



Original Investigation | Geriatrics

# Bimagrumab vs Optimized Standard of Care for Treatment of Sarcopenia in Community-Dwelling Older Adults

## A Randomized Clinical Trial

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### Abstract

**IMPORTANCE** The potential benefit of novel skeletal muscle anabolic agents to improve physical function in people with sarcopenia and other muscle wasting diseases is unknown.

**OBJECTIVE** To confirm the safety and efficacy of bimagrumab plus the new standard of care on skeletal muscle mass, strength, and physical function compared with standard of care alone in community-dwelling older adults with sarcopenia.

**DESIGN, SETTING, AND PARTICIPANTS** This double-blind, placebo-controlled, randomized clinical trial was conducted at 38 sites in 13 countries among community-dwelling men and women aged 70 years and older meeting gait speed and skeletal muscle criteria for sarcopenia. The study was conducted from December 2014 to June 2018, and analyses were conducted from August to November 2018.

**INTERVENTIONS** Bimagrumab 700 mg or placebo monthly for 6 months with adequate diet and home-based exercise.

**MAIN OUTCOMES AND MEASURES** The primary outcome was the change in Short Physical Performance Battery (SPPB) score after 24 weeks of treatment. Secondary outcomes included 6-minute walk distance, usual gait speed, handgrip strength, lean body mass, fat body mass, and standard safety parameters.

**RESULTS** A total of 180 participants were recruited, with 113 randomized to bimagrumab and 67 randomized to placebo. Among these, 159 participants (88.3%; mean [SD] age, 79.1 [5.3] years; 109 [60.6%] women) completed the study. The mean SPPB score increased by a mean of 1.34 (95% CI, 0.90 to 1.77) with bimagrumab vs 1.03 (95% CI, 0.53 to 1.52) with placebo ( $P = .13$ ); 6-minute walk distance increased by a mean of 24.60 (95% CI, 7.65 to 41.56) m with bimagrumab vs 14.30 (95% CI, -4.64 to 33.23) m with placebo ( $P = .16$ ); and gait speed increased by a mean of 0.14 (95% CI, 0.09 to 0.18) m/s with bimagrumab vs 0.11 (95% CI, 0.05 to 0.16) m/s with placebo ( $P = .16$ ). Bimagrumab was safe and well-tolerated and increased lean body mass by 7% (95% CI, 6% to 8%) vs 1% (95% CI, 0% to 2%) with placebo, resulting in difference of 6% (95% CI, 4% to 7%) ( $P < .001$ ).

**CONCLUSIONS AND RELEVANCE** This randomized clinical trial found no significant difference between participants treated with bimagrumab vs placebo among older adults with sarcopenia who had 6 months of adequate nutrition and light exercise, with physical function improving in both groups. Bimagrumab treatment was safe, well-tolerated, increased lean body mass, and decreased

(continued)

### Key Points

**Question** What is the effect on physical function of adding bimagrumab treatment to optimized standard of care in community-dwelling older adults with sarcopenia?

**Findings** In this randomized clinical trial in 180 adults aged 70 years and older meeting the criteria for sarcopenia, there was no statistically significant difference in improvement in physical function between bimagrumab vs placebo. Participants who received bimagrumab had increased lean body mass and reduced fat mass vs placebo.

**Meaning** These findings suggest that the addition of bimagrumab does not substantially enhance the effect of adequate diet and habitual light exercise, which can improve physical function and reduce the impact of sarcopenia in older adults.

+ [Visual Abstract](#)

+ [Supplemental content](#)

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Abstract (continued)

fat body mass. The effects of sarcopenia, an increasing cause of disability in older adults, can be reduced with proper diet and exercise.

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## Introduction

The global population is aging rapidly, leading to an exponential increase in the number of older people and the proportion of those with chronic, noncommunicable diseases.<sup>1</sup> Sarcopenia is a chronic, progressive muscle disease characterized by a loss of intrinsic physical capacity that is seen with aging and numerous acute and chronic conditions.<sup>2-6</sup> Originally defined as the loss of skeletal muscle mass associated with reduced strength and physical function seen with advanced age,<sup>7</sup> sarcopenia is now additionally used to describe adverse body composition changes observed with chronic illnesses and injuries.<sup>8-10</sup> Sarcopenia is currently defined as the presence of low lean body mass (LBM), based on sex, geographic and body size-adjusted cutoffs, accompanied by muscle weakness and impaired physical performance.<sup>2,11-14</sup> Sarcopenia is common, occurring in up to 13% of older adults.<sup>15</sup> Typically manifesting as slower walking speed and difficulty with transitioning from sitting to standing and climbing stairs<sup>16</sup> sarcopenia is associated with a greater incidence of falls and fractures, loss of independent living, and death and worse outcomes in those with concurrent chronic illness and injuries.<sup>17,18</sup>

While there is no universally effective treatment for sarcopenia, potential options are being studied. Recently, international treatment guidelines for sarcopenia<sup>19</sup> recommend an improved nutritional status, habitual physical activity, and exercise as first-line therapy, although adoption of these lifestyle behaviors may be difficult.<sup>20</sup> Adding to the evolving evidence of the effectiveness of diet and exercise to improve physical function in later life<sup>21</sup> is a surge in the evaluation of new and repurposed pharmacotherapies as potential treatments.<sup>22,23</sup> One novel approach targets the myostatin/activin type II receptor (ActRII) pathway to induce the systemic hypertrophy of skeletal muscles, with the expectation of increased muscle strength and improved functional capability.<sup>23-26</sup>

Bimagrumab (BYM338; Novartis) is a fully human monoclonal antibody that prevents ligand binding and promotes differentiation of human myoblasts.<sup>27</sup> Muscle hypertrophy is enhanced by the blockade of both receptor subtypes (ActRIIA and ActRIIB) achieved with bimagrumab, with muscle mass increase approximately 2-fold that seen with myostatin inhibition alone.<sup>28</sup> A 2017 proof-of-concept study<sup>26</sup> with bimagrumab demonstrated good safety and increased LBM and muscle strength in patients with sarcopenia with gait speeds of less than 1.0 m/s. Clinically relevant improvement in walking performance was observed in a subset of study participants with slower baseline gait speeds (ie, <0.8 m/s). This study was performed to confirm and better define the clinical benefit of bimagrumab treatment in a global population of older adults meeting the most widely accepted criteria for sarcopenia.<sup>11,13</sup>

## Methods

### Study Design

This was a 28-week, double-blind, placebo-controlled, parallel-arm, multicenter, phase II randomized clinical trial. All participants, investigators, and sponsor representatives associated with the study were masked to treatment assignment.

The institutional review board or independent ethics committee at each site approved the study, and each participant gave written informed consent. The study complied with the

International Council for Harmonisation Guidelines for Good Clinical Practice, applicable local regulations, and the ethical principles established in the Declaration of Helsinki.<sup>29</sup> The Trial Protocol is provided in [Supplement 1](#). An external data monitoring committee reviewed safety data throughout the trial. This study is a primary analysis reported in line with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Approximately 1 year after the first patient was randomized, the study design was modified in response to communications from health authorities suggesting that the Short Physical Performance Battery (SPPB) was becoming the preferred clinical end point for drug trials in sarcopenia. The original 4-arm dose range (700 mg, 210 mg, 70 mg bimagrumab or placebo every 4 weeks for 24 weeks) finding design was modified to 2 arms (eFigure in [Supplement 2](#)) to confirm efficacy of bimagrumab with the SPPB, which had not been used in prior studies. The decision was made to reduce potential risk to patients on the lower 2 dose levels before treatment efficacy was established.

### Study Population

Community-living adults aged 70 years and older with gait speeds greater than 4 m of 0.3 m/s or more to less than 0.8 m/s, and appendicular skeletal muscle index (ASMI; kg/m<sup>2</sup>) values meeting cutoffs for non-Asian<sup>11</sup> and Asian<sup>13</sup> countries, were enrolled. Race/ethnicity was self-reported. To attempt to control key potential confounders of skeletal muscle anabolism, participants were required to consume at least 20 kcal/kg of body weight and at least 0.8 g protein/kg of body weight daily.<sup>30,31</sup> A dietary assessment was administered in person by a dietician or comparably trained professional using an established method.<sup>32</sup> Volunteers who did not meet the diet criteria were disqualified or offered nutritional counseling. Those who received nutritional counseling were re-evaluated approximately 4 weeks later and enrolled if they met the dietary criteria or disqualified if they did not. In addition, participants had Mini-Mental State Examination (MMSE) scores of 21 or higher. Key exclusion criteria were the presence of health conditions that could increase a participant's risk of a safety issue, inability to complete performance outcomes, and concurrent conditions (eg, protein-calorie malabsorption) or medications (eg, prednisone) known to affect skeletal muscle mass or function. Participants with uncontrolled chronic conditions (eg, hypertension) were also excluded.

### Interventions

Participants were provided with a personalized exercise program and recording diary, diet analysis and counseling, an oral nutritional supplement, and vitamin D throughout the study period (eAppendix 1 in [Supplement 2](#)). The top dose of intravenous bimagrumab, 700 mg bimagrumab every 4 weeks, was chosen for the revised study design to maximize potential improvement with bimagrumab. This study presents data from all participants randomized to receive bimagrumab 700 mg or placebo for 24 weeks ([Figure 1](#)).

### Study Procedures and End Points

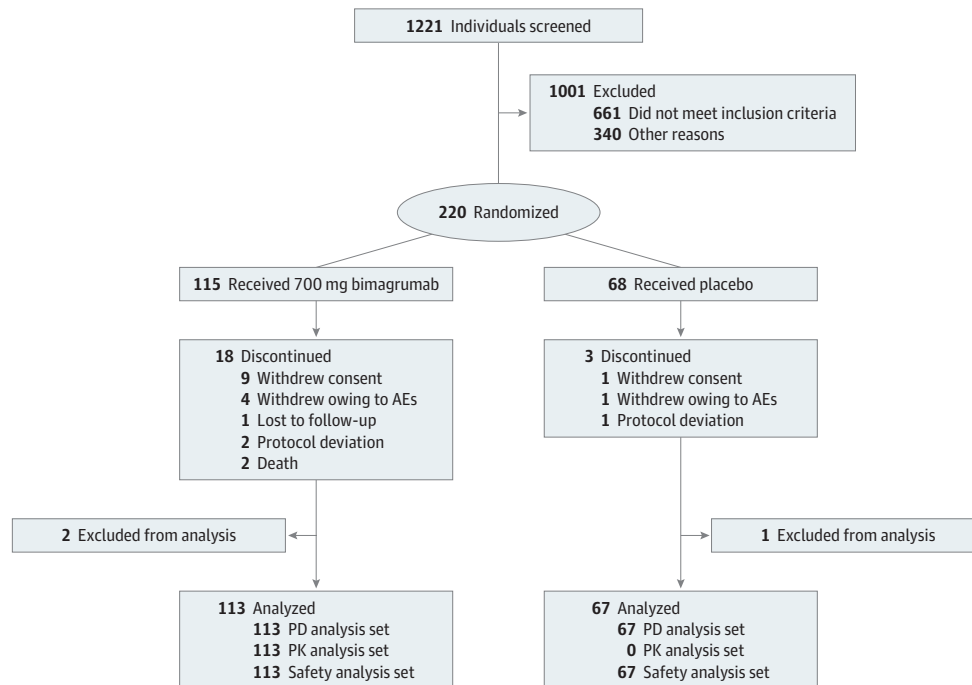
The primary end point was the treatment effect of bimagrumab vs placebo on improved physical performance, assessed by the change in SPPB<sup>33</sup> score, after 24 weeks of treatment. The SPPB was selected as the primary end point because of its association with adverse health outcomes and mortality in older adults by either a reduction of 1 or more points over time, or a total score of 9 points or fewer.<sup>34,35</sup> A change of 1 point on the 0 to 12 scale was considered clinically meaningful, with a higher score reflecting greater function.<sup>36</sup> The change from baseline in 6-minute walk distance (6MWD), measured in m,<sup>37</sup> and usual gait speed, measured in m/s over 4 m,<sup>38</sup> further assessed mobility performance. We quantified LBM and fat body mass (FBM) using standard methods of data acquisition with dual-energy x-ray absorptiometry (DXA), and ASMI was calculated from DXA data.<sup>11</sup> Safety was assessed from results of standard laboratory tests, vital signs, electrocardiogram, echocardiography, and reports of adverse events (AEs) and serious AEs.

In addition, we assessed bilateral handgrip strength with a dynamometer (Jamar; Lafayette Instruments),<sup>39</sup> the number of self-reported falls, health status by patient-reported outcomes (European Quality of Life-5 Dimensions-5 Levels<sup>40</sup> and Short Form-36),<sup>41</sup> and differences between participants who improved by 1 or more point on the SPPB score and those who did not improve with treatment.

**Statistical Analysis**

Change from baseline in SPPB total score, 6MWD, gait speed, and handgrip strength at week 25 was analyzed using a mixed-effect model repeated measure with a covariate for treatment, visit, baseline, visit × baseline, visit × treatment, and region (Asian and non-Asian). No adjustment was made for multiplicity. The ratios of baseline to week 25 of LBM, FBM, and ASMI (DXA parameters) were analyzed by mixed-effect model repeated measure. Data were transformed using natural logarithms and then analyzed using baseline, treatment, subgroup (Asian and non-Asian), and visit as covariates. A saturated covariance structure was used for observations from the same patient. The results were back-transformed to the original scale to present the adjusted geometric mean ratio with 95% CIs, and a P value to reflect the 1-sided evaluation of treatment vs placebo was reported, with significance set at P < .05. The sample size of 135 (85 bimagrumab; 50 placebo) participants was calculated to demonstrate a statistical significance at 1-sided 2.5% level and a point estimate increase (improvement) of at least 1 point in change from baseline SPPB total score compared with placebo.<sup>36</sup> Descriptive statistics were used to report an a priori comparison between participants in the bimagrumab and placebo groups who had baseline SPPB scores of 9 points or fewer and no longer met the criteria of lean mass or gait speed or both criteria for sarcopenia. Analysis was conducted using SAS statistical software version 9.4 (SAS Institute). Data were analyzed from August to November 2018.

Figure 1. Study Flow Diagram of Participant Screening and Enrollment



AE indicates adverse events; PD, pharmacodynamics; and PK, pharmacokinetics.

## Results

### Population

Between December 2014 and June 2018, 1221 individuals were screened at 58 sites (screen failure rate, 82.0%) (Figure 1). A total of 180 participants were randomized, including 113 assigned to bimagrumab 700 mg and 67 assigned to placebo; of these, 159 participants (88.3%) completed the study, and 89 participants (78.8%) in the bimagrumab group and 62 participants (92.5%) in the placebo group received all 6 doses. The study population had a mean (SD) age of 79.1 (5.3) years, mean (SD) MMSE score of 28 (2.0) points, and 109 participants (60.6%) were women. Baseline characteristics were balanced between groups (Table 1). Pharmacokinetic assessment confirmed that exposure to bimagrumab in this population was comparable to that seen in previous studies and exceeded the threshold needed for consistent target engagement, as further confirmed by changes in LBM and FBM. Adherence to the exercise and diet requirements were maintained throughout the study in both groups. At each clinic visit, participants reviewed their exercise diary and were encouraged to perform their program 2 to 3 times per week. Dietary protein was assessed every 1 to

Table 1. Baseline Characteristics of Older Adults With Sarcopenia

Characteristic	Mean (SD)	
	Bimagrumab (n = 113)	Placebo (n = 67)
Age, y	79.5 (5.46)	78.3 (5.03)
Median (range)	79 (70-95)	78 (70-88)
Sex, No. (%)		
Men	47 (41.6)	24 (35.8)
Women	66 (58.4)	43 (64.2)
Race, No. (%)		
White	93 (82.3)	54 (80.6)
Asian	17 (15.0)	11 (16.4)
Other	0	1 (1.0)
Ethnicity, No. (%)		
Other	56 (49.6)	31 (46.3)
Not Hispanic/Latino	30 (26.5)	16 (23.9)
Hispanic/Latino	19 (16.8)	19 (28.4)
Height, cm	163.6 (12.50)	161.9 (9.55)
Median (range)	162 (138-200)	160 (145-184)
Weight, kg	65.6 (16.61)	62.3 (11.17)
Median (range)	63.4 (36-111)	62.8 (42-94)
BMI	24 (3.55)	23.6 (2.84)
Median (range)	24 (15-32)	23.6 (17-31)
Total SPPB score	7.1 (1.73)	7.3 (1.68)
6MWD, m	294.3 (83.60)	312.4 (93.92)
Gait speed, m/s	0.642 (0.1079)	0.656 (0.0836)
Grip strength, kg		
Right hand	20.4 (7.79)	19.5 (7.36)
Left hand	19.4 (7.63)	18.1 (7.09)
LBM, kg	35.4 (8.89)	33.6 (6.89)
FBM, kg	22.7 (8.74)	21.2 (7.5)
ASMI, kg/m <sup>2</sup>	5.7 (0.82)	5.5 (0.75)
Non-Asia		
Men	6.64 (0.421)	6.38 (0.586)
Women	5.13 (0.351)	5.07 (0.373)
Asia		
Men	6.12 (0.628)	6.29 (0.527)
Women	4.92 (0.213)	5.33 (0.265)

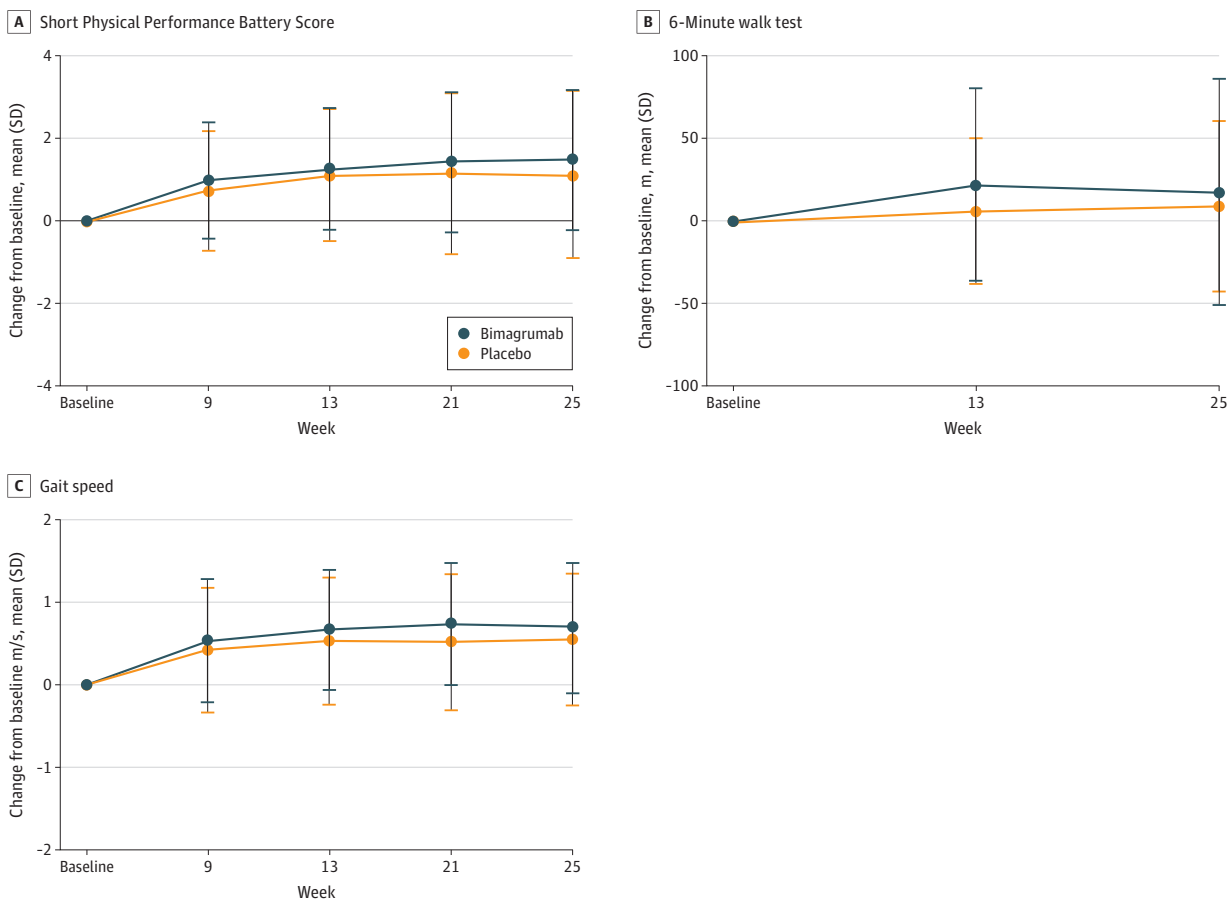
Abbreviations: 6MWD, 6-minute walk distance; ASMI, appendicular skeletal muscle index (calculated as lean mass of upper and lower extremities in kilograms divided by height in meters squared); BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FBM, fat body mass; LBM, lean body mass; SPPB, Short Physical Performance Battery.

2 clinic visits, and results suggested that protein intake was maintained above 0.8 g/kg/d in both groups (eTable 1 in Supplement 2).

