Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial

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Summary

Background Myostatin inhibits skeletal muscle growth. The humanised monoclonal antibody LY2495655 (LY) binds and neutralises myostatin. We aimed to test whether LY increases appendicular lean body mass (aLBM) and improves physical performance in older individuals who have had recent falls and low muscle strength and power.

Methods In this proof-of-concept, randomised, placebo-controlled, double-blind, parallel, multicentre, phase 2 study, we recruited patients aged 75 years or older who had fallen in the past year from 21 investigator sites across Argentina, Australia, France, Germany, Sweden, and the USA. Eligible patients had low performance on hand grip strength and chair rise tests, tested with the procedure described by Guralnik and colleagues. Participants were stratified by country, age, hand grip strength, and performance on the chair rise test, and were randomly assigned (1:1) by a computer-generated random sequence to receive subcutaneous injections of placebo or 315 mg LY at weeks 0 (randomisation visit), 4, 8, 12, 16, and 20, followed by 16 weeks observation. The primary outcome was change in aLBM from baseline to 24 weeks. We measured physical performance as secondary outcomes (four-step stair climbing time, usual gait speed, and time to rise five times from a chair without arms, or with arms for participants unable to do it without arms) and exploratory outcomes (12-step stair climbing test, 6-min walking distance, fast gait speed, hand grip strength, and isometric leg extension strength). Efficacy analyses included all randomly assigned patients who received at least one dose and had a baseline and at least one subsequent measure. The primary analysis and all other tests of treatment effect (except physical performance tests) were done at a two-sided alpha level of 0·05. Tests of treatment effect on physical performance tests were done at a pre-specified two-sided alpha level of 0·1. This trial is registered with ClinicalTrials.gov, number NCT01604408.

Findings Between June 19, 2012, and Dec 12, 2013, we screened 365 patients. 99 were randomly assigned to receive placebo and 102 to receive LY. Treatment was completed in 85 (86%) of patients given placebo and in 82 (80%) given LY. At 24 weeks, the least-squares mean change in aLBM was –0·123 kg (95% CI –0·287 to 0·040) in the placebo group and 0·303 kg (0·135 to 0·470) in the LY group, a difference of 0·43 kg (95% CI 0·192 to 0·660; p<0·0001). Stair climbing time (four-step and 12-step tests), chair rise with arms, and fast gait speed improved significantly from baseline to week 24 with differences between LY and placebo of respectively –0·46 s (p=0·093), –1·28 s (p=0·011), –4·15 s (p=0·054), and 0·05 m/s (p=0·088). No effect was detected for other performance-based measures. Injection site reactions were recorded in nine (9%) patients given placebo and in 31 (30%) patients given LY (p<0·0001), and were generally mild, and led to treatment discontinuation in two patients given LY.

Interpretation Our findings show LY treatment increases lean mass and might improve functional measures of muscle power. Although additional studies are needed to confirm these results, our data suggest LY should be tested for its potential ability to reduce the risk of falls or physical dependency in older weak fallers.

Funding Eli Lilly and Company.

Introduction

Skeletal muscle strength and power decrease with ageing, leading to mobility disability, reduced physical activity, high risk for falls and related injuries, reduced quality of life, institutionalisation, and death.[1,2] The current standard of care for decreased lower limb muscle strength or power (risk factors for mobility impairment or falls) relies on resistance exercise,[3,4] but its efficacy is variable[5] and its implementation is often limited by medical and logistical challenges commonly experienced by older adults who are mobility limited.[6,7] A drug that increases muscle strength and power in older people could prevent poor outcomes that often affect people in the last decades of life.[1]

Myostatin, a member of the TGFβ superfamily, binds to activin receptor IIb[8] and inhibits muscle protein synthesis through the AKT–mTOR pathway.[9] Postnatal inhibition of myostatin stimulates muscle protein synthesis resulting in muscle hypertrophy in mice.[10] This hypertrophy translates into increased physical performance in rodent models.[11,12] Conversely, it was reported that muscle quality and specific force (force/mass) is decreased in myostatin-knockout mouse models.[13] It is unknown whether these results will translate to human beings.

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See Online for appendix

Panel: **Research in context**

Evidence before this study

Age-associated muscle weakness is responsible for several poor outcomes in older people, including mobility disability, fall-related injuries, institutionalisation, and death. The standard of care for low muscle strength or power relies on resistance exercise training, but its efficacy is variable and its implementation often challenging in older disabled people. A drug that increases muscle power could prevent these poor outcomes. We searched PubMed up to April 1, 2015, with the search terms "clinical" and "trial" and [myostatin or activin] for clinical trials testing drugs that target myostatin or its receptor (AcRIIb) with no language restrictions. Although several molecules have been reported that increase muscle mass or its surrogate, lean mass, the data available about physical performance are limited. Positive effects were reported on 6 min walking distance with bimagrumab (AcRIIb antibody) in 11 patients with sporadic inclusion body myositis versus three patients given placebo, and with follistatin (natural myostatin inhibitor) gene therapy in six patients with Becker muscular dystrophy in an open-label clinical trial. Apart from the design and size limitations of these previous trials, it was unknown whether effects recorded in a purely muscular disorder (such as sporadic inclusion body myositis or Becker muscular dystrophy) would translate into older fallers whose impaired physical performance is generally multifactorial.

