Safety and efficacy of intravenous bimagrumab in inclusion body myositis (RESILIENT): a randomised, double-blind, placebo-controlled phase 2b trial

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Summary

Background Inclusion body myositis is an idiopathic inflammatory myopathy and the most common myopathy affecting people older than 50 years. To date, there are no effective drug treatments. We aimed to assess the safety, efficacy, and tolerability of bimagrumab—a fully human monoclonal antibody—in individuals with inclusion body myositis.

Methods We did a multicentre, double-blind, placebo-controlled study (RESILIENT) at 38 academic clinical sites in Australia, Europe, Japan, and the USA. Individuals (aged 36–85 years) were eligible for the study if they met modified 2010 Medical Research Council criteria for inclusion body myositis. We randomly assigned participants (1:1:1:1) using a blocked randomisation schedule (block size of four) to either bimagrumab (10 mg/kg, 3 mg/kg, or 1 mg/kg) or placebo matched in appearance to bimagrumab, administered as intravenous infusions every 4 weeks for at least 48 weeks. All study participants, the funder, investigators, site personnel, and people doing assessments were masked to treatment assignment. The primary outcome measure was 6-min walking distance (6MWD), which was assessed at week 52 in the primary analysis population and analysed by intention-to-treat principles. We used a multivariate normal repeated measures model to analyse data for 6MWD. Safety was assessed by recording adverse events and by electrocardiography, echocardiography, haematological testing, urinalysis, and blood chemistry. This trial is registered with ClinicalTrials.gov, number NCT01925209; this report represents the final analysis.

Findings Between Sept 26, 2013, and Jan 6, 2016, 251 participants were enrolled to the study, of whom 63 were assigned to each bimagrumab group and 62 were allocated to the placebo group. At week 52, 6MWD change from baseline did not differ between any bimagrumab dose and placebo (least squares mean treatment difference for bimagrumab 10 mg/kg group, 17·6 m, SE 14·3, 99% CI –19·6 to 54·8; p=0·22; for 3 mg/kg group, 18·6 m, 14·2, –18·2 to 55·4; p=0·19; and for 1 mg/kg group, –1·3 m, 14·1, –38·0 to 35·4; p=0·93). 63 (100%) participants in each bimagrumab group and 61 (98%) of 62 in the placebo group had at least one adverse event. Falls were the most frequent adverse event (48 [76%] in the bimagrumab 10 mg/kg group, 55 [87%] in the 3 mg/kg group, 54 [86%] in the 1 mg/kg group, and 52 [84%] in the placebo group). The most frequently reported adverse events with bimagrumab were muscle spasms (32 [51%] in the bimagrumab 10 mg/kg group, 43 [68%] in the 3 mg/kg group, 25 [40%] in the 1 mg/kg group, and 13 [21%] in the placebo group) and diarrhoea (33 [52%], 28 [44%], 20 [32%], and 11 [18%], respectively). Adverse events leading to discontinuation were reported in four (6%) participants in each bimagrumab group compared with one (2%) participant in the placebo group. At least one serious adverse event was reported by 21 (33%) participants in the 10 mg/kg group, 11 (17%) in the 3 mg/kg group, 20 (32%) in the 1 mg/kg group, and 20 (32%) in the placebo group. No significant adverse cardiac effects were recorded on electrocardiography or echocardiography. Two deaths were reported during the study, one attributable to subendocardial myocardial infarction (secondary to gastrointestinal bleeding after an intentional overdose of concomitant sedatives and antidepressants) and one attributable to lung adenocarcinoma. Neither death was considered by the investigator to be related to bimagrumab.

Interpretation Bimagrumab showed a good safety profile, relative to placebo, in individuals with inclusion body myositis but did not improve 6MWD. The strengths of our study are that, to the best of our knowledge, it is the largest randomised controlled trial done in people with inclusion body myositis, and it provides important natural history data over 12 months.

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Research in context

Evidence before this study

We searched PubMed for randomised clinical studies of inclusion body myositis published up to Sept 11, 2018, using the term "inclusion body myositis", with no language restrictions. We identified nine randomised controlled trials. The duration of intervention varied from 3 months to 17 months. One very small trial of oxandrolone suggested positive results, but this work has not been repeated. Other larger trials reported no improvement with methotrexate, intravenous immunoglobulin, etanercept, or interferon-beta. Currently, no evidence is available to support any specific treatment in clinical practice. To date, there are no effective or approved treatment options for inclusion body myositis.

Added value of this study

RESILIENT is, to the best of our knowledge, the first phase 2b clinical study of a myostatin inhibitor in adults, and it is the largest randomised controlled study in inclusion body myositis and in any idiopathic inflammatory myopathy.

Implications of all the available evidence

RESILIENT did not meet its primary endpoint, which was an improvement in the 6-min walk distance (6MWD) test at week 52. Among the secondary endpoints, there was no effect in isometric muscle strength, as measured by quadriceps quantitative muscle testing, dynamometer measurements, number of falls, swallowing function, or short physical performance battery, but a positive effect was noted in lean body mass and self-reported physical function, as assessed by sporadic inclusion body myositis physical functioning assessment. The large number of participants in RESILIENT helps us to better understand the natural history of inclusion body myositis over 1 year, which will assist in powering future clinical trials of this disorder. Furthermore, the problems we had with the 6MWD test in this population might lead to better primary outcome measures being implemented in future trials.

Introduction

Inclusion body myositis is an idiopathic inflammatory myopathy and the most common myopathy affecting people older than 50 years. It is characterised by slowly progressive asymmetric muscle weakness and atrophy of the proximal and distal muscle groups, mainly quadriceps and deep finger flexors.[1–3] Results of a systematic review and meta-analysis in people of all ages showed that the pooled meta-prevalence of inclusion body myositis was 24·8 (95% CI 20·0–29·6) per million when the analysis was restricted to the highest quality prevalence papers (data obtained from nine reports).[4] Inclusion body myositis affects men two to three times more often than women.[5] Progression of leg weakness can cause frequent falls[6] and loss of ambulation, leading to use of assistive devices for mobility and eventual wheelchair dependence.[1,2] Progressive loss of hand function reduces activities of daily living, and dysphagia can result in choking, weight loss, aspiration, and pneumonia.[6] Reviews of inclusion body myositis provide understanding of pathogenesis of this disease and effective therapeutic targets.[7–11] To date, no effective drug treatments are available for inclusion body myositis.[12] However, treatments that target atrophy pathways in muscle might be effective in this disease. The Inclusion Body Myositis Guideline Development Group have developed a protocol to produce best practice clinical guidelines for inclusion body myositis.[13]

