Title page

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

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RESILIENT, A **R**andomized, double-blind, placebo-controlled, multicenter, parallel group, dose-finding, pivotal, phase IIb/III study to evaluate the **E**fficacy, **S**afety and tolerability of **I**ntravenous BYM338 at 52 weeks on **L**ean body mass, muscle strength, physical function and mobility and additional long-term safety up to 2 years in pat**IENT**s with sporadic inclusion body myositis

Summary (300 words; Limit 300)

Background: To assess the efficacy, safety, and tolerability of bimagrumab (fully human monoclonal antibody) in participants with inclusion body myositis (IBM).

Methods: This multicentre, double-blind, placebo-controlled study (RESILIENT; ClinicalTrials.gov, number NCT01925209) was conducted between September 26, 2013 and January 06, 2016 at academic clinical sites in Europe, the USA, Australia, and Japan. Eligible participants (aged 36–85 years [inclusive]; modified 2010 MRC criteria) were randomly assigned (1:1:1:1) using blocked randomisation schedule (block size=4) to receive intravenous infusions of bimagrumab 10, 3, 1 mg/kg, or placebo every 4 weeks for at least 48 weeks. All study participants, sponsor, investigators, site personnel, and those performing assessments were masked to treatment assignment. 6-minute walking distance (6MWD; primary outcome measure) was assessed at Week 52 in the primary analysis population. A multivariate normal repeated measures model was used to analyse data on 6MWD. Safety was assessed by recording adverse events (AEs), electrocardiography, echocardiography, hematology, urinalysis, and blood chemistry.

Findings: At Week 52, there were no statistically significant differences in 6MWD change from baseline for any of the bimagrumab groups (10, 3, 1 mg/kg) versus placebo (least squares mean treatment difference (SE;99%CI): 17·6 m (14·3;−19·6,54·8) p=0·2210, 18·6 m (14·2;−18·2,55·4) p=0·1909, and −1·3 m (14·1;−38·0,35·4) p=0·9263, respectively). There were 63(100%) participants in each bimagrumab group and 61(98.4%) in the placebo group who experienced at least one AE. Proportion of participates reporting at least serious AE was 21(33·3%), 11(17·5%), 20(31·7%), and 20(32·3%) in the respective groups. No significant adverse cardiac effects were observed on electrocardiography or echocardiography testing.
Interpretation: Bimagrumab demonstrated a good safety profile in the IBM population but did not improve 6MWD. Strengths of the study are that it is the largest RCT conducted in IBM and provides important natural history data over 12 months.

Funding: Novartis Pharma AG

Keywords: Activin type II receptors, bimagrumab, inclusion body myositis, myostatin

Research in context

Evidence before this study: We searched PubMed for randomised clinical studies in participants with inclusion body myositis (IBM) published up to September 11, 2018, using the terms “inclusion body myositis”, with no language restrictions. We identified nine randomised controlled trials. The duration of intervention varied from 3 to 17 months. One very small trial using oxandrolone suggested positive results, but this has not been repeated. The other larger trials observed no improvement using methotrexate, intravenous immunoglobulin, etanercept, or β-interferon. There is currently no evidence to support any specific treatment in clinical practice. To date, there are no effective or approved treatment options for IBM.

Added value of this study: RESILIENT is the first Phase 2b clinical study of a myostatin inhibitor in adults and is the largest randomised controlled study in IBM and in any idiopathic inflammatory myopathy.

Implications of all the available evidence: RESILIENT study did not meet the primary endpoint of improving 6-minute walk distance (6MWD) test at Week 52. Among all 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 there was a positive effect in lean body mass and self-reported physical function as assessed by sporadic IBM physical functioning assessment. The large number of participants in this study helps in better understanding of the natural history of IBM over one year which will assist in powering future clinical trials in IBM. In addition, the problems of using the

6MWD test in this population should lead to better primary outcome measures in future trials.

Introduction (3598 words; Limit 4500)

Inclusion body myositis (IBM) is an idiopathic inflammatory myopathy and the most common myopathy affecting people over 50 years of age. It is characterised by slowly progressive asymmetric weakness and atrophy of the proximal and distal muscle groups, mainly quadriceps and deep finger flexors.[1–3] Results from a systematic review and meta-analysis in people of all age categories showed that the pooled meta-prevalence of IBM was 24·8 per million (95% confidence interval [CI], 20·0–29·6), when limited to the highest quality prevalence papers (data from nine articles).[4] IBM affects men more often than women (ratio: 2:1 to 3:1).[5] The progression of leg weakness leads to frequent falls[6] and results in the loss of ambulation, leading to the use of assistive devices for mobility and eventual wheelchair dependence.[1,2] Progressive loss of hand function gives rise to decrease in the activities of daily living and dysphagia can result in choking, weight loss, aspiration and pneumonia.[6] Recent reviews on IBM provide understanding of pathogenesis of this disease and effective therapeutic targets.[7–11] To date, there are no effective drug treatments for IBM.[12]

Bimagrumab (BYM338) is a novel fully human monoclonal antibody that binds competitively to activin type II receptors (ActRII) with greater affinity than the natural ligands activin and myostatin, which usually function to limit muscle mass growth.[13] SMAD2 phosphorylation, activated downstream of ActRII, is increased in IBM muscle relative to other muscle diseases—indicating enhanced signaling via this receptor.[14,15]

The results from a pre-clinical *in vivo* study in mice showed that blockade of ActRII with bimagrumab increased body weight and led to marked skeletal muscle hypertrophy.[13] A proof-of-concept study in participants with IBM (N=14; 11 active, 3 placebo) showed that a single intravenous dose of bimagrumab 30 mg/kg improved thigh muscle volume measured by muscle imaging and lean body mass (LBM) at 8 weeks, as well as 6-minute walk distance (6MWD) at 16 weeks, versus placebo.[15] However, in the RESILIENT study bimagrumab 10 mg/kg was selected as the highest dose as it was expected, based on the analysis of exposure–response relationship in increasing thigh muscle volume in the healthy adults, that repeated treatment with 10 mg/kg would achieve similar efficacy as 30 mg/kg every two months but with a better safety profile.

The study, therefore, investigated whether designated dosing regimens of bimagrumab improve physical function and mobility relative to placebo in IBM participants after 52 weeks of monthly treatment. Treatment beyond 52 weeks varied per participant up to a maximum of 52 additional weeks in the maintenance treatment period, thereby allowing for evaluation of the long-term efficacy and safety in the IBM population. The data on efficacy beyond 52 weeks of treatment (40% participants had 104 week visits) will be presented in a separate follow-up article

Methods

Study design and Participants

This randomised, double-blind, placebo-controlled, dose-finding, phase 2b study (Fig. 1) was conducted between September 26, 2013 and January 06, 2016 at the academic

clinical sites in Europe, the USA, Australia, and Japan. Members of the steering committee collaborated with Novartis Pharma AG to develop the protocol. There was no protocol amendment after start of the study. The protocol and informed consent form were reviewed and approved by the Institutional Review Board/Independent Ethics Committee at each participating site, and written informed consent was obtained from all participants. The study was performed in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice,[16] in compliance with applicable local regulations, and with the ethical principles established in the Declaration of Helsinki of 1964, as revised in 2013.[17] An independent, external data monitoring committee reviewed safety data of the study at regular intervals.

The 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 maintenance treatment period, and approximately 28-day treatment-free follow-up period. The treatment duration for all participants was determined by the last subject completing the 52-week treatment period; once the last subject had completed the Week 48 dose, no other subjects received the study treatment. While the reported efficacy results represent only the 52-week treatment period, the safety results encompass the overall study (treatment and maintenance treatment periods).

