo antibody-sensitised sheep red blood cell (sRBC) lysis assay to assess the classical pathway of complement activation.(18)

Exploratory pharmacokinetic/pharmacodynamic outcomes included evaluation of classical complement pathway activation utilising the sRBC lysis assay.

Following the initiation of the study, the objectives and endpoints were updated to encompass evaluation of long-term efficacy, safety, and tolerability during the open label extension part of the study.

Statistical analyses

The planned enrolment was for approximately 24 participants. A sample size of 12 study participants per group yielded approximately 95% power to detect a difference in the percent reduction from baseline CK between the active and placebo groups using a Wilcoxon rank-sum test at the 2-sided 0·05 type 1 error rate. These power calculations assumed that the percent reduction in creatine kinase in the active dose group was approximately normally distributed with a mean of 80% and a standard deviation of 8%; that four of the placebo participants had a percent reduction similar to the active dose group; and the remaining eight placebo participants had a percent reduction normally distributed with a mean of 10% and a standard deviation of 8%.

Study populations

The following study populations were defined: the intention-to-treat (ITT) population included all participants randomised; the per-protocol (PP) population included all participants in the ITT population who had completed the main 8-week study period and had no major protocol deviations; the safety population included all participants who received at least 1 dose of study drug, with participants to be analysed based on the actual study treatment received.

Efficacy analysis

A two-sided stratified Wilcoxon rank sum test (Van Elteren test) was utilised in the final analysis to assess potential differences in the percentage change from baseline between treatments. The magnitude of association was expressed by Wilcoxon-Mann-Whitney odds (WMWodds) and the corresponding 95% confidence interval (CI).

ACR/EULAR minimal response at Week 8 was assessed by logistic regression model with treatment and strata (anti-HMGCR+/anti-SRP+) as fixed factors. Treatment group differences for each of the secondary efficacy change from baseline endpoints at Week 8, were assessed using an analysis of covariance model with treatment, randomization strata (anti-HMGCR+/anti-SRP+), and baseline endpoint as covariates. The least squares means (LSMs) of each treatment group and the least squares mean differences between zilucoplan and placebo were reported for the Week 8 change from baseline along with the two-sided 95% CIs and p-values.

Treatment group differences for each of the secondary efficacy change from baseline endpoints at Week 8 were assessed using a linear mixed effect model with repeated measures (MMRM) analysis of covariance (ANCOVA) with treatment and strata (anti-HMGCR+/anti-SRP+) as fixed factors and, visit, baseline score as a covariate, treatment×visit (interaction term), and baseline score×visit (interaction term) as fixed effects and participant as a random effect.

Change from baseline for the exploratory evaluation of the classical complement pathway activation and assessment of C5 levels was assessed using an ANCOVA model with treatment as a factor and the corresponding baseline value as a covariate. The active dose was compared to the placebo treatment group based on the ANCOVA model; corresponding 90% CIs were produced.

Safety analysis

Data on duration of exposure was summarised as number and percentage of study participants with cumulative study treatment duration (e.g., any duration, ≥1 week, ≥2 weeks, ≥3 weeks, etc.), duration of exposure in years (or participant exposure years [PEY])=[(min(date of last dose+40 days, last visit)-date of first dose+1)]/365 ·25. Exposure was adjusted for the 5 half-lives of active treatment, which was 40 days.

AEs were captured for the duration of the study from informed consent (SAEs only) or time of first administration, through until administration of the last study dose plus 40 days (or last visit, depending on which occurred first). TEAEs were defined as AEs starting on or after the time of first administration of study treatment. AEs were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5·0. TEAE summaries were reported separately within the main and open-label extension parts of the study.

Role of the funding source

This study was funded by Ra Pharmaceuticals Inc, now part of UCB Pharma. The funding source contributed to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication.

Results

The study was conducted across 15 sites in the USA, UK, France, and the Netherlands, and participants were enrolled between 07 November 2019 and 07 January 2021. Twenty-seven participants were enrolled in the study and randomised (figure 1), and all received zilucoplan or placebo; all 27 participants completed the 8-week blinded study period and 25 continued to the open-label extension.

Baseline demographic and clinical characteristics for each treatment group are shown in table 1. Overall, baseline characteristics were similar between treatment groups, with the exception of weight: compared with the placebo group, the zilucoplan group had a lower mean weight (81·1kg vs 91·5kg). Overall, 25 study participants (92·6%) received prior or concomitant IMNM-related medications.

Primary outcome

The primary efficacy endpoint in this study of change from baseline to Week 8 in CK levels was not met. There was no statistically significant difference between treatment arms Wilcoxon-Mann-Whitney odds: 0·55 95% CI: [0·19-1·57] (p=0·464) and no clinically relevant reduction in CK levels over time within treatment arms (table 2, figure 2).

As previously described the sample size calculation was based on the assumption of 80% CK reduction; none of the participants in either group reached this level of response. Individual CK levels over the main study period are shown in figure 3. The outlier in the zilucoplan group did not meet the 80% threshold.

Secondary outcomes

Similarly, there were no clinically relevant differences in secondary (clinical) endpoints such as the ACR/EULAR TIS at least minimal response at Week 8 or the 3TUG test (supplementary table 1) between the treatment arms.

Subgroup analysis

There were no clinically relevant differences in subgroup analysis endpoints such as the change from baseline in CK to Week 4 and Week 8 by sex, age or stratification factor (supplementary table 2).