**Efficacy**

No minimum clinically important difference was seen between groups in any performance-based end point. The mean change in total SPPB score from baseline increased at the end of the study by 1.34 (95% CI, 0.90 to 1.77) points with bimagrumab vs 1.03 (95% CI, 0.53 to 1.52) points with placebo ( $P = .13$ ). Scores improved in both groups at 13 weeks and remained through treatment completion (Figure 2A). Mean changes in 6MWD from baseline to weeks 13 and 25 were below clinically relevant levels of 35 to 54 m for both treatment groups (bimagrumab: 24.60 [95% CI, 7.65 to 41.56] m; placebo: 14.30 [95% CI, -4.64 to 33.23]; ( $P = .16$ ).<sup>37</sup> The mean distance walked improved by week 13 and plateaued in both groups for the remainder of the study (Figure 2B). At week 13, gait speed increased from baseline in both groups by the clinically relevant level of at least 0.1 m/s (bimagrumab: 0.14 [95% CI, 0.09 to 0.18] m/s; placebo: 0.11 [95% CI, 0.05 to 0.16] m/s;  $P = .16$ ),<sup>36</sup> and remained stable for the remainder of the study (Figure 2C). No noteworthy change (ie, <1.4 kg) was seen in the mean bilateral handgrip strength with either treatment, and no clinically meaningful change was seen in patient-reported outcome scores. In addition, no significant differences were seen in participants with improved SPPB scores of at least 1 point compared with those with no improvement (eTable 2 in Supplement 2).

**Figure 2. Effect of Bimagrumab Compared With Placebo on Physical Performance Assessed**



A repeated measure mixed model with a covariate for treatment (placebo or bimagrumab), visit, baseline, visit × baseline, visit × treatment, and region (Asian and non-Asian) was used. No adjustment for multiplicity was made. The baseline value considered for the calculation of the change from baseline is the last value before Day 1.

In a subgroup of the sample with baseline SPPB scores fewer than 9 points, 44 of 63 participants (69.8%) in the bimagrumab group and 23 of 37 participants (62.2%) in the placebo group no longer met the criteria for sarcopenia at the end of the study. However, differences were seen in the patterns of improvement between treatments. Based on the 2 key criteria in the definition of sarcopenia (ie, lean mass as ASMI and gait speed) participants who received bimagrumab improved similarly on 1 or both characteristics (improved gait speed: 19 participants; improved ASMI: 11 participants; or improved ASMI and gait speed: 14 participants). More participants who received the placebo improved on gait speed (18 participants) compared with ASMI (4 participants) or both (1 participant).

There was a significant increase in mean LBM in the bimagrumab group vs placebo at week 13 (mean [SD] change, 1.93 kg [1.74] kg vs 0.37 [1.24] kg;  $P < .001$ ) and week 25 (mean [SD] change, 2.02 [1.95] vs 0.08 [1.17] kg;  $P < .001$ ). The increase in LBM with bimagrumab was reflected in the ASMI values, which increased by 7% (95% CI, 6% to 8%) with bimagrumab vs 1% (95% CI, 0% to 2%) with placebo at week 25, resulting in difference of 6% (95% CI, 4% to 7%) ( $P < .001$ ). Conversely, FBM showed a progressive decrease at week 13 (mean [SD] change, -1.39 [1.8] kg) and week 25 (mean [SD] change, -3.24 [2.5] kg) in the bimagrumab group, compared with no change in the placebo group (mean [SD] change: week 13: 0.1 [1.3] kg; week 25: 0.6 [1.6] kg) ( $P < .001$ ).

## Safety

Bimagrumab 700 mg administered intravenously every 4 weeks over 24 weeks was generally safe and well-tolerated in the study population of older adults with sarcopenia. The most frequently reported AEs were falls, involuntary muscle contractions (eg, muscle spasms), and diarrhea (**Table 2**).