The study population included men and women (aged 36–85 years, inclusive) with a pathologically or clinically defined diagnosis of IBM according to the modified 2010 Medical Research Council criteria.[18,19] All patients had a biopsy as part of their diagnostic evaluation and this was reviewed. Although intermittent use of wheelchairs

was allowed, the study participants had to be able to walk at least 1 m without assistance from another person. The use of assistive aids (e.g., canes, walkers, rollators) during the test was permitted. The proportion of participants who could walk more than 400 m in 6 minutes was limited to 20% based on an observational study[20] where the 6MWD decline in more functional IBM participants (>400 m 6MWD at baseline) was much slower, thus representing a lesser unmet need. Key exclusion criteria were conditions other than IBM that significantly limited the participant's mobility; the use of concomitant medications with an immunomodulatory effect or biological effect on muscle anabolism or catabolism; use of prohibited systemic treatments (within past 6 months prior to randomisation) or any therapies known to affect muscle mass (within past 3 months prior to randomisation); any active chronic condition associated with cachexia or muscle atrophy other than IBM; severe vitamin D deficiency; any uncontrolled medical condition that might limit the ability of the subject to participate in the study procedures. Pregnant or nursing women were also excluded from the study.

Randomisation and masking

Eligible participants were randomly assigned (1:1:1:1) to receive intravenous infusions of bimagrumab 10, 3, 1 mg/kg, or matching placebo. Participants were assigned a treatment according to a blocked randomisation schedule. The randomisation list was created by Cenduit (Cenduit, Durham, NC, USA); reviewed as well as approved by Novartis Biostatistics Quality Assurance group. A blocked randomization schedule was generated with block size of 4. Randomisation was stratified by geographic region. Within each 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 study was supported by Interactive Response Technology for randomisation and medication management (Cenduit, Durham, NC, USA). The study sponsor, participants, investigators, site personnel, and those performing the assessments were masked to treatment assignment. The study medication was prepared by an independent non-blinded pharmacist/designee appointed at the study site before administration. The identity of the treatments (bimagrumab or placebo) was concealed by the use of study drugs treatments in forms of opaque sleeve-covered infusion bags filled with active or placebo solutions identical in appearance, but the actual bimagrumab or placebo vials were supplied “open-label”. To maintain blinding, the study medication was administered only by blinded study centre personnel. Emergency treatment code breaks were to be performed using an interactive voice response system, and were only to be undertaken when it is essential to treat the participant safely and efficaciously. The study medication was to be discontinued after emergency unblinding.
In this study no interim analysis was performed.

Study procedures

Bimagrumab and matching placebo were administered intravenously every 4 weeks as a slow infusion over no less than 30 minutes. The first dose administration occurred on Day 1 and the final dose for the treatment period was administered at the Week 48 visit,

defining the minimum treatment duration of 52 weeks. The European Medicines Agency and US Food and Drug Administration agreed that 12 months was adequate for inclusion body myositis (IBM) studies, all participants received at least 48 weeks of treatment. In this study subjects remained until the last participant received the Week 48 dose or up to 104 weeks, whichever was shorter. Scheduled study visits, including safety assessments, took place at screening, baseline, treatment period, maintenance treatment period, and the post-treatment follow-up period. On-going participants who had already reached the Week 48 dose continued in the maintenance treatment period until the last participant received the Week 48 dose, up to a maximum of 104 weeks. Participants who had received Week 48 treatment but did not complete the 52-week treatment period completed the end of treatment visit approximately 28 days following their last study dose. Following completion of the end of treatment visit, participants entered into the post-treatment follow-up period. These participants were not eligible to enter into the maintenance treatment period. Participants who had entered the maintenance treatment period completed the end of maintenance treatment visit approximately 28 days following their last study dose. Following completion of the end of maintenance treatment visit, all participants entered the post-treatment follow-up period. The end of follow-up visit for a participant occurred approximately 4 weeks after completion of the treatment period and approximately 8 weeks after the last study dose. The end of follow-up visit was completed for all participants regardless of whether they completed or prematurely discontinued.

Outcomes

The primary endpoint was change from baseline in 6MWD relative to placebo at Week 52. Secondary endpoints included the following assessments relative to placebo at Week 52: isometric muscle strength, as measured by quadriceps quantitative muscle testing (QMT; BTE Evaluator portable fixed dynamometer [BTE Technologies, Hanover, MD, USA or equivalent]); LBM, as measured by dual-energy x-ray absorptiometry; self-reported physical function using a patient-reported outcome (PRO) measure, the Sporadic Inclusion Body Myositis Physical Functioning Assessment (sIFA); number of falls; and in-clinic physical performance as measured by the Short Physical Performance Battery (SPPB).

The SPPB was used to evaluate lower extremity physical function through tests of gait speed, ability to maintain standing balance, and time to rise from a chair five times. sIFA is an IBM-specific PRO measure designed to assess physical function and clinical progression and physical function in IBM from the patient perspective (Supplementary material, Appendix 2). sIFA was developed following FDA PRO guidance[21] and included item generation based on review of the literature, input from key opinion leaders, and in-depth face-to-face patient interviews. sIFA items were generated directly from concepts captured during the qualitative research. A separate series of in-person cognitive debriefing interviews confirmed the content validity of the sIFA and the appropriateness and comprehension of the items, instructions, and response options. The sIFA has been evaluated in three observational studies and demonstrated to have highly satisfactory psychometric properties.[22,23] A comprehensive psychometric analysis of data from the RESILIENT study established the reliability of sIFA (internal consistency alpha=0.88,

0.90; test-retest=0.85), responsiveness (effect size=0.22), and construct validity of sIFA in patients with IBM (unpublished data). sIFA items are rated on an 11-point numerical rating scale from 0 (no difficulty) to 10 (unable to do) across three domains: upper body functioning (e.g., “carry a 5-pound object”), lower body functioning (e.g., “step up and down sidewalk or street curbs”), and general functioning (e.g., “get on and off a toilet”).

Safety was assessed by recording adverse events (AEs), serious AEs throughout the study (with their severity and relationship to study drug), and additional measures that included physical examination, monitoring of vital signs, hematology and blood chemistry, urinalysis, electrocardiography, and echocardiography testing.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Statistical analysis

The study was planned to enroll 240 participants (60 per group). The assumptions used for sample size calculations were based on the proof-of-concept study[15] and observational data.[20] The sample size of 60 participants per arm was determined to power ≥90% under most realistic scenario (assuming a treatment effect 50 and a SD of 55, the study is more than 90% powered). The study was powered to detect a significant difference from placebo in the primary endpoint (6MWD). A blinded sample size re-estimation was performed once approximately 120 participants (half the sample size) have completed 16 weeks of treatment. The statistical power to detect a significant

difference from placebo under different assumed treatment effects and SD was tabulated (Supplementary material, Appendix 3); higher the effect size, the higher the statistical power. The testing procedure protects the family-wise type-I-error of alpha=1% (2 sided). The full analysis set was used for efficacy analysis. The full analysis set comprised all randomised participants who received at least one dose of the study drug after randomisation and had at least one post-baseline efficacy assessment. The safety analysis set included all randomised participants who took at least one dose of bimagrumab. All safety evaluations were performed on the safety analysis set. A multivariate normal mixed model for repeated measures (MMRM) was used to analyse data for the primary efficacy analysis. The following MMRM model was used for analysis of change from baseline in 6MWD: change from baseline in 6MWD = intercept + treatment + baseline 6MWD + region + visit + treatment*visit + baseline 6MWD*visit + error. The 6MWD at each post-baseline visit (Weeks 8, 16, 24, 32, 40, 48, and 52) was analysed using MMRM. A similar MMRM model was used to analyse secondary outcomes of QMT, sIFA, LBM, and SPPB; however, by including appropriate baseline values. The graphical approach of Bretz et al.[24] was used to adjust for multiplicity for 6MWD, sIFA, and falls, with a family wise type I error of 1% (2-sided). The following primary and key secondary endpoints were tested in a hierarchical manner: change from baseline in 6MWD test at week 52 (primary), change from baseline in QMT on 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.

Statistical analyses were performed with SAS program, version 9.3 (SAS Institute, Cary, NC, US). The study (RESILIENT) was registered with ClinicalTrials.gov, number

NCT01925209. An independent data monitoring committee (DMC) reviewed the safety data every 3 months during the first year and every 4 months during the second year of this study. DMC provided recommendations to the Sponsor concerning safety and study continuation or discontinuation. An independent adjudication committee monitored specific safety events, including, but potentially not limited to clinically significant cardiovascular events.

Role of the funding source

The study sponsor participated in the study design, conduct of the study, data collection, data management, data analysis, data interpretation, and preparation, review, and approval of the manuscript. The authors had full access to the data in the study, participated in data analysis, interpretation, development of the manuscript, and had final responsibility for the decision to submit for publication.

Results

A total of 222 (88%) participants completed the 52-week treatment period; 85·7−88·9% across bimagrumab treatment groups versus 91·9% for placebo. In this study, there were 73 (29.1%) participants who met pathologically defined- and 178 (70.9%) who met clinically defined-diagnosis of IBM according to the modified 2010 Medical Research Council criteria. The reasons for study drug discontinuation are shown in Figure 1a. Demographics and baseline disease characteristics were similar across the treatment groups (Table 1), except for the bimagrumab 10 mg/kg group. While the mean (SD) total distance walked (6MWD) at baseline was 292·2 (119·2) m, with 17% (n=43) of

participants having a 6MWD of ≥400 m, there was a trend for the high-dose group to include participants with greater functional limitation (requiring the use of walking aids during the 6MWD test) than the lower dose or placebo groups--a difference that was associated with lower 6MWD test performance (the mean (SD) total distance walked at baseline was 267·7 (131·1) m for participants in the bimagrumab 10 mg/kg group compared with 303·3 (124·4) m in the placebo group).

6-minute walking distance: There were no evidence of effect in any of the three bimagrumab groups in change from baseline on 6MWD versus placebo at Week 52 (least squares mean [LS mean] treatment difference for bimagrumab 10, 3 and 1 mg/kg vs placebo (SE; 99%CI): 17·6 m (14·3; −19·6, 54·8) p=0·2210, 18·6 m (14·2; −18·2, 55·4) p=0·1909, and −1·3 m (14·1; −38·0, 35·4) p=0·9263, respectively) (Fig. 2a; Table 2a).

Lean body mass: Bimagrumab showed a dose-dependent increase in LBM versus placebo at Week 52, with 3 and 10 mg/kg treatments (3.3% difference; treatment ratio of bimagrumab 10 mg/kg vs placebo exp (LS mean) (exp (SE)): 1·1 (1·0) (95% CI 1·0, 1·1), P=0·0001 and 5.8% difference; treatment ratio of bimagrumab 3 mg/kg vs placebo exp (LS mean) (exp (SE)) 1·0 (1·0) (95% CI 1·0, 1·1), P<0·0001, respectively) (Supplementary Fig 1, Appendix 4; Table 2b).

Quantitative muscle testing: QMT showed a progressive deterioration in right quadriceps strength over the course of the study (Fig. 2b). There was no difference

between the bimagrumab and placebo groups at 52 weeks (LS mean treatment difference for bimagrumab 10, 3 and 1 mg/kg vs placebo (SE; 99%CI): 4·05 (7·0; –14·0, 22·1) P=0.5618, –3·87 (6·8; –21·7, 13·9) P=0.5723 and 1·59 (6·8; –16·1, 19·3) P=0.8153, respectively) (Table 2c).

sIFA: A dose-dependent difference in the mean change of sIFA total score from baseline was observed at Week 52 (Table 2d); participants treated with bimagrumab 10 mg/kg reported preservation of physical functioning whereas a slowly progressing deterioration was reported in the bimagrumab 1 mg/kg and placebo groups (LS mean treatment difference for bimagrumab 10 mg/kg vs placebo (SE; 99%CI): –5·11 (2·4; –11·3, 1·1) p=0.0338) (Fig. 2c; Table 2d). Moreover, there was an increase in the proportion of responders (defined as a change in sIFA score of ≤0) in the bimagrumab 10 mg/kg group versus placebo at 52 weeks (55% vs. 30%; P=0·0115) (Supplementary Fig 2, Appendix 4).

Falls: The mean number of falls at 52 weeks was 4·33, 4·02, 4·70, and 5·13 in the bimagrumab 10, 3, 1 mg/kg, and placebo groups, respectively; no differences in the rate of falls between bimagrumab and placebo groups (fall rate ratio for bimagrumab 10 mg/kg vs placebo (99%CI): 0·8 (0·5, 1·5) p=0·4361, 0·8 (0·5, 1·4) p=0·2579, and 0·9 (0·5, 1·6) p=0·6812, respectively) (Supplementary Table 1, Appendix 4).

SPPB: There was no improvement in physical performance as measured by the SPPB in the bimagrumab 10 and 3 mg/kg groups versus placebo at 52 weeks (LS mean

treatment difference for bimagrumab 10 mg/kg vs placebo (SE; 99%CI): 0.5 (0·3; –0·1, 1·1) p=0.0833, 0·5 (0·3; –0·1, 1·1), p=0·1059, and 0·0 (0.3; –0·6, 0·6), p=0·9303) (Table 2e).

Swallowing efficiency (by videofluoroscopy): There were no differences between the 3 bimagrumab groups versus placebo in swallowing efficiency at Week 52 (Supplementary Table 2, Appendix 4).

Hand-grip and pinch-grip dynamometry: At Week 52 treatment with bimagrumab was not associated with benefits for either right hand-grip (LS mean treatment difference for bimagrumab 10, 3 and 1 mg/kg vs placebo (SE; 95%CI): 0·2 (6·4; –12·5, 12·9) p=0·9781, 5·2 (6·3; –7·3, 17·6) p=0·4169, and 5·0 (6·3; –7·5, 17·5) p=0·4339) or right pinch-grip strength (LS mean treatment difference for bimagrumab 10, 3 and 1 mg/kg vs placebo (SE; 95%CI): 0·1 (3·7; –7·3, 7·4) p=0·9804, 1·4 (3·7; –5·8, 8·6) p=0·6953, and 1·4 (3·6; –5·8, 8·6) p=0·7108, respectively) (Supplementary Tables 3 and 4, Appendix 4).

