The Safety, Pharmacokinetics, and Effects of LGD-4033, a Novel Nonsteroidal Oral, Selective Androgen Receptor Modulator, in Healthy Young Men

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Background. Concerns about potential adverse effects of testosterone on prostate have motivated the development of selective androgen receptor modulators that display tissue-selective activation of androgenic signaling. LGD-4033, a novel nonsteroidal, oral selective androgen receptor modulator, binds androgen receptor with high affinity and selectivity.

Objectives. To evaluate the safety, tolerability, pharmacokinetics, and effects of ascending doses of LGD-4033 administered daily for 21 days on lean body mass, muscle strength, stair-climbing power, and sex hormones.

Methods. In this placebo-controlled study, 76 healthy men (21–50 years) were randomized to placebo or 0.1, 0.3, or 1.0 mg LGD-4033 daily for 21 days. Blood counts, chemistries, lipids, prostate-specific antigen, electrocardiogram, hormones, lean and fat mass, and muscle strength were measured during and for 5 weeks after intervention.

Results. LGD-4033 was well tolerated. There were no drug-related serious adverse events. Frequency of adverse events was similar between active and placebo groups. Hemoglobin, prostate-specific antigen, aspartate aminotransferase, alanine aminotransferase, or QT intervals did not change significantly at any dose. LGD-4033 had a long elimination half-life and dose-proportional accumulation upon multiple dosing. LGD-4033 administration was associated with dose-dependent suppression of total testosterone, sex hormone–binding globulin, high density lipoprotein cholesterol, and triglyceride levels. Follicle-stimulating hormone and free testosterone showed significant suppression at 1.0-mg dose only. Lean body mass increased dose dependently, but fat mass did not change significantly. Hormone levels and lipids returned to baseline after treatment discontinuation.

Conclusions. LGD-4033 was safe, had favorable pharmacokinetic profile, and increased lean body mass even during this short period without change in prostate-specific antigen. Longer randomized trials should evaluate its efficacy in improving physical function and health outcomes in select populations.

Key Words: Selective androgen receptor modulators—SARMs—Sarcopenia—Function promoting anabolic therapies—Cachexia.

Received December 8, 2011; Accepted February 2, 2012

Decision Editor: Luigi Ferrucci, MD, PhD

As men and women grow old, they lose muscle mass, muscle strength, and leg power (1,2,3,4,5,6), mostly due to the preferential loss of type II muscle fibers (5). Sarcopenia, the age-associated loss of muscle mass and strength, increases the risk of falls, fractures, physical disability, and poor quality of life (1,3,6,7). Similarly, the course of many illnesses, such as chronic obstructive lung disease, end-stage renal disease, and some types of cancer, is punctuated by the loss of muscle mass and physical function, which contributes to mobility limitation and disability (7,8). Thus, there is an unmet need for anabolic therapies that improve physical function and reduce the burden of disability in persons experiencing functional limitations due to aging or illness. Among the various candidate function-promoting anabolic therapies that are in development, androgens are the farthest along in development.

Testosterone administration increases muscle mass and strength (9,10,11,12,13,14,15), but concerns regarding its potential adverse effects on the prostate have restrained enthusiasm for its use as an anabolic therapy and have motivated efforts to develop selective androgen receptor modulators (SARMs), a new class of androgen receptor
ligands that are tissue selective (8,16,17,18,19). The last decade has witnessed substantial pharmaceutical efforts to develop nonsteroidal SARMS to treat muscle wasting and functional limitations associated with acute and chronic illness and aging (8,16,17,18,19). LGD-4033 is a novel nonsteroidal, oral SARM that binds to androgen receptor with high affinity (Ki of ~1 nM) and selectivity. In animal models, LGD-4033 has demonstrated anabolic activity in the muscle, anti-resorptive and anabolic activity in bone, and robust selectivity for muscle versus prostate.

