

# Selective Androgen Receptor Modulators (SARMs): A Mini-Review



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## Abstract

Selective Androgen Receptor Modulators (SARMs) were discovered in the late 1990's. They may have an application in treatments of various diseases, including muscle wasting, cancer cachexia, breast cancer, osteoporosis, andropause and sarcopenia. In this mini-review the development, pharmacodynamics, and the phase 1 and 2 trial results of the SARMs are discussed with a special emphasis on the illicit use of the SARMs.

## Introduction

The androgen receptor (AR) is a member of the steroid hormone receptor family that plays important roles in the physiology and pathology of diverse tissues. AR ligands, which include circulating testosterone and locally synthesized dihydrotestosterone bind to activate the AR to elicit their effects. Ubiquitous expression of the AR metabolism and cross reactivity with other receptors limit broad therapeutic utilisation of steroidal androgens. However, the discovery of selective androgen receptor modulators (SARMs) provide an opportunity to promote the beneficial effects with greatly unwanted side effects. In the last two decades SARMs have been proposed as treatments of choice for various diseases, including muscle wasting, breast cancer and osteoporosis. In addition, they may have an application in andropause, sarcopenia, cancer cachexia and as selective anabolic steroids in performing body building sports [1-6]. In this mini-review the development, pharmacodynamics and the phase 1 and 2 trial results of the SARMs are discussed, with a special emphasis on the illicit use of the SARMs.

## Development of SARMs

Synthesized steroidal androgens due to their ability to mimic the actions of their endogenous counterparts have been used clinically as valuable therapeutic agents to target a variety of male and female disorders resulting from androgen deficiency. The principle clinical indication of androgens is as replacement therapy for hypogonadal men [1,2]. Other documented clinical uses

of androgens include delayed puberty in boys, anemias, primary osteoporosis, hereditary angioneurotic edema, endometriosis, estrogen receptor-positive breast cancer and muscular diseases, as Duchenne's muscular dystrophy [3-6].

Since the discovery of the therapeutic benefits of testosterone in the 1930's a variety of androgen preparations have been introduced and tested clinically.

Unfortunately, all current available androgen preparations have severe limitations [2,6]. Unmodified testosterone is impractical for oral administration due to its low systematic bioavailability [7]. Testosterone esters (e.g., testosterone propionate and testosterone enanthate) are presently the most widely used testosterone preparations, usually administered by intramuscular injection in oil-vehicles [8,9]. A prolonged duration of action is achieved with these esters. However, they produce highly variable testosterone levels. 17-alpha alkylated testosterone (e.g., methyltestosterone and oxandrolone) can be given orally. Nevertheless, they often cause unacceptable hepatotoxicity and are less efficacious; hence they are not recommended for long-term androgen therapy [9-11].

At the end of the 1990's studies with affinity ligands for the androgen receptor started. The discovery of these nonsteroidal androgens offered an opportunity for the development of a new generation of selective androgen receptor modulators

(SARMs) superior to current androgens. Theoretically, SARMs are advantageous over their steroidal counterparts in that they can obtain better receptor selectivity and allow greater flexibility in structural modification. Thus SARMs can potentially avoid the undesirable side effects caused by cross-reactivity and achieve superior pharmacokinetic properties [12].

### Pharmacodynamics of SARMs

Structural modifications of the acryl propionamide analogues bicalutamide and hydroxyflutamide led to the discovery of the first generation SARMs. The compounds S1 and S4 in this series bind AR with high affinity and demonstrate tissue selectivity in the Herzberger assay, that utilizes a castrated rat model [13-20]. Both S1 and S4 prevented castration induced atrophy of the levator ani muscle and acted as weak agonists in the prostate. At a dose of 3mg/kg/day, S4 partially restored the prostate weight to <20% of intact weight, but fully restored the levator ani weight, skeletal muscle strength, bone mineral density, bone strength and lean body mass and suppressed LH (luteinizing hormone) and FSH (follicle stimulating hormone) [20,21].

S4 also prevented ovariectomy-induced bone loss in a female rat model of osteoporosis [22]. The ability of SARMs to promote both muscle strength and bone mechanical strength constitutes a unique advantage over other therapies for osteoporosis, that only increase bone density. S1 and S4 are partial agonists thus in intact male rats [20,21]. S1 and S4 compete with endogenous androgens and act as antagonists in prostate, such SARMs with antagonistic or low intrinsic activity in prostate might be useful in the treatment of benign prostate hyperplasia (BPH) or prostate cancer. The suppressive effects of this class of SARMs on gonadotrofin secretion in rats suggests a potential application for male contraception [21]. The ether linkage and B-ring para-position substitution are critical for agonist activity of the acryl propionamide SARMs [19]. Based on crystal structures, compounds with ether linkage appear to adapt a more compact conformation than bicalutamide due to formation of an intramolecular H-bond, allