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INVITED REVIEW

Male Endocrinology

Selective androgen receptor modulators for the treatment of late onset male hypogonadism

Christopher C Coss, Amanda Jones, Michael L Hancock, Mitchell S Steiner, James T Dalton

Several testosterone preparations are used in the treatment of hypogonadism in the ageing male. These therapies differ in their convenience, flexibility, regional availability and expense but share their pharmacokinetic basis of approval and dearth of long-term safety data. The brevity and relatively reduced cost of pharmacokinetic based registration trials provides little commercial incentive to develop improved novel therapies for the treatment of late onset male hypogonadism. Selective androgen receptor modulators (SARMs) have been shown to provide anabolic benefit in the absence of androgenic effects on prostate, hair and skin. Current clinical development for SARMs is focused on acute muscle wasting conditions with defined clinical endpoints of physical function and lean body mass. Similar regulatory clarity concerning clinical deficits in men with hypogonadism is required before the beneficial pharmacology and desirable pharmacokinetics of SARMs can be employed in the treatment of late onset male hypogonadism.
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INTRODUCTION

As the population ages, longitudinal and cross-sectional studies have shown that a significant portion of men over the age of 60 have serum testosterone (T) levels below the lower limits of those seen in healthy younger men (20−30 years).[1,2] Late onset hypogonadism (LOH) encompasses a broad list of signs and symptoms including sexual dysfunction, fatigue and reduced lean body mass and bone mineral density (BMD) that are associated with low T and are what typically drives the patient to seek medical attention.[3] Due to the often varied intensity of these symptoms and their association with non-pathological general ageing processes, a significant effort has been made to clearly define LOH and thus patients who might benefit from therapy.[4] Despite such efforts, LOH prevalence remains controversial as does the treatment of men who do not display overt hypothalamic-pituitary-gonadal pathology where the risk benefit profile of androgen supplementation is more clearly established.[5] Diagnostic tools like ANDROTEST have estimated a disease incidence of 10%−40% in men aged over 45 years and suggest that up to 60 million men in the United States, Europe and Japan suffer from LOH.[3,6,7] Conversely, more stringent criteria have placed LOH rates at as little as 2.1% in similarly aged men.[8] Regardless of the diagnostic criteria employed, the current gold standard for the treatment of hypogonadism in older men is T therapy.[3]

TESTOSTERONE REPLACEMENT THERAPY FOR LATE ONSET HYPOGONADISM

The goal of T therapy in the treatment of LOH is to return serum T levels to the normal eugonadal range. Diagnosing LOH involves serial measurements of an individual's T levels.[4] Based on a host of factors including body mass index (BMI), circulating sex hormone binding globulin SHBG and concurrent disease states, an individual's total circulating T may fall below the eugonadal range despite being asymptomatic. Decreased sex hormone binding globulin resulting from any number of separate pathologies may allow eugonadal levels of free T (unbound) despite hypogonadal levels of total T. Likewise, elevated levels of sex hormone binding globulin might result in hypogonadal symptoms, due to reduced levels of free T, despite eugonadal levels of total T. For these reasons it has been suggested that free T levels, along with associated symptoms of hypogonadism, be used in the positive diagnoses of LOH.[3,8] Though it is accepted that eugonadal levels of total T are variable and patient specific, the range of approximately 300−1000 ng dl^{-1} (10.4−34.7 nmol l^{-1}) has been adopted and is used to gauge the success of TRT. When T therapy is indicated, minimally therapeutic T levels are desired and the upper end of the eugonadal range for young men (1000 ng dl^{-1}) is generally avoided as the risks associated with T therapy are thought to increase with the levels of exogenous T administered.[9] Currently available T product labeling suggests monitoring serum T and dose adjustments to maintain appropriate T levels.