Similar proportions of participants (98·4–100%) reported AEs across all treatment groups (Table 3). Falls were the most frequent AEs, occurring in >75% participants in each treatment group (10, 3, 1 mg/kg and placebo: 76·2% [n=48], 87·3% [n=55], 85·7% [n=54], and 83·9% [n=52], respectively). Muscle spasm and diarrhea were the next most frequently reported AEs in the bimagrumab groups (Table 3). The majority of AEs were mild or moderate in intensity. The overall incidence of severe AEs was higher in

the active treatment groups than in the placebo group (Table 3). In this study, Sjogren's syndrome was reported in 3 (4.8%), 3 (4.8%), 2 (3.2%), and 5 (8.1%) participants in the bimagrumab 10, 3, 1 mg/kg and placebo groups, respectively. AEs leading to discontinuation were reported in the same number of participants in the three bimagrumab groups (6·3%) compared with 1·6% participants in the placebo group (Table 3; Supplementary Table 5, Appendix 4). Two deaths were reported during the study: one due to subendocardial myocardial infarction (secondary to gastrointestinal bleeding following an intentional overdose of concomitant sedative and antidepressant medications), and one due 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 (Supplementary Table 6, Appendix 4). On echocardiography, there were no findings suggestive of effects on cardiac heart muscle or its contractility (Supplementary Table 7, Appendix 4).

Discussion

RESILIENT is the first Phase 2b clinical study of a myostatin inhibitor in adults and the largest randomised controlled study to date of any therapeutic agent in idiopathic inflammatory myopathy in general (which encompasses IBM). IBM is a myopathy that is characterised by progressive muscle weakness and wasting; therefore, treatments that target atrophy pathways in muscle may be effective in this disease. Myostatin belongs to the transforming growth factor-β family and is an endogenous negative regulator of the skeletal muscle mass.[25] Although a number of strategies involving myostatin

inhibition are currently being investigated,[26] blockade of myostatin binding to ActRII by the receptor-neutralizing antibody bimagrumab represents a novel approach for the treatment of muscle-wasting disorders such as IBM. Recently, the IBM guideline development group developed a protocol to produce best practice clinical guidelines for IBM.[27]

In this study, the 6MWD (primary efficacy endpoint) was chosen as the physical performance measure of choice in the IBM population based on data from the proof-of-concept study.[15] The 6MWD is a standardised test,[28,29] approved by the US FDA as an acceptable measure of physical function in IBM participants to assess therapeutic drug effects. The 6MWD reflects muscle endurance and has been used extensively in research to assess functional exercise capacity in heart and lung diseases; more recently, this measure of walking distance has also supported regulatory approval of neuromuscular drugs.

Bimagrumab in doses ranging from 1 to 10 mg/kg had no beneficial effect (relative to placebo) on the selected primary endpoint, 6MWD, after 52 weeks of treatment. The 6MWD had a lower than expected rate of deterioration in the placebo group over 52 weeks (8·96 m, i.e., less than 1/3 of the expected change). This might be attributable to the performance of exercises (in all participants) that have shown some benefit in IBM. Participants who received the highest doses of bimagrumab were the weakest at study entry (based on baseline 6MWD) and therefore may have lacked the potential for sufficient compensatory muscle hypertrophy due to fatty changes of their muscle. We

also found larger than expected variations in 6MWD results of participants between visits. Variability in 6MWD may be attributable to comorbities (e.g., peripheral neuropathy, arthritis, recent falls, pain or musculoskeletal injuries) unrelated to IBM. We mention this not as an excuse as to why bimagrumab failed in this study, but because of a growing concern amongst neuromuscular clinicians that the 6MWD may not be the most appropriate primary outcome measure to use in future trials of IBM. Based on findings from our study we discuss that 6MWD may not be the most appropriate primary outcome measure to evaluate the full spectrum of physical functioning in IBM.

Despite the lack of improvement in 6MWD, a dose-dependent effect on LBM was observed with bimagrumab treatment, confirming its biological activity on skeletal muscle mass. These results suggest that bimagrumab increases muscle mass and sustains the effect up to 52 weeks in the two higher dose bimagrumab groups (3 and 10 mg/kg), thus attenuating the loss of LBM observed with the lowest dose of bimagrumab or placebo. However, our results are clear that the modest increase in LBM was not sufficient to lead to an improvement in muscle strength or physical function as measured by 6MWD and QMA. However, more participants treated with bimagrumab 10 mg/kg self-reported stable or improved *physical function* on the sIFA scale after 52 weeks. The sIFA is a novel PRO measure designed to collect standardized data related to IBM patient experience and impacts and it is intended to augment objective measures of physical functioning. While sIFA was developed in accordance with standards outlined in the FDA PRO guidance[21] and is aligned with recent FDA emphasis on patient-focused drug development and the capture of patient experience

data,[30] evaluation of the psychometric properties of sIFA in IBM has been limited to data from three observational studies.[19]

Bimagrumab demonstrated a good safety profile and was well-tolerated in the IBM participant population. Falls, a major source of morbidity in IBM caused by severe quadriceps weakness (and associated knee instability) and/or dropped foot, were the most frequently reported AE in all bimagrumab- and placebo-treated groups. Common AEs occurring at a greater frequency in the bimagrumab-treated participants relative to placebo included muscle spasms and diarrhea, although only rarely did this lead to study discontinuation. There was no increase in serious AEs and no evidence of cardiac hypertrophy in bimagrumab-treated participants, suggesting an overall favorable safety profile.

In conclusion, treatment with bimagrumab did not improve 6MWD (primary outcome measure), muscle strength as measured by quadriceps QMT, or grip and pinch strength measured by dynamometry. However, at 10 mg/kg, there was evidence that bimagrumab improved LBM and patient-reported physical function after 52 weeks of therapy, although the clinical significance of these effects is unclear. Based on the study results, the sponsor is not planning to pursue bimagrumab in inclusion body myositis indication. Future studies may require more refined functional indices to fully gauge if there are therapeutic effects of bimagrumab in IBM.

Contributors

The RESILIENT study investigators contributed to patient recruitment. **MGH** contributed to data analysis, writing and revision of the manuscript. **UAB** contributed to the study design, data collection, data interpretation, and writing of the manuscript. **OB** contributed to the study design, data collection, data interpretation, literature search, and critical revision of the manuscript. **TEL** contributed to data collection, data interpretation, and writing of the manuscript. **MN** contributed to data collection and writing of the manuscript. **HC** contributed to data collection, data interpretation, writing and critical revision of the manuscript. **MA** contributed to the study design and data collection. **PMM** contributed to data collection, data analysis, data interpretation, and provided guidance during manuscript as well as figures/tables development. **CL** contributed to data collection, data interpretation, and critical revision of the manuscript. **KAR** contributed to data collection, data analysis, data interpretation, and read manuscript for important scientific content. **MDV** contributed to data collection and critical revision of the manuscript. **DPA** contributed to data collection, writing/ editing of the manuscript. **RJB** contributed to data collection and writing of the manuscript. **MMD** contributed to the study design, data collection, data analysis, data interpretation, and review of the manuscript. **JALM** contributed data collection and critical revision of the manuscript. **JTK** contributed to data collection and review of the manuscript. **NCJ** contributed to data collection and interpretation, writing of the manuscript and figures. **PVDB** contributed to data collection, data analysis and interpretation, and critical revision of the manuscript. **JB** contributed to data collection and interpretation, and critical revision of the manuscript. **JLDB** contributed to data collection, data analysis and interpretation, and read manuscript for important scientific content. **CK** contributed

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the study design, data collection, data analysis and interpretation as well as preparation, review, and approval of the manuscript. **AAA** contributed to the study design, data collection, data analysis and interpretation, and writing of the manuscript.

Declaration of interests

MGH has served on an advisory board for Novartis and received fees. **UAB** reports support from Novartis AG, during the conduct of the study; support from Argen X, outside the submitted work. **OB** reports grants and personal fees from Novartis, during the conduct of the study; grants and non-financial support from Shire, personal fees and non-financial support from: LFB and CSL Behring, grants and personal fees from Neovacs, outside the submitted work. **TEL** reports grants, personal fees and non-financial support from Novartis, during the conduct of the study. **MN** has served on an advisory board for Novartis in the initial study design. **HC** reports grants from The University of Manchester, during the conduct of the study; personal fees and grants from UCB, personal fees from Lilly, support from: Janssen and Abbvie, personal fees from Momenta, outside the submitted work; received personal compensation for activities with Novartis, UCB, Lilly and Momenta as a speaker and/or advisory board member; received travel support from Abbvie and Janssen. **MA** reports grants from: Research on Psychiatric and Neurological Diseases and Mental Health from the Japanese Ministry of Health Labor and Welfare, Grants-in-Aids for Scientific Research,

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Institutions wishing to analyse data from the study can apply online.

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Tables

Table 1. Demographic and baseline characteristics (Full analysis set)

	Bimagrumab 10 mg/kg N=63	**Bimagrumab 3 mg/kg N=63**	**Bimagrumab 1 mg/kg N=63**	**Placebo N=62**
Age, years	68·0 (7·9) (range, 41–79)	66·5 (8·7) (range, 42–84)	69·4 (7·9) (range, 51–85)	68·4 (8·1) (range, 49–83)
Gender, n (%)				
Men	41 (65·1)	42 (66·7)	40 (63·5)	39 (62·9)
Women	22 (34·9)	21 (33·3)	23 (36·5)	23 (37·1)
Race, n (%)				
Caucasian	53 (84·1)	56 (88·9)	53 (84·1)	57 (91·9)
Time since diagnosis (years)#	5·3 (3·98)	4·4 (3·22)	4·2 (3·44)	4·4 (3·39)
Proposed modified 2010 MRC IBM diagnostic criteria type				
Pathologically defined	17 (27·0)	21 (33·3)	18 (28·6)	17 (27·4)
Clinically defined	46 (73·0)	42 (66·7)	45 (71·4)	45 (72·6)
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, n (%)				
No assistance	23 (36·5)	24 (38·1)	31 (49·2)	35 (56·5)
Unilateral assistance	19 (30·2)	24 (38·1)	18 (28·6)	14 (22·6)
Bilateral assistance	5 (7·9)	2 (3·2)	1 (1·6)	2 (3·2)
Walker	16 (25·4)	13 (20·6)	13 (20·6)	11 (17·7)
Muscle strength of the right quadriceps, Newton	57·3 (72·8)	72·8 (89·3)	57·7 (54·7)	69·2 (71·6)
Total LBM, kg	38·5 (8·9)	40·4 (9·2)	38·9 (8·9)	39·9 (10·3)
sIFA total score	57·8 (17·9) (range, 9·1–90·9)	52·4 (17·2) (range, 10·0–90·9)	51·1 (18·1) (range, 15·5–86·4)	51·3 (21·4) (range, 5·5–95·5)

Data are shown as mean (SD), unless specified otherwise.
Reference date is the screening visit
6MWD, 6-minute walk distance test; IBM, inclusion body myositis; LBM, lean body mass; MRC Medical Research Council; sIFA, sporadic inclusion body myositis physical functioning assessment; SD, standard deviation

Table 2. MMRM of change from baseline at week 52 in **(a)** 6MWD, **(b)** log transformed total LBM, **(c)** QMT of right quadriceps, **(d)** sIFA total score **(e)** and SPPB (Full analysis set)

(a) 6MWD

		Change from baseline in 6MWD (m)		Treatment difference comparison (bimagrumab versus placebo)		
Treatment	**n**	**LS mean (SE)**	**95% CI**	**LS mean (SE)**	**99% CI**	**p-values**
Bimagrumab 10 mg/kg	61	8·6 (10·9)	–12·9, 30·2	17·6 (14·3)	–19·6, 54·8	0·2210
Bimagrumab 3 mg/kg	63	9·6 (10·8)	–11·6, 30·8	18·6 (14·2)	–18·2, 55·4	0·1909
Bimagrumab 1 mg/kg	63	–10·3 (10·7)	–31·4, 10·8	–1·3 (14·1)	–38·0, 35·4	0·9263
Placebo	62	–9·0 (10·8)	–30·2, 12·2			

n=number of patients included in analysis
Baseline is defined as the last assessment before the first dose of study drug
6MWD, 6-minute walking distance test; CI, confidence interval; LS mean, least squares mean; MMRM, Mixed Model for Repeated Measures; SE, standard error of the mean

(b) Total LBM

		LBM at visit/LBM at baseline in %		Treatment ratio (bimagrumab versus placebo)		
Treatment	**n**	**exp (LS mean) (exp (SE))**	**95% CI**	**exp (LS mean) (exp (SE))**	**95% CI**	**p-values**
Bimagrumab 10 mg/kg	62	102·8 (100·7)	101·4, 104·2	1·1 (1·0)	1·0, 1·1	<0·0001
Bimagrumab 3 mg/kg	61	100·4 (100·7)	99·1, 101·8	1·0 (1·0)	1·0, 1·1	0·0001
Bimagrumab 1 mg/kg	63	98·3 (100·7)	97·0, 99·6	1·0 (1·0)	1·0, 1·0	0·1714
Placebo	61	97·2 (100·7)	95·9, 98·5			

n=number of patients included in analysis
Baseline is defined as the last assessment before the first dose of study drug
CI, confidence interval; LBM, lean body mass; LS mean, least squares mean; MMRM, Mixed Model for Repeated Measures; SE, standard error of the mean

(c) QMT of right quadriceps

		Change from baseline in QMT (N)		Treatment difference comparison (bimagrumab versus placebo)		
Treatment	**n**	**LS mean (SE)**	**95% CI**	**LS mean (SE)**	**99% CI**	**p-values**
Bimagrumab 10 mg/kg	60	–12·4 (6·0)	–24·3, –0·59	4·05 (7·0)	–14·0, 22·1	0.5618
Bimagrumab 3 mg/kg	63	–20·4 (5·8)	–31·9, –8·85	–3·87 (6·8)	–21·7, 13·9	0.5723
Bimagrumab 1 mg/kg	63	–14·9 (5·8)	–26·4, –3·42	1·59 (6·8)	–16·1, 19·3	0.8153
Placebo	61	–16·5 (5·8)	–28·0, –5·01			

n=number of patients included in analysis
Baseline is defined as the last assessment before the first dose of study drug
CI, confidence interval; LS mean, least squares mean; MMRM, Mixed Model for Repeated Measures; QMT, quantitative muscle testing; SE, standard error of the mean

(d) sIFA total score

		Change from baseline in sIFA (%)		Treatment difference comparison (bimagrumab versus placebo)		
Treatment	**n**	**LS mean (SE)**	**95% CI**	**LS mean (SE)**	**99% CI**	**p-values**
Bimagrumab 10 mg/kg	61	1·7 (1·9)	–2·0, 5·5	–5·11 (2·4)	–11·3, 1·1	0.0338
Bimagrumab 3 mg/kg	63	3·6 (1·9)	–0·1, 7·3	–3·29 (2·4)	–9·4, 2·8	0.1636
Bimagrumab 1 mg/kg	60	6·1 (1·9)	2·4, 9·9	–0·73 (2·4)	–6·9, 5·4	0.7580
Placebo	61	6·9 (1·9)	3·1, 10·6			

n=number of patients included in analysis
Baseline is defined as the last assessment before the first dose of study drug
sIFA total score is between 0 (lowest level of difficulty) and 100 (highest level of difficulty/unable to complete)
CI, confidence interval; LS mean, least squares mean; MMRM, Mixed Model for Repeated Measures; SE, standard error of the mean; sIFA, sporadic inclusion body myositis physical functioning assessment