Added value of this study

We did a clinical trial testing an antimyostatin antibody in 201 older fallers with low muscle strength. In addition to achieving the primary endpoint (increase in appendicular lean mass), this antibody showed efficacy on several measures of physical performance, predominantly those that are heavily dependent on muscle power (consistent with the mechanism of action) and that are functional (eg, climbing stairs). This trial provides the first robust demonstration that inhibiting myostatin increases lean mass in older weak fallers and most importantly that these changes in lean mass translate into an improved physical performance which is what matters to these patients.

Implications of all the available evidence

Although the clinical importance of these improvements and this antibody's safety remain to be formally shown in larger confirmatory trials, LY might provide significant benefits to this high-risk older population, both in terms of quality of life and prevention of adverse outcomes such as fall related injuries or mobility disability.

LY2495655 (LY) is a humanised monoclonal antibody that neutralises the activity of the myostatin protein. In a dose-escalation phase 1 trial,[14] LY treatment increased thigh muscle volume of healthy volunteers. Here, we present the efficacy and safety results of a 36-week, phase 2 study of LY in older fallers with low muscle strength and power, a population at high risk for future falls.

Methods

Study design and patients

This phase 2 randomised, proof-of-concept, double-blind, placebo-controlled, parallel group, outpatient study was done at 21 investigator sites across Argentina, Australia, France, Germany, Sweden, and the USA. Eligible patients were aged 75 years or older, had fallen once or more in the past year, had a hand grip strength of 37 kg or less for men or 21 kg or less for women, and took 12 s or longer to rise five times from a chair with arms folded on the chest or were unable to complete this test.[15] Study participants also had to be able to rise from a chair at least once (using the arms if necessary), and walk at least 10 m and climb at least one stair step without assistance from another person. Potentially eligible patients were identified by consultations, hospital records, advertising, and at assisted living facilities.

Patients were excluded if they had an obvious cause of disability independent of muscle strength (eg, dementia); severe uncontrolled cardiac, respiratory, liver, diabetic, or renal comorbidities; or severe 25-hydroxyvitamin D deficiency (<9·2 ng/mL). Patients with a 25-hydroxyvitamin D concentration higher than 9·2 but lower than 20 ng/mL could be enrolled but were required to receive 25-hydroxyvitamin D supplementation during the trial, at doses determined based on local standard of care. Other exclusion criteria included recent lower limb fracture or major lower limb surgery (to avoid high variability in physical performance measures), surgery planned within the next 24 weeks, muscle disease, current or previous use of drugs altering muscle mass or performance (androgens, anti-androgens, luteinising hormone-releasing hormone [LHRH] agonists and antagonists, and growth hormones and analogues), or BMI 35 kg/m² or higher. The appendix provides a complete list of eligibility criteria (appendix pp 3–5).

The study was done in accordance with the Declaration of Helsinki, the International Conference on Harmonisation, and local laws and regulations. The study protocol and informed consent forms were approved by applicable ethics review boards. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) by a computer-generated random sequence using an interactive voice response system (IVRS). Randomisation was stratified according to country, age (75–80 years or ≥81 years), hand grip strength (<25 kg for men and <17 kg for women, or ≥25 for men and ≥17 kg for women), and chair rise test (<20 s or ≥20 s including patients who could not perform

the test at all). Patients, investigators, study site personnel, and the funder were masked to treatment allocation. When reconstituted and drawn up in a syringe, the active preparation and placebo were visually similar. All investigator sites remained masked until the study was complete. The site pharmacy or designated personnel were not masked during preparation of the investigational product; these personnel were not involved in any clinical aspects of the study after the screening visit, including investigational product administration or assessment of efficacy or adverse events. At each dosing administration, all patients received three injections irrespective of treatment assignment. An assessment committee separate from the study team met during the trial to review interim unmasked safety and efficacy data. These pre-planned analyses were included in the protocol but did not lead to early termination.

Procedures

At weeks 0, 4, 8, 12, 16, and 20, patients received either placebo (0·9% sodium chloride) or 315 mg LY given as three sequential 1·5 ml subcutaneous injections in the abdomen, with the injection sites at least 2 cm apart (appendix). We closely monitored patients for signs or symptoms of hypersensitivity reactions and patients were instructed to contact the investigator as soon as possible if they had any complaints or problems. Patients were observed for 16 weeks after the last injection. Physical therapy and protein supplementation were allowed and monitored at every visit, but were not controlled. Whole-body dual-energy x-ray absorptiometry (DXA) scans were done, and performance-based tests were assessed, at weeks 0, 12, 24, and 36.

Outcomes

The primary endpoint was the change in appendicular lean body mass (aLBM) as measured by DXA 24 weeks after treatment initiation. DXA scans were done on Hologic or GE Healthcare (Lunar) scanners and were analysed by a central reader (BioClinica).

Secondary efficacy endpoints were changes in the following performance-based measures: four-step stair climbing time (best of two attempts in minimum time to climb four steps, with two handrails, using electronic switch mats, and with step height range of 15–18 cm), five chair rise test (minimum time to rise from a chair five times without arms[15] for patients who could perform this test, and minimum time using arms for the others), and usual gait speed (second of two attempts in usual gait speed over 4 m, assessed with electronic switch mats). The other physical performance-based tests (exploratory endpoints) were changes in 6-min walking distance (maximum distance walked in 6 min),[16] fast gait speed (best of two attempts over 4 m, assessed with electronic switch mats), isometric leg extension strength (using a hand-held dynamometer strapped between the patient's ankle and the chair foot),[17] hand grip strength (JAMAR hand dynamometer), and 12-step stair climbing time (addendum in a subset of sites, minimum time to climb 12 steps).