T therapy has well-established beneficial effects on body composition, including increases in lean body mass and decreases in fat mass.[10,11] These effects are rapid (apparent after as little as 3 months of therapy) and durable (maintained after 3 years).[12,13] Increases in muscle strength are less consistently reported due to training effects and technical challenges in measuring maximal muscle strength.[14] However, durable muscle strength benefits are reported in placebo controlled TRT trials performed in a hypogonadal population.[15] Improvements in lumbar spine and hip BMD require extended treatment, but have been reported following T therapy in a placebo controlled setting.[16] Rapid improvements in sexual function are a hallmark of T administration

with increases in sexual desire, motivation and performance in several studies.[11,12,17] Likewise, durable improvements are reported in positive mood scores.[13,18]

The success of TRT in treating the symptoms of LOH is supported by a rapidly expanding market.[3] Annual T prescriptions increased by nearly 300% in the US between the years of 2000 and 2008 mirroring a trend seen in European nations as well.[19] Critics of this trend instead believe that TRT is overprescribed and more the result of successful marketing than successful therapeutic intervention.[20,21] Detractors also cite a paucity of long-term safety data especially concerning cardiovascular and prostate disease risk. Current registration trials for TRT products are short (~3 months), driven by pharmacokinetic endpoints and of relatively low cost. The low development-cost barrier has resulted in a plethora of TRT delivery options, but provides no incentive to develop novel therapies addressing risks associated with prolonged androgen administration to older men. A new class of drugs currently being developed for acute muscle wasting conditions, selective androgen receptor modulators (SARMs), could provide once daily oral androgen supplement with reduced side effects for the treatment of LOH.

SELECTIVE ANDROGEN RECEPTOR MODULATOR DEVELOPMENT

SARMs were initially reported in the 1990s as nonsteroidal androgen receptor agonists.[22] Early nonclinical work demonstrated these orally active agents had unique pharmacology operating as full agonists in anabolic tissues (muscle and bone), but partial agonists in androgenic tissues (prostate, skin and hair).[23] The utility of this pharmacology in expanding androgen therapy to women and men at risk for prostate disease was recognized immediately and followed with extensive worldwide drug discovery efforts.[24] The result of one such effort, GTx-024 or enobosarm, is a first in class SARM in late clinical development.

Enobosarm has been evaluated for its effect on body composition and physical function in three clinical studies. In a phase I study in 48 postmenopausal women, enobosarm 3.0 mg or placebo was administered for 12 weeks.[25] Enobosarm 3.0 mg significantly increased total lean body mass compared to placebo (1.54 kg; $P < 0.001$). Enobosarm also increased thigh muscle volume by 0.17 L from baseline to day 84 compared to a decrease of 0.12 l in the placebo group. Correspondingly, a 22 lb increase in leg muscle strength was observed in the enobosarm treatment group relative to 1.5 lb in patients that received placebo.

A dose-response phase II study was conducted in 120 healthy elderly men (>60 years of age) and postmenopausal women.[26] Subjects received placebo or enobosarm at a daily dose of 0.1, 0.3, 1.0 or 3.0 mg for 12 weeks. Enobosarm dose-dependently increased total lean body mass, while decreasing total fat mass. At 3.0 mg, enobosarm increased lean body mass by 1.3 kg ($P < 0.001$), which was accompanied by a decrease of approximately 0.6 kg ($P = 0.049$) in total fat mass relative to placebo. Subjects also exhibited a dose-dependent increase in stair climb power ($P = 0.013$) and an improvement in the time required to climb 12 steps.

A second phase II study was performed in 159 patients with a variety of cancers.[27] After 4 months of treatment, subjects experienced a significant increase in total lean body mass at 1.0 mg (1.5 kg; $P = 0.0012$) and 3.0 mg (1.3 kg; $P = 0.046$). Additionally, an average increase of 18.0% for 1 mg ($P = 0.001$) and 21.7% for 3 mg ($P = 0.001$) was observed in stair climb power with significant improvements in the time required to climb 12 steps ($P = 0.0019$ at 1.0 mg; $P = 0.0065$ at 3.0 mg). Enobosarm 3.0 mg is currently being evaluated in two phase III studies in a larger patient population ($n \approx 650$) with non-small cell lung cancer with key endpoints of total lean body mass and physical function (i.e., stair climb test) after 3 and 5 months of treatment.

The principal challenge in developing SARMs for the treatment of male hypogonadism is the definition of acceptable clinical endpoints. Unlike a T product registration trial, eugonadal levels of SARM cannot be used as a primary endpoint. Furthermore, though established improvement in body composition, muscle strength, BMD and sexual function follow successful T therapy; little agreement exists on what constitutes clinical deficits in these areas within a hypogonadal population let alone meaningful therapeutic amelioration.[3] These challenges aside, SARMs' unique pharmacology could provide therapeutic benefit in the treatment of male hypogonadism.