Myostatin belongs to the transforming growth factor β family and is an endogenous negative regulator of the skeletal muscle mass.[14] Although several strategies involving myostatin inhibition are currently being investigated for treatment of inclusion body myositis,[15] blockade of myostatin binding to activin type 2 receptors by the receptor-neutralising antibody bimagrumab represents a novel approach for the treatment of such muscle-wasting disorders. Bimagrumab is a novel, fully human, monoclonal antibody that binds competitively to activin type 2 receptors with greater affinity than the natural ligands activin and myostatin, which usually function to limit muscle mass growth.[16] SMAD2 phosphorylation, which is activated downstream of activin type 2 receptors, is increased in muscle tissue of people with inclusion body myositis relative to other muscle diseases, indicating enhanced signalling via this receptor.[17,18] Results of a preclinical study in mice showed that blockade of activin type 2 receptors with bimagrumab increased bodyweight and led to striking skeletal muscle hypertrophy.[16] A proof-of-concept study in 14 participants with inclusion body myositis (11 received active treatment and three received matching placebo) showed that one intravenous dose of bimagrumab 30 mg/kg improved thigh muscle volume—measured by muscle imaging and lean body mass at 8 weeks and 6-minute walk distance (6MWD) at 16 weeks—versus placebo.[18]

RESILIENT is a randomised, double-blind, phase 2b study to assess the safety, efficacy, and tolerability of intravenous bimagrumab. We assessed three dosing regimens (10 mg/kg, 3 mg/kg, and 1 mg/kg administered every 4 weeks), which are doses lower than that used in the proof-of-concept study.[18] We selected 10 mg/kg as the highest dose because we expected—based on analysis of the exposure–response relation in increasing thigh muscle volume in healthy adults (unpublished data)—that repeated treatment with 10 mg/kg would achieve activity similar to that achieved with a single dose of 30 mg/kg, but with a better safety profile. We investigated whether the designated dosing regimen of bimagrumab would improve lean body mass, muscle strength, physical function, and mobility relative to placebo in participants with sporadic inclusion body myositis after 52 weeks of

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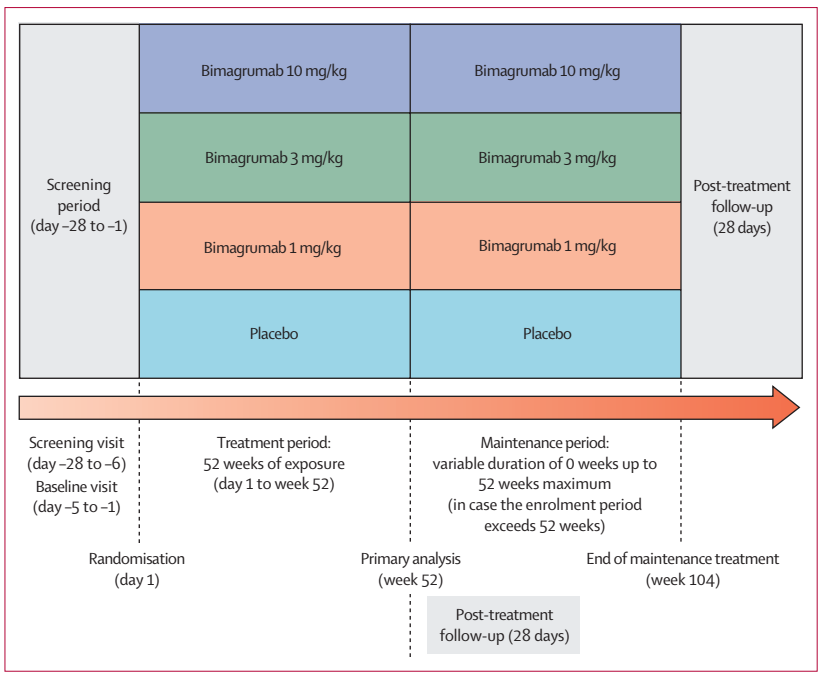

Figure 1: **Study design**

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monthly treatment. Efficacy data beyond 52 weeks of treatment will be presented separately.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled, dose-finding, phase 2b study at 38 academic clinical sites in Australia, Belgium, Denmark, France, Italy, Japan, the Netherlands, Switzerland, the UK, and the USA (appendix pp 1–11). We enrolled men and women (aged 36–85 years) with a pathologically or clinically defined diagnosis of inclusion body myositis, per modified 2010 Medical Research Council (MRC) criteria (appendix pp 97, 98).[19,20] All participants had a biopsy as part of their diagnostic assessment, which was reviewed by the treating clinician. Although we allowed intermittent use of wheelchairs, study participants had to be able to walk at least 1 m without assistance from another individual. Use of assistive aids (eg, canes, walkers, or rollators) during the walking test was permitted. We restricted the proportion of participants who could walk more than 400 m in 6 min to 20%, based on data from an observational study[21] in which the decline in 6MWD in participants with more functional inclusion body myositis (ie, >400 m 6MWD at baseline) was much slower, thus representing a lesser unmet need.

Key exclusion criteria were disorders other than inclusion body myositis that substantially limited the participant's mobility, use of concomitant drugs with an immunomodulatory effect or biological effect on muscle anabolism or catabolism, use of prohibited systemic treatments (within the past 6 months before randomisation) or any treatments known to affect muscle mass (within the past 3 months before randomisation), any active chronic disorder associated with cachexia or muscle atrophy other than inclusion body myositis, severe vitamin D deficiency, and any uncontrolled medical disorder that might limit the ability of the individual to participate in study procedures. We also excluded pregnant women or breastfeeding mothers.

The RESILIENT study comprised a 28-day screening period (days –28 to –1), a 52-week treatment period (day 1 to week 52), a subsequent variable 52-week or shorter maintenance period, and an approximately 28-day treatment-free follow-up period (figure 1). The treatment duration for all participants was ascertained by the last individual to be enrolled completing the 52-week treatment period; once the last participant had received the week 48 dose, no other participants received study treatment.

Members of the RESILIENT Steering Committee (appendix p 11) collaborated with the funder (Novartis Pharma, Basel, Switzerland) to develop the protocol. No protocol amendments were made after the start of the study. The protocol and informed consent form were reviewed and approved by the Institutional Review Board or Independent Ethics Committee at every participating site. Written informed consent was obtained from all participants. The study was done in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice, in compliance with applicable local regulations, and with the ethical principles established in the Declaration of Helsinki.