The choice to include several different performance-based measures was driven by the need to assess the effects of LY on various types of performance-based measures: those that are more functional (used in activities of daily living—eg, 6-min walking distance, gait speed, stair climbing, chair rise) or less functional (grip strength, leg extension strength); those that are demanding in terms of muscle power (stair climbing, fast gait speed, chair rise), isometric strength (grip strength, leg strength), or endurance or aerobic capacity (6-min walking distance); or those that are less demanding in terms of endurance or aerobic capacity (usual gait speed). Evidence suggests that muscle power is more important to functional task performance and to dynamic balance than isometric strength.[18,19] Finally, we chose the 12-step stair climb as a power-intensive test (hence more likely to respond to a drug that increases muscle power),[20–22] but the four-step

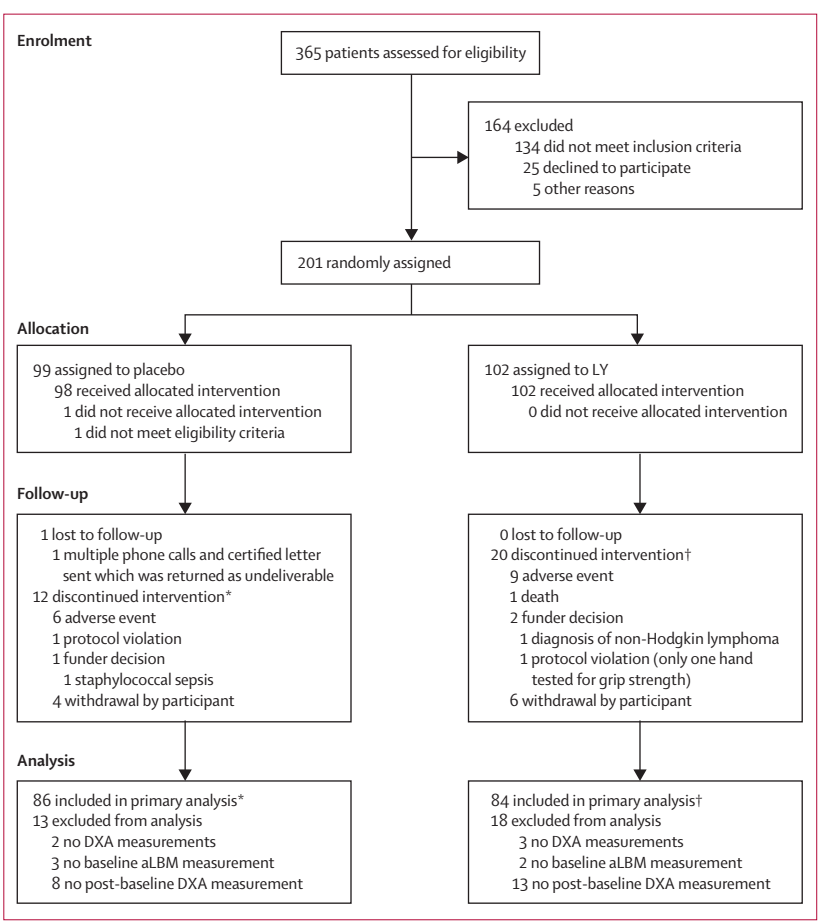

***Figure 1*: Trial profile**

LY=LY2495655. DXA=dual-energy x-ray absorptiometry. aLBM=appendicular lean body mass. *Four placebo patients discontinued intervention but had DXA measurements and were therefore included in the analysis of the primary efficacy measure. Four placebo patients completed intervention but had missing DXA measures and were therefore not included in the primary efficacy analysis. †Of the 20 LY patients who discontinued intervention, six had DXA measurements and were therefore included in the primary efficacy analysis. Four LY patients completed intervention but were not included in the primary efficacy analysis due to missing DXA measurements.

stair climb was added because not all sites had access to a 12-step staircase. Study personnel were trained and certified by academic experts to undertake the performance-based measure assessments and received an operations manual specifying the detailed procedure for each assessment.

Other exploratory endpoints included changes in total lean mass and fat mass (assessed by DXA), changes in bodyweight, changes in serum myostatin concentrations (assessed by enzyme-linked immunosorbent assay), and the rate of falls (captured at every visit) using the PROFANE definition[23] but excluding falls resulting from major intrinsic events (eg, seizure, stroke, syncope) or overwhelming environmental hazards (eg, a pedestrian being hit by a car).

For safety assessment, adverse events were recorded at every visit, irrespective of treatment assignment, and coded to Medical Dictionary for Regulatory Activities terms by blinded Eli Lilly and Company clinical personnel. The following safety measures were recorded throughout the study according to a predetermined study schedule: bodyweight, vital signs, concomitant medications, haematology and clinical chemistry, faecal occult blood test, and immunogenicity.

Statistical analysis

Efficacy analyses were done on a modified intention-to-treat (ITT) population consisting of all randomly assigned patients who received at least one dose of study drug and who had a baseline and at least one post-baseline DXA. Safety analyses were done on all enrolled patients irrespective of adherence to protocol. Statistical analyses were done by original assigned groups.

The primary analysis and all other tests of treatment effect (except for performance-based tests of physical function) were done at a two-sided alpha level of 0·05. Tests of treatment effect on performance-based tests of physical function were done at a pre-specified two-sided alpha level of 0·1. A sample size of 75 completers per group was predicted to provide 85% power to detect a 2% difference between LY and placebo for the change from baseline to 24 weeks in aLBM.

We used a mixed-effect longitudinal model for the primary analysis, with change from baseline in aLBM as the response variable. In the model, treatment, visit (up to week 24), and the treatment-by-visit interaction were included as fixed effects, and baseline value as a covariate. An appropriate covariance structure was chosen based on Akaike's information criterion. This method enabled testing of the overall treatment significance including all timepoints up to week 24 and the treatment effect at each timepoint. We used the same method to investigate the effect of treatment on performance-based measures. This mixed effect model adequately accounts for missing observations; therefore, no imputation was necessary.

Treatment comparisons for baseline characteristics were made by two sample t tests for continuous variables, Fisher's Exact test for categorical variables, and Poisson or negative binomial regression models for count variables. Numbers of falls were compared between treatment groups by fitting a negative binomial regression model as follows:

Log (number of falls since baseline) = intercept + number of falls between screening and randomisation visits + treatment.

In a post-hoc exploratory analysis, a risk-adjusted approach was used to study the treatment effect on fractures. A logistic regression model adjusted by pre-existing osteoporosis and previous fracture was fit to the data. Other exploratory post-hoc analyses investigated the effect of baseline physical performance on the difference between LY and placebo for the change from baseline to 24 weeks on respective measures of physical performance. Each treatment group was subdivided into tertiles with low, medium, or high physical performance at baseline. The model used to analyse the primary endpoint was applied for each tertile subgroup for the following performance measures: four-step stair climb time, chair rise time, 6-min walking distance, hand grip strength, and leg strength (appendix pp 7–8). Chair rise with arms and 12-step stair climb were not included in this subgroup analysis due to their small sample size. Analyses were done using SAS (version 9.2).

This trial is registered with ClinicalTrials.gov, number NCT01604408.

	Placebo group (n=99)	LY2495655 group (n=102)
Age (years)	83 (75–99)	82 (75–96)
Women	65 (66%)	75 (74%)
White	98 (99%)	101 (99%)
Weight (kg)	69·3 (13·7)	69·1 (13·4)
Height (cm)	161·4 (10·2)	161·3 (10·6)
Appendicular lean body mass/height²	6·02 (0·8)	6·1 (0·8)
Sarcopenia*	29 (31%)	25 (26%)
BMI (kg/m²)	26·5 (4·0)	26·4 (3·8)
Number of pre-existing conditions	8·8 (6·9)	11·5 (8·1)
Number of concomitant drugs (mean per patient)	8·6 (4·9)	9·3 (5·1)
Number of falls between visit one (screening) and visit two (randomisation; mean per patient)	0·15	0·23
Previous fractures (total number per group)	61	105
Number of patients with previous fractures (%)	32 (33%)	41 (40%)
Pre-existing osteoporosis† (%)	33 (33%)	48 (47%)
Patients with 25-hydroxyvitamin D <20 ng/mL before the first dose (%)	20 (20%)	28 (28%)
Chair rise test without arms (s)	16·4 (4·9)	16·8 (5·8)
Patients performing chair rise test without arms (%)	78 (79%)	76 (75%)
Hand grip strength (kg)	19·9 (7·7)	20·0 (7·2)

Data are mean (range), n (%), mean (SD), or n, unless otherwise stated. *Sarcopenia defined according to the Baumgartner criteria for DXA based sarcopenia (<5·45 kg/m² for women and <7·26 kg/m² for men).[24] †Osteoporosis reported by investigator as a pre-existing disorder as part of medical history.

Table 1: **Baseline characteristics**

Role of funding source

The funder of the study approved the trial design and appointed study monitoring committees. Statistical analysis and data management were done by the funder or with funder's oversight. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 19, 2012, and Dec 12, 2013, we screened 365 patients. After application of our exclusion criteria, we randomly assigned 201 patients to receive either placebo (n=99) or LY (n=102; figure 1). Of these patients, 167 (83%) completed treatment (85 [86%] patients given placebo and 82 [80%] patients given LY), and 169 (84%) completed the study. Table 1 shows baseline characteristics: the study population had a mean age of 82 years, with 140 (70%) women. The LY group had a higher number of pre-existing disorders (p=0·011). Baseline values for efficacy outcomes were well balanced between the two groups (table 2). At baseline, 54 (28%) of 192 patients had sarcopenia according to Baumgartner's criteria (aLBM/height^2 <5·45 kg/m^2 for women and <7·26 kg/m^2 for men;[24] table 1).

