Selective androgen receptor modulators for the prevention and treatment of muscle wasting associated with cancer

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Purpose of review
This review highlights selective androgen receptor modulators (SARMs) as emerging agents in late-stage clinical development for the prevention and treatment of muscle wasting associated with cancer.

Recent findings
Muscle wasting, including a loss of skeletal muscle, is a cancer-related symptom that begins early in the progression of cancer and affects a patient's quality of life, ability to tolerate chemotherapy, and survival. SARMs increase muscle mass and improve physical function in healthy and diseased individuals, and potentially may provide a new therapy for muscle wasting and cancer cachexia. SARMs modulate the same anabolic pathways targeted with classical steroidal androgens, but within the dose range in which expected effects on muscle mass and function are seen androgenic side-effects on prostate, skin, and hair have not been observed. Unlike testosterone, SARMs are orally active, nonaromatizable, nonvirilizing, and tissue-selective anabolic agents.

Summary
Recent clinical efficacy data for LGD-4033, MK-0773, MK-3984, and enobosarm (GTx-024, ostarine, and S-22) are reviewed. Enobosarm, a nonsteroidal SARM, is the most well characterized clinically, and has consistently demonstrated increases in lean body mass and better physical function across several populations along with a lower hazard ratio for survival in cancer patients. Completed in May 2013, results for the Phase III clinical trials entitled Prevention and treatment Of muscle Wasting in patiEnts with Cancer1 (POWER1) and POWER2 evaluating enobosarm for the prevention and treatment of muscle wasting in patients with nonsmall cell lung cancer will be available soon, and will potentially establish a SARM, enobosarm, as the first drug for the prevention and treatment of muscle wasting in cancer patients.

Keywords
cachexia, enobosarm, muscle wasting, selective androgen receptor modulator

INTRODUCTION

Muscle wasting is a cancer-related symptom that begins early during the course of malignancy leading to weakness and physical function limitations. As the cancer progresses, muscle wasting may, along with anorexia, fatigue, and weight loss, contribute to the multifactorial syndrome known as cancer cachexia. Historically, cancer cachexia was perceived to be a condition that occurred in terminally ill cancer patients in the months preceding death, fostering the decades old illusion that emaciated patients with cachexia could be easily identified and that body weight alone, or the loss thereof, could be used as the sole criterion for its diagnosis. This view has been replaced by a better conceptual and mechanistic understanding of cancer cachexia as a progressive syndrome of ongoing loss of skeletal muscle mass (with or without the loss of fat mass), which begins at or before the time of cancer diagnosis (precachexia) and eventually advances to a stage in which patients have lost more than 5% body weight (cachexia) or are unresponsive to anticancer and supportive treatments and near death (refractory cachexia) [1–4]. Oncologists and cancer supportive care specialists (palliative care

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KEY POINTS

- Muscle wasting is a cancer-related symptom that can occur without weight loss. It begins early during the course of malignancy and is already present in the majority of cancer patients at the time of diagnosis.
- Muscle wasting associated with cancer (precachexia, cachexia, and refractory cachexia) is an unmet clinical need affecting approximately 60–80% of advanced cancer patients.
- SARMs are being developed as an early intervention to prevent or treat muscle wasting in cancer patients.
- Enobosarm was generally safe and well tolerated during Phase II clinical trials. Statistically significant increases in LBM and improvements in physical function were observed in cancer patients and healthy elderly men and postmenopausal women.
- Results of the POWER1 and POWER2 Phase III trials for enobosarm as first-line therapy with chemotherapy for the prevention and treatment of muscle wasting in patients with advanced NSCLC are discussed *infra*.

physicians) now realize that muscle wasting is likely one of the first symptoms of cancer, exacerbated by treatment (chemotherapy, radiation therapy, and surgery) and/or tumor progression, and more closely associated with diminished survival, physical function, quality of life, and tolerance to chemotherapy than changes in body weight alone [2,5–7]). The prevalence of weight and/or muscle loss ranges from 50 to 80% at the time of cancer diagnosis and varies with the type of malignancy, with the greatest frequency observed in gastrointestinal, pancreatic, lung, and colorectal cancers [8,9]. Muscle wasting is associated with a poorer prognosis and shorter survival, regardless of body weight whether the cancer patients are obese, overweight, normal weight, or underweight and despite the presence of stable disease [3]. Waiting until cancer patients have lost 5% of their body weight to be formally diagnosed with cancer cachexia may delay treatment of muscle wasting, at the very time the patient has the greatest capacity to respond to anabolic intervention.