Randomisation and masking

Eligible participants were randomly assigned (1:1:1:1) to receive either intravenous infusions of bimagrumab (10 mg/kg, 3 mg/kg, or 1 mg/kg) or matching placebo. Participants were assigned a treatment according to a blocked randomisation schedule (block size of four). The randomisation list was created by Cenduit (Durham, NC, USA) and reviewed and approved by Novartis Biostatistics Quality Assurance Group. Randomisation was stratified by geographical region. Within every region, participants were randomised to one of the four treatment arms via an interactive voice response system or interactive web response system. The interactive response technology assigned a randomisation number to the participant, which was used to link the participant to a treatment arm and specify unique medication numbers for packages of the investigational treatment to be prepared for the participant. The funder, participants, investigators, site personnel, and people doing the assessments were unaware of treatment assignments. Study medication was prepared by an independent, non-masked, pharmacist or designee appointed at the study site before administration. The identity of the treatments (bimagrumab or placebo) was concealed by opaque sleeve-covered infusion bags filled with active or placebo solutions identical in appearance, but the actual bimagrumab or placebo vials were

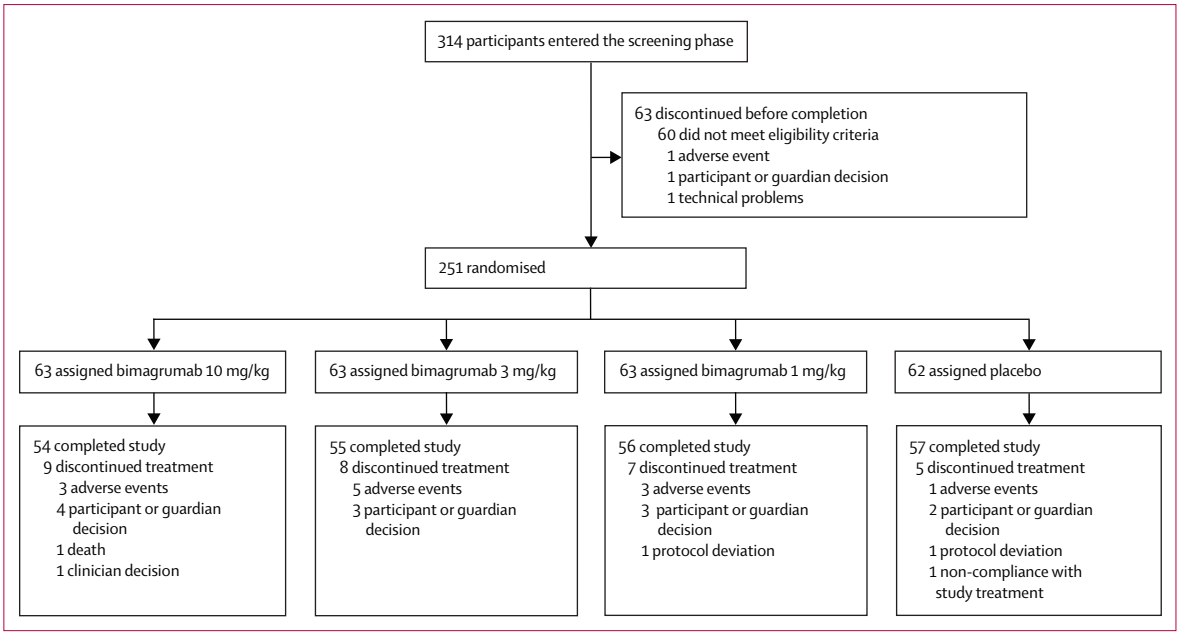

Figure 2: **Trial profile**
One participant was erroneously randomised (assigned to placebo) and was discontinued immediately before receiving study treatment. This participant was re-randomised to bimagrumab 10 mg/kg group and was counted only once in the analysis set.

supplied open-label. To maintain masking, study medication was administered only by study centre personnel who were unaware of treatment assignments. Emergency treatment code breaks were to be done using an interactive voice response system and were only to be done when essential to treat the participant safely and effectively. Study medication was to be discontinued after emergency unmasking.

Procedures

Bimagrumab or matching placebo was administered intravenously every 4 weeks as a slow infusion over a period no shorter than 30 min. The first dose was administered on day 1 and the final dose for the treatment period was given at week 48, defining the minimum treatment duration of 52 weeks. The European Medicines Agency and US Food and Drug Administration (FDA) agreed that 12 months of treatment might be adequate for studies of inclusion body myositis. Participants remained in the study and could receive maintenance treatment (same assigned treatment) until either the last enrolled participant received the week 48 dose or they reached week 104, whichever was shorter.

Scheduled study visits—including safety assessments—took place at screening, baseline, week 2, week 4, every 4 weeks during the treatment and maintenance periods, and after the post-treatment follow-up period. Efficacy assessments took place at screening, baseline, every 12 weeks during the treatment and maintenance periods, and at the end of treatment.

Participants could opt to discontinue the study at any time for any reason. Participants who discontinued the study at any time or who completed the study had an end-of-treatment study visit approximately 4 weeks after their last study dose and a post-treatment follow-up visit 4 weeks after the end-of-treatment visit. The end-of-treatment and follow-up visits were completed for all participants, regardless of whether they completed or discontinued prematurely.

At all monthly study visits, we did a physical examination, monitored vital signs, and did haematological testing, blood chemistry, urinalysis, and falls assessment. We did electrocardiography every 12 weeks and echocardiography at weeks 24 and 48. At screening, baseline, and every 8 weeks, we asked participants to take the 6MWD test and we measured physical performance with the Short Physical Performance Battery (SPPB) and quadriceps strength using portable fixed dynamometry. Lean body mass was measured every 12 weeks.

Participants self-reported their physical function at baseline and every 12 weeks with the Sporadic Inclusion Body Myositis Physical Functioning Assessment (sIFA) score. This test is a self-reported outcome measure specific to inclusion body myositis that is designed to assess clinical progression and physical function from the participant's perspective (appendix pp 12–15). The sIFA score was developed using guidance on self-reported outcomes from the FDA[22] and included item generation based on review of published work, input from key opinion leaders, and in-depth face-to-face interviews with participants. Items in the sIFA score were generated directly from ideas captured during qualitative research. A separate series of in-person cognitive debriefing interviews confirmed the content validity of the sIFA score and

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See **Online** for appendix

	Bimagrumab 10 mg/kg (n=63)	Bimagrumab 3 mg/kg (n=63)	Bimagrumab 1 mg/kg (n=63)	Placebo (n=62)
Age (years)	69 (64–74)	68 (61–73)	69·0 (65–75)	68 (64–75)
Sex				
Men	41 (65%)	42 (67%)	40 (63%)	39 (63%)
Women	22 (35%)	21 (33%)	23 (37%)	23 (37%)
Ethnic origin				
White	53 (84%)	56 (89%)	53 (84%)	57 (92%)
Other	10 (16%)	7 (11%)	10 (16%)	5 (8%)
Time since diagnosis (years)*	5·0 (2·0–8·0)	4·0 (2·0–7·0)	3·0 (2·0–6·0)	3·5 (2·0–7·0)
Disorder defined pathologically by MRC criteria	17 (27%)	21 (33%)	18 (29%)	17 (27%)
Disorder defined clinically by MRC criteria	46 (73%)	42 (67%)	45 (71%)	45 (73%)
6MWD (m)	267·7 (131·1)	291·6 (98·7)	306·3 (119·1)	303·3 (124·4)
Walking aid used in the 6MWD test				
No assistance	23 (37%)	24 (38%)	31 (49%)	35 (56%)
Unilateral assistance	19 (30%)	24 (38%)	18 (29%)	14 (23%)
Bilateral assistance	5 (8%)	2 (3%)	1 (2%)	2 (3%)
Walker	16 (25%)	13 (21%)	13 (21%)	11 (18%)
Muscle strength of the right quadriceps (N)	57·3 (72·8)	72·8 (89·3)	57·7 (54·7)	69·2 (71·6)
Total lean body mass (kg)	38·5 (8·9)	40·4 (9·2)	38·9 (8·9)	39·9 (10·3)
sIFA total score†	60·0 (43·6–68·2)	56·4 (42·7–65·5)	47·7 (36·8–64·6)	51·8 (32·7–70·0)