SELECTIVE ANDROGEN RECEPTOR MODULATORSS FOR THE TREATMENT OF LATE ONSET HYPOGONADISM

Pharmacokinetics

The vast majority of T products approved for the treatment of hypogonadism require parenteral administration.[3] Through varied formulation and delivery techniques, often combined with chemical modifications to the parent steroid T, T levels can be restored to steady-state eugonadal levels in roughly a week's time. Though effective in restoring T levels, intramuscular (IM) injections of T esters (TE) result in large fluctuations in circulating T and are long acting (2–14 weeks), which prevents rapid dose adjustments or cessation in case of an adverse event. IM injections are also frequently associated with pain and irritation at the injection site and often require a doctor's visit increasing the end cost of therapy to the patient.[28] Treatment frequency can be reduced with surgical implantation of slow release T pellets. However, this modality suffers from the same therapeutic rigidity as long-acting IM injections with increased invasiveness. Several transdermal preparations offer therapeutic flexibility, more tightly controlled physiologic T levels and noninvasive administration. Transdermal T is rapidly becoming the therapy of choice for many hypogonadal men.[5,20] The disadvantages of these therapies are their increased cost, site irritation and contact transfer risk.[5,29] The daily administration of a lipophilic T patch or gel can result in significant unintended drug transfer which is of particular concern when women and children are exposed to high levels of androgen.[30–32]

T undecanoate (TU) is available as an oral capsule though not in the US. Unmodified T is subject to extensive first pass metabolism and suffers from a half-life on the order of minutes.[33] The increased lipophilicity of TU relative to other TEs, affords increased absorption by the intestinal lymphatic system without the well characterized overt hepatotoxicity associated with orally administered 17-alkylated androgens such as methyl T.[34,35] Consistent therapeutic levels of T are often challenging to achieve following oral TU administration. Despite an improved formulation, 300 mg twice daily dosing of TU, or roughly 50 molar equivalents of the T generated daily by healthy testes, is required to maintain physiological nadir levels of serum T. The risk associated with the super physiological serum 5α-dihydrotestosterone (DHT) levels and increased androgen burden on the liver that result from this dosing regimen are disputed.[35] However, the reduced utilization of oral TU relative to the multiple parenteral T formulations available suggests that the perceived risks outweigh the convenience of an oral dosage form in the minds of patients and their physicians.

The SARMs under current clinical development are orally bioavailable and capable of anabolic benefit at low milligram doses.[26,36] These drugs also have prolonged elimination half-lives that results in

minimal peak-to-trough fluctuations and makes them amenable to once-daily dosing.[25] The multiple nonsteroidal SARM pharmacophores discovered to date offer a great deal of flexibility in that small chemical modifications can be made that are neutral to the drugs inherent activity, but have a large impact on its pharmaceutical properties.[23,37] This situation differs greatly from the exhausted field of modified steroidal androgens, which produced the TEs in use today more than 50 years ago.[33]

Effects on prostate

The prostate is an androgen-dependent organ. The requirement of a functioning androgen axis for prostatic development and homeostasis is well-characterized. Androgens are also implicated in benign prostatic hyperplasia and prostate carcinogenesis, raising obvious concerns around the potential impact of TRT on prostatic disease.[38] The effects of T supplementation on prostate cancer risk remain controversial. Retrospective studies evaluating 5 years of TRT found that men who developed prostate cancer while on TRT had steeper increases in prostate specific antigen (PSA); however, the total rate of disease was no different than the general population.[39] In a prospective setting, multiple aspects of prostatic physiology were compared between TRT and placebo-treated controls with few differences in molecular markers and no differences in disease instance or severity reported.[40] Alternatively, a meta-analysis of nearly 700 patients across 19 placebo-controlled trials reported a higher risk (odds ratio [OR] =1.78, 95% confidence interval [CI] = 1.07−2.95) of all prostatic events defined as prostate biopsies, prostate cancers, increase in International Prostate Symptom Score >4, PSA >4 ng ml^{-1} or PSA increment ≥1.5 ng ml^{-1} during treatment and acute urinary retention.[41] The primary prostatic androgen, DHT, has been implicated in the development of prostate cancer by the clinical evaluation of several 5α-reductase inhibitors. 5α-reductase drives the conversion of T to the more potent androgen DHT. Prostatic levels of DHT are known to be several fold higher than prostatic levels of T, owing to elevated expression of 5α-reductase in the prostate, and an order of magnitude higher than circulating levels of DHT.[16,40,42] 5α-reductase inhibitor administration reduced the chance of at risk men developing prostate cancer by nearly 25% over a 4−7 year period, suggesting the importance of DHT formation in the natural disease course of prostate cancer.[43,44] When T supplementation is combined with a 5α-reductase inhibitor, T-mediated increases in serum PSA and prostate volume were completely and partially reversed, respectively.[16] Amory et al. and Page et al. demonstrated in a hypogonadal population that DHT is not required for the anabolic bone or muscle benefits associated with T supplementation and may instead provide a prostatic liability[15,16] (**Figures 1 and 2**). Enobosarm is not subject to 5α-reduction and tissue selective pharmacology suggests its potential to stimulate diseases of benign prostatic hyperplasia is greatly reduced. To this end, enobosarm does not cause increases in serum PSA in healthy older men at anabolic doses (**Figures 1 and 2**).

Cardiovascular and hematologic effects

The most common adverse event associated with T supplementation is increased erythrocytosis which can lead to increased blood viscosity and consequently ischemic events. Calof et al.'s survey of trials reported that T-treated men were nearly four times (OR = 3.69, 95% CI = 1.82−7.51) more likely to have a hematocrit value >50% when compared to placebo-treated men.[41] Despite elevating this cardiovascular risk factor, cardiac event rates were similar between T-treated and placebo-treated men (33.2 per 1000 patient-years and 44.3 per 1000 patient-years, respectively). Steidle et al. reported at least one hematocrit value >55% in 3%, 6% and 1% of patients in the 50 mg per day AA2500, 100 mg per day AA2500 and T patch groups, respectively, compared to 1% in placebo. Similarly, Amory et al. reported dose reductions in 30% of subjects receiving TE injections based on hematocrit values >52%, but reported no significant cardiovascular events.[16] Enobosarm minimally stimulated erythrocytosis in healthy older men and women and resulted in only one hematocrit value >50% (3-mg group) during 3 months of daily administration (**Figure 3**). Increased iron incorporation by erythrocytes results in the stimulation of hemoglobin production.[33] As such, hemoglobin levels are elevated following T administration, closely resembling hematocrit inductions (**Figure 4**). Enobosarm's minimal effects on hemoglobin production in healthy men and women similarly reflected its effects on hematocrit.

The role of T and TRT in atherogenic cardiovascular disease is poorly understood and controversial. Increased cardiovascular events and mortality in men relative to women is dogmatically associated with increased endogenous circulating T levels despite ample evidence to the contrary.[45,46] In a case-controlled comparison between healthy men with eugonadal levels of total T and age- and ethnicity-matched controls with low total T, an increased risk in all metabolic cardiovascular risk factors was reported for the low T group.[47] This early study was limited in terms of its size (n = 50) and methodology, but its findings have been substantiated in larger studies evaluating free as well as total T.[48,49] Despite being extensively characterized, the cardiovascular risk associated with exogenous T administration remains controversial.
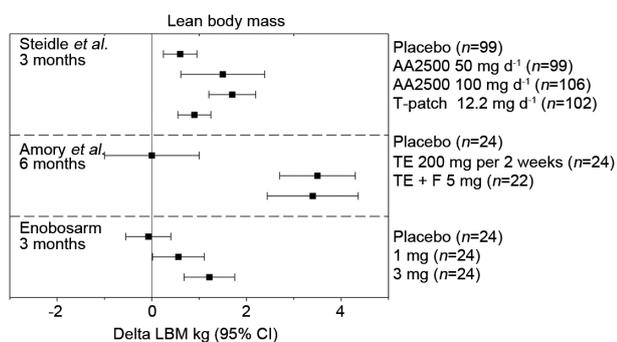

Figure 1: Changes in lean body mass (LBM) following testosterone or enobosarm treatment. Mean changes from baseline at the indicated treatment times are reported along with 95% confidence intervals (CIs) from Steidle et al.,[12] Page et al.,[15] and Dalton et al.[26] AA2500: testim© gel; F: finasteride; T-patch, Androderm©; TE: testosterone enanthanate injection.
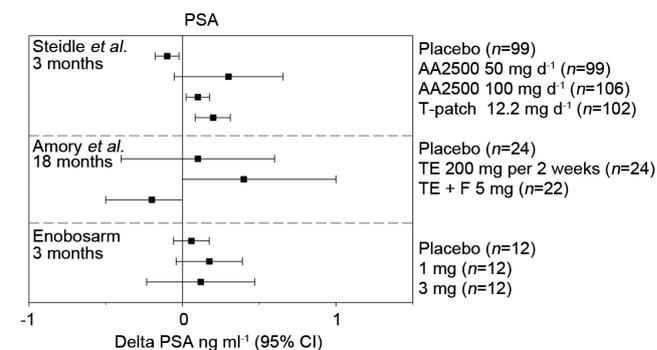