Open label extension efficacy outcomes

There were also no clinically relevant changes in efficacy endpoints in the extension portion of the study.

Exploratory outcomes

Zilucoplan administration led to a sustained and complete inhibition of the terminal complement pathway measured by the sRBc lysis assay from participants on active treatment in the main study. In the zilucoplan group, baseline mean (SD) was 84·65 (34·74) compared with 3·67 (3·37) at Week 8, whereas in the placebo group, the baseline mean (SD) was 91·54 (28·13 vs 100·00 (0·00) at Week 8) (figure 4). Two participants during the main study, one in the zilucoplan group and one in the placebo group, had low complement activity at baseline.

Safety

During the main study, for participants who received zilucoplan, the mean (SD) duration of exposure was 56·3 (3·0) days, for participants who received placebo the mean (SD) duration of exposure was 55·2 (10·1) days and for participants who received at least 1 dose of zilucoplan during the main/extension study, the mean duration of exposure was 149·2 (92·9) days.

No new or unexpected safety findings or relevant differences between the zilucoplan and placebo arms were reported (table 3). The rate of TEAEs and serious TEAEs in the zilucoplan group was numerically lower than in the placebo group. The most frequently reported TEAEs (headache and nausea) had a similar rate across both treatment groups. No treatment-related serious TEAEs and no deaths were reported in the double-blind portion of the study. The incidence of treatment-related TEAEs was similar between treatment groups, and included headache, nausea, and vertigo. No *Neisseria* infections were reported in this study.

TEAEs of interest included infections and injection site reactions. Three participants [25·0%] who received zilucoplan and 2 participants [13·3%] who received placebo reported infection and infestation TEAEs during the main study (none were treatment related), and eight participants (32·0%) in the open-label extension study. Two participants receiving zilucoplan during the open-label extension experienced events of herpes zoster and sinusitis, which were related to treatment. Mild and moderate injection site reactions were reported in 5 participants (3 in the zilucoplan group and 2 in the placebo group) in the main study and 4 participants during the open-label extension. Of these, most were treatment related (2/3 in the zilucoplan and 1/2 in the placebo group [1 participant experienced two related injection site events] in the main study and 3/4 in the open-label extension).

Open label extension safety

In the open-label extension part of the study no unexpected safety findings were reported or observed.

Discussion

In this study, C5 inhibition as a potential treatment in participants with IMNM was tested based on the hypothesis that classical complement pathway activation has a primary pathogenic role in the disease. Sustained, complete inhibition of the terminal complement pathway, was confirmed in all participants on active treatment in the double-blind period, confirming that the intended pharmacologic effect of zilucoplan administration was achieved. Daily SC self-injection of zilucoplan was well tolerated in study participants, in line with prior data in research trials in generalised myasthenia gravis.(10)

Unexpectedly, terminal complement pathway inhibition did not show an effect on either CK levels or clinical symptoms in this study. The lack of a demonstrable effect on laboratory and clinical markers of disease within a timeframe when other therapeutics such as glucocorticoids or IVIg are known to have an effect (14) suggests that complement activation may not be the primary pathomechanistic driver for disease activity in this participant population. In a recent humanized mouse model, blocking complement activation through C5 inhibition by zilucoplan protected mice from IMNM onset whereas therapeutic administration of zilucoplan following disease onset failed to significantly restore muscle strength.(8) This model also demonstrated reduced C5b9 deposits on myofibers. In combination, these preclinical and clinical findings contradict the current hypothesis that MAC deposition via the classical complement pathway activation through anti-HMGCR or anti-SRP antibodies drives the histopathological hallmark of the disease, (7, 19) and are more consistent with in vitro data showing that anti-SRP or HMGCR autoantibodies induce muscle fibre atrophy and impair myoblast fusion in complement independent mechanisms.(20)

Thus, the results of our study provide insight into the pathophysiology of IMNM in that, based on the inability of complement inhibition to reduce disease activity, the prominent presence of complement components in muscle tissue appears to be reactive rather than to cause the necrotic process. Whether or not anti-HMGCR and anti-SRP autoantibodies may be pathogenic via a non-complement mediated mechanism or are just a hallmark of the disease with no relevance to its pathobiology remains to be explored further.

In the absence of prior clinical studies in IMNM, we developed an efficient study design for evaluating a potential treatment effect in these participants. Our study allowed us to obtain results in a small number of participants over a short period of time in a placebo-controlled setting as is essential in a severe, rare disease such as IMNM. This was possible with the selection of CK as the primary endpoint, using a high threshold of 80% reduction of CK levels over the 8–week study period, in line with expectations for a treatment effect above the currently available treatment options for these participants.(14) Moreover, we identified the ACR/EULAR scale (21) as a suitable option for clinical assessment in this population, though as the study was designed to be double–blinded, CK readouts along with ALT and AST could not be provided to sites. This study design not only helped us answer the important question of whether complement inhibition is a potential treatment for IMNM participants but should also serve as a starting point for future studies on this disease.

There are a number of potential limitations of our study. The majority of study participants had previously received other treatments for IMNM, including glucocorticoids and IVIg, therefore the results may not be generalizable to treatment-naïve patients with IMNM. The study duration may not have been sufficient to allow for an effect of complement inhibition on the chosen endpoints. The chosen endpoints, notably CK, may not be sensitive to the effect of complement inhibition, though they respond well to glucocorticoids and IVIg treatment. The participants included may have been a group of participants who do not respond to complement inhibition or may have been too far advanced in the course of the disease to respond to C5 inhibition.

Despite these caveats, and although the results are disappointing from the clinical perspective, our study provides valuable insight into the pathophysiology of IMNM, may support evidence-based treatment decisions in the future, and is paving a way for future clinical trials in IMNM using an efficient study design.

Contributors

Study concept and Design: ALM, AAA, MD, BB, RFF, PWD, OB

Acquisition, analysis, or interpretation of data: ALM, AAA, MD, HC, YH, JL, IPF, YA, BB, MV, ED, HK, RFF, PWD, CS, OB

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Statistical analysis: ED

All authors had full access to the data in the study and had final responsibility for the decision to submit for the manuscript publication.

Declaration of interests

ALM is a patent author for the anti-HMGCR test.

AAA has participated in medical advisory boards/acted as a consultant for Argenx, Ra Pharmaceuticals, Alexion, EMD Serono, OnoPharma, Horizon Therapeutics, Takeda, Johnson & Johnson (COVID-19 vaccination program)

MD has served or recently served as a consultant for Amazentis, ArgenX, Catalyst, Cello, Covance/Labcorp, CSL-Behring, EcoR1, Janssen, Kezar, Medlink, Momenta, NuFactor, Octapharma, RaPharma/UCB, Roivant Sciences Inc, RMS Medical, Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, Abata/Third Rock, UCB Biopharma, and UpToDate. Dr. Dimachkie received research grants or contracts or educational grants from Alexion, Alnylam Pharmaceuticals, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, Corbus, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Kezar, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, UCB Biopharma / RaPharma, Viromed/Healixmith & TMA.

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BB, HK, PWD, CS* and OB are employees and stockholders of UCB Pharma

IPF and YH have no competing interests to declare

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Data sharing

Underlying data from this manuscript may be requested by qualified researchers six months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymised individual patient-level data and redacted trial documents which may include: analysis-ready datasets, study protocol, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password-protected portal.

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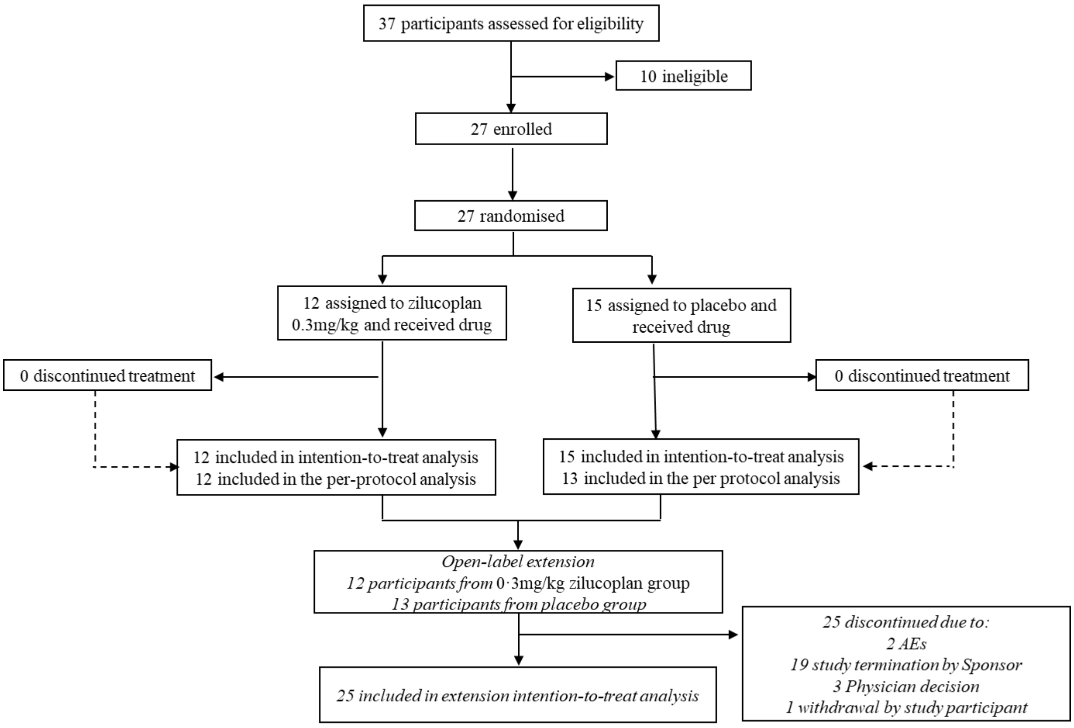
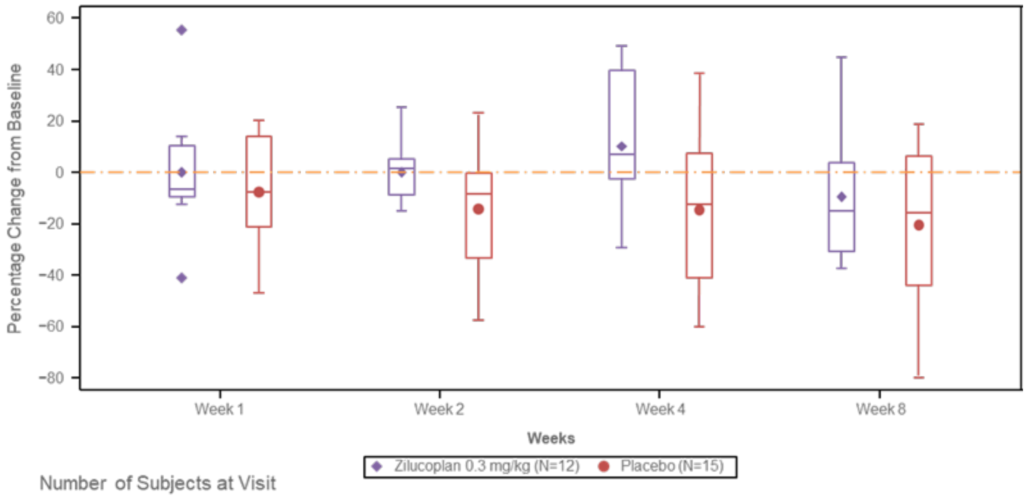
Figures

Figure 1. Study disposition



AEs, adverse events

Figure 2. Percent changes in Creatine Kinase Levels from Baseline to Week 8 (ITT population)



Number of Subjects at Visit				
Zilucoplan:	11	9	11	10
Placebo:	15	15	14	14
p-value:			0.048	0.464

Figure 3. Individual CK Levels (U/L) Over the Main Study Period (ITT population)

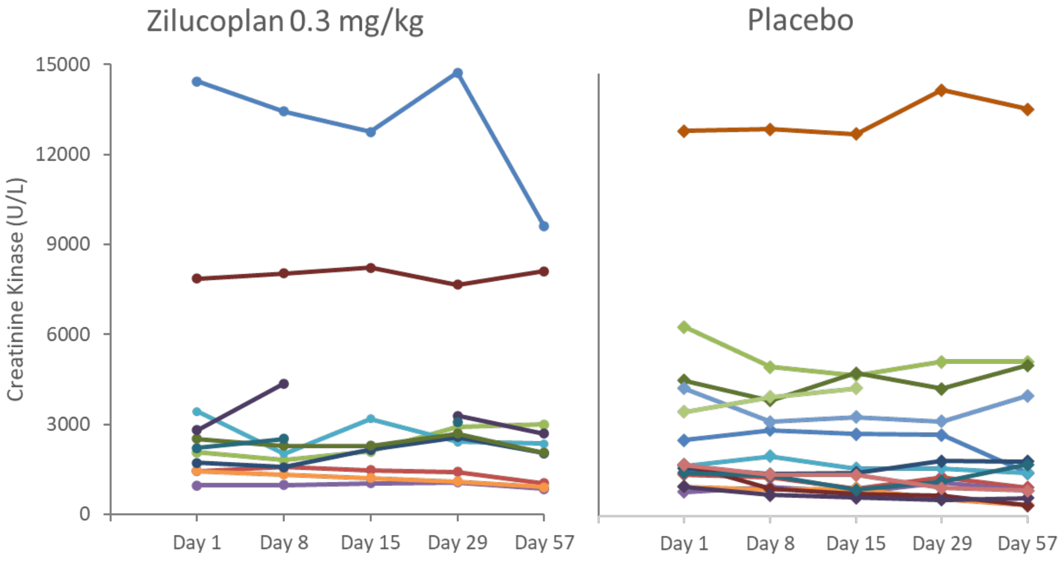
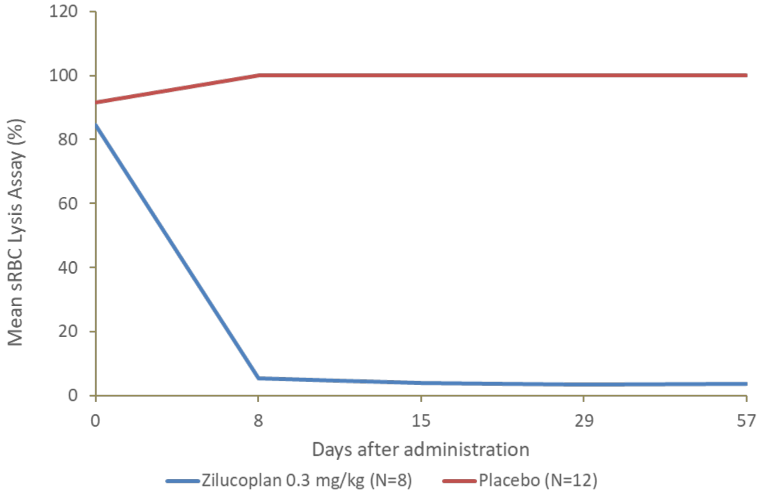


Figure 4. Mean complement inhibition levels, based on sRBC lysis assay in the main study period (PD-PPS population)



Tables

Table 1. Demographics and Baseline Characteristics (ITT population)

		Zilucoplan 0·3mg/kg N=12	Placebo N=15	All Participants N=27
Age (years)				
	Mean (SD)	56·9 (9·0)	52·8 (13·6)	54·6 (11·8)
Sex				
F	n (%)	6 (50·0)	7 (46·7)	13 (48·1)
M	n (%)	6 (50·0)	8 (53·3)	14 (51·9)
Weight (kg)				
	Mean (SD)	81·1 (17·5)	91·5 (27·1)	86·9 (23·5)
Countries				
France	n (%)	2 (16·7)	2 (13·3)	4(14·8)
United Kingdom	n (%)	2 (16·7)	2 (13·3)	4 (14·8)
Netherlands	n (%)	0	1(6·7)	1 (3·7)
United States	n (%)	8 (66·7)	10 (66·7)	18 (66·7)
Months since Initial Diagnosis*	n	12	14	26
	Mean (SD)	35·6 (35·2)	21·5 (24·1)	28·0 (30·0)
Age at Initial IMNM Diagnosis (years)†	n	12	14	26
	Mean (SD)	54·2 (9·8)	52·2 (13·9)	53·1 (12·0)
HMGCR/SRP Antibodies				
Positive/Negative	n (%)	10 (83·3)	11 (73·3)	21 (77·8)
Negative/Positive	n (%)	2 (16·7)	4 (26·7)	6 (22·2)
Muscle Biopsy performed				
Y	n (%)	11 (91·7)	15 (100)	26 (96.3)
Complement C5b-9 or C9 staining performed	n (%)	4 (33·3)	5 (33·3)	9 (33·.3)
Positive	n (%)	3 (25.0)	5 (33.3)	8 (29·6)
Negative	n (%)	1 (8.3)	0	1 (3·7)
IMNM Treatment history				
Any medication received for IMNM	n (%)	11 (91·7)	14 (93·3)	25 (92·6)
Prednisone	n (%)	11 (91·7)	11 (73·3)	22 (81·5)
Methotrexate	n (%)	8 (66·7)	7 (46.7)	15 (55.6)
Azathioprine	n (%)	3 (25·0)	3 (20·0)	6 (22·2)
Mycophenolate mofetil	n (%)	2 (16·7)	3 (20·0)	5 (18·5)
Cyclophosphamide	n (%)	1 (8·3)	1 (6·7)	2 (7·4)
Cyclosporine	n (%)	0	0	0
Tacrolimus	n (%)	0	0	0
Rituximab	n (%)	3 (25·0)	6 (40·0)	9 (33·3)
Plasma Exchange	n (%)	2 (16·7)	3 (20·0)	5 (18·5)
Intravenous immunoglobulin	n (%)	9 (75·0)	10 (66·7)	19 (70·4)
Other	n (%)	1 (8·3)	3 (20·0)	4 (14·8)

HMGCR=3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, IMNM=Immune mediated necrotizing myopathy, SD= standard deviation, SRP=signal recognition particle. *Months since initial diagnosis was calculated as: (Date of Randomization – Date of Initial IMNM Diagnosis + 1)/30.5. ‡Age at initial diagnosis was calculated as: Year of Initial IMNM Diagnosis - Year of Birth.

Table 2. Changes in Creatine Kinase Levels from Baseline to Week 8 (ITT population)

	Zilucoplan 0·3mg/kg N=12	**Placebo N=15**
	n=10	**n=14**
Mean percent change from baseline (SD) *	-9·9 (26·1)	-20·7 (31·2)
Median (Min, Max)	-15·1 (-37·3, 44·5)	-16.3 (-80·0, 18·2)
Stratified†		
p-value‡		0·464
Wilcoxon-Mann-Whitney odds		0·55
95% CI		0·19, 1·57

CI=confidence interval, Max=maximum, Min=minimum, SD=standard deviation.
*Week 8 CK values were not available for 3 participants (two in the zilucoplan arm and one in the placebo arm)
†Primary efficacy analysis.
‡Based on a 2-sided Van Elteren test.

Table 3. Summary of treatment-emergent adverse events (safety analysis population)

	Zilucoplan 0·3mg/kg N=12 n (%)*	**Placebo N=15 n (%)***
Any TEAE	9 (75·0)	13 (86·7)
Most Frequent TEAE†		
Headache	4 (33·3)	4 (26·7)
Nausea	3 (25·0)	3 (20·0)
Serious TEAE	0	3 (20·0)
TEAE Resulting in Permanent Withdrawal from Study Medication	0	0
Treatment-related TEAE	4 (33·3)	5 (33·3)
Headache	2 (16·7)	2 (13·3)
Nausea	2 (16·7)	1 (6·7)
Vertigo	0	2 (13·3)
Treatment Related Serious TEAE	0	0
Deaths (TEAEs leading to death)	0	0

TEAE=treatment-emergent adverse event. *n=number of participants reporting at least one TEAE in that category; †TEAEs reported in >2 participants in either treatment group.

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Supplementary Appendix

Contents

Complete Inclusion and Exclusion Criteria

In order to be considered eligible for this study, all of the following criteria must have been met:

1. Male or female ≥18 years and <75 years.

2. Were able to provide informed consent, including signing and dating the ICF.

3. Clinical diagnosis of IMNM.

4. Positive serology for anti-HMGCR or anti-SRP autoantibodies.

5. Clinical evidence of weakness (≤Grade 4 out of 5) on manual muscle testing (MMT) in at least 1 proximal limb muscle group.

6. Creatine kinase of >1000U/L at Screening.

7. No change in corticosteroid dose for at least 30 days prior to Baseline or anticipated to occur during the first 8-weeks on study.

8. No changes in immunosuppressive therapy, including dose, for at least 30 days prior to Baseline or anticipated to occur during the first 8-weeks on study.

9. Female study participants of childbearing potential must have had a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of the IMP.

10. Sexually active female study participants of childbearing potential (ie, women who were not postmenopausal or who had not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male study participants (who had not been surgically sterilized by vasectomy) must have agreed to use effective contraception during the study. Postmenopausal women were defined as women who had gone 12 consecutive months without menstruation.