Data are n (%), median (IQR), or mean (SD). 6MWD=6-min walk distance. MRC=Medical Research Council. sIFA=sporadic inclusion body myositis physical functioning assessment. *Reference date is the screening visit. †Data missing for three participants in the bimagrumab 1 mg/kg group and one participant in the placebo group.

Table 1: **Demographic and baseline characteristics**

the appropriateness and comprehension of the items, instructions, and response options. The sIFA score has been evaluated in three observational studies and shown to have highly satisfactory psychometric properties.[23,24] A comprehensive psychometric analysis of data from the RESILIENT study established the reliability of the sIFA score (internal consistency, α=0·88, 0·90; test–retest 0·85), its responsiveness (effect size 0·22), and the construct validity of the sIFA score in individuals with inclusion body myositis (unpublished data). Items in the sIFA score are rated on an 11-point scale from 0 (no difficulty) to 10 (unable to do) across three domains comprising upper body functioning (eg, "carry a 5-pound object"), lower body functioning (eg, "step up and down sidewalk or street curbs"), and general functioning (eg, "get on and off a toilet").

We used the SPPB to measure participants' physical performance in the clinic. SPPB assesses lower extremity physical function through tests of gait speed, ability to maintain standing balance, and time to rise from a chair five times.

Safety was assessed at scheduled visits and by recording adverse events and serious adverse events throughout the study (with severity and relation to study drug). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Outcomes

The primary endpoint was change from baseline in 6MWD, relative to placebo, at week 52. Secondary endpoints were assessments, relative to placebo, at week 52: isometric muscle strength, as measured by quadriceps quantitative muscle testing (using a BTE Evaluator portable fixed dynamometer [BTE Technologies, Hanover, MD, USA] or equivalent); lean body mass, as measured by dual-energy x-ray absorptiometry; self-reported physical function (sIFA score); number of falls; and in-clinic physical performance (SPPB score).

Statistical analysis

We planned to enrol 240 participants (60 per group). The assumptions used for sample size calculations were based on the proof-of-concept study[18] and observational data.[21] The sample size of 60 participants per group was calculated for 90% power or greater under the most realistic scenario (assuming a treatment effect of 50 m [SD 55], the study has >90% power). The study was powered to detect a significant difference relative to placebo in the primary endpoint. We did a blinded sample size re-estimation when approximately 120 participants (half the sample size) had completed 16 weeks of treatment. We tabulated the statistical power to detect a significant difference from placebo under different assumed treatment effects and SDs (appendix pp 16, 17)—the higher the effect size, the higher the statistical power. This testing procedure protects the family-wise type I error (α=1%; two-sided).

The full analysis set was used for efficacy analysis, which comprised all participants who received at least one dose of study drug after randomisation and had at least one post-baseline efficacy assessment. The safety analysis set included all randomised participants who received at least one dose of bimagrumab. All safety assessments were done in the safety analysis set.

A multivariate normal mixed model for repeated measures (MMRM) was used to analyse data for the primary efficacy analysis. The MMRM model used for analysis of change from baseline in 6MWD was:

change from baseline in 6MWD = (intercept + treatment + baseline 6MWD + region + visit + treatment) × (visit + baseline 6MWD) × (visit + error)

The 6MWD at every post-baseline visit was analysed using MMRM. A similar MMRM model was used to analyse the secondary outcomes of quantitative muscle testing, sIFA score, lean body mass, and SPPB, including appropriate baseline values. We used the graphical approach of Bretz and colleagues[25] to adjust for multiplicity for 6MWD, sIFA score, and falls, with a family-wise type I error of 1% (two-sided). We tested primary and key secondary endpoints in a hierarchical manner: change from baseline in 6MWD at week 52 (primary), change from baseline in quantitative muscle testing on

	Change from baseline	Difference (bimagrumab *vs* placebo)	p value
6MWD (m)			
Bimagrumab 10 mg/kg (n=61)	8·6 (95% CI −12·9 to 30·2)	17·6 (99% CI −19·6 to 54·8)	0·22
Bimagrumab 3 mg/kg (n=63)	9·6 (95% CI −11·6 to 30·8)	18·6 (99% CI −18·2 to 55·4)	0·19
Bimagrumab 1 mg/kg (n=63)	−10·3 (95% CI −31·4 to 10·8)	−1·3 (99% CI −38·0 to 35·4)	0·93
Placebo (n=62)	−9·0 (95% CI −30·2 to 12·2)	..	..
Total lean body mass (%)*			
Bimagrumab 10 mg/kg (n=62)	102·8% (95% CI 101·4 to 104·2)	1·1 (95% CI 1·0 to 1·1)	<0·0001
Bimagrumab 3 mg/kg (n=61)	100·4% (95% CI 99·1 to 101·8)	1·0 (95% CI 1·0 to 1·1)	0·0001
Bimagrumab 1 mg/kg (n=63)	98·3% (95% CI 97·0 to 99·6)	1·0 (95% CI 1·0 to 1·0)	0·17
Placebo (n=61)	97·2% (95% CI 95·9 to 98·5)	..	..
Quantitative muscle testing of right quadriceps (N)			
Bimagrumab 10 mg/kg (n=60)	−12·4 (95% CI −24·3 to −0·6)	4·1 (99% CI −14·0 to 22·1)	0·56
Bimagrumab 3 mg/kg (n=63)	−20·4 (95% CI −31·9 to −8·9)	−3·9 (99% CI −21·7 to 13·9)	0·57
Bimagrumab 1 mg/kg (n=63)	−14·9 (95% CI −26·4 to −3·4)	1·6 (99% CI −16·1 to 19·3)	0·82
Placebo (n=61)	−16·5 (95% CI −28·0 to −5·0)	..	..
sIFA total score			
Bimagrumab 10 mg/kg (n=61)	1·7 (95% CI −2·0 to 5·5)	−5·1 (99% CI −11·3 to 1·1)	0·034
Bimagrumab 3 mg/kg (n=63)	3·6 (95% CI −0·1 to 7·3)	−3·3 (99% CI −9·4 to 2·8)	0·16
Bimagrumab 1 mg/kg (n=60)	6·1 (95% CI 2·4 to 9·9)	−0·7 (99% CI −6·9 to 5·4)	0·76
Placebo (n=61)	6·9 (95% CI 3·1 to 10·6)	..	..
SPPB score			
Bimagrumab 10 mg/kg (n=60)	0·0 (95% CI −0·4 to 0·5)	0·5 (95% CI −0·1 to 1·1)	0·083
Bimagrumab 3 mg/kg (n=63)	0·0 (95% CI −0·5 to 0·4)	0·5 (95% CI −0·1 to 1·1)	0·11
Bimagrumab 1 mg/kg (n=61)	−0·5 (95% CI −1·0 to −0·1)	0·0 (95% CI −0·6 to 0·6)	0·93
Placebo (n=61)	−0·5 (95% CI −1·0 to −0·1)	..	..
Falls rate†			
Bimagrumab 10 mg/kg (n=63)	4·3 (95% CI 2·9 to 6·4)	0·8 (99% CI 0·5 to 1·5)	0·44
Bimagrumab 3 mg/kg (n=63)	4·0 (95% CI 2·7 to 5·9)	0·8 (99% CI 0·5 to 1·4)	0·26
Bimagrumab 1 mg/kg (n=63)	4·7 (95% CI 3·2 to 6·9)	0·9 (99% CI 0·5 to 1·6)	0·68
Placebo (n=62)	5·1 (95% CI 3·6 to 7·2)	..	..