(e) SPPB

	Change from baseline in score		Treatment difference comparison (bimagrumab versus placebo)		
Treatment	**LS mean (SE)**	**95% CI**	**LS mean (SE)**	**99% CI**	**p-values**
Bimagrumab 10 mg/kg	0.0 (0.24)	–0.4, 0.5	0.5 (0.3)	–0.1, 1.1	0.0833
Bimagrumab 3 mg/kg	0.0 (0.23)	–0.5, 0.4	0.5 (0.3)	–0.1, 1.1	0.1059
Bimagrumab 1 mg/kg	–0.5 (0.23)	–1.0, –0.1	0.0 (0.3)	–0.6, 0.6	0.9303
Placebo	–0.5 (0.23)	–1.0, –0.1			

n=number of patients included in analysis
Baseline is defined as the last assessment before the first dose of study drug
CI, confidence interval; LS mean, least squares mean; MMRM, Mixed Model for Repeated Measures; SPPB, short physical performance battery; SE, standard error of the mean

Table 3. Number (%) of participants with AEs and serious AEs (Safety analysis set)

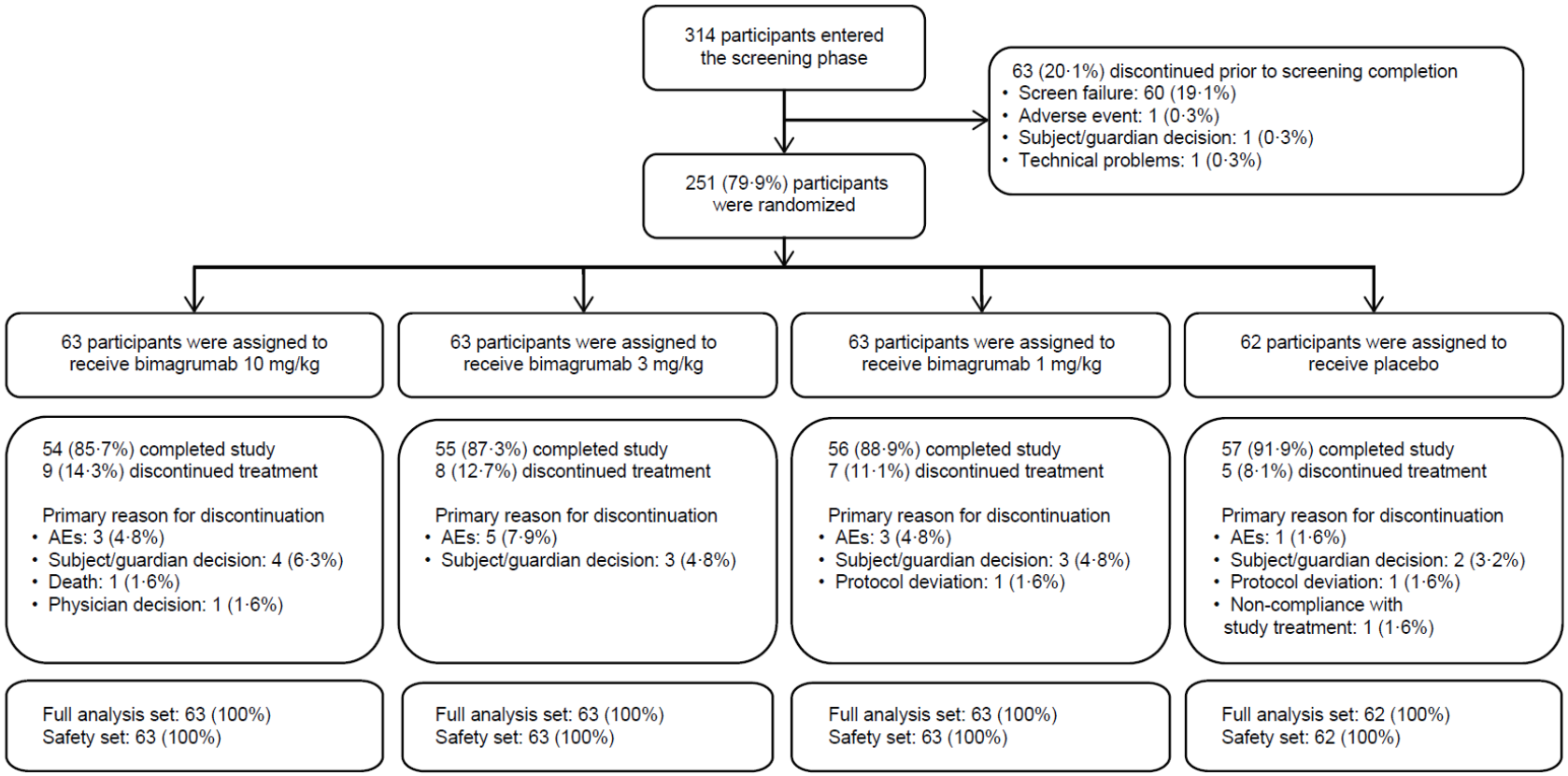
	Bimagrumab 10 mg/kg N=63 n (%)	**Bimagrumab 3 mg/kg N=63 n (%)**	**Bimagrumab 1 mg/kg N=63 n (%)**	**Placebo N=62 n (%)**
Participants with at least one AE*	63 (100)	63 (100)	63 (100)	61 (98·4)
Mild	17 (27·0)	20 (31·7)	18 (28·6)	21 (33·9)
Moderate	28 (44·4)	27 (42·9)	25 (39·7)	29 (46·8)
Severe	18 (28·6)	16 (25·4)	20 (31·7)	11 (17·7)
Participants with at least one serious AE	21 (33·3)	11 (17·5)	20 (31·7)	20 (32·3)
Death	1 (1·6)	0	1 (1·6)	0
Discontinuation due to AE(s)*	4 (6·3)	4 (6·3)	4 (6·3)	1 (1·6)
AEs with ≥5% higher frequency in the 10 mg/kg bimagrumab versus placebo group				
Muscle spasms	32 (50·8)	43 (68·3)	25 (39·7)	13 (21·0)