The primary endpoint, change in aLBM from randomisation to week 24 in least-squares mean, was–0·123 kg (95% CI –0·287 to 0·040) in the placebo group and 0·303 kg (0·135 to 0·470) in the LY group (p<0·0001), with an absolute difference of 0·43 kg (95% CI 0·192 to 0·660; p<0·0001), equivalent to a 2·5% difference (figure 2A, table 2). This difference was not significant at week 12 (p=0·083), but was maintained

	Baseline			12 weeks				24 weeks				p value for overall treatment effect including 12 and 24 weeks*
	N, Placebo/ LY2495655	Placebo	LY2495655	N, Placebo/ LY2495655	Change from baseline, actual value	95% CI	p value	N, Placebo/ LY2495655	Change from baseline, actual value	95% CI	p value	
Serum myostatin concentration (ng/mL)†	89/90	6·6 (2·7)	7·5 (4·3)	88/90	17·48	15·39 to 19·56	0<0·001	85/86	15·85	13·42 to 18·28	<0·0001	<·001
Bodyweight (kg)†	99/102	69·3 (13·7)	69·1 (13·4)	89/89	-0·05	–0·50 to 0·40	0·831	86/86	-0·40	–1·04 to 0·24	0·221	0·354
Body composition												
Appendicular lean body mass (kg)†	94/97	17·2 (4·3)	16·9 (3·8)	85/84	0·20	–0·03 to 0·44	0·083	82/77	0·43	0·19 to 0·66	<0·0001	0·003
Total body lean mass (kg)*	95/98	41·0 (9·1)	40·3 (7·8)	86/85	0·51	0·09 to 0·92	0·018	83/78	0·71	0·28 to 1·13	0·001	0·001
Total body fat mass (kg)†	95/98	24·7 (7·2)	25·2 (7·4)	86/85	–0·48	–0·82 to –0·14	0·007	83/78	–1·00	–1·49 to –0·51	<0·0001	<0·0001
Performance-based measures												
Four-step stair climb time (s)‡	98/102	3·6 (2·0)	3·6 (1·5)	83/86	–0·21	–0·47 to 0·04	0·166	84/80	–0·46	–0·88 to –0·04	0·073	0·093
12-step stair climb time (s)‡	43/44	12·0 (5·9)	12·0 (6·5)	34/39	–1·33	–2·34 to –0·32	0·031	35/35	–1·28	–2·66 to 0·10	0·127	0·011
Five chair rise time without arms (s)‡	78/76	16·4 (4·9)	16·8 (5·8)	64/64	–1·45	–2·96 to 0·05	0·111	64/53	–1·06	–2·40 to 0·28	0·191	0·118
Five-chair rise with arms (s)‡	17/24	23·6 (7·9)	22·5 (8·3)	8/18	-7·67	–12·64 to –2·70	0·013	10/16	-4·15	–8·87 to 0·58	0·147	0·054
Fast gait speed (m/s)‡	98/102	1·2 (0·4)	1·2 (0·3)	83/86	0·04	–0·004 to 0·08	0·135	85/79	0·05	–0·01 to 0·10	0·150	0·088
Usual gait speed (m/s)‡	98/102	0·9 (0·3)	0·9 (0·2)	83/86	0·01	–0·02 to 0·05	0·496	85/80	0·02	–0·02 to 0·06	0·478	0·422
Six minute walk distance (m)‡	97/102	314·4 (115·1)	313·0 (98·4)	83/85	-2·33	–17·42 to 12·76	0·761	84/78	-4·19	–21·20 to 12·82	0·627	0·525
Average leg extension strength (Nm/kg)†	98/100	0·8 (0·3)	0·7 (0·3)	82/83	0·01	–0·05 to 0·078	0·660	84/76	-0·02	–0·09 to 0·06	0·646	0·919
Average hand grip strength (kg)†	98/102	19·9 7·7)	20·0 (7·2)	85/86	0·22	–0·55 to 0·99	0·579	86/81	0·51	–0·41 to 1·43	0·276	0·357

Data are n, mean (SD) unless otherwise stated. *Statistically significant at a level of p<0·1 for all performance based measures and p<0·05 for all other measures.†95% CI. ‡90% CI.

Table 2: **Least squares mean differences between LY2495655 and placebo for the change from baseline in main pharmacodynamics and efficacy measures**

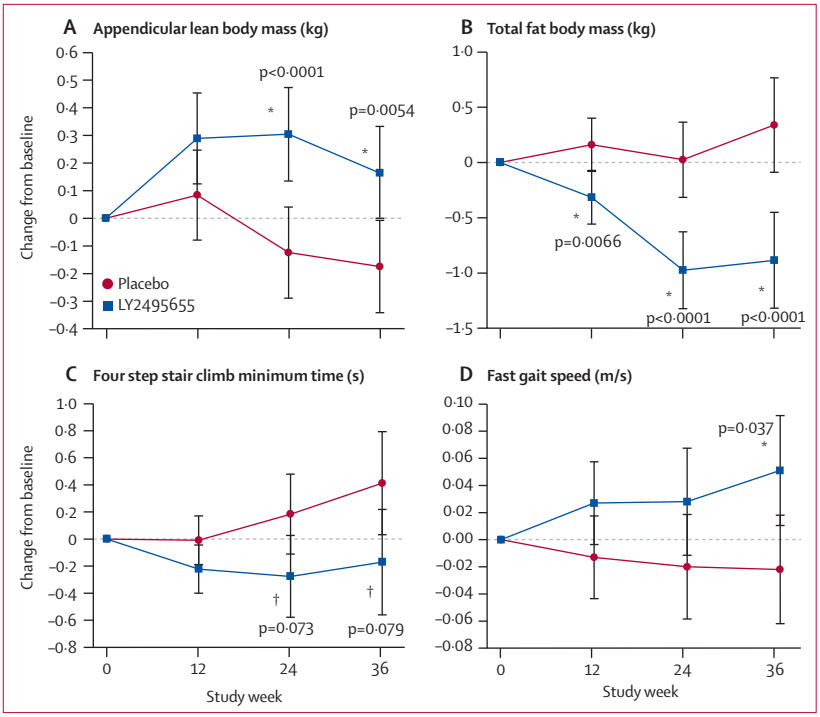

***Figure 2*: Change from baseline in body composition and performance-based measures**
Data are least-squares means. Error bars indicate 95% CIs for body composition data and 90% CIs for performance-based measures. Treatment was given at weeks 0, 4, 8, 12, 16, and 20, with observational follow-up until week 36. *p<0·05. †p<0·1.