Data are least squares mean (CI), unless otherwise indicated. Baseline was the last assessment before the first dose of study drug. 6MWD=6-min walking distance. sIFA=sporadic inclusion body myositis physical functioning assessment. SPPB=Short Physical Performance Battery. *Data for total lean body mass were log-transformed. †Data for falls are change from baseline in falls rate (95% CI), and rate ratio (99% CI).

Table 2: **Change from baseline at week 52 in primary and secondary outcome measures, and difference relative to placebo**

the right quadriceps at week 52, change from baseline in sIFA score at week 52, and incidence of self-reported falls up to week 52. Reported efficacy results represent only the 52-week treatment period. Safety results encompass the overall study (treatment and maintenance periods).

Statistical analyses were done with SAS, version 9.3. No interim analysis was done during the study. An independent Data Monitoring Committee (appendix p 11) reviewed safety data every 3 months during the first year then every 4 months until completion of the study. The Data Monitoring Committee provided recommendations to the funder about safety and study continuation or discontinuation. An Independent Adjudication Committee (appendix p 11) monitored specific safety events, including—but potentially not restricted to—clinically significant cardiovascular events.

RESILIENT is registered with ClinicalTrials.gov, number NCT01925209.

Role of the funding source

The funder had a role in study design, study implementation, data collection, data management, data analysis, data interpretation, and preparation, review, and approval of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 26, 2013, and Jan 6, 2016, 314 individuals were screened for the study, of whom 63 were excluded, mainly because they did not meet inclusion criteria (figure 2). 251 participants were randomised, 63 to each bimagrumab group and 62 to placebo. 222 (88%) participants completed the 52-week treatment period and two (1%) participants reached the 104-week visit. 78 (31%) individuals completed 72 weeks of treatment and 34 (14%) completed 60 weeks of treatment. Most participants were between week 52 and week 72 when the study completed,

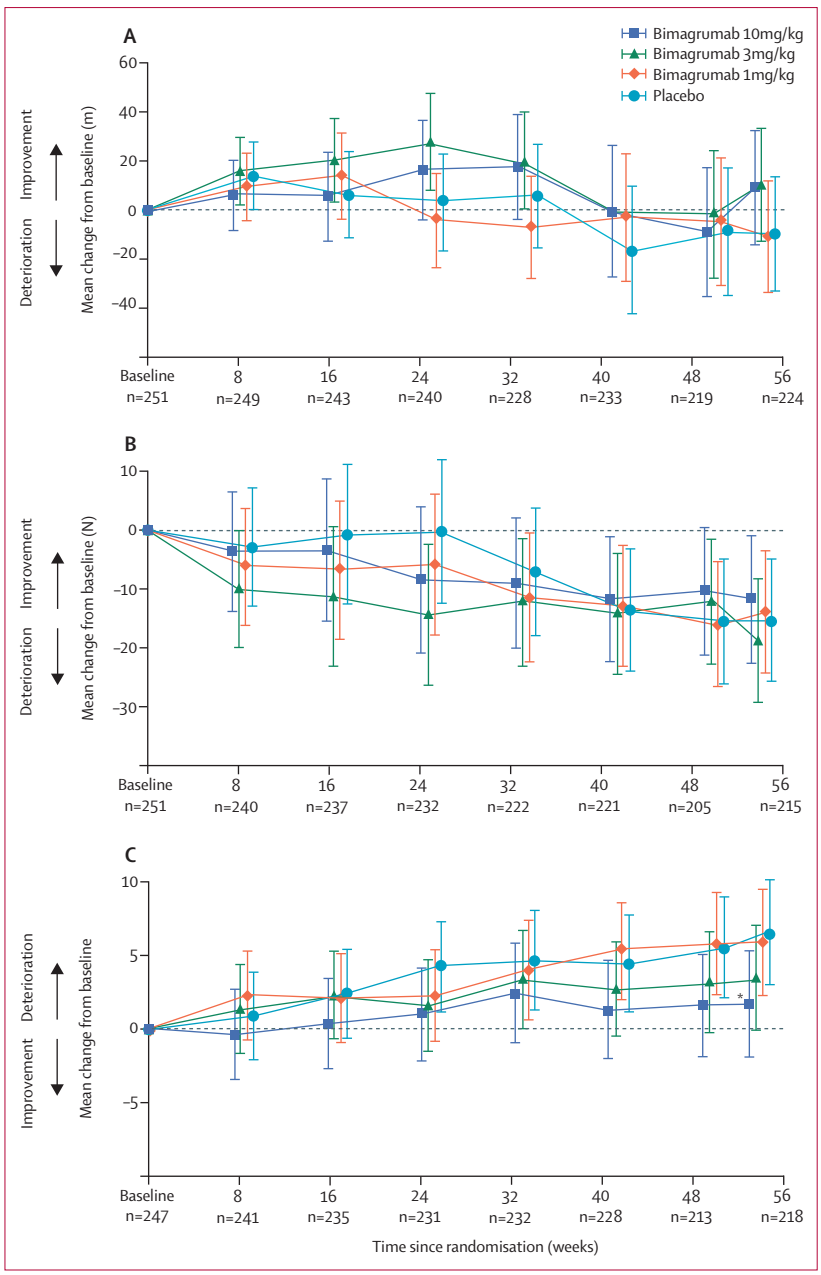

***Figure 3*: Mean change from baseline at week 52 in primary and secondary outcomes**
Change from baseline in 6MWD (A), right quadriceps strength as measured by quantitative muscle testing (B), and total sIFA score (C). Error bars represent 95% CI. 6MWD=6-min walk distance. sIFA=sporadic inclusion body myositis physical functioning assessment. *p=0·034.