Although there are many potential therapeutic approaches to the treatment of cancer cachexia (nutritional supplementation and appetite stimulants), few of these potential therapies directly address the prevention or treatment of muscle wasting in cancer patients. Enobosarm (Fig. 1) is a first-in-class nonsteroidal SARM recently evaluated in two Phase III clinical trials (NCT01355497 and NCT01355484) for the prevention and treatment of muscle wasting in patients with stage III or IV nonsmall cell lung cancer (NSCLC) at the time they initiate first-line standard platinum doublet chemotherapy. Although many investigations are currently attempting to treat muscle wasting through a variety of interventions (i.e. physical activity, inflammatory modulation, muscle protein modulation, hormonal signaling, etc.), this review briefly summarizes some of the preclinical pharmacology studies with SARMs and provides an overview of recently published clinical data with SARMs, with an emphasis on enobosarm studies to define its safety and efficacy in NSCLC patients with muscle wasting.

PRECLINICAL PHARMACOLOGY OF SELECTIVE ANDROGEN RECEPTOR MODULATORS

Selective androgen receptor modulators (SARMs) are androgen receptor (AR) agonists that selectively stimulate the anabolic pathways of the AR in muscle and bone, but differ from classical steroidal androgens (testosterone, oxandrolone, and nandrolone) that stimulate androgen-dependent tissues (prostate), cause virilization (skin and hair), require injection or topical administration, and have unacceptable safety [10,11]. Several molecular mechanisms contribute to the observed tissue selectivity of SARMs: differences in the three-dimensional conformation of the AR ligand binding domain, coactivator and corepressor recruitment, nongenomic signaling, and gene regulation induced by SARMs as compared to testosterone or other steroidal androgens have been shown to play a role in the observed tissue selectivity of SARMs in muscle, bone, skin, and prostate [12–17]. SARMs have been extensively investigated in the preclinical setting using animal models relevant to muscle wasting, hypogonadism, osteoporosis, and other indications [17–28]. Enobosarm was discovered in 2004 as a hyper-myoanabolic SARM that dissociated the anabolic from androgenic effects of AR in terms of potency (ED_{50}) and efficacy (E_{max}) [29]. Levator ani muscle weight was increased to 131 and 136% of intact controls in intact and castrated (maintenance mode) rats, respectively, without significant increases in ventral prostate and seminal vesicles weights. Importantly, increases in levator ani muscle weight were associated with increases in muscle strength (soleus) in rats. Enobosarm also exerted in-vivo osteoanabolic effects alone and synergistically with alendronate in terms of bone density, strength, and structure [30▪▪], which was explained by in-vitro mechanistic studies that demonstrated antiresorptive (osteoclast inhibition) and anabolic (osteoblast differentiation) effects [31]. Additionally, enobosarm lacked the limitations of

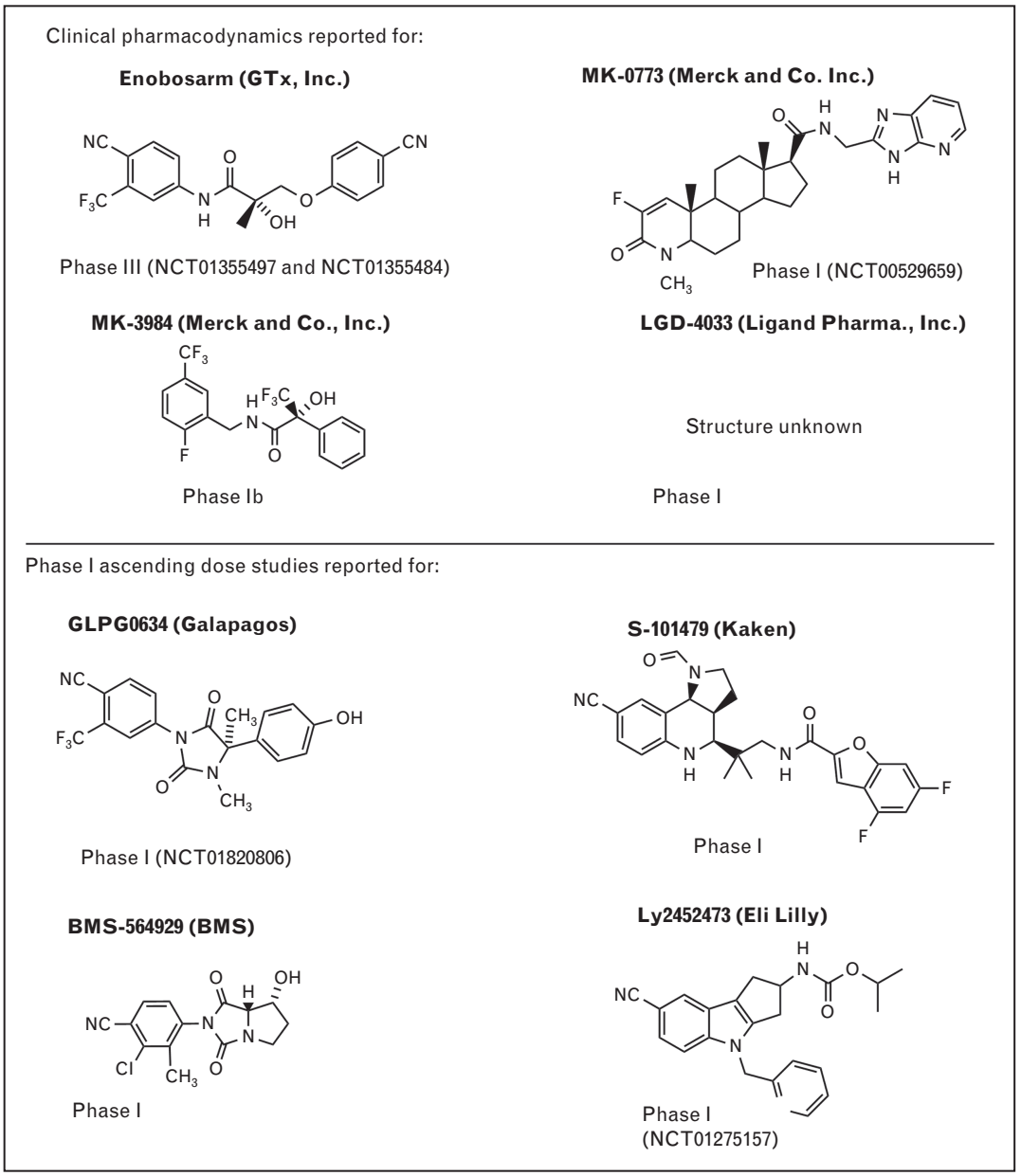

FIGURE 1. SARMs that have been evaluated in clinical trials. The preclinical development of SARMs has produced several clinical candidates, some of which are shown in this figure. However, clinical efficacy data have been published for only a few SARMs. SARMs, selective androgen receptor modulators.

currently available steroidal androgens such as testosterone and oxandrolone due its nonvirilizing and nonandrogenic tissue-selectivity profile, high oral bioavailability, preclinical safety profile, and inability to be aromatized or 5-α reduced to estrogenic and androgenic metabolites, respectively.

CLINICAL TRIALS WITH SELECTIVE ANDROGEN RECEPTOR MODULATORS

Although Phase I clinical trials have been conducted for many SARMs (Fig. 1) [25,32–36], clinical efficacy data have only been reported for LGD-4033 (Ligand Pharmaceuticals, one Phase I trial), MK-0773 (Merck & Co., one Phase II trial), and enobosarm (GTx, Inc., one Phase I and two Phase II trials).

LGD-4033

Basaria *et al.* [37▪▪] recently described the pharmacokinetics, safety, and efficacy of LGD-4033, a novel nonsteroidal SARM in healthy young men. Seventy-six men between the ages of 21 and 50 years were randomized to receive placebo, 0.1, 0.3, or 1.0 mg of

drug daily for 21 days in a Phase I dose escalation study. LGD-4033 was generally safe and well tolerated at all doses. None of the individuals discontinued the study because of an adverse event or had a clinically significant change in liver enzymes, hematocrit, or prostate specific antigen (PSA). Similar to other SARMs, decreases in sex hormone binding globulin (SHBG), high-density lipoprotein (HDL) cholesterol, and triglycerides were observed. LGD-4033 demonstrated a 24–36 h terminal half-life, amenable for once daily administration. A statistically significant increase (1.21 kg) in lean body mass (LBM) was observed only for individuals in the 1 mg dose arm ($P = 0.047$). Increases in leg press strength and physical function (stair climb power) were observed, but did not reach statistical significance at any dose compared with placebo. Notably, LGD-4033 caused dose-dependent suppression of serum total testosterone, serum-free testosterone, and follicle-stimulating hormone (FSH), indicating that the drug significantly suppressed gonadal function at the dose required to affect LBM. Overall, LGD-4033 was reported to be safe and well tolerated, and the authors indicated that the observed increase in LBM supports further development in longer randomized trials. In this same publication, the authors also summarized the results from an earlier Phase I single ascending dose study, reporting that safety was determined in doses up to 22 mg of LGD-4033.

MK-0773 and MK-3984

The safety and efficacy of MK-0773 (Fig. 1), a steroidal SARM, was evaluated in sarcopenic, elderly women [38▪,39]. Individuals received either 50 mg of MK-0773 ($n = 81$) or placebo ($n = 89$) twice daily for 6 months in combination with vitamin D and protein supplementation. A statistically significant increase in total (1.26 vs.0.29 kg for placebo; $P < 0.001$) and appendicular LBM (0.72 vs.0.15 kg for placebo; $P < 0.001$) was observed after 6 months of treatment, with the majority of the increases in LBM achieved within 3 months. The MK-0773-induced improvements in LBM were not accompanied by statistically significant improvements in physical function as measured by stair climb power, bilateral leg press, short physical performance battery, or gait speed, but were associated with elevations in liver transaminases (the most common reason for discontinuation) and hematocrit. However, it is important to note that the physical function tests (one repetition maximum leg press, four-step stair climb, and 4 m gait speed) employed in these otherwise healthy women were of limited duration and/or intensity. The authors concluded that a higher dose of MK-0773 or longer duration of therapy might have resulted in improvements in physical function, but liver transaminase elevations likely preclude further development of this SARM. Merck has also clinically investigated MK-3984 (Fig. 1), reporting increased total LBM and thigh volume in healthy postmenopausal women [40].

Enobosarm (GTx-024, ostarine, and S-22)

The safety of enobosarm, a nonsteroidal SARM, and its effects on total LBM and physical function in healthy elderly men and postmenopausal women [41], postmenopausal women [30▪▪], and cancer individuals with muscle wasting [42▪▪] have been recently reported. A proof-of-concept Phase II trial was conducted during the early stages of clinical development to evaluate four doses of enobosarm (0.1, 0.3, 1, and 3 mg) as compared to placebo in 120 elderly men and postmenopausal women [41]. Enobosarm increased total LBM and improved physical function at the 3 mg dose, with statistically significant increases of 1.3 kg ($P < 0.001$) and 29 W ($P = 0.049$), respectively, compared with placebo. Improvements in insulin sensitivity were also observed in individuals in the 3 mg dose group. Decreases in serum total testosterone, SHBG, HDL, and triglycerides were reported, but, in contrast to LGD-4033, there were no changes in serum-free testosterone, luteinising hormone, FSH, or estradiol observed in men treated with enobosarm. Infrequent transient elevations in liver transaminase (ALT) that resolved while the individuals received enobosarm were observed, but only one individual was discontinued from the trial for this reason, corroborating preclinical studies demonstrating AR-mediated expression of ALT [43▪].

Another clinical efficacy trial was conducted in 88 postmenopausal women [30▪▪,40]. Individuals received enobosarm 3 mg ($n = 25$), MK-3984 (a SARM by Merck & Co.), or placebo ($n = 23$) once daily for 12 weeks. A statistically significant increase (1.54 kg; $P < 0.001$) in total LBM was observed in individuals that received enobosarm compared with placebo and was accompanied by increases in physical function. Leg muscle strength (measured by weight lifted during bilateral leg press) increased by 22 lbs from baseline following administration of enobosarm, compared with 1.5 lbs in the placebo group. Total serum cholesterol, HDL, and triglyceride concentrations declined by $\sim$ 9, 24, and 18%, respectively, by week 12 in enobosarm-treated individuals. Additional endpoints to examine the safety and tissue selectivity of enobosarm showed that enobosarm had no meaningful effects on the uterus (transvaginal ultrasound, endometrial biopsies, and

medroxyprogesterone challenge), skin (sebaceous gland volume, sebum excretion rate, and biopsy gene expression), or liver transaminases. This study confirmed the promising efficacy of enobosarm and provided compelling evidence of its tissue-selectivity in postmenopausal women, which is in contrast to the virilization seen with oxandrolone [10].

