Efficacy and Safety of Bimagrumab in Sporadic Inclusion Body Myositis: Long-Term Extension of RESILIENT

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ABSTRACT

Objective: To assess long-term (2 years) effects of bimagrumab in participants with sporadic inclusion body myositis.

Methods: Participants (aged 36–85 years) who completed the core study (RESILIENT) were invited to join an extension study. Individuals continued on same treatment as in the core study (10 mg/kg, 3 mg/kg, 1 mg/kg bimagrumab, or matching placebo administered as intravenous infusions every 4 weeks). The co-primary outcome measures were 6-minute walk distance (6MWD) and safety.

Results: Between November 2015 and February 2017, 211 participants entered double-blind placebo-controlled period of the extension study. Mean change in 6MWD from baseline was highly variable across treatment groups, but indicated progressive deterioration from weeks 24 to 104 in all treatment groups. Overall, 91·0%(n=142) participants in the pooled bimagrumab group and 89·1%(n=49) in the placebo group had ≥1 treatment-emergent adverse event (AE). Falls were slightly higher in the bimagrumab 3 mg/kg group versus 10 mg/kg, 1 mg/kg and placebo groups (69·2%[n=36 of 52] vs. 56·6%[n=30 of 53], 58·8%[n=30 of 51], and 61·8%[n=34 of 55], respectively). The most frequently reported AEs in pooled bimagrumab group were diarrhea 14·7%(n=23), involuntary muscle contractions 9·6%(n=15), and rash

5·1%(n=8). Incidence of serious AEs was comparable between the pooled bimagrumab and the placebo group (18·6%[n=29] vs. 14·5%[n=8], respectively).

Conclusion: Extended treatment with bimagrumab up to 2 years produced a good safety profile and was well-tolerated, but did not provide clinical benefits in terms of improvement in mobility. The extension study was terminated early due to core study not meeting its primary endpoint.

CLASSIFICATION OF EVIDENCE

This study provides Class IV evidence that for patients with sIBM, long-term treatment with bimagrumab was safe, well tolerated and did not provide meaningful functional benefit. The study is rated Class IV because of the open label design of Extension Treatment Period 2.

INTRODUCTION

Sporadic inclusion body myositis (sIBM) represents the most common form of idiopathic inflammatory myopathy in participants aged ≥50 years, affecting men more often than women (ratio: 2:1 to 3:1).[1] As the disease progresses, muscle weakness in the quadriceps may cause difficulties with rising from a seated position, mobility

limitation, frequent falls and injuries,[2] and ultimately many participants opt to use a wheelchair.[3,4]

Currently, there are no approved treatment options to slow down or reverse the progression of muscle weakness and atrophy in sIBM.[5,6] As there is pathological muscle loss in sIBM the treatments target muscle atrophy pathways. Bimagrumab is a fully human, monoclonal antibody against activin type II receptors (ActRII) that prevents binding of muscle-regulating ligands (ie activin and myostatin) to these receptors, thereby inhibiting downstream signaling-induced muscle loss.[7,8] Activin and myostatin (muscle-regulating ligands) are known to signal through ActRII trigger increases in Smad2/3 phosphorylation, resulting in inhibiting muscle-specific gene upregulation and downregulation of Akt phosphorylation ultimately leading to muscle atrophy.[9] A proof-of-concept study in participants with sIBM (N=14; 11 active, 3 placebo) showed that a single exposure to bimagrumab 30 mg/kg i.v. – resulting in 2-month continuous exposure – increased thigh muscle volume over 8 weeks followed by an increase of 49 m in the 6-minute walk distance (6MWD) from baseline to 16 weeks.[9] Findings from the largest clinical study RESILIENT (core study) in participants with sIBM (N=251) showed that treatment with bimagrumab did not improve mobility relative to placebo as assessed by changes of the 6MWD (primary endpoint) from baseline to week 52 despite increases in lean body mass (LBM).[10]

Here, we report on the long-term extension of the RESILIENT study (up to 2 years) to further assess efficacy and safety of bimagrumab beyond the initial 12-month treatment period.