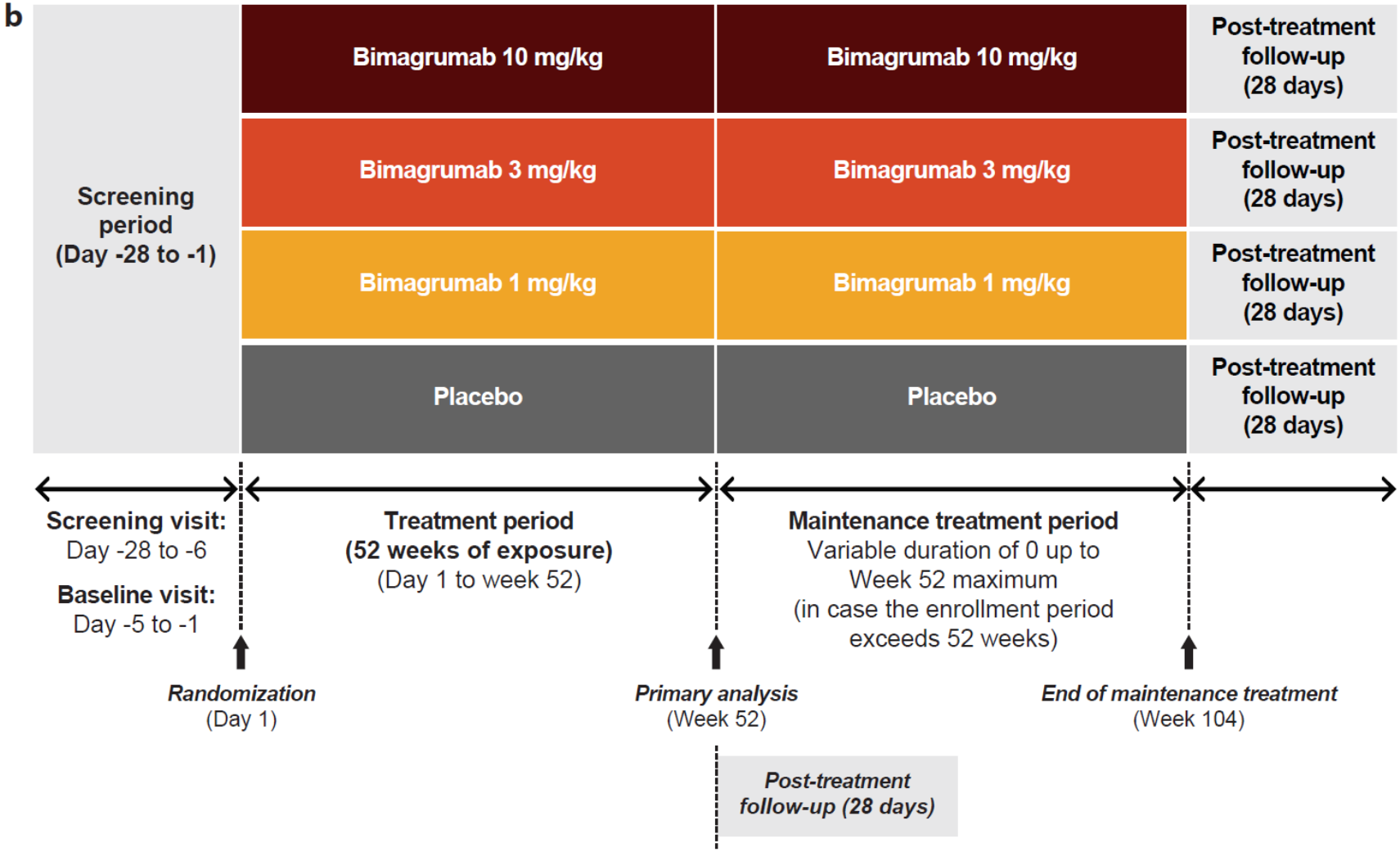
Diarrhea	33 (52·4)	28 (44·4)	20 (31·7)	11 (17·7)
Acne	12 (19·0)	19 (30·2)	8 (12·7)	6 (9·7)
Rash	13 (20·6)	8 (12·7)	10 (15·9)	8 (12·9)
Nausea	11 (17·5)	4 (6·3)	9 (14·3)	5 (8·1)
Weight decreased	9 (14·3)	4 (6·3)	8 (12·7)	3 (4·8)
Decreased appetite	10 (15·9)	3 (4·8)	3 (4·8)	1 (1·6)
Pruritus	6 (9·5)	6 (9·5)	6 (9·5)	1 (1·6)
Anemia	5 (7·9)	3 (4·8)	1 (1·6)	1 (1·6)
Insomnia	5 (7·9)	0	2 (3·2)	1 (1·6)
Dysgeusia	5 (7·9)	1 (1·6)	0	1 (1·6)
Hypomagnesemia	4 (6·3)	2 (3·2)	0	0

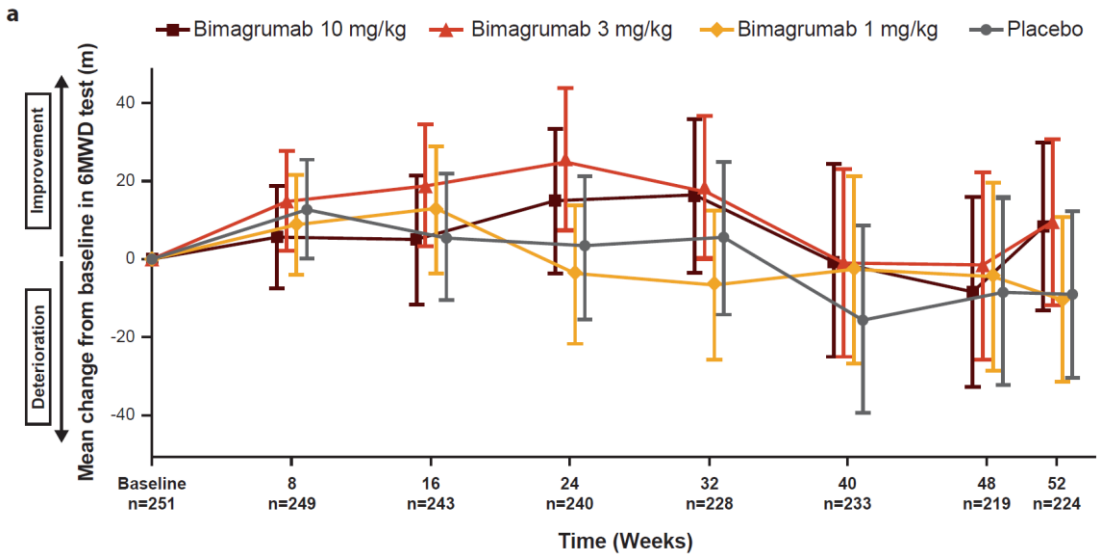
*AEs starting on or after the day of first administration of study drug until last administration of study drug + 56 days are considered.
A participant with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the maximum severity.
AEs, adverse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