	Placebo (N=99)	315 mg LY (N=102)	p-value
Deaths	0	1 (1%)	1·000
Serious adverse events	18 (18%)	26 (26%)	0·235
Early treatment discontinuation	14 (14%)	20 (20%)	0·351
Adverse events leading to treatment discontinuation	6 (6%)	10 (10%)	0·436
Injection site reactions			
Mild	8 (8%)	22 (22%)	<0·001*
Moderate	1 (1%)	8 (8%)	
Severe	0	1 (1%)	
Patients with ≥1 fracture	6 (6%)	10 (10%)	0·403
Patients with ≥1 TEAE considered by investigators as possibly related to study drug	23 (23%)	42 (41%)	0·007
All TEAEs considered by investigators as possibly related to study drug (by frequency and alphabetic order):			
Injection site pain	5 (5%)	20 (20%)	0·002
Blood creatine phosphokinase increased	0	5 (5%)	0·060
Fatigue	1 (1%)	3 (3%)	0·621
Injection site bruising	0	4 (4%)	0·121
Injection site erythema	1 (1%)	3 (3%)	0·621
Rash	0	4 (4%)	0·121
Diarrhoea	1 (1%)	2 (2%)	1·000
Injection site rash	0	3 (3%)	0·246
Anaemia	2 (2%)	0	0·241
Constipation	0	2 (2%)	0·498
Dysgeusia	2 (2%)	0	0·241

(Table 3 continues on next page)

until week 36 (p=0·005)—ie, 16 weeks after the last injection (figure 2). Patients given LY also had a greater increase in total lean mass (p=0·0007) and a larger reduction in total fat mass (p<0·0001) compared with placebo over the course of the study (table 2 and figure 2B). Total bodyweight showed numerical decreases in patients given LY versus those given placebo, especially at 24 weeks, but these differences were not significant (table 2). During the trial, 37 (38%) of 98 patients given placebo performed at least one physical therapy session versus 34 (34%) of 100 patients given LY. The appendix shows additional exploratory analyses of bone parameters (DXA and biochemical markers; appendix p 9).

Several performance-based measures improved in the LY group compared with the placebo group. Compared with placebo, the overall treatment effect of LY including 12-week and 24-week timepoints was significant for four-step stair climb time, 12-step stair climb time and power, five-chair rise using arms, and fast gait speed (table 2). At selected individual timepoints (12, 24, or 36 weeks), statistically significant improvements versus placebo were also detected for usual gait speed, and four-step stair climb power (table 2, figure 2, and appendix). Of the performance-based measures that showed a difference between groups over the 24 week treatment period, the effect size of LY compared with placebo ranged from 4% (fast gait speed) to 18% (5-chair rise with arms). We did not record a significant difference for other performance-based measures (6-min walking distance, leg extension strength, usual gait speed, or hand grip strength; appendix p 6). Post-hoc exploratory analyses were done to investigate the effect of baseline physical performance on the effect of LY versus placebo on each physical performance test respectively. The slowest or weakest tertiles of baseline physical performance responded better to LY versus placebo than the fastest or strongest tertiles for all the time dependent tests (stair climb time, chair rise time, fast gait speed, usual gait speed, and 6-min walking distance), but not for isometric hand and leg strength (appendix pp 7–8).

During the 36-week study period, at least one fall was reported by 52 (53%) of 98 patients given placebo (total 127 falls) and 46 (46%) of 100 given LY (105 falls). The incidence rate was 2 falls per patient-year in the placebo group versus 1·6 falls per patient-year in the LY group (p=0·357).

As a demonstration of molecular target engagement, the amount of serum myostatin increased by more than 200% in the LY group versus the placebo group (p<0·0001 at weeks 12 and 24).

We reported more patients with at least one adverse event, one serious adverse event, or discontinuation due to an adverse event in the LY group than in the placebo group, although these differences were not significant. Table 3 provides an overview of adverse events and the list of all adverse events considered as possibly related to study drug by investigators; the appendix provides a complete list of adverse events irrespective of their

relatedness (appendix pp 11–18). We recorded one death due to ischaemic colitis in an 87-year old man receiving LY who had hypercholesterolaemia and previous surgery for abdominal aortic aneurysm. During the 36-week study period, ten adverse events of fractures were reported by six (6%) of 99 patients in the placebo group compared with 15 fractures in ten (10%) of 102 patients receiving LY, including one vertebral fracture in each group. A risk-adjusted analysis of fracture showed no significant treatment effect (p=0·403).

Adverse events deemed as possibly related to study drug by investigators were more frequent in the LY group (p=0·007), and this difference was driven by injection site reactions, which occurred among 9 (9%) placebo patients versus 31 (30%) of LY patients and led to treatment discontinuation in two patients given LY. The type of reactions included injection site pain, bruising, erythema, rash, and pruritus. No case of anaphylaxis was reported. Of 102 patients with LY, 22 (22%) had mild reactions, and eight (8%) had moderate reactions. The only severe injection site reaction (pain) occurred after the first injection but did not prevent further dosing, and subsequent injections induced only mild pain.

We recorded non-specific adverse events more frequently in the LY group than in the placebo group: fatigue (three placebo patients [3%] *vs* 12 LY patients [12%]; p=0·029) and back pain (four placebo patients [4%] *vs* 13 LY patients [13%]; p=0·040). Raised serum creatine phosphokinase (CPK) concentrations were reported by investigators as an adverse event possibly related to study drug in five patients receiving LY (5%) versus one placebo patient (1%; p=0·212). 21 (22%) of 94 patients given placebo and 23 (25%) of 92 patients given LY had at least one CPK increase above the upper limit of normal after baseline, independently of whether the investigator reported this increase as an adverse event. Five patients (four in the LY group and one in the placebo group) had at least one serum CPK value greater than two times the upper limit of normal after baseline. Of the four patients in the LY group, the CPK concentration was already above the upper limit of normal at baseline, but this was not the case in the patient in the placebo group. Of these patients, none was taking a statin, but one patient given LY and the patient given placebo were receiving fenofibrate. The highest post-baseline CPK concentration in the placebo patient was 5·2 times the upper limit of normal, and 3·2 times the upper limit of normal in patients given LY.

Discussion

This study showed that 24 weeks of LY treatment increases aLBM compared with placebo in older fallers with low muscle strength and power. We also recorded a treatment effect of LY on several performance-based measures assessed, including stair climbing, fast gait speed, and a chair rise test.

These results are consistent with the increase in thigh muscle volume (assessed by MRI) reported during LY

	Placebo (N=99)	315 mg LY (N=102)	p value
(Continued from previous page)			
Headache	1 (1%)	1 (1%)	1·000
Hyponatraemia	1 (1%)	1 (1%)	1·000
Injection site pruritus	0	2 (2·0)	0·498
Muscle spasms	0	2 (2%)	0·498
Musculoskeletal stiffness	2 (2%)	0	0·241
Myalgia	0	2 (2%)	0·498
Occult blood positive	1 (1%)	1 (1%)	1·000
Pain	1 (1%)	1 (1%)	1·000
Pruritus	0	2 (2%)	0·498
Abdominal pain upper	1 (1%)	0	0·493
Amnesia	0	1 (1%)	1·000
Application site rash	0	1 (1%)	1·000
Arthralgia	1 (1%)	0	0·493
Asthenia	1 (1%)	0	0·493
Blood potassium increased	1 (1%)	0	0·493
Bone pain	1 (1%)	0	0·493
Burning sensation	1 (1%)	0	0·493
Contusion	0	1 (1%)	1·000
Dry mouth	0	1 (1%)	1·000
Dry skin	1 (1%)	0	0·493
Dyspnoea	0	1 (1%)	1·000
Ear discomfort	1 (1%)	0	0·493
Energy increased	0	1 (1%)	1·000
Epistaxis	0	1 (1%)	1·000
Erythema	0	1 (1%)	1·000
Feeling hot	1 (1%)	0	0·493
Gastritis	1 (1%)	0	0·493
Gastrointestinal hypermotility	1 (1%)	0	0·493
Gastro-oesophageal reflux disease	1 (1%)	0	0·493
Haematochezia	0	1 (1%)	1·000
Head injury	0	1 (1%)	1·000
Hot flush	1 (1%)	0	0·493
Hypersensitivity	0	1 (1%)	1·000
Hypertonia	0	1 (1%)	1·000
Hypoxia	0	1 (1%)	1·000
Infusion site pain	0	1 (1%)	1·000
Injection site haematoma	0	1 (1%)	1·000
Injection site haemorrhage	0	1 (1%)	1·000
Injection site mass	0	1 (1%)	1·000
Injection site oedema	0	1 (1%)	1·000
Injection site warmth	1 (1%)	0	0·493
Ligament sprain	0	1 (1%)	1·000
Lymphocyte count decreased	1 (1%)	0	0·493
Malaise	1 (1%)	0	0·493
Muscular weakness	1 (1%)	0	0·493
Musculoskeletal pain	0	1 (1%)	1·000
Nausea	1 (1%)	0	0·493
Pain in extremity	1 (1%)	0	0·493
Parosmia	1 (1%)	0	0·493
Pulmonary arterial hypertension	0	1 (1%)	1·000

(Table 3 continues on next page)

	Placebo (N=99)	315 mg LY (N=102)	p value
(Continued from previous page)			
Pyrexia	1 (1%)	0	0·493
Skeletal injury	0	1 (1%)	1·000
Sleep disorder	0	1 (1%)	1·000
Somnolence	0	1 (1%)	1·000
Tic	1 (1%)	0	0·493
Toxic epidermal necrolysis	0	1 (1%)	1·000
Transaminases increased	0	1 (1%)	1·000
Type 2 diabetes	0	1 (1%)	1·000
Vertigo	1 (1%)	0	0·493

LY=LY2495655. TEAE=treatment-emergent adverse event. MedDRA=Medical Dictionary for Regulatory Activities. *Fisher exact test comparing proportions for each severity across treatment groups.

Table 3: **Summary of treatment-emergent adverse events (all randomly assigned patients)**

treatment in a single dose phase 1 trial in healthy volunteers.[14] Other compounds targeting myostatin directly are a myostatin monoclonal antibody that showed consistent increases in thigh muscle volume (as assessed by MRI) but inconsistent effects on lean body mass (assessed by DXA) in older healthy participants,[25] and a myostatin peptibody that increased lean mass by 2·2% versus control at 29 days and 1·7% at 58 days in older men receiving androgen deprivation treatment for prostate cancer.[26]

Progressive resistance training increases lean mass but its effect decreases with ageing.[27] Although they are heterogeneous, data obtained in randomised controlled trials testing progressive resistance training versus control in populations with a mean age of at least 75 years suggest that differences in lean mass are smaller than or equivalent to those recorded with LY versus control in the present trial.[28–30]

Our findings show, for the first time with a drug specifically targeting myostatin, that increases in lean mass translate into improvement of several measures of physical performance. Consistent with LY's mechanism of action, which induces hypertrophy preferentially of fast twitch fibres,[31] we recorded treatment effects for performance-based measures that are power intensive and require the patients to perform a task as quickly as possible (eg, stair climbing, five-chair rise, and fast gait speed), but not for less power-intensive performance-based measures (eg, 6-min walking distance and usual gait speed, which are measures of endurance and general mobility).[32,33] Hand grip strength showed some consistent but non-significant improvement over time in the LY group, but we noted no treatment effect for isometric leg extension strength, which contrasts with preclinical findings.[12] This finding might be the result of the predominant effect of myostatin inhibition on muscle power versus isometric strength, the high variability of leg extension strength recorded in this multicentre study, or the fact that isometric strength is less natural for frail older individuals than functional measures such as stair climbing or standing up from a chair.

Compared with the heterogeneous effects of progressive resistance training reported in randomised controlled trials done in populations with a mean age of at least 75 years, the effects of LY in our trial seem to be similar for stair climbing time,[34–38] smaller for usual gait speed[34–39] and isometric leg strength,[40] and difficult to compare for other measures of physical performance (as published studies included different populations or used different methods of assessment). The effect of progressive resistance training is smaller in studies with clear allocation concealment and in studies using masked assessors,[4] suggesting that the absence of a full double-blind design in progressive resistance training trials makes it difficult to compare with our trial, which was double-blinded.

Our trial did not show any safety signals preventing further clinical development of LY. The only adverse events probably related to LY were injection site reactions. The higher number of fractures in the LY group (non-significant) is probably not related to LY use because there was no concomitant increase in falls in this group, which appeared to have a higher baseline risk for fracture.

A limitation of this trial was the baseline imbalance in pre-existing disorders, which translated into a higher prevalence of risk factors for falls and fractures at baseline in patients given LY versus those given placebo. The absence of adjustment for multiplicity testing on performance-based measures is another study limitation because it increases the risk of detecting a false signal; this a-priori study design choice relates to the exploratory nature of this proof-of-concept trial. Another limitation is that the primary analysis necessarily included only patients with at least one post-baseline aLBM assessment, which could be a potential source of bias. However, post-hoc exploratory analyses were used to assess the baseline characteristics of patients who had DXA assessments up to at least week 24; these patients were similar to the overall population randomly assigned (appendix p 10). Additionally, because of limited sample size, our study was not statistically powered to detect a difference in terms of falls, so any finding related to these endpoints should be interpreted cautiously. Finally, exercise and protein intake were not standardised; whereas this might be deemed as a study limitation, it allowed testing LY in a setting closer to routine practice.

In conclusion, compared with placebo treatment, 24 weeks of LY treatment resulted in increased aLBM and improvements in several measures of physical performance in older fallers with reduced muscle strength. These findings open up the possibility of testing LY for improvement in various disorders characterised by disabling muscle wasting.

Contributors

CB, SRL, SAS, SJW, CPR, SLF, HB, EFB, YR, SLM, SP, KRP, LH, EVG, and OB created the concept and developed the design of this trial. CB, CPR, EFB, YR, QIA, and KRP acquired the data and provided administrative, technical, and material support. LH and EVG did the statistical analyses. SLM, KRP, and OB supervised the study. All authors analysed and interpreted the data. CTB, OB, and EVG drafted the Article with support from Barbara M Coffey, a professional medical writer and employee of Eli Lilly and Company. All authors revised the Article.

Declaration of interests

CB has received consultation fees from Lilly and and Robert Bosch Healthcare. SRL reports personal fees from Lilly during the conduct of the study. SAS reports personal fees from Lilly during the conduct of the study; personal fees from Novartis, Abbott Nutrition, and Ammonette outside the submitted work. SJW reports personal fees and non-financial support from Lilly during the conduct of the study. RAF reports personal fees from Lilly during the conduct of the study; grants and personal fees from Regeneron; personal fees from Cytokinetics, Pronutria, Astellas, Ammonett, and GSK; grants and personal fees from Nestlé; non-financial support from Inside Tracker and Myosyntax outside the submitted work. MCH reports personal fees from Lilly during the conduct of the study. SLF reports grants and personal fees from AMGEN and MSD; personal fees from Lilly; personal fees from UCB and AGNOVOS outside the submitted work. CPR, HB, and SP have nothing to disclose. EFB reports grants and personal fees from Lilly during the conduct of the study; grants and personal fees from Regeneron Pharmaceuticals outside the submitted work. YR reports grants and personal fees from Lilly during the conduct of the study; grants from LACTALIS and NOVARTIS outside the submitted work. SLM and QIA were employees of Eli Lilly and Company during the conduct of the study. CTB, LH, KRP, EVG, and OB are employees of Eli Lilly and Company.

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