METHODS

Primary research question

RESILIENT (core study) is the largest (N=251) Phase 2b clinical study of an activin type II receptor antagonist in participants with sIBM. Currently, there are no effective or approved options for the treatment of sIBM. The extension study assessed the long-term (2 years) effects of bimagrumab administered as i.v. infusion every 4 weeks in participants with sIBM. This study provides Class IV evidence that for patients with sIBM, long-term treatment with bimagrumab was safe, well tolerated and did not provide meaningful functional benefit. The study is rated Class IV because of the open label design of Extension Treatment Period 2.

Study design and participants

RESILIENT (core study; ClinicalTrials.gov number, NCT01925209) was a randomised, double-blind, placebo-controlled, dose-finding, phase 2b study.[10] The core study enrolled men and women aged 36–85 years with a pathologically or clinically defined diagnosis of sIBM according to the modified 2010 Medical Research Council (MRC) criteria.[11,12] Participants who had completed the core study were invited to join this extension study. The extension study was conducted between November 2015 and February 2017 (early termination) at 38 academic clinical sites in Australia, Belgium,

Denmark, France, Italy, Japan, the Netherlands, Switzerland, the UK, and the USA. The extension study was prematurely terminated, as findings from the core study did not meet its primary objective when all participants had completed week 52.

The extension study comprised a screening period (to assess participant eligibility), an Extension Treatment Period 1 (double-blind and placebo-controlled), an Extension Treatment Period 2 (open-label), and a post-treatment follow-up (Figure 1a). In the study, intermittent use of wheelchairs was allowed; however, participants had to be able to walk at least 1 m without assistance from another person. The use of assistive aids including canes, walkers, or rollators were permitted during the walking test. Key exclusion criteria preventing further participation were (i) a history of severe hypersensitivity reaction in the core study, adverse event(s) (AEs; including those from the core study) prior to the start of the study medication in the extension study that, in the judgment of the investigator, prevented the participant from entering the extension study; and (ii) clinically significant abnormal liver function tests. Participants on current use of prohibited treatments were also excluded (e.g., prohibited during Treatment period 1: androgen modulators, anabolic steroids, anti-androgens, anti-estrogens, progestins, insulin, dronabinol, systemic glucocorticoids [short-term (<14 days) irregular use if medically indicated was permitted], oral beta-adrenergic agonists, systemic beta blockers, gonadotropin-releasing hormone analogues, growth hormone receptor antagonists, human growth hormone and/or mimetics and ghrelin, drug inhibiting angiogenesis, and vascular endothelial growth factor inhibitors; prohibited during

Extension Treatment Period 1 and 2: immunomodulators). Finally, women who were pregnant, or of child-bearing potential were excluded from the study.

Standard protocol approvals, registrations, and patient consents

Members of the Steering Committee gathered from known medical experts supported Novartis Pharma AG in developing the protocol. The study protocol, protocol amendments, and informed consent forms were all reviewed and approved by the Institutional Review Board/Independent Ethics Committee at each participating site. Informed consent was obtained from each participant in writing before any study-specific procedures were performed. The study was performed in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice,[13] in compliance with applicable local regulatory bodies, and with the ethical principles established in the Declaration of Helsinki.

The extension study was registered with ClinicalTrials.gov, number NCT02573467.

Masking

This was an extension of a randomised core study (RESILIENT). In the core study eligible participants were randomly assigned (1:1:1:1) to receive intravenous infusions of bimagrumab 10, 3, 1 mg/kg, or matching placebo every 4 weeks. Further details about the core study randomisation are provided elsewhere.[10] The participants who completed the core study entered the extension study and continued on the same study medication to which they were randomised in the core study. Once the last participant

completed week 48 visit in the core study, all ongoing participants who completed the end of treatment / end of maintenance treatment visit entered the screening period of the extension study after signing the informed consent.

The study medication for the Extension Treatment Period 1 (double-blind and placebo-controlled) was prepared by an unblinded pharmacist/designee appointed at the study site, and administered to the participants by blinded study site personnel. Participants who were assigned to study treatment remained blinded. Investigators and their site personnel and persons performing the assessments remained blinded to the identity of the treatment. No other person had access to the medication and drug administration documentation, except the unblinded Novartis monitor. The identity of the bimagrumab or placebo treatments was concealed by sleeve-covered infusion bags filled with active or placebo solutions identical in appearance, but the actual bimagrumab or placebo vials were supplied “open-label”.