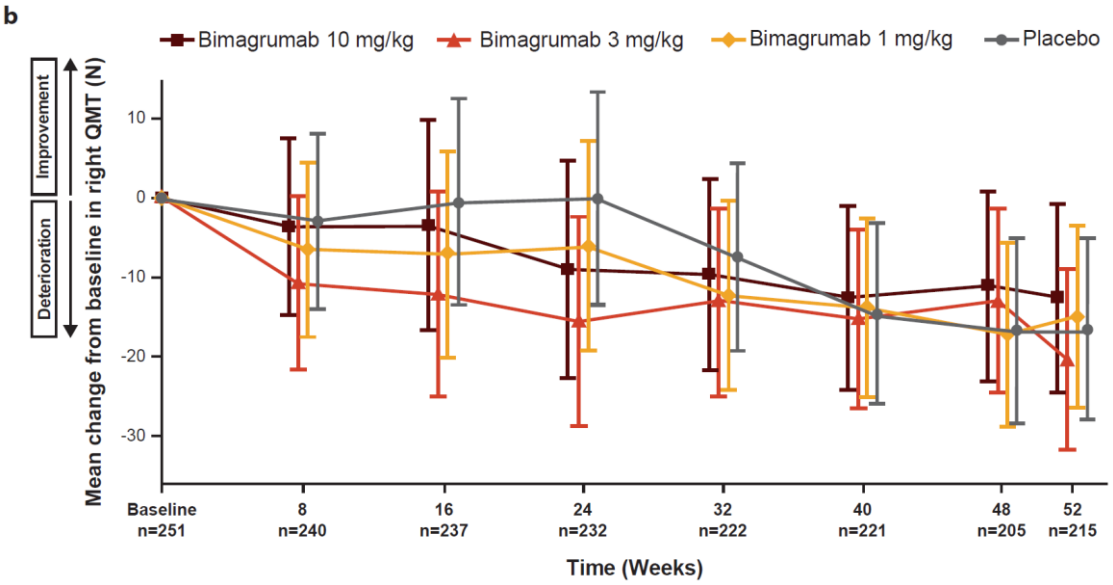
Figures

a


314 participants entered the screening phase
63 (20·1%) discontinued prior to screening completion
• Screen failure: 60 (19·1%)
• Adverse event: 1 (0·3%)
• Subject/guardian decision: 1 (0·3%)
• Technical problems: 1 (0·3%)
251 (79·9%) participants were randomized
63 participants were assigned to receive bimagrumab 10 mg/kg
63 participants were assigned to receive bimagrumab 3 mg/kg
63 participants were assigned to receive bimagrumab 1 mg/kg
62 participants were assigned to receive placebo
54 (85·7%) completed study
9 (14·3%) discontinued treatment
Primary reason for discontinuation
• AEs: 3 (4·8%)
• Subject/guardian decision: 4 (6·3%)
• Death: 1 (1·6%)
• Physician decision: 1 (1·6%)
55 (87·3%) completed study
8 (12·7%) discontinued treatment
Primary reason for discontinuation
• AEs: 5 (7·9%)
• Subject/guardian decision: 3 (4·8%)
56 (88·9%) completed study
7 (11·1%) discontinued treatment
Primary reason for discontinuation
• AEs: 3 (4·8%)
• Subject/guardian decision: 3 (4·8%)
• Protocol deviation: 1 (1·6%)
57 (91·9%) completed study
5 (8·1%) discontinued treatment
Primary reason for discontinuation
• AEs: 1 (1·6%)
• Subject/guardian decision: 2 (3·2%)
• Protocol deviation: 1 (1·6%)
• Non-compliance with study treatment: 1 (1·6%)
Full analysis set: 63 (100%)
Safety set: 63 (100%)
Full analysis set: 63 (100%)
Safety set: 63 (100%)
Full analysis set: 63 (100%)
Safety set: 63 (100%)
Full analysis set: 62 (100%)
Safety set: 62 (100%)


b
Screening period (Day -28 to -1)
Bimagrumab 10 mg/kg
Bimagrumab 10 mg/kg
Post-treatment follow-up (28 days)
Bimagrumab 3 mg/kg
Bimagrumab 3 mg/kg
Post-treatment follow-up (28 days)
Bimagrumab 1 mg/kg
Bimagrumab 1 mg/kg
Post-treatment follow-up (28 days)
Placebo
Placebo
Post-treatment follow-up (28 days)
Screening visit: Day -28 to -6
Baseline visit: Day -5 to -1
Treatment period (52 weeks of exposure) (Day 1 to week 52)
Maintenance treatment period Variable duration of 0 up to Week 52 maximum (in case the enrollment period exceeds 52 weeks)
Randomization (Day 1)
Primary analysis (Week 52)
End of maintenance treatment (Week 104)
Post-treatment follow-up (28 days)


a
Bimagrumab 10 mg/kg
Bimagrumab 3 mg/kg
Bimagrumab 1 mg/kg
Placebo
Improvement
Deterioration
Mean change from baseline in 6MWD test (m)
40
20
0
-20
-40
Baseline n=251
8 n=249
16 n=243
24 n=240
32 n=228
40 n=233
48 n=219
52 n=224
Time (Weeks)


b
Bimagrumab 10 mg/kg
Bimagrumab 3 mg/kg
Bimagrumab 1 mg/kg
Placebo
Improvement
Deterioration
Mean change from baseline in right QMT (N)
10
0
-10
-20
-30
Baseline n=251
8 n=240
16 n=237
24 n=232
32 n=222
40 n=221
48 n=205
52 n=215
Time (Weeks)

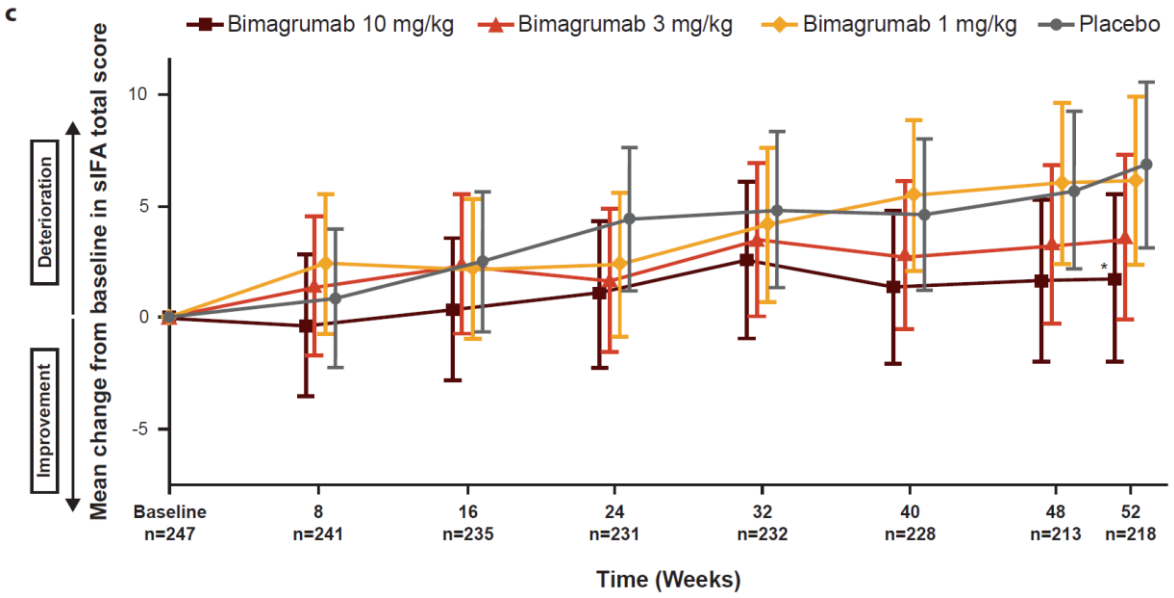

c
Bimagrumab 10 mg/kg
Bimagrumab 3 mg/kg
Bimagrumab 1 mg/kg
Placebo
Mean change from baseline in sIFA total score
Deterioration
Improvement
10
5
0
-5
*
Baseline n=247
8 n=241
16 n=235
24 n=231
32 n=232
40 n=228
48 n=213
52 n=218
Time (Weeks)

Figure Legends

Figure 1. Participant disposition **(a)** and study design **(b)**

(a)

AEs, adverse events

Note: One participant was erroneously randomised and was discontinued immediately prior to receiving the study treatment. The participant who was erroneously randomised (assigned to placebo group) was re-randomised to bimagrumab 10 mg/kg group and was counted only once in the analysis set. Of the 314 participants who entered the screening phase, 251 were randomised: 63 participants to each of the bimagrumab 10, 3, and 1 mg/kg groups and ultimately 62 participants to the placebo group.

Figure 2. Mean change from baseline at Week 52 on **(a)** 6MWD, **(b)** right quadriceps strength, and **(c)** sIFA (full analysis set)

(a)

6MWD, 6-minute walk distance test; CI, confidence interval; LS mean, least-squares mean; SE, standard error

Error bars represents 95% CI

(b)

CI, confidence interval; LS mean, least-squares mean; QMT, quantitative muscle testing; N, newton; SE, standard error

Error bars represents 95% CI

(c)

CI, confidence interval; LS mean, least-squares mean; sIFA, sporadic inclusion body myositis physical functioning assessment; SE, standard error

Error bars represents 95% CI

P=0·03*