Here we report the results of a randomized, double-blind, placebo-controlled, ascending-dose study, which evaluated the safety, tolerability, and pharmacokinetics (PK) of LGD-4033 in healthy men. We also evaluated the effects of graded doses of LGD-4033 on lean body mass (LBM), muscle strength, and physical function. LGD-4033 doses of 0.1, 0.3, and 1.0 mg were selected for multiple dosing over 21 days because a previous phase I single ascending-dose study had established the safety of up to 22 mg LGD-4033. We also tested the hypothesis that the LGD-4033 increases muscle mass by stimulating fractional synthetic rate (FSR) of mixed-muscle proteins, measured using continuous steady state infusion of labeled phenylalanine in men randomized to either placebo or 0.3-mg daily dose of LGD-4033. This dose was selected for FSR study because preclinical data suggested that this dose was the most likely to increase LBM.

Study Design
This was a double-blind, placebo-controlled, multiple once-daily dose escalation study of LGD-4033 in healthy men, approved by Boston University’s Institutional Review Board. All subjects provided written, informed consent.

Subjects
Nonsmoking, healthy men, 21–50 years, with body mass index between 18 and 32 kg/m², who were capable of providing informed consent, were eligible. We excluded subjects who had an active disease, prostate-specific antigen >3 ng/mL, aspartate aminotransferase or ALT >1.5 times the upper limit of normal, hematocrit <37% or >48%, creatinine >2.0 mg/dL, and (HDL) cholesterol <40 mg/dL; had used anabolic steroids, recombinant human growth hormone, dehydroepiandrosterone, and androstenedione during the past year; or were using any recreational drug.

Study Intervention
Three dose levels—0.1, 0.3, and 1.0 mg—were evaluated against placebo. Each dose of LGD-4033 or placebo was administered daily orally with 8 ounces of water after an overnight fast. A total of 20 doses were administered over 21 days; no dose was given on day 2 to allow PK sampling for 48 hours after the first dose. The 21-day treatment period was followed by a 5-week observation period.

Randomization
The subjects were randomized to the active drug or placebo group based on protocol-defined randomization schema: six active and two placebo in 0.1-mg cohort; 10–12 active and 10–12 placebo in 0.3-mg and 1.0-mg cohorts. A protocol amendment after the completion of 1.0-mg cohort added 12 active and six placebo subjects in the 0.1-mg cohort. Randomization lists, generated by the biostatistician, were sent directly to Investigational Drug Service.

The subjects were initially assigned to either placebo or 0.1 mg LGD-4033 daily. At the completion of each dose level, the safety data were reviewed by a Safety Panel and separately by a Data and Safety Monitoring Board, which determined whether the dose could be escalated to a higher level, based on prespecified safety criteria. Dose escalation proceeded only if an acceptable safety profile with no clinically significant and/or unexpected toxicity was observed at the lower dose.

Blinding
The study was a double-blind trial with concealed randomization. The subjects and study personnel were unaware of the intervention. Only the biostatistician and Investigational Drug Service were aware of the subject’s group allocation. The Investigational Drug Service maintained the randomization code and dispensed the study medication based on the randomization list.

Outcomes
The primary aim was to assess the safety and tolerability of escalating doses of LGD-4033 following repeated once-daily oral administration for 21 days. Secondary aims included the determination of the PK and pharmacodynamics of LGD-4033 and its effects on mixed-muscle FSR. Additionally, we investigated the effects of 21 days of treatment with LGD-4033 on LBM measured by dual-energy x-ray absorptiometry, maximal voluntary strength measured by one repetition maximum method, and physical function, assessed by the stair-climbing power, recognizing that a 21-day duration may not be sufficiently long to fully elucidate the anabolic effects of the SARM on LBM, muscle strength, and physical function.

Schedule of Events
LGD-4033 concentrations were measured using a validated liquid chromatographic–tandem mass spectrometry method in venous blood collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 28, 32, and 48 hours after the first dose. Once-daily dosing recommenced on day 3 for 20 days, and on day 21, venous blood was collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 28, 32, 48, 72, 96, 120, and 168 hours after day 21 dosing.
Luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone, cortisol, total and free testosterone, sex hormone–binding globulin levels, and plasma lipids were measured periodically throughout the 21-day intervention period and 7 and 35 days after drug cessation. LBM and fat mass were measured at baseline and on days 20 and 28. Leg press strength and stair-climbing power and speed were assessed at baseline and between days 23 and 25.