Study procedures

Scheduled study visits took place at screening, day 1, week 2, week 4, every 4 weeks during Extension Treatment Period 1 and at the end of Extension Treatment Period 1 (week 52; week 52 resembles week 104 as from the core study). During the Extension Treatment Period 1 efficacy assessments (6MWD, short physical performance battery [SPPB], quantitative muscle testing [QMT]) were at week 24 and week 52, and safety was assessed at scheduled visits and by recording of adverse events and serious adverse events throughout the study. Sporadic inclusion body

myositis functional assessment (sIFA) was assessed at screening, week 24 and week 52 of Extension Treatment Period 1 (Extension Treatment Period 2: week 52 and 6-month post treatment follow-up). Physical examination, vital signs, haematological testing, blood chemistry, and urinalysis were performed at week 24 and week 52. Assessment of falls was performed at all scheduled visits, whereas electrocardiography was assessed every 12 weeks. Extension Treatment Period 1 was a double-blind placebo-controlled period. Bimagrumab or matching placebo was administered intravenously every 4 weeks as slow infusion over no less than 30 minutes. Starting at Day 1 and at all subsequent site visits during Treatment Period 1, the unblinded pharmacist/designee contacted the Interactive Response Technology (IRT) to obtain unique medication numbers to prepare the investigational treatment for each participant. Participants were allowed to voluntarily discontinue from the study treatment for any reason at any time. Participants who discontinued prematurely during Extension Treatment Period 1 for any other reason entered the post-treatment follow-up period.

Extension Treatment Period 2 was open-label (no blinding). As per protocol, all participants were scheduled for transition to the Extension Treatment Period 2 to receive continuing treatment with the optimal dose of bimagrumab as indicated by the 52-week data. However, the extension study protocol allowed for early termination of the study if no bimagrumab dose elicited statistically and clinically significant increase in the 6MWD at week 52.

Outcomes

The primary outcome measures were 6MWD as well as incidence of AEs and serious AEs. Additional safety outcome measures included physical examination, monitoring of vital signs, laboratory evaluations (hematology, clinical chemistry, coagulation testing, and urinalysis), electrocardiography, and assessment of immunogenicity. Secondary outcomes included physical function (sIFA) and muscle strength measurements (quantitative muscle testing of right quadriceps and hand-grip). The latter were performed using BTE Evaluator portable fixed dynamometry (BTE Technologies, Hanover, MD) or equivalent. sIFA is a patient-reported outcome measure developed specifically for sIBM in alignment with the FDA PRO guidance[14] and evaluated in three observational studies and demonstrated to have good psychometric properties.[15,16] Falls were reported by participants. The SPPB is a physical performance test that evaluates lower extremities function by using tests of gait speed, standing balance, and time to rise from a chair five times.

Statistical analysis

In the extension study, no hypothesis testing was performed (summary analyses were planned). For evaluation of efficacy the double-blind treatment period of the extension study was combined with the initial core study. Enrollment of participants in the extension study was determined based on the number completing the core study, and not more than 240 participants were planned to be enrolled into this study. The full analysis set (FAS) comprised participants to whom the study treatment was assigned in the core study. The safety set included all participants who received at least one dose of

study drug in the extension study. The 6MWD results from the pooled double-blind treatment periods of the core and extension studies were summarised descriptively by visits for the FAS. Efficacy assessments were performed at the core study baseline. Patient demographics and baseline characteristics were at the extension study baseline (i.e., prior to intake of any study medication in extension study). The change from core study baseline in 6MWD was computed for each visit. For secondary efficacy variables (quantitative muscle testing of right quadriceps, sIFA, falls, and hand-grip), analyses were performed similar to 6MWD. Crude group-level annualised falls rate was calculated as the total number of falls of all individuals within a treatment group/total days of risk of all individuals of the treatment arm x 365.25. Efficacy analyses were performed from the core study baseline to end of Treatment Period 1, whereas safety was only from the extension phase.

An independent, external Data Monitoring Committee (DMC) of the entire bimagrumab program continued to review the safety data at regular intervals. DMC provided recommendations to the Sponsor concerning safety and study continuation or discontinuation. An independent adjudication committee monitored specific safety events, including, but not limited to clinically significant cardiovascular events.