Figure 2: Changes in prostate specific antigen (PSA) following testosterone or enobosarm treatment. Mean changes from baseline at the indicated treatment times are reported along with 95% confidence intervals (CIs) from Steidle et al.,[12] Page et al.,[15] and Dalton et al.[26] AA2500: testim© gel; F: finasteride; T-patch, Androderm©; TE: testosterone enanthanate injection.
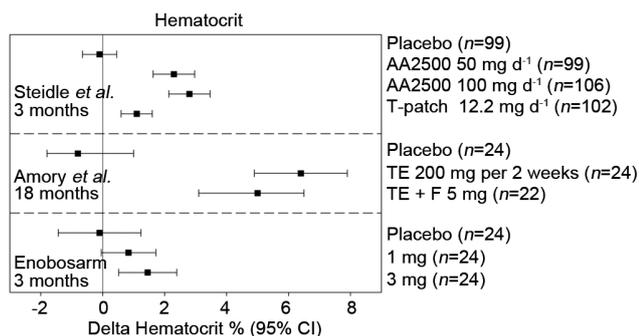
Figure 3: Changes in hematocrit following testosterone or enobosarm treatment. Mean changes from baseline at the indicated treatment times are reported along with 95% confidence intervals (CIs) from Steidle *et al.*,[12] Page *et al.*,[15] and Dalton *et al.*[26]AA2500, Testim© gel; F: finasteride; T-patch, Androderm©; TE: testosterone enanthanate injection.
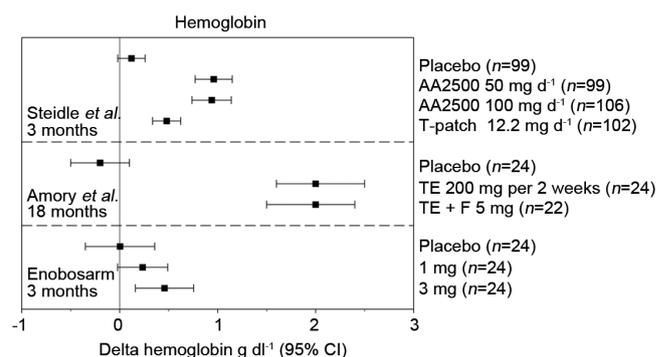

Figure 4: Changes in hemoglobin following testosterone or enobosarm treatment. Mean changes from baseline at the indicated treatment times are reported along with 95% confidence intervals (CIs) from Steidle *et al.*,[12] Page *et al.*,[15] and Dalton *et al.*[26] AA2500, Testim© gel; F: finasteride; T-patch, Androderm©; TE: testosterone enanthanate injection.

A recent meta-analysis of placebo-controlled trials included nearly 3000 patients experiencing a total of 180 cardiovascular events and found an increased risk associated with T therapy (OR–1.54, 95% CI=1.09−2.18).[50] Alternatively, an analysis of over 1000 patients involved in placebo-controlled trials reported no association between T therapy and an increase in cardiovascular events.[41] A recent trial involving hypogonadal community-dwelling men was terminated early due to treatment-related cardiovascular events.[9] It was suggested by the investigators that the elevated total cardiac event rate in this study was related to the chronic disease prevalence and limited mobility of the test subjects. This assertion is supported by the reduced number of cardiac events reported in much larger trials using similar T gel products.[12,13,18]

The lack of consensus concerning T and cardiovascular outcomes is likely due in part to T's myriad effects on body composition. Low T levels are also associated with metabolic syndrome and increases in visceral fat.[51] Increased adiposity is a well-characterized cardiovascular risk factor, but its status as a cause or an effect of hypogonadal T remains an open question.[52] In either case, T administration has been shown to reduce fat mass and improve insulin sensitivity amongst other aspects of metabolic syndrome.[53] Similarly, enobosarm administration to a healthy elderly population of men and women improved insulin resistance (according to the HOMA-IR criteria[54]) in the 1- and 3-mg treated groups (placebo: 2.6% ± 8.6%, 1 mg: -9.3% ± 5.5%, 3 mg: -27.5% ± 7.6%, $P = 0.013$ for 3 mg *vs* placebo).[26]