Most AEs were mild or moderate in intensity (Common Terminology Criteria for Adverse Events grade 1).<sup>42</sup> Muscle spasms and diarrhea, both associated with bimagrumab in prior studies, were reported more frequently by patients receiving bimagrumab. Five participants discontinued the study owing to AEs, 4 of whom received bimagrumab and 1 of whom received placebo. Fourteen participants (12.4%) in the bimagrumab group and 5 participants (7.5%) participants in the placebo group experienced serious AEs; no serious AEs reported in the bimagrumab group were considered related to the study drug. No clinically meaningful changes in vital signs, echocardiography, or electrocardiogram were observed during the study in either treatment group (eAppendix 2 in [Supplement 2](#)). Safety findings were similar to the earlier proof-of-concept study in older adults with sarcopenia.<sup>26</sup>

## Discussion

This randomized clinical trial found that 24 weeks of bimagrumab treatment in adults with sarcopenia, defined as those aged 70 years or older with low LBM for their height and slow gait speed (ie,  $<0.8$  m/s), had no significant effect on physical performance (measured by SPPB) but increased participants' LBM by a mean of 2.0 kg and decreased FBM by a mean of 3.8 kg compared with placebo. The gain in LBM did not result in clinically relevant treatment differences in muscle strength or mobility. These changes were observed with a background treatment of an optimized diet, vitamin D intake, and exercise, which resulted in improved physical performance and mobility of participants in both groups. The favorable safety profile seen in this trial was consistent with prior studies with bimagrumab in adults receiving the same dose level with a similar or longer duration.<sup>43,44</sup>

To our knowledge, this is the largest study evaluating a drug targeting the myostatin-ActRII pathway in an international population of community-dwelling older adults with confirmed sarcopenia. Our results are consistent with prior studies in older adults of drugs acting on the myostatin-ActRII pathway. Three mechanisms of action have been evaluated to drug the pathway: antiligand (primarily to myostatin),<sup>25,45,46</sup> a soluble ActRIIB,<sup>24</sup> and a receptor antagonist,<sup>26,27,47-49</sup> all of which have increased LBM in adults to varying degrees. Among the 3 approaches evaluated in humans, blocking activity at the ActRIIA and ActRIIB receptors with bimagrumab results in larger

increases in LBM compared with inhibiting myostatin alone (2.0 kg vs 0.7 kg).<sup>25</sup> However, despite the increase in LBM, no corresponding improvement in clinically relevant muscle strength or physical performance has been reported in adults with sarcopenia or other conditions with reduced muscle mass, strength, or physical function.<sup>24,25,48,50</sup> This pattern of muscle hypertrophy without improved function has been seen in other pharmacotherapeutic approaches as well, including agents that target other receptor pathways, such as selective androgen receptor modulators.<sup>51</sup> Mixed results have also been reported with testosterone treatment. Data from the HORMA trial<sup>52</sup> in men aged 65 to 90 years who received 16 weeks of testosterone or human growth hormone showed a median increase of 1.8 kg in LBM, which corresponded to statistically significant gains in muscle strength and physical function. Other trials with testosterone treatment of a longer duration did not find a sustained positive effect on muscle mass, strength, or function and showed an increased safety risk.<sup>53,54</sup> The lack of functional improvement seen with pharmacotherapies is contrary to that seen with exercise, which can improve physical function and strength without muscle hypertrophy.<sup>55-57</sup> Therefore, future considerations of drug candidates may need to more closely mimic the neuromuscular and metabolic effects of exercise to compensate for the morphological and physiological changes seen with aging, and in sarcopenia in particular.<sup>58</sup>

Our findings do not confirm the results of a 2017 proof-of-concept study<sup>26</sup> evaluating bimagrumab in a similar patient population with sarcopenia that showed significant, clinically relevant improvements in muscle strength, gait speed, and 6MWD after 16 weeks of treatment compared with placebo. Several key differences may explain the discrepancy between studies. The

Table 2. Adverse Events by Reported Description for Both Treatment Groups

AE <sup>a</sup>	No. (%)	
	Bimagrumab (n = 113)	Placebo (n = 67)
Participants with ≥1 AE	100 (88.5)	52 (77.6)
Fall	28 (24.8)	24 (35.8)
Muscle spasms	37 (32.7)	10 (14.9)
Diarrhea	22 (19.5)	2 (3.0)
Hypertension	9 (8.0)	4 (6.0)
Contusion	5 (4.4)	7 (10.4)
Upper respiratory tract infection	5 (4.4)	5 (7.5)
Back pain	5 (4.4)	4 (6.0)
Pain in extremity	6 (5.3)	3 (4.5)
Headache	5 (4.4)	3 (4.5)
Nausea	8 (7.1)	0
Bronchitis	6 (5.3)	2 (3.0)
Constipation	6 (5.3)	1 (1.5)
Urinary tract infection	6 (5.3)	1 (1.5)
Dizziness	6 (5.3)	0
Increased lipase	6 (5.3)	0
Osteoarthritis	4 (3.5)	2 (3.0)
Viral infection	5 (4.4)	1 (1.5)
Decreased appetite	5 (4.4)	0
Fatigue	5 (4.4)	0
Nasopharyngitis	5 (4.4)	0
Rash	5 (4.4)	0
Sinusitis	4 (3.5)	1 (1.5)
Increased amylase	4 (3.5)	0
Cough	4 (3.5)	0
Dysgeusia	4 (3.5)	0
Dyspnea	4 (3.5)	0
Vomiting	4 (3.5)	0

Abbreviation: AE, adverse event.

<sup>a</sup> AEs with more than 3% in bimagrumab group have been listed.



2017 study<sup>26</sup> we performed had the same nutritional intake and oral nutritional supplement requirements as this study but did not include exercise. Our study attempted to control for the variability of exercise participation by providing a personalized, home-based program to promote regular muscle contraction without improving cardiovascular fitness or increasing functional strength. The combination of a high exercise adherence rate and the enhanced nutritional status in this study may have provided the necessary stimuli to improve performance on the functional end points. The other key difference between the studies relates to outcomes. The SPPB was not included in the proof-of-concept study,<sup>26</sup> so a comparison of participant responses between studies cannot be made. While performance-based testing administration and training were standardized across both studies, the 2017 study<sup>26</sup> was performed in a smaller sample of adults (40 participants) at 5 sites in the United States, compared with our study, which was conducted among 180 participants in 38 sites in 13 countries.

### Limitations

Our study has several limitations. While this well-characterized sample is one of the largest in a study of sarcopenia and involved participants from North America, Europe, Asia, and Asia-Pacific, the unbalanced racial distribution limits the broad generalization of the findings. Rather than usual care, which is difficult to quantify and not standardized for an emerging diagnostic entity, like sarcopenia, the study used optimized standard of care as the comparator to determine what clinical benefits bimagrumab might provide when combined with ideal self-care.

### Conclusions

Three key conclusions can be drawn from this randomized clinical trial with its well-characterized, international sample of older adults with sarcopenia after 24 weeks of treatment with bimagrumab. First, bimagrumab safely increases LBM within 4 to 8 weeks, and this is maintained with continuous exposure. Second, drugs that promote skeletal muscle hypertrophy exclusively without affecting other aspects of muscle function, such as neuromotor or metabolic activity, likely will not improve muscle strength or functional performance sufficiently as monotherapy to have a clinical impact. Third, adequate nutritional intake (including protein, calories, and vitamin D) and habitual light exercise can improve physical performance in men and women with sarcopenia to the extent that they no longer meet the disease criteria. These data, when combined with clearer diagnostic criteria, a new *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification* code, and the recent clinical practice treatment guidelines, support the consideration of sarcopenia as a treatable muscle disease with dietary and exercise prescription, and a reversible cause of disability in older adults. Physicians should be encouraged to evaluate older patients for the presence of sarcopenia and provide nutritional and physical therapy prescriptions and referrals to reliable, convenient exercise programs accordingly.

### ARTICLE INFORMATION

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**Conflict of Interest Disclosures:** Drs Rooks, Swan, Filosa, Mr Bunte, Drs Panchaud, Coleman, Miller, Garcia Garayoa, Praestgaard, Laurent, and Petricoul, Ms Hemsley, Drs Lach-Trifilieff, Papanicolaou, and Roubenoff are employees of Novartis and may be eligible for Novartis stock and stock options. Dr Rooks reported having a patent for use of bimagrumab in sarcopenia pending. Dr Coleman had a patent for PAT058683 pending. Dr Fogarty reported receiving grants from Novartis during the conduct of the study. Dr Lach-Trifilieff reported having a patent for WO2010/125003 pending, a patent for US13/485399 issued, a patent for US14/806997 pending, a patent for US15/906703 pending, and a patent for US12/767509 issued. Dr Roubenoff reported having a patent for bimagrumab issued for Novartis. No other disclosures were reported.

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#### SUPPLEMENT 1.

##### Trial Protocol

#### SUPPLEMENT 2.

eAppendix 1. Supplementary Methods

eAppendix 2. Supplementary Results

eTable 1. Baseline Characteristics and Changes in Outcomes of All Participants Receiving Study Drug

eTable 2. Baseline Characteristics for Responders and Nonresponders

eFigure. Study Design

#### SUPPLEMENT 3.

##### Data Sharing Statement