In this study, the statistical analyses were performed with SAS program, version 9·3 (SAS Institute, Cary, NC, US). Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18·1.

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.

Data Availability

Anonymised data will be shared by request from any qualified investigator. Individual participant data will not be shared.

RESULTS

Of the 215 screened participants (38 sites) from the core study, 211 entered the extension study Treatment Period 1. There were four participants who were not enrolled in the extension study as they were screen failures. The primary reason for discontinuation were subject/guardian decision (n=1), screen failure (n=2), study terminated by sponsor (n=1). As the core study did not meet its primary endpoint of significantly improving the 6MWD from baseline to week 52, the study medication in the extension study was terminated per study protocol before any participant entered the Extension Treatment Period 2. During Extension Treatment Period 1 there were 204 participants who discontinued study treatment (Figure 1b). Subsequently, 178 participants entered the post-treatment follow-up period following Treatment Period 1.

Of 178 participants, 154 (86·5%) completed the follow-up period and 24 (13·5%) discontinued before completion.

The baseline demographics were well balanced between all treatment groups participating in the extension study (Table 1). There were more men than women (65·4% [n=138] vs. 34·6% [n=73]) in the extension study. The mean (SD) age of participants was 69·1 (8·24) years, and the majority were Caucasian (87·2%; n=184). Participants in the bimagrumab 10 mg/kg group had numerically lower mean [SD] 6MWD at baseline (268·6 [133·5]); and sIFA total score in the 10 mg/kg group was higher (i.e. greater difficulty) compared with the other bimagrumab groups (10 mg/kg vs. 3 mg/kg or 1 mg/kg: 56·9 [18·7] vs. 51·0 [18·1] or 50·9 [18·2]) and the placebo group (10 mg/kg vs. placebo: 56·9 [18·7] vs. 50·0 [20·6]), raising the possibility that those included in the bimagrumab 10 mg/kg dose group had on average more severe underlying disease.

6-minute walk distance test

The mean change in 6MWD from baseline was highly variable across treatment arms and showed progressive decline from week 24 to week 104 in all treatment groups (following a small transient increase during the first 6 months of the core study) (Figure 2).

Sporadic inclusion body myositis physical functioning assessment

The differences in changes in sIFA total score from the core study baseline increased progressively between the placebo and the 10 mg/kg bimagrumab groups up to week 78. The number of participants was sustained until this visit. At week 104, only 150 participants completed sIFA, limiting the interpretation of the curve as a continuum. At week 104, the bimagrumab 10 mg/kg dose group experienced a relative worsening, whereas the placebo group remained largely stable, resulting in convergence of responses toward the end of the observation period (Figure 3).

Quantitative muscle testing of right quadriceps

Absolute changes in the quadriceps muscle strength (N) were highly variable in each of the treatment arms and there was no indication of a dose-response relationship based on the mean changes from baseline. The overall trend of changes suggested slow but progressive decline over the 104-week observation period. The differences in the changes of muscle strength between bimagrumab and placebo groups were not clinically meaningful at any time point during the treatment period (Figure 4).

Hand-grip strength

The absolute changes in handgrip strength were also highly variable. The differences in muscle strength per hand grip between bimagrumab and placebo groups were not clinically meaningful at any time point (Figure 5).

Falls

The annualised rates of all falls were slightly higher in the bimagrumab 10 mg/kg group compared with the other bimagrumab groups and placebo group (all falls: 4·164 [10 mg/kg] vs. 3·480 [1 mg/kg], 3·879 [3 mg/kg], and 3·835 [placebo]).

Safety

Ninety-one percent of participants in the pooled bimagrumab group and 89·1% in the placebo group had at least one treatment-emergent adverse event (AE). Overall, 5 deaths were reported during the study. One death in the bimagrumab 1 mg/kg group and one in the placebo group occurred during Treatment Period 1. The remaining 3 deaths (one each in the 10 mg/kg and 3 mg/kg bimagrumab groups and placebo group) occurred during the post-treatment follow-up period. The causes of deaths were respiratory failure, pneumonia and aspiration pneumonia, which are all regarded as relatively frequent and fatal complications in this population. None of these deaths were considered to be related to the study medication by the investigator. The incidence of AEs (91·0% vs. 89·1%) and SAEs (18·6% vs. 14·5%) was comparable between the pooled bimagrumab versus the placebo group. No dose-dependent increases in the overall incidence of AEs were observed. The incidence of SAEs was comparable between the pooled bimagrumab and placebo groups (Table 2). The most frequently reported exposure-adjusted AESI (AEs of special interest; incidence rate greater than 15 per 100 patient-years) in the pooled bimagrumab group were diarrhea (49·4), acne (24·7), involuntary muscle contractions (18·8), and hypersensitivity (17·8). Hypersensitivity was defined as per SMQ (standardised MedDRA query) and included

the following AE preferred terms (rash, rhinitis allergic, dermatitis, dermatitis contact, hand dermatitis, lip swelling, rash erythematous, and urticaria).

Fall was reported by more than 50% of the participants across all the treatment groups. The incidence of falls was slightly higher in the bimagrumab 3 mg/kg group compared with the bimagrumab 10 mg/kg, 1 mg/kg and placebo groups (69·2% vs. 56·6%, 58·8%, and 61·8% respectively) without any clear dose-dependent trend or statistically significant difference observed. The most frequently reported AEs (>5% incidence) in the pooled bimagrumab group were diarrhea (14·7%), involuntary muscle contractions (9·6%), and rash (5·1%) (Table 2).

DISCUSSION

The primary analysis of the core study (i.e., changes in 6MWD from baseline to week 52) did not reveal statistically and clinically meaningful improvements of physical performance in any of the doses of bimagrumab when compared to placebo; therefore, administration of the study medication in the extension study was stopped prematurely. As a consequence, about one-third of the participants did not reach week 104. None of the assessed outcome measures revealed clinical benefits to treatment during the study. However, this study provides a 2-year insight into the history of sIBM utilizing multiple types of outcome measures including clinical indices as well as both performance-based and patient self-reported.

Compared to week 52 findings, extension of the treatment period did not change the overall conclusions based on objective measures of muscle function. Changes of these parameters from the core baseline suggested a slow but progressive decline, with no significant differences between treatment arms. Bimagrumab showed a dose-dependent improvement of self-reported physical function from baseline to week 52 as assessed by sIFA. In the extension study, the relative benefits of the 10 mg/kg bimagrumab group appeared to increase compared to the changes in the placebo group at week 78. However, progressive separation of treatment curves were not observed at week 104 when responses seemed to converge rather than diverge further. A significant drop in the number of participants attending this visit, which was mainly caused by stopping the double-blind treatment period based on the core study results related to 6MWD represents, an important caveat in the interpretation of apparent changes between week 78 and week 104.

In this study, quadriceps muscle strength seemed to deteriorate in all treatment groups, although the absolute changes in muscle strength were highly variable. No clinically meaningful differences were observed between the bimagrumab and placebo groups at any time. The variability in the reported results is due to, at least in part, the heterogeneity of the study population in terms of disease duration, distribution of muscle weakness, and severity. In contrast to the proof-of-concept study conducted in 2 centres that showed improvement favoring a single dose of bimagrumab 30 mg/kg i.v. in right quadriceps QMT,[9] the lack of significant differences between treatment groups of the RESILIENT study may also involve difficulties in standardisation of these methods

between centres in a worldwide multicentre study. Conversely, the proof-of-concept study was not powered for efficacy and is prone to spurious results.[9]

The long-term use of bimagrumab was well-tolerated. Falls were observed in more than 50% of all participants in line with this being a common complication of the underlying muscle disease. Less than a quarter of AEs were suspected to be related to the study drug. The bimagrumab 3 mg/kg group showed slightly higher incidence of AEs and suspected AEs as compared with the other treatment groups. Diarrhea and involuntary muscle contractions were the most common suspected AEs. The majority of cases of diarrhea were mild or moderate in severity.