Enobosarm was also evaluated in a Phase II clinical trial of cancer patients with muscle wasting using two doses of enobosarm (1 and 3 mg) vs. placebo in men (>45 years old) and postmenopausal women with NSCLC, colorectal cancer, breast cancer, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia (NCT00467844) [42▪▪]. One hundred fifty-nine patients with a median weight loss of 8.8% in the 6 months prior to enrollment were randomized. Following 4 months of treatment, total LBM, as measured by dual-energy X-ray absorptiometry, was assessed as the primary endpoint. A total of 100 patients who completed both baseline and day 84 assessments of LBM and stair climb power were included in the evaluable efficacy population (placebo, $n=34$; enobosarm 1 mg, $n=32$; enobosarm 3 mg, $n=34$) with statistically significant median increases in total LBM observed in both doses of enobosarm (1 mg, 1.5 kg, $P=0.0012$; 3 mg, 1.0 kg, $P=0$ 0.046) as compared to baseline. Both doses of enobosarm also resulted in significant improvements in stair climb power (1 mg, 14.26 W, $P=0.0008$; 3 mg, 16.81 W, $P=0.0006$) from baseline. No significant changes in total LBM or physical function were observed in the placebo-treated individuals. No changes in hair growth in women or serum PSA in men were observed. All groups had a similar frequency of adverse events. The observed benefits of enobosarm on total LBM and physical function in cancer patients with established muscle wasting, coupled with a favorable side-effect profile across all cancer types studied, and more specifically NSCLC, provided strong evidence to advance enobosarm 3 mg into Phase III clinical trials.

Two international, pivotal Phase III clinical trials, entitled Prevention and treatment Of muscle Wasting in patiEnts with Cancer1 [(POWER1) (NCT01355484) and POWER2 (NCT01355497)], were initiated in mid-2011 and the final individuals completed the trials in May 2013. Each of the POWER1 (platinum and paclitaxel or docetaxel)