with fewer than ten participants per group having completed more than 80 weeks of treatment

73 (29%) participants met the modified 2010 MRC pathological definition for inclusion body myositis and 178 (71%) were diagnosed clinically (table 1). Demographics and baseline disease characteristics were mostly similar across treatment groups, except for participants assigned to the bimagrumab 10 mg/kg group, who had greater functional limitation. Overall, the mean total distance walked (6MWD) at baseline was 292·2 m (SD 119·2), with 43 (17%) participants having a 6MWD of 400 m or longer. However, the bimagrumab 10 mg/kg group included more participants who required assistance during the 6MWD test compared with lower dose bimagrumab groups or the placebo group, a difference that was associated with diminished 6MWD test performance. The mean 6MWD at baseline was 267·7 m (SD 131·1) for participants in the bimagrumab 10 mg/kg group compared with 303·3 m (124·4) in the placebo group.

No change from baseline in 6MWD was noted with any dose of bimagrumab versus placebo at week 52 (table 2). The least squares mean treatment difference was 17·6 m (SE 14·3, 99% CI −19·6 to 54·8; p=0·22) for the 10 mg/kg dose versus placebo, 18·6 m (14·2, −18·2 to 55·4; p=0·19) for the 3 mg/kg dose, and −1·3 m (14·1, −38·0 to 35·4; p=0·93) for the 1 mg/kg dose (figure 3A, table 2).

A dose-dependent increase in lean body mass was noted with bimagrumab versus placebo at week 52, with significant differences recorded with bimagrumab 3 mg/kg and 10 mg/kg versus placebo (table 2; appendix pp 18–20). Quantitative muscle testing showed a progressive deterioration in strength of the right quadriceps over the course of the study in all study groups (figure 3B). No difference was noted between bimagrumab and placebo at 52 weeks (table 2).

A dose-dependent difference was recorded between bimagrumab and placebo in mean change of total sIFA score from baseline at week 52 (table 2). Participants in the bimagrumab 10 mg/kg group reported preservation of physical functioning whereas a slowly progressing deterioration in physical function was reported in the bimagrumab 1 mg/kg group and with placebo (figure 3C, table 2). Moreover, an increase was seen in the proportion of responders (ie, participants who improved or had no deterioration in sIFA score, defined as a change ≤0) in the bimagrumab 10 mg/kg group versus placebo at 52 weeks (55% *vs* 30%; p=0·012; appendix pp 19, 21). No improvement was noted in physical performance as measured by the SPPB with any dose of bimagrumab versus placebo at 52 weeks (table 2).

The fall rate at 52 weeks was 4·33 (95% CI 2·92–6·42) in the bimagrumab 10 mg/kg group, 4·02 (2·73–5·92) with bimagrumab 3 mg/kg, 4·70 (3·22–6·86) in the bimagrumab 1 mg/kg group, and 5·13 (3·64–7·24) with placebo. The fall rate did not differ between bimagrumab and placebo (table 2, appendix pp 22, 23).

Swallowing efficiency, as measured by videofluoroscopy, did not differ between bimagrumab and placebo at week 52 (appendix pp 24–27). Moreover, bimagrumab was not associated with benefits for either right handgrip (appendix pp 28–36) or right pinch-grip strength (appendix pp 37–45).

Falls were the most frequent adverse event, occurring in more than three-quarters of participants in each treatment group (48 [76%] in the bimagrumab 10 mg/kg group,

55 [87%] in the 3 mg/kg group, 54 [86%] in the 1 mg/kg group, and 52 [84%] in the placebo group). Muscle spasms and diarrhoea were the most frequently reported adverse events with bimagrumab (table 3). Most adverse events were mild or moderate in intensity. At least one serious adverse event was reported by 21 (33%) participants in the 10 mg/kg group, 11 (17%) in the 3 mg/kg group, 20 (32%) in the 1 mg/kg group, and 20 (32%) in the placebo group. Serious adverse events that occurred in more than one participant in any group were diarrhoea (three in bimagrumab 10 mg/kg group), falls (two in bimagrumab 10 mg/kg group, two in bimagrumab 3 mg/kg group, four in bimagrumab 1 mg/kg group, one in placebo group), tibial fracture (one in bimagrumab 10 mg/kg group, two in bimagrumab 1 mg/kg group), and basal cell carcinoma (three in bimagrumab 10 mg/kg group, three in bimagrumab 3 mg/kg group, one in bimagrumab 1 mg/kg group, three in placebo group). Sjogren's syndrome was reported in three (5%) individuals in the bimagrumab 10 mg/kg group, three (5%) in the 3 mg/kg group, two (3%) in the 1 mg/kg group, and five (8%) in the placebo group.

The reasons for study drug discontinuation are shown in figure 2. Adverse events leading to discontinuation were reported in four (6%) participants in each bimagrumab group compared with one (2%) individual in the placebo group (table 3; appendix pp 46–48). Two deaths were reported during the study. One death was attributable to subendocardial myocardial infarction (secondary to gastrointestinal bleeding after an intentional overdose of concomitant sedatives and antidepressants) and one was attributable to lung adenocarcinoma. Neither death was considered by the investigator to be related to bimagrumab. Bimagrumab treatment had no effect on blood pressure, heart rate, or standard electrocardiography measures including QT and PR interval (appendix pp 49, 50). On echocardiography, there were no findings suggestive of effects on cardiac heart muscle or its contractility (appendix pp 51–96).

	Bimagrumab 10 mg/kg (n=63)	Bimagrumab 3 mg/kg (n=63)	Bimagrumab 1 mg/kg (n=63)	Placebo (n=62)
Participants with at least one adverse event	63 (100%)	63 (100%)	63 (100%)	61 (98%)
Mild	17 (27%)	20 (32%)	18 (29%)	21 (34%)
Moderate	28 (44%)	27 (43%)	25 (40%)	29 (47%)
Severe	18 (29%)	16 (25%)	20 (32%)	11 (18%)
Participants with at least one serious adverse event	21 (33%)	11 (17%)	20 (32%)	20 (32%)
Deaths	1 (2%)	0	1 (2%)	0
Discontinuations due to adverse events	4 (6%)	4 (6%)	4 (6%)	1 (2%)
Adverse events reported with ≥5% higher frequency in the bimagrumab 10 mg/kg group *vs* placebo				
Muscle spasms	32 (51%)	43 (68%)	25 (40%)	13 (21%)
Diarrhoea	33 (52%)	28 (44%)	20 (32%)	11 (18%)
Acne	12 (19%)	19 (30%)	8 (13%)	6 (10%)
Rash	13 (21%)	8 (13%)	10 (16%)	8 (13%)
Nausea	11 (17%)	4 (6%)	9 (14%)	5 (8%)
Weight decreased	9 (14%)	4 (6%)	8 (13%)	3 (5%)
Decreased appetite	10 (16%)	3 (5%)	3 (5%)	1 (2%)
Pruritus	6 (10%)	6 (10%)	6 (10%)	1 (2%)
Anaemia	5 (8%)	3 (5%)	1 (2%)	1 (2%)
Insomnia	5 (8%)	0	2 (3%)	1 (2%)
Dysgeusia	5 (8%)	1 (2%)	0	1 (2%)
Hypomagnesaemia	4 (6%)	2 (3%)	0	0

Adverse events starting on or after the first day of study drug administration until 56 days after the last dose of study drug are counted. A participant with multiple occurrences of an adverse event under one treatment is counted only once in the adverse event category for that treatment at the maximum severity.

Table 3: **Adverse events and serious adverse events**

Discussion

The findings of our study show that bimagrumab in doses ranging from 1 mg/kg to 10 mg/kg had no beneficial effect relative to placebo on 6MWD after 52 weeks of treatment. 6MWD had a lower than expected rate of deterioration in the placebo group over 52 weeks (less than a third of the expected change), which might be attributable to the performance of exercises (in all participants) that have shown some benefit in inclusion body myositis. Participants who received the 10 mg/kg dose of bimagrumab turned out to be the weakest at study entry (based on baseline 6MWD) and, therefore, might not have had the potential for sufficient compensatory muscle hypertrophy because of fatty changes in their muscle. We also noted larger than expected variations in 6MWD between study visits. Variability in 6MWD could be attributable to comorbidities (eg, peripheral neuropathy, arthritis, recent falls, pain, or musculoskeletal injuries) unrelated to inclusion body myositis. We mention these reasons not as an explanation as to why bimagrumab did not achieve the primary endpoint in this study but because of a growing concern expressed by some neuromuscular clinicians that the 6MWD test might not be the most appropriate primary outcome measure to use in future trials of inclusion body myositis if a substantial proportion of individuals cannot walk without assistance, as was the case in this study. We chose 6MWD as the primary endpoint to measure physical performance in our study based on data from a proof-of-concept study.[18] The 6MWD is a standardised test[26,27] approved by the FDA as an acceptable measure of physical function in people with inclusion body myositis to assess therapeutic drug effects. The test reflects muscle endurance and has been used extensively in research to assess functional exercise capacity in heart and lung diseases. This measure of walking distance has also supported regulatory approval of neuromuscular drugs. However, based on findings from our study, we propose that 6MWD might not have been the most appropriate primary outcome measure to assess the full range of physical functioning in inclusion body myositis in this study: 2MWD or other measures, such as quantitative MRI, might have been more appropriate.

Despite no improvement in 6MWD, a dose-dependent effect on lean body mass was seen with bimagrumab

treatment, confirming the biological activity of this drug on skeletal muscle mass. These results suggest that higher doses of bimagrumab (3 mg/kg and 10 mg/kg) increase muscle mass and can sustain the effect up to 52 weeks, thus attenuating the loss of lean body mass noted with 1 mg/kg bimagrumab or placebo. However, our results are clear that the modest increase in lean body mass was not sufficient to lead to an improvement in muscle strength or physical function, as measured by 6MWD and quantitative muscle testing. However, more participants treated with bimagrumab 10 mg/kg self-reported stable or improved physical function on the sIFA score after 52 weeks. The sIFA score is a novel self-reported outcome measure designed to collect standardised data related to the individual's experience of inclusion body myositis and its effects, and the sIFA score is intended to augment objective measures of physical functioning. Although the sIFA score was developed in accordance with standards outlined in the FDA self-reported outcome guidance[22] and is aligned with recent FDA emphasis on patient-focused drug development and the capture of patient experience data,[28] evaluation of the psychometric properties of the sIFA score in inclusion body myositis has been restricted to data from three observational studies.[20]

Bimagrumab showed a good safety profile and was well-tolerated in our population with inclusion body myositis. Falls—a major source of morbidity in inclusion body myositis caused by severe weakness of quadriceps (and associated knee instability) or dropped foot—were the most frequently reported adverse event in all study groups. Common adverse events occurring at a greater frequency in bimagrumab-treated participants relative to placebo included muscle spasms and diarrhoea, although only rarely did adverse events lead to study discontinuation. No increase was noted in serious adverse events relative to placebo and no evidence of cardiac hypertrophy was seen in bimagrumab-treated participants, suggesting an overall favourable safety profile.

In conclusion, treatment with bimagrumab did not improve 6MWD, muscle strength, or grip and pinch strength in individuals with inclusion body myositis. However, at a dose of 10 mg/kg, bimagrumab improved lean body mass and self-reported physical function after 52 weeks of treatment, although the clinical relevance of these effects is unclear. Based on our study findings, the funder is not planning to pursue bimagrumab for inclusion body myositis. Future studies might need more refined functional indices to fully gauge if there are therapeutic effects of bimagrumab in inclusion body myositis.

Contributors

The RESILIENT study investigators contributed to participants' recruitment. MGH contributed to data analysis and writing and revision of the report. UAB contributed to study design, data collection, data interpretation, and writing of the report. OB contributed to study design, data collection, data interpretation, and revision of the report, and did the literature search. TEL contributed to data collection, data interpretation, and writing of the report. MN, DPA, and RJB contributed to data collection and writing of the report. HC contributed to data collection, data interpretation, and writing and revision of the report. MA contributed to study design and data collection. PMM contributed to data collection, data analysis, data interpretation, and provided guidance during writing of the report and for development of figures and tables. CL contributed to data collection, data interpretation, and revision of the report. KAR and JLDB contributed to data collection, data analysis, data interpretation, and read the report for important scientific content. MdV and JALM contributed to data collection and revision of the report. MMD contributed to study design, data collection, data analysis, and data interpretation, and reviewed the report. JTK contributed to data collection and reviewed the report. BO contributed to study design and implementation. NCJ contributed to data collection, data interpretation, writing of the report, and preparation of figures. PVdB, MM, and JV contributed to data collection, data analysis, data interpretation, and revision of the report. JB, HHJ, LM, and MF contributed to data collection, data interpretation, and revision of the report. CK contributed to data interpretation and reviewed the report. WSD, SY, MK, and KM contributed to data collection. SPN and LZA contributed to data analysis, data interpretation, and development of the report. EP contributed to data collection, data interpretation, and development of the report. CR contributed to revision of the report. AIS and NS contributed to data collection and data analysis. KS, HN, and IN contributed to data collection and data interpretation. NAG contributed to study design and data collection. MM-Y contributed to data collection, data analysis, data interpretation, and development of the report. CDR and VSLW contributed to data analysis, data interpretation, and revision of the report. MW contributed to data analysis, data interpretation, and writing of the report. AdV contributed to data collection, data analysis, data interpretation, and writing of the report. DAP contributed to study design, data collection, data analysis, data interpretation, and preparation and review of the report. AAA contributed to study design, data collection, data analysis, data interpretation, and writing of the report.