Study participants who met any of the following exclusion criteria were ineligible for participation in the study:

1. History of meningococcal disease.

2. Current or recent systemic infection within 2 weeks prior to Screening or infection requiring intravenous antibiotics within 4 weeks prior to Screening.

3. Pregnant, planning to become pregnant, or nursing female study participants.

4. Recent surgery requiring general anesthesia within 2 weeks prior to Screening or expected to have surgery requiring general anesthesia during the 8-week Treatment Period.

5. Treatment with a complement inhibitor or an experimental drug within 30 days or 5 half-lives of the drug (whichever was longer) prior to Baseline.

6. Statin use within 30 days prior to Baseline or anticipated to occur during study.

7. Rituximab use within 90 days prior to Baseline or anticipated to occur during study. NOTE: For study participants who received rituximab more than 90 days but less than 6 months prior to Baseline, prophylactic antibiotics (eg, ciprofloxacin, erythromycin, penicillin V) were given upon initiation of IMP until 6 months after the last rituximab dose.

8. Recent initiation of IVIG (ie, first cycle administered less than 90 days prior to Baseline).

9. Plasma exchange within 4 weeks prior to Baseline or expected to occur during the 8-week Treatment Period.

10. Active malignancy (except curatively resected squamous or basal cell carcinoma of the skin) requiring surgery, chemotherapy, or radiation within the prior 12 months (study participants with a history of malignancy who underwent curative resection or otherwise did not require treatment for at least 12 months prior to Screening with no detectable recurrence were allowed).

11. History of any significant medical, psychiatric disorder, or laboratory abnormality that in the opinion of the Investigator made the study participant unsuitable for participation in the study.

12. Participation in another concurrent clinical trial involving an experimental therapeutic intervention (participation in observational studies and/or registry studies was permitted).

13. Were unable or unwilling to comply with the requirements of the study.

14. Study participants who had a known hypersensitivity to ZLP or any of its excipients (as per

Inclusion criteria for the Extension Portion of the study

1. Completion of the Main Portion of the study.

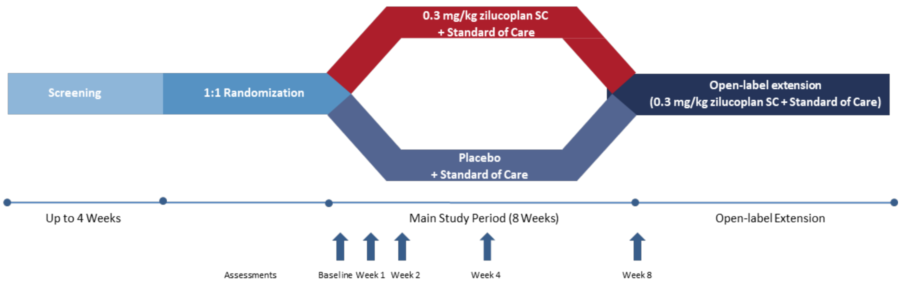
2. Continued to meet inclusion criteria 2, 9, and 10, from the Main Portion of the study.

3. Did not start any disallowed medication per the exclusion criteria from the Main Portion of the study or alter the dose of any other concomitant medication, unless medically indicated.

4. Were able and willing to comply with the requirements of the study.

5. Did not have any new medical condition (since entry into the Main Portion) or any other reason that, in the opinion of the Investigator or Sponsor, disqualified the study participant from participation in the Extension Portion of the study.

Figure S1: IMNM 01 Study Design



SC, subcutaneous.

Table S1. Change from baseline to Week 8 in secondary endpoints (ITT population)

	ZLP 0·3mg/kg N=12	PBO N=15
ACR/EULAR Total Improvement Score		
N	11	14
Responder*, n (%)	6 (54·5)	7 (50·0)
Non-responder, n (%)	5 (45·5)	7 (50·0)
Odds ratio vs placebo* (95% CI)	1·088 (0·214, 5·535)	
p-value†	0·919	
Triple Timed Up and Go test		
N	10	10
Baseline mean	12·8	11·6
LS mean change (SE) at Week 8	-1·401 (0·788)	-0·712 (0·789)
LS mean difference (95% CI)	-0·688 (-2·781, 1·404)	
p-value‡	0·496	
Proximal MMT		
N	11	14
Baseline mean	115·3	99·5
LS mean change (SE) at Week 8	3·71 (3·81)	-0·18 (3·44)
LS mean difference (95% CI)	3·89 (-6.18, 13·95)	
p-value‡	0·431	
Physician Global Activity VAS		
N	11	15
Baseline mean	4·48	4.89
LS mean change (SE) at Week 8	-0·830 (0·671)	-0·626 (0·557)
LS mean difference (95% CI)	-0·204 (-1·855, 1·448)	
p-value‡	0·800	
Patient Global Activity VAS		
N	11	15
Baseline mean	5·94	6·71
LS mean change (SE) at Week 8	-1·966 (0·854)	-0·685 (0·707)
LS mean difference (95% CI)	-1·281 (-3·390, 0·829)	
p-value‡	0·221	
HAQ		
N	11	15
Baseline mean	1·19	1·55
LS mean change (SE) at Week 8	-0.125 (0.183)	0·022 (0·151)
LS mean difference (95% CI)	-0·147 (-0·601, 0·307)	
p-value‡	0·508	
MDAAT		
N	11	15
Baseline mean	0·55	0·73
LS mean change (SE) at Week 8	-0·287 (0·398)	-0·144 (0·336)
LS mean difference (95% CI)	-0·143 (-1·123, 0·837)	
p-value‡	0·765	
FACIT-Fatigue scale		
N	11	15
Baseline mean	27·8	27·1
LS mean change (SE) at Week 8	8·98 (4·08)	3·45 (3·41)
LS mean difference (95% CI)	5·53 (-4·49, 15·55)	
p-value‡	0·265	

ACR=American College of Rheumatology, CI=confidence interval, EULAR=European League Against Rheumatism, LS=least square, Max=maximum, Min=minimum, SD=standard deviation, SE=standard error.
[*]Threshold of 20 in the ACR/EULAR corresponds to a minimal response based on the criterion scale

[†]P-values for the comparison of treatment groups have been calculated using logistic regression with IMP and strata as fixed factors.