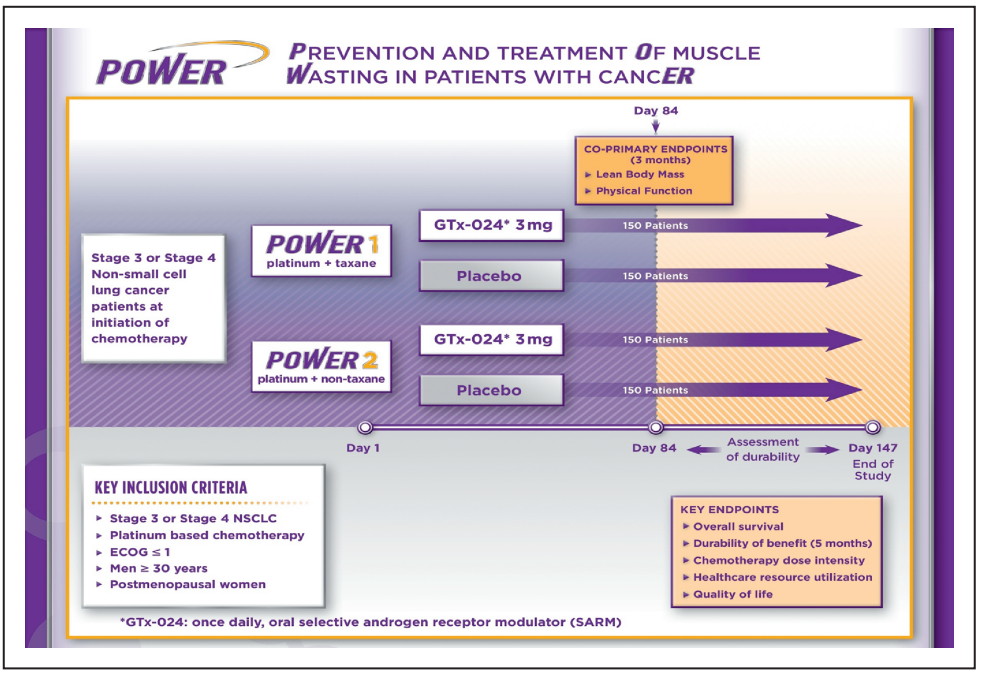

FIGURE 2. Phase III enobosarm study design. POWER1 and POWER2 trials focus on early intervention to prevent and treat muscle wasting in NSCLC. Inclusion of only stage 3 and 4 NSCLC patients at initiation of chemotherapy seeks to control variability because of multiple cancer types and stages, chemotherapy regimens, and severity of muscle wasting. The coprimary endpoints of LBM and physical function were measured at day 84, with the durability of these endpoints assessed at day 147 as a secondary endpoint. Other endpoints include overall survival across both trials, chemotherapy dose intensity, healthcare resource utilization, and quality of life assessments. Enobosarm (GTx-024) has achieved positive results for these endpoints in the previous clinical trials reviewed herein. ECOG, Eastern Cooperative Oncology Group; GTx-024, enobosarm; LBM, lean body mass; NSCLC, nonsmall cell lung cancer; POWER, prevention and treatment of muscle wasting in patients with cancer.

and POWER2 (platinum and gemcitabine, pemetrexed, or vinorelbine) Phase III clinical trials randomized approximately 325 patients to receive placebo or enobosarm 3 mg for 147 days beginning at the time that they initiated first-line chemotherapy for stage III/IV NSCLC (Fig. 2). The trials had identical coprimary endpoints of total LBM response and physical function response for enobosarm vs. placebo after 3 months of treatment, with response (clinical benefit) defined as no loss or a gain of total LBM and at least a 10% increase in stair climb power, respectively, at day 84. Secondary endpoints for the trials include survival for safety, durability of benefit in LBM and stair climb power at 147 days, tolerability to chemotherapy, and quality of life. GTx announced in 2013 that the US Food and Drug Administration designated enobosarm for the prevention and treatment of muscle wasting in patients with NSCLC as a Fast Track development program, identifying muscle wasting in NSCLC as an indication for an unmet medical need.

In August of 2013, GTx, Inc. announced top line results of the POWER1 and POWER2 trials indicating mixed results for the coprimary endpoints of LBM and physical function. Although enobosarm demonstrated beneficial effects on LBM in both trials, statistically significant effects on physical function (stair climb power) were observed only in patients receiving taxane-based chemotherapy and enobosarm (POWER1) as compared to placebo. Enobosarm was well tolerated in both trials. Although the data have not yet been formally presented or published, the POWER trial data are under intense review to better understand the impact of the chemotherapy regimen and the relationship between LBM benefit and performance in NSCLC patients. These findings will be the subject of future reports.

The strategy in the POWER trials differed significantly from that of previous (and ongoing) cancer cachexia trials using other agents (e.g., anamorelin), which required patients to have already lost 5% of their body weight at the time of randomization. Despite equivocal physical function data in the POWER2 trial, we still believe that enobosarm, as a SARM, is well positioned to benefit cancer patients with a predisposition for the development of muscle wasting (e.g., NSCLC patients) via their ability to increase LBM and improve physical function.

In total, eight other clinical trials involving over 600 patients (not including POWER1 and POWER2) to assess the pharmacokinetic and safety of single and multiple ascending doses of enobosarm have also been completed.

CONCLUSION

Enobosarm and other SARMs have demonstrated increases in total LBM and improvements in physical function. The ability of SARMs to increase LBM with a short-treatment period (e.g., 21 days) suggests that the benefits of therapy may be quickly realized. The ability of SARMs to increase LBM and improve physical function can be achieved without nutritional supplementation or an exercise regimen. SARMs appear to be generally safe and well tolerated. Decreases in HDL have been observed for all SARMs, including enobosarm although the relevance of this effect is questionable in a cancer population, with suppressive effects on serum hormones (LGD-4033) [37▪▪] and increases in liver transaminases (MK-0773 and MK-3984) [38▪,40] being the most commonly observed adverse events for other drugs in the class. The forthcoming reports of the enobosarm POWER1 and POWER2 studies should shed light on many of these important but unanswered questions, and potentially provide a novel agent for the prevention and treatment of muscle wasting associated with cancer.

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None.

Conflicts of interest

All authors are employees of GTx, Inc. and receive compensation for their work related to the development of enobosarm. J.T.D. and M.L.M. receive royalties on enobosarm as inventors through the University of Tennessee Research Foundation.

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43. ■ Coss CC, Bauler M, Narayanan R, *et al.* Alanine aminotransferase regulation by androgens in nonhepatic tissues. Pharm Res 2012; 29:1046–1056.

This publication reports an interesting preclinical perspective on the clinical relevance of monitoring 'hepatic' enzymes in patients receiving anabolic agents.