Declaration of interests

MGH has served on an advisory board for and received reimbursement from Novartis. UAB declares reimbursement of study costs paid to his institution from Novartis, during the conduct of the study; and consultancy fees paid to his institution from Argen X, outside of the submitted work. OB declares grants and personal fees from Novartis, during the conduct of the study; grants and non-financial support from Shire, outside of the submitted work; personal fees and non-financial support from LFB and CSL Behring, outside of the submitted work; and grants and personal fees from Neovacs, outside of the submitted work. TEL declares grants, personal fees, and non-financial support from Novartis, during the conduct of the study. MN has served on an advisory board for Novartis during the initial study design. HC declares grants from the University of Manchester, during the conduct of the study; personal fees and grants from UCB, outside of the submitted work; personal fees from Lilly and Momenta, outside of the submitted work; travel support from Janssen and Abbvie, outside of the submitted work; personal compensation for being a speaker or advisory board member from Novartis, UCB, Lilly, and Momenta, outside of the submitted work; and travel support from Abbvie and Janssen, outside of the submitted work. MA declares research grants from the Japanese Ministry of Health Labor and Welfare, the National Center of Neurology and Psychiatry, the Japanese Ministry of Education, Culture, Sports, Science and Technology, and the Japan Agency for Medical Research and Development, during the conduct of the study; and personal fees from Mitsubishi Tanabe Pharma, Astellas Pharma, Takeda Pharmaceutical Company, Sanofi, Novartis Pharma, and Dainippon Sumitomo Pharma, during the conduct of the study. PMM declares personal fees from Novartis, during the conduct of the study; and personal fees from AbbVie, Centocor, Janssen, MSD, Novartis, Pfizer, and UCB, outside of the submitted work. CL declares compensation for attending investigator meetings from Novartis, during the conduct of the study; and compensation for attending investigator meetings from Bristol-Myers Squibb, outside of the submitted work. KAR reports grants from Novartis, during the conduct of the study. MdV declares personal fees from Avexis and Bristol-Myers Squibb, outside of the submitted work. RJB has served as a consultant for

NuFactor and Momenta Pharmaceutical, outside of the submitted work; and declares research support from PTC Therapeutics, Ra Pharma, Orphazyme, Sanofi Genzyme, the US Food and Drug Administration Office of Orphan Products Development, the National Institutes of Health, and the Patient-Centered Outcomes Research Institute, outside of the submitted work. MMD declares grants from University of Kansas Medical Center, during the conduct of the study; consultancy or speaker's fees from Alnylam, Audentes, Biomarin, Catalyst, CSL-Behring, Genzyme, Mallinckrodt, Momenta, Novartis, NuFactor, Octapharma, Sanofi, Shire, and Terumo, outside of the submitted work; and grants from Alexion, Alnylam, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, CSL-Behring, the US Food and Drug Administration Office of Orphan Products Development, GlaxoSmithKline, Genentech, Grifols, MDA, the National Institutes of Health, Novartis, Genzyme, Octapharma, UCB Biopharma, Viromed, and TMA, outside of the submitted work. JALM declares speaker's fees or compensation for advisory board membership from CSL Bering, Octapharma, and Grifols, outside of the submitted work. JTK declares grants from Cytokinetics, Genzyme, Alexion, Novartis, and AveXis, outside of the submitted work. BO declares research support from Novartis, Biogen, Genentech, GSK, Flexpharma and consulting from Biogen and Mitsubishi Tanabe. NCJ declares support for this clinical trial from Novartis, during the conduct of the study; support for running a clinical trial and personal fees from Biogen, outside of the submitted work; and support for running a clinical trial from Acceleron, Cytokinetics, and FlexPharma, outside of the submitted work. PVdB reports personal fees from Genzyme, Pfizer, Alnylam, CSL Behring, LFB France, and UCB Pharma, outside of the submitted work. JB reports personal fees and travel support from Novartis, during the conduct of the study; and consultancy fees from Sanofi and CSL Behring, outside of the submitted work. MM declares grants, personal fees, consultancy or speaking fees, research support, travel grants, and reimbursement for participation in scientific advisory boards from Bayer Schering, Biogen, Sanofi Genzyme, Novartis, TEVA, Ultragenix, and Merck Serono, outside of the submitted work; and travel grants and reimbursement for participation in scientific advisory boards from CSL Behring, outside of the submitted work. SPN declares personal fees from Grifols and Bio Products Laboratory, outside of the submitted work. EP declares grants and non-financial support from Santhera, outside of the submitted work; personal fees from Sarepta and Roche, outside of the submitted work; non-financial support from Genzyme, outside of the submitted work; and grants from PTC Pharmaceuticals, outside of the submitted work. LM declares support related to running of this clinical trial from Novartis Pharma, during the conduct of the study; and grants from Sanofi Genzyme, outside of the submitted work. NAG has served on an advisory board for Novartis. MK declares a clinical trial fee from Novartis, during the conduct of the study; personal fees from Novartis, Daiichi-Sankyo, Sumitomo Dainippon, Takeda, and Tanabe-Mitsubishi, outside of the submitted work; grants from the Japan Agency for Medical Research and Development, the Japanese Ministry of Education, Culture, Sports, Science and Technology, the Japanese Ministry of Health Labor and Welfare, the Naito Foundation, the Uehara Memorial Foundation, Otsuka, Nihonseiyaku, Sanofi, Astellas, Sumitomo Dainippon, and Pfizer, outside of the submitted work; and patent loyalty from Takeda, outside of the submitted work. IN declares grants from Astellas Pharma and Daiichi Sankyo, outside of the submitted work; grants and personal fees from Sanofi Japan, outside of the submitted work; and personal fees from Japan Blood Products Organization and Eisai, outside of the submitted work. CDR and VSLW declare support for doing this clinical trial from Novartis, during the conduct of the study; collaborated with Novartis on the development of the Sporadic Inclusion Body Myositis Physical Functioning Assessment (sIFA) before this study; and are both employed by RTI Health Solutions, which runs research projects for multiple pharma and biotech companies. JV declares support for doing this clinical trial from Novartis, during the conduct of the study. LZA, AdV, MW, and DAP are employees of Novartis. MW and DAP hold stock or shares in Novartis. AAA declares personal fees from Novartis, during the conduct of the study. DPA, JLDB, CK, WSD, HHJ, CR, MF, AIS, KS, MM-Y, SY, NS, KM, and HN declare no competing interests.

Data sharing

Investigators wishing to analyse data from this study can apply online at Clinical Study Data Request.

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