In this study, diarrhea, acne, involuntary muscle contractions, and hypersensitivity were the most frequently reported exposure-adjusted AEs of special interest (IR frequency exceeding 15/100 patient years in the pooled bimagrumab group). These findings are similar to earlier clinical studies testing bimagrumab, in which transient acne, involuntary muscle contractions and diarrhea were the most frequently reported AEs with higher frequency of reporting accompanying higher doses of the antibody.[9,10]

The study limitations include the wide heterogeneity of the study population in terms of disease severity, distribution of muscle weakness, and physical performance at baseline. Although the broad spectrum of disease manifestations in each arm pinned down the representativeness of the study population to the real world patient population,

yet it may have impacted the statistical probability of demonstrating significant differences between placebo and bimagrumab-treated patients. In addition, although the use of physical performance measures as well as the procedures of measuring muscle strength were guided by standardised methods, variations in the method leading to differences in the measured responses of participants between clinical sites is another limitation of using muscle strength measurements in multicenter clinical trials. Measuring thigh muscle volume by MRI or limb LBM by dual-energy X-ray absorptiometry, DEXA, in the core study and/or quadriceps strength in the core and extension study might have helped to deal with collective analysis and better understanding of the data. Furthermore, mobility/physical performance in sIBM participants may be a function of multiple etiopathological factors beyond muscle mass and weakness. This may include injuries, illnesses, mood changes, sleeping problems, etc., which possibly also influenced the variation in responses over time in the different treatment arms. The study design and some of the deviations from it during the operational execution have also led to limitations driven by differences in total exposure time. Similarly, therapeutic gaps of variable duration between the end of treatment in the core study and initiation of the treatment in the extension study may have impacted results from affected participant. Another limitation of this extension study is that after demonstrating significant increases and sustained responses of lean body mass in the core study, monitoring of this parameter with DEXA was not continued. Conversely, the lean body mass changes observed in the core study seem to be of no clinical relevance. In addition, announcement of the failure of the core study may have theoretically affected self-reported results of sIFA. Finally, the limited number of visits after week 52

resulting from premature termination of the study treatment likely introduced significant changes to the conduct of the study, limiting the number of participants contributing to the number of observations at the week 104 visit data.

CONCLUSION

Extended treatment and observation of participants with sIBM beyond week 52 suggest that bimagrumab had a good safety profile and well tolerated, though it did not demonstrate meaningful functional benefits in participants treated with bimagrumab versus placebo. Outcome measures described the slow but progressive decline in function. Findings from this study, which is the largest and longest ever conducted in sIBM participants, may help to understand disease progression and provide important input to consider when designing clinical trials testing the anticipated benefits of new investigational drugs.

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Tables

Table 1. Demographic and participant baseline characteristics at extension study baseline (FAS)

	Bimagrumab 10 mg/kg N=53	**Bimagrumab 3 mg/kg N=52**	**Bimagrumab 1 mg/kg N=51**	**Placebo N=55**
Age, years	69·2 (8·19) (range: 43–80)	67·3 (9·04) (range: 43–85)	70·0 (7·69) (range: 54–87)	69·9 (7·95) (range: 50–84)
Gender, n (%)				
Men	35 (66·0)	33 (63·5)	34 (66·7)	36 (65·5)
Women	18 (34·0)	19 (36·5)	17 (33·3)	19 (34·5)
Race, n (%)				
Caucasian	43 (81·1)	46 (88·5)	44 (86·3)	51 (92·7)
BMI (kg/m^2)	24·2 (3·71)	25·5 (4·8)	24·9 (3·3)	25·8 (4·2)
6MWD, m	n=53 268·6 (133·5)	n=52 296·3 (94·2)	n=51 315·44 (125·0)	n=55 310·7 (125·5)
QMT of right quadriceps (N)	n=53 58·3 (76·5)	n=52 77·41 (93·8)	n=51 58·1 (55·3)	n=55 72·63 (74·7)
Right hand-grip strength (N)	n=52	n=52	n=51	n=54

	89·1 (63·2)	103·30 (59·5)	110·30 (70·8)	108·3 (63·3)
Right pinch-grip strength (N)	n=50 47·2 (25·2)	n=52 67·74 (136·5)	n=51 45·6 (23·9)	n=54 48·6 (19·3)
sIFA total score	n=53 56·9 (18·7) (range, 9·1–90·9)	n=52 51·0 (18·1) (range, 10·0–90·9)	n=49 50·9 (18·2) (range, 15·5–86·4)	n=52 50·0 (20·6) (range, 5·5–81·8)
Short physical performance test total score (points)	n=53 6·0 (2·5)	n=52 6·7 (1·9)	n=51 6·8 (2·0)	n=55 7·1 (2·2)

Data are shown as mean (SD), unless specified otherwise; body mass index: BMI (kg/m^2) = baseline weight (kg) / screening height (m)^2

6MWD, 6-minute walk distance test; BMI, body mass index; FAS, full analysis set; sIFA, sporadic inclusion body myositis physical functioning assessment; SD, standard deviation; QMT, quantitative muscle testing

Table 2. Participants with AEs and serious AEs during extension study (safety set)

	Bimagrumab 10 mg/kg N=53 n (%)	**Bimagrumab 3 mg/kg N=52 n (%)**	**Bimagrumab 1 mg/kg N=51 n (%)**	**Placebo N=55 n (%)**	**Pooled active treatment groups N=156 n (%)**

Subjects with at least one AE *	48 (90·6)	50 (96·2)	44 (86·3)	49 (89·1)	142 (91·0)
Diarrhea †	9 (17·0)	5 (9·6)	9 (17·6)	5 (9·1)	23 (14·7)
Involuntary muscle contractions †	4 (7·5)	8 (15·4)	3 (5·9)	1 (1·8)	15 (9·6)
Rash †	2 (3·8)	3 (5·8)	3 (5·9)	1 (1·8)	8 (5·1)
Subjects with at least one serious AE ‡	12 (22·6)	10 (19·2)	7 (13·7)	8 (14·5)	29 (18·6)
Serious AEs or AE discontinuations					
Death	1 (1·9)	1 (1·9)	1 (2·0)	2 (3·6)	3 (1·9)
Discontinuation due to AE(s) *	1 (1·9)	0	1 (2·0)	0	2 (1·3)
Discontinuation due to serious AE(s) ‡	1 (1·9)	0	1 (2·0)	0	2 (1·3)

A participants could have discontinued study treatment due to both a SAE and non-SAE

* AEs starting on or after the day of first administration of extension study drug until last administration of study drug + 56 days are considered

† Most frequently reported AEs (>5% incidence) in the pooled bimagrumab group

‡ SAEs starting on or after the day of first administration of extension study drug are considered. Deaths which occurred on or after the day of first administration of extension study drug are considered

AEs, adverse events; SAEs, serious adverse events

Figure Legends

Figure 1. Study design and subject disposition (a) Study design. (b) Subject disposition in the extension study during double-blind Extension Treatment Period 1 (excluding follow-up period) (full analysis set)

Maximum duration of Extension Treatment Period was 52 weeks

Figure 2. Mean change from core baseline in 6MWD during double-blind treatment.

Error bars represent SEM

At each visit, only participants with a value at both core baseline and the post core-baseline visit were included. Number of participants contributing to the data analyzed for means of 6MWD at week 104 was considerably lower than earlier visits. Baseline was defined as the last assessment before the first dose of core study drug. All participants were included regardless of intervening drug holiday. Treatment for participants in the double-blind period of the extension study was stopped as the core study (RESILIENT) did not meet the primary endpoint, and all participants were switched to a 6-month off-drug follow-up period.

Figure 3. Mean change from core baseline in sIFA total score during double-blind treatment

Error bars represent SEM

The number of participants contributing to the means analyzed for sporadic inclusion body myositis functional assessment (sIFA) total scores across all treatment groups at week 104 decreased by 13 to 15 due to early termination of study medication in the extension study. sIFA total score is between 0 and 100 with 0 indicating no difficulties. Baseline is defined as the last assessment before the first dose of study drug. Results from tests performed more than 56 days after discontinuation of study drug are not shown. All participants were included regardless of any drug holiday.

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”).

Figure 4. Mean change from core baseline in quantitative muscle testing of the right quadriceps muscle during the double-blind treatment period

Error bars represent SEM

At each visit, only subjects with a value at both core baseline and the post core-baseline visit were included. Baseline is defined as the last assessment before the first dose of core study drug. All participants were included regardless of any drug holiday.

Figure 5. Mean change from core baseline in right hand-grip strength during double-blind treatment

Error bars represent SEM

At each visit, only subjects with a value at both core baseline and the post core-baseline visit were included. Baseline is defined as the last assessment before the first dose of core study drug. All participants were included regardless of their drug holiday.

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