**METHODS**

Body composition was assessed using dual-energy x-ray absorptiometry (Hologic 4500) scanner, calibrated using a soft tissue phantom before each scan. To measure the leg press strength (15,20,21), subjects underwent whole-body warm up, followed by one set of 5–10 repetitions using 40%–60% of the estimated maximum. Following appropriate rest periods between attempts, subjects lifted progressively heavier weights until the subject could not complete the lift. The last successfully completed lift was recorded as the one repetition maximum.

The 12-step stair-climb test required subjects to ascend a staircase with step rise of 17 cm as fast as possible with time recorded by activation of switchmats on the 8th and 12th stair (15,20,21). The test–retest reliability is 0.85 and coefficients of variation 2%. After familiarization, two trials were given with the best time taken as the stair-climb score. Power was calculated from the time elapsed, body weight, and vertical distance.

**Fractional Protein Synthesis Rates**

On days 1 and 20, at 7 am, an 18-gauge catheter was inserted into the forearm vein of each arm, one for blood sampling and one for tracer infusion. Baseline blood samples were drawn for analysis of amino acid enrichments from one arm, heated with a heating pad. At 8 am, a primed (2.0 μmol/kg) constant infusion (0.06 μmol/kg/minutes) of l-[ring-13C6]-phenylalanine was started and maintained for 6 hours. Venous blood was obtained at 0, 60, 120, 150, 165, 180, 195, 210, 240, 300, 330, 345, and 360 minutes during the infusion. Two muscle biopsies (100–300 mg) were taken at 180 and 360 minutes from vastus lateralis, ~10 to 15 cm above the knee, using a 5-mm Bergstrom biopsy needle, and snap frozen in liquid nitrogen for storage in a −80°C freezer until analysis.

Phenylalanine enrichments in arterialized venous blood was determined after deproteinization with sulfosalicylic acid, extraction with cation exchange chromatography (Dowex AG 50W-8X, 100–200 mesh H+ form; BioRad Laboratories, Richmond, CA), derivatization using tert-butyldimethylsilyl, followed by gas chromatography–mass spectrometry in electron impact mode (GC HP 5890, MSD HP 5898, Hewlett Packard, Palo Alto, CA; 22).

Muscle samples were weighed and the proteins precipitated with 800 μl of 10% sulfosalicylic acid. Intracellular phenylalanine enrichment was determined by extraction with cation exchange chromatography (Dowex AG 50W-8X, 200–400 mesh H+ form; BioRad Laboratories, Inc.), tert-butylidimethylsilyl derivatization, and gas chromatography–mass spectrometry in electron impact mode (22). The remaining pellet containing bound mixed-muscle proteins was repeatedly washed, dried at 50°C overnight, and hydrolyzed in 3 mL of 6 N HCl at 110°C for 24 hours. Amino acids in the hydrolysate were extracted and derivatized and analyzed by monitoring the ions 238 and 240 (22).

Mixed-muscle FSR was calculated by measuring the incorporation of l-[ring-13C6]-phenylalanine into protein using the precursor–product model:

\[
FSR = \frac{(E_{P2} - E_{P1})}{(E_{M} \times t)60 \times 100}
\]

where \(E_{P1}\) and \(E_{P2}\) are enrichments of bound l-[ring-13C6]-phenylalanine in the first and second muscle biopsies, \(t\) is the time between biopsies, and \(E_{M}\) is the mean l-[ring-13C6]-phenylalanine enrichment in muscle intracellular pool (22).

**Hormone Assays**

Total testosterone was measured using liquid chromatography–tandem mass spectrometry (23), and free testosterone was calculated using a published law–of–mass–action equation (24). Serum luteinizing hormone, follicle-stimulating hormone, and sex hormone–binding globulin were measured using two site-directed immunofluorometric assays (9,21).

**Statistical Analyses**

Safety parameters were listed and summarized by study intervention, dose, and time point. Adverse events were tabulated by System Organ Class and Preferred Term based on MedDRA dictionary version 12.