Compared to parenteral therapy, oral androgens are associated with greater effects on serum lipids, namely reductions in high density lipoprotein (HDL).[55] Though colloquially considered 'good cholesterol', new research suggests that the cholesterol efflux capacity of circulating HDL is an improved predictor of atherosclerosis.[56] Efflux capacity is a distinct metric from both total serum HDL, as is routinely measured, and HDL subfractionation. Several studies have evaluated the effects of T therapy on various HDL subfractions with widely varying results.[57–59] The effects of therapy on the HDL efflux capacity of T-treated men are yet to be determined. Like other oral anabolic agents SARMs reduce total serum cholesterol and HDL dose dependently.[36] Enobosarm treatment resulted in 17% and 27% reductions in HDL at the 1.0 and 3.0 mg dose levels, respectively. However, the average total cholesterol/HDL ratio in these treatment groups remained in the low risk category between 3.5 and 5.0 for the duration of the study.[26]

Role of aromatase
The composite pharmacologic actions of T include its conversion to estradiol (E_2) as well as DHT. CYP19 (aromatase) is responsible for this largely peripheral conversion, however T administration does result in increased circulating E_2.[16] In rare cases, usually associated with long-acting IM T injections, E_2 overproduction can even result in painful gynecomastia.[28] The importance of E_2 to the male skeleton is apparent in men who are naturally aromatase deficient and present with stunted bone development and greatly reduced BMD.[60,61] Likewise, men who are hypogonadal often have low BMD putting them at greater risk for fractures and their associated comorbidities.[62] Direct effects of androgens on both cortical and trabecular bone are suggested by knockout animal models and supported by several nonaromatizable, non-estrogenic SARMs demonstrating the ability to maintain bone in preclinical models of osteopenia.[63–66] To date the clinical evaluation of SARMs has been of insufficient duration (3 months or less) to characterize effects on relatively slow changing bone parameters.

Sexual dysfunction is the primary cause of hypogonadal men seeking treatment.[51] It follows that any broadly applicable therapy for LOH needs to alleviate sexual symptoms as well as improve body composition and physical function. Though the benefits of TRT on multiple sexual parameters is established, the relative contributions of E_2 to this effect remains a rather poorly studied open question.[67] To date no sexual parameters have been monitored clinically following SARM administration. Nonclinical evidence suggests nonaromatizable, non-estrogenic SARM administration benefits male sexual function.[68]

CONCLUSION
Despite registration trials based on purely pharmacokinetic endpoints, in practice TRT doses are more often adjusted based on symptoms and safety monitoring than on the levels of serum total T actually achieved in the patient.[46] The inter-patient variability in the pharmacokinetics of T products and patient specific levels of effective TRT combine to all but obviate truly useful T monitoring. Thus, successful TRT is ultimately symptom and not pharmacokinetic driven. Unlike TRT, a SARMs approval for the treatment of LOH would likely require proven amelioration of hypogonadal symptoms in a large otherwise healthy cohort of older men. Agreement from regulatory bodies as to what constitutes clinically relevant efficacy would requisitely precede initiation of such a trial. The lack of consensus amongst physicians in diagnosing LOH suggests that broad agreement on clinically relevant efficacy in LOH remains out of reach. In light of this regulatory challenge, current SARM development is focused on acute and chronic muscle wasting diseases with defined clinical deficits in physical function and lean body mass. It stands to reason that the accumulation of efficacy and safety

data, especially pertaining to benefits in physical function, will inform discussions with regulatory bodies as to acceptable clinical endpoints in an ageing hypogonadal population. SARM's beneficial pharmacology and desirable pharmacokinetics offer considerable promise in the treatment of LOH. The convenience of once daily oral therapy combined with defined safety margins surrounding a proven efficacious dosage form may one day challenge TRT as the gold standard in treating LOH.

COMPETING INTERESTS

All authors were employees of GTx Inc and hold stock options in GTx Inc at the time this article was written. GTx Inc. is developing GTx-024 (enobosarm) for the treatment of cachexia in late stage NSCLC patients.

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