[‡]Based on a linear model with treatment and strata (anti-HMGCR+/anti-SRP+) as fixed factors with baseline Triple Timed Up and Go, baseline proximal MMT, baseline Physician Global Activity Visual Analogue Scale, Patient Global Activity Visual Analogue Scale, baseline Health Assessment Questionnaire, baseline MDAAT or baseline FACIT-Fatigue Scale as a covariate

Table S2. Subgroup analysis (Sex, age and stratification factor, ITT population)

	ZLP 0·3mg/kg N=12	PBO N=15	ZLP 0·3mg/kg N=12	PBO N=15	ZLP 0·3mg/kg N=12	PBO N=15	ZLP 0·3mg/kg N=12	PBO N=15	ZLP 0·3mg/kg N=12	PBO N=15	ZLP 0·3mg/kg N=12	PBO N=15
	Sex Female		Sex Male		Age <55 years		Age ≥55 years		Anti-HMGCR+		Anti-SRP+	
Percentage change from baseline in CK levels[*]												
N	6	5	6	8	3	7	8	7	9	10	2	4
Week 4 Mean percent change from baseline (SD)	21·2 (18·7)	-10·1 (27·0)	0·41 (27·9)	-17·7 (29·3)	7·6 (-)	-2·0 (26·4)	10·7 (22·8)	-26·8 (24·2)	13·5 (25·6)	-19·3 (23·4)	-6·7 (-)	-2·3 (36·9)
N	6	4	6	8	3	7	7	7	8	10	2	4
Week 8 Mean percent change from baseline (SD)	0·16 (31·3)	-17·1 (27·7)	-16·6 (22·4)	-23·5 (35·2)	-5·4 (-)	-18·0 (22·2)	-11·8 (27·1)	-23·5 (40·0)	-6·2 (27·4)	-24·2 (32·8)	-24·5 (-)	-11·9 (29·2)
ACR/EULAR Response Criteria Scale, TIS ≥20 at Week 4 and Week 8[†]												
N	6	5	6	7	3	6	9	6	10	9	2	3
Week 4 responder, n (%)	3 (50%)	3 (60%)	4 (67%)	3 (43%)	2 (67%)	2 (33%)	5 (56%)	4 (67%)	5 (50%)	5 (56%)	2 (100%)	1 (33%)
N	5	6	6	8	3	7	8	7	9	10	2	4
Week 8 responder, n (%)	2 (40%)	3 (50%)	4 (67%)	4 (50%)	2 (67%)	5 (71%)	4 (50%)	2 (29%)	5 (56%)	6 (60%)	1 (50%)	1 (25%)
Change from baseline in 3TUG[‡]												
N	4	4	6	5	3	3	7	6	8	8	2	1
Week 4 Mean percent change from baseline (SD)	-0·43 (2·9)	0.68 (0·97)	-0·98 (1·8)	0·18 (1·7)	-2·1 (-)	0·63 (-)	-0·19 (-2·1)	0·28 (1·4)	-0·65 (2·4)	0·45 (1·4)	-1·2 (-)	0
N	4	4	6	6	3	3	7	7	8	8	2	2
Week 8 Mean percent change from baseline (SD)	-1·7 (2·7)	-0·05 (1·2)	-0·62 (2·6)	-0·50 (2·0)	-2·4 (-)	0·13 (-)	-0·44 (2·7)	-0·51 (1·4)	-0·88 (2·8)	0·01 (1·5)	-1·7 (-)	-1·7 (-)
Change from baseline in proximal MMT[‡]												
N	6	5	6	7	3	6	9	6	10	9	2	3
Week 4 Mean percent change from baseline (SD)	1·3 (15·5)	3·4 (5·8)	7·8 (9·4)	5·4 (2·4)	7·0 (-)	3·3 (4·6)	3·8 (13·7)	5·8 (3·4)	5·6 (13.8))	6·1 (3·1)	-0·5 (-)	0
N	5	6	6	8	3	7	8	7	9	10	2	4

Week 8 Mean percent change from baseline (SD)	2·2 (16·6)	10·2 (13·2)	8·3 (12·7)	-0·13 (7·0)	10·3 (-)	8·3 (13·0)	3·8 (14·4)	0·29 (7·5)	7·1 (15·1)	6·6 (11·1)	-1·5 (-)	-1·5 (9·5)
Change from baseline in Physician global activity VAS‡												
N	6	6	6	8	3	7	9	7	10	10	2	4
Week 4 Mean percent change from baseline (SD)	-1·5 (1·3)	-1·6 (1·3)	-1·3 (1·9)	-0·51 (1·1)	-1·5 (-)	-1·3 (1·6)	-1·3 (1·2)	-0·67 (0·95)	-1·4 (1·7)	-1·2 (1·2)	-1·3 (-)	-0·55 (1·6)
N	5	7	6	8	3	7	8	8	9	11	2	4
Week 8 Mean percent change from baseline (SD)	-1·1 (2·3)	-1·5 (2·0)	-1·3 (2·8)	-0·54 (1·2)	-1·1 (-)	-1·3 (2·3)	-1·3 (2·0)	-0·69 (0·87)	-1·5 (2·3)	-1·3 (1·7)	0·05 (-)	0·03 (1.3)
Change from baseline in Patient global activity VAS‡												
N	6	6	6	8	3	7	9	7	10	10	2	4
Week 4 Mean percent change from baseline (SD)	-1·3 (1·1)	-1·7 (1·4)	-2·3 (2·4)	1·3 (2·0)	-3·4 (-)	0·41 (2·8)	-1·2 (1·8)	-0·39 (1·8)	-1·7 (2·0)	-0·15 (2·5)	-2·3 (-)	0·43 (2.0)
N	5	7	6	8	3	7	8	8	9	11	2	4
Week 8 Mean percent change from baseline (SD)	-1·3 (1·3)	-1·6 (2·5)	-2·4 (4·0)	-0·16 (1·4)	-4·7 (-)	-0·89 (2·9)	-0·86 (2·2)	-0·75 (1·2)	-2·0 (3·3)	-0·84 (2·1)	-1·4 (-)	-0·75 (2·2)
Change from baseline in HAQ[c]												
N	6	6	6	8	3	7	9	7	10	10	2	4
Week 4 Mean percent change from baseline (SD)	-0·13 (0·41)	-0·25 (0·37)	-0·38 (0·68)	-0·09 (0·50)	-0·83 (-)	-0·36 (0·33)	-0·06 (0·35)	0·04 (0·47)	-0·25 (0·60)	-0·29 (0·33)	-0·25 (-)	0·16 (0·56)
N	5	7	6	8	3	7	8	8	9	11	2	4
Week 8 Mean percent change from baseline (SD)	-0·10 (0·64)	-0·18 (0·79)	-0·31 (0·55)	-0·03 (0·33)	-0·67 (-)	-0·25 (0·76)	-0·05 (0·50)	0·03 (0·33)	-0·25 (0·63)	-0·25 (0·58)	0·06 (-)	0·31 (0·33)
Change from baseline in MDAAT Extramuscular Disease Activity Score‡												
N	6	6	6	8	3	7	9	7	10	10	2	4
Week 4 Mean percent change from baseline (SD)	-0·22 (0·33)	-0·40 (1·1)	-0·45 (0·95)	0·26 (0·53)	-0·50 (-)	-0·03 (1·2)	0·28 (0·38)	-0·01 (0·21)	-0·33 (0·73)	0·09 (0·36)	-0·35 (-)	-0·30 (1·6)
N	5	7	6	8	3	7	8	8	9	11	2	4
Week 8 Mean percent change from baseline (SD)	-0·24 (0·37)	-0·34 (2·0)	0·02 (1·6)	0·14 (0·41)	-0·70 (-)	-0·46 (1·8)	0·13 (0·96)	0·24 (0.92))	-0·06 (1·24)	0·20 (0·77)	-0·30 (-)	-0·88 (2·4)
Change from baseline in FACIT-Fatigue Scale[c]												

N	6	6	6	7	3	7	9	6	10	10	2	3
Week 4 Mean percent change from baseline (SD)	7·7 (7·8)	7·7 (7·3)	9·7 (14·4)	5·0 (5·7)	20·7 (-)	4·6 (5·4)	4·7 (7·8)	8·2 (7·3)	8·6 (12·3)	8·0 (5·6)	9·0 (-)	0·33 (-)
N	5	7	6	8	3	7	8	8	9	11	2	4
Week 8 Mean percent change from baseline (SD)	3·3 (16·3)	3·3 (10·9)	13·8 (17·5)	4·1 (7·1)	27·0 (-)	3·0 (7·7)	2·3 (12·5)	4·4 (10·1)	8·6 (19·0)	3·6 (10·1)	11·0 (-)	4·3 (4·0)

[*]The percentage change from baseline of CK levels was defined as %CHG = 100 x (Post Baseline - Baseline) / Baseline; Baseline during the Main Portion was defined as the closest non-missing value obtained prior to the first study drug administration; Baseline mean was defined as the Baseline results for those participants who were also assessed at the specified visit.

[†]Percentages are based on the number of participants with a non-missing result at the specific visit. A total improvement score of >=20 represents Minimal Improvement, a score of >=40 represents Moderate Improvement, and a score of >=60 represents Major Improvement.

[‡]The change from baseline is defined as CHG = Post Baseline - Baseline. Baseline during the Main Portion was defined as the closest non-missing value obtained prior to the first study drug administration. Baseline mean was defined as the Baseline results for those participants who were also assessed at the specified visit.

ACR=American College of Rheumatology, CI=confidence interval, CHG= change from baseline, CK=creatinine kinase, EULAR=European League Against Rheumatism, FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy, HAQ=health assessment questionnaire, LS=least square, Max=maximum, MDAAT=myositis disease activity assessment tool, Min=minimum, MMT=manual muscle testing, SD=standard deviation, SE=standard error, 3TUG=triple timed up and go test, VAS=visual analogue scale.

Table S3. List of Investigators

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