Plasma drug concentration–time data were analyzed using noncompartmental methods. PK parameters were summarized by dose group, and selected PK parameters were analyzed using comparative statistics. Dose proportionality of PK parameters was assessed by linear regression.

Pharmacodynamic assessments were summarized for each dose and time point. Changes from baseline in hormone levels, lipids, and FSR were analyzed using repeated measures analyses of variance, with a dose factor and time-in-treatment factor and baseline value as covariate. A similar approach was used to analyze change from baseline in LBM, one repetition maximum strength, and stair-climbing power.

For dual-energy x-ray absorptiometry, muscle strength, and stair-climbing power, a trend analysis of change from baseline was applied using a mixed-model analysis of repeated measures and adjusted for baseline value. Two post-baseline measures up to day 28 were utilized in repeated measure model. This analysis was performed on evaluable subjects who had baseline measures and at least one
post-baseline measure. Placebo subjects from the three cohorts were pooled for analysis. This resulted in sample sizes of 30 men for dual-energy x-ray absorptiometry analysis and 29 men for muscle strength analysis in the placebo group, 17 in the 0.1-mg, 10 in the 0.3-mg, and 11 in the 1.0-mg dose groups.

RESULTS

Flow of Subjects
A total of 389 subjects were screened in person, 131 were eligible, and 76 were randomized (CONSORT diagram, Supplementary Appendix Figure 1). Eight subjects were either lost to follow-up or discontinued and 68 subjects completed the trial.

Subjects
The participants were young (mean age 37 years), lean (body mass index 25.8 kg/m²), and had normal testosterone, luteinizing hormone, and follicle-stimulating hormone levels (Table 1). The groups were similar in their baseline characteristics.

Compliance
The compliance, assessed by drug logs and by counting the unused tablets, was 100%, among men who were included in the efficacy analysis.

Safety Data
LGD-4033 was safe and well tolerated at all doses. The frequency of adverse events was similar between the placebo and any dose group. Headache, pain related to muscle biopsy, and dry mouth were the most common events and did not show dose relationship (Supplementary Appendix Table 1). More upper respiratory tract infections were observed in LGD-4033 1.0-mg group, but these events were not considered drug related. No drug-related severe or serious adverse events occurred. One cellulitis (in placebo group) and one gastroenteritis (0.3 mg group) were severe but were not considered study drug related. There was no study discontinuation due to adverse events. There were no clinically significant changes in liver enzymes, hematocrit, prostate-specific antigen, or electrocardiogram at any dose.

Pharmacokinetics
LGD-4033 displayed a prolonged elimination half-life (24–36 hours) and linear PK (Figure 1). There was a dose-proportional increase in LGD-4033 concentrations on days 1 and 21. Serum LGD-4033 concentrations were nearly threefold higher on day 21 than on day 1, reflecting accumulation upon multiple dosing. The mean areas under the drug concentration curve on day 21 were 19, 85, and 238 ng 24 hour/mL, respectively, in men receiving 0.1, 0.3, and 1.0 mg LGD-4033 daily.

Hormone Levels
There was a dose-dependent suppression of total testosterone and sex hormone–binding globulin levels from baseline to day 21 (Figure 2). Free testosterone suppression was noted at the 1.0-mg dose only. The suppression of total testosterone was greater than that of free testosterone. Serum luteinizing hormone levels did not show any meaningful changes from baseline, whereas the follicle-stimulating hormone levels were suppressed only in the 1.0-mg dose group (Figure 2D and E). Upon discontinuation of LGD-4033, the hormone levels returned to baseline by day 56.
biopsy, and dry mouth were the most common events and
Compliance characteristics.

luteinizing hormone, and follicle-stimulating hormone (body mass index 25.8 kg/m²), and had normal testosterone,
eligible, and 76 were randomized (CONSORT diagram,

Placebo/LGD Dose Group Placebo 0.1-mg 0.3-mg 1.0-mg

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>0.1 mg</th>
<th>0.3 mg</th>
<th>1.0 mg</th>
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<td>6</td>
<td>6</td>
<td>10</td>
<td>11</td>
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<tr>
<td>Cohort 2</td>
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<td>10</td>
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<tr>
<td>Cohort 3</td>
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and one gastroenteritis (0.3 mg group) were severe but were
observed in LGD-4033 1.0-mg group, but these events were
did not show dose relationship (Supplementary Appendix Table 1).

**Table 1.** Baseline Characteristics of the Subjects

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<tr>
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<th>All Subjects</th>
<th>0.1 mg</th>
<th>0.3 mg</th>
<th>1 mg</th>
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<td>60.6 (9.1)</td>
<td>58.9 (7.6)</td>
<td>60.6 (8.7)</td>
<td>63.9 (4.7)</td>
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<td>Prostate-specific antigen</td>
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<td>0.7 (0.2)</td>
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<td>Follicle-stimulating hormone</td>
<td>4.0 (3.4)</td>
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<td>Body mass index</td>
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<td>27.0 (2.7)</td>
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<td>Body weight</td>
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<td>78.2 (13.9)</td>
<td>80.5 (13.5)</td>
<td>84.6 (10.2)</td>
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<tr>
<td>Total testosterone</td>
<td>549 (136)</td>
<td>564 (153)</td>
<td>543 (111)</td>
<td>551 (144)</td>
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<tr>
<td>Total T4</td>
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Figure 2. (A) The effects of LGD-4033 selective androgen receptor modulator on serum total testosterone levels. Change from baseline in serum total testosterone levels are shown. The data are mean ± standard error of the mean (SEM). \( n = 33 \) in the placebo group, 18 in the 0.1-mg dose, 11 in the 0.3-mg group, and 14 in the 1.0-mg group. BL = baseline. The shaded area highlights the 21-day treatment period. (B) Change in the free testosterone levels from baseline. Change from baseline in serum follicle-stimulating hormone levels is shown. The data are mean ± SEM, \( n = 33 \) in the placebo group, 18 in the 0.1-mg dose, 11 in the 0.3-mg group, and 14 in the 1.0-mg group. BL = baseline. The shaded area highlights the 21-day treatment period. (C) Change in sex hormone–binding globulin levels from baseline. Change from baseline in serum sex hormone–binding globulin levels is shown. The data are mean ± SEM, \( n = 33 \) in the placebo group, 18 in the 0.1-mg dose, 11 in the 0.3-mg group, and 14 in the 1.0-mg group. BL = baseline. The shaded area highlights the 21-day treatment period. (D) Change in luteinizing hormone levels from baseline. Change from baseline in serum luteinizing hormone levels is shown. The data are mean ± SEM, \( n = 33 \) in the placebo group, 18 in the 0.1-mg dose, 11 in the 0.3-mg group, and 14 in the 1.0-mg group. BL = baseline. The shaded area highlights the 21-day treatment period. (E) Change in prostate-specific antigen (ng/mL) levels from baseline. Change from baseline in prostate-specific antigen levels is shown. The data are mean ± SEM, \( n = 33 \) in the placebo group, 18 in the 0.1-mg dose, 11 in the 0.3-mg group, and 14 in the 1.0-mg group. BL = baseline. The shaded area highlights the 21-day treatment period.
predictable accumulation upon multiple dosing. There was a robust relationship between the dose and the plasma concentrations. The mean area-under-the-curves (AUC) in men receiving the 0.3- and 1.0-mg dose were above the drug AUC estimated to be efficacious in monkeys, and all three doses produced AUCs that exceeded the AUC estimated to be efficacious in orchidectomized rats.

In a manner typical of all oral androgens (25,26,27), the oral administration of LGD-4033 was associated with significant suppression of HDL cholesterol at the 1.0-mg dose. Triglyceride levels also decreased, but LDL cholesterol did not change. Neither the mechanism nor the clinical significance of the HDL suppression with orally administered androgens is well understood (25). HDL cholesterol has been negatively associated with the risk of coronary artery disease in epidemiological studies (25,28); however, pharmacologically induced changes in HDL cholesterol have not been necessarily associated with changes in cardiovascular risk. In animal models, the degree of anti-atherogenic effect of HDL cholesterol is determined more by the mechanism of HDL modification than by the changes in HDL levels (28,29). Thus, the increases in HDL cholesterol due to overproduction of apoA1, but not due to inhibition of HDL catabolism, have been found to be atheroprotective (28,29,30,31,32). The HDL lowering effect of oral androgens has been attributed to the upregulation of scavenger receptor B1 and the hepatic lipase, both of which are involved in HDL catabolism (32,33). Neither the hyperexpression of scavenger receptor B1 nor that of hepatic lipase has been associated with acceleration of atherogenesis, even though increased expression of each is associated with reduced HDL cholesterol (28,29,30,31). Thus, clinical significance of the HDL decrease associated with oral androgens remains unclear. Long-term studies are needed to clarify the effects of long-term SARM administration on cardiovascular risk. In the interim, the initial trials are likely to be conducted for acute or subacute

<table>
<thead>
<tr>
<th>Treatment Group*</th>
<th>Mean (SD) Baseline</th>
<th>Mean (SE) Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>163.4 (28.1)</td>
<td>Day 21 −1.6 (2.9) 5.2 (4.2)</td>
</tr>
<tr>
<td>0.1 mg</td>
<td>163.3 (33.5)</td>
<td>Day 21 −10.8 (3.6) 0.4 (3.5)</td>
</tr>
<tr>
<td>0.3 mg</td>
<td>168.6 (16.6)</td>
<td>Day 21 −18.0 (4.8) 6.4 (5.0)</td>
</tr>
<tr>
<td>1 mg</td>
<td>175.1 (33.5)</td>
<td>Day 21 −14.3 (8.1) 0.3 (4.4)</td>
</tr>
</tbody>
</table>

Notes: * Number of subjects with at least one post-baseline test: placebo = 33, 0.1 mg = 17, 0.3 mg = 10, and 1 mg = 14. LDL = Low density lipoprotein.
indications, such as cancer cachexia and functional limitations associated with acute illness or hip fracture, where the short-term changes in HDL cholesterol may not be clinically important.

Exogenous androgens would be expected to lower endogenous testosterone levels. However, LGD-4033 has been shown to increase bone mineral density, periosteal bone formation, and femur bending strength in preclinical models. Other SARMs have also been shown to maintain measures of sexual function in the orchietomized rodent model (18).

The mechanisms by which androgens increase muscle mass remain incompletely understood. Testosterone administration induces hypertrophy of both type I and type II muscle fibers (34). Muscle fiber hypertrophy can result from either increased muscle protein synthesis or decreased muscle protein degradation. Our studies did not reveal a significant difference in fractional muscle protein synthesis between the placebo and the active drug groups at the 0.3-mg dose. These studies were conducted in the fasted state when the fractional muscle protein synthesis is low; however, testosterone trials that have reported an increase in FSR have also been conducted in the fasted state as have trials that failed to show improvements in FSR (35). Previous human and animal studies have shown inhibition of muscle proteolysis and muscle protein degradation pathways during testosterone administration, as potential mechanisms for increased muscle mass (36,37). Testosterone also increases the number of satellite cells (38) by promoting the proliferation of satellite cells and the differentiation of muscle progenitor cells (39,40). Those mechanisms were not investigated in this study.

The past decade has witnessed the emergence of a number of nonsteroidal SARMs from several pharmaceutical companies. Currently, SARMs are being developed as a new class of function-promoting anabolic therapies to treat the loss of muscle mass and function associated with aging and illness, cancer cachexia, osteoporosis, and other conditions associated with muscle loss. This 3-week phase I study, by demonstrating the safety and tolerability of LGD-4033 and significant gains in muscle mass and strength, paves the way for longer term efficacy trials in one or more populations of older individuals for which SARMs may be indicated. Short-term indications for grievous conditions, such as cancer cachexia or functional limitations following an acute illness or hip fracture, might provide a more attractive risk:benefit profile for initial trials of SARMs than long-term indications such as aging-associated sarcopenia.

Funding
This trial was supported by Ligand Pharmaceuticals.

Supplementary Material
Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

Acknowledgment
The authors thank the Data and Safety Monitoring Board: Glenn Cunningham, MD, and Ronal S. Swerdloff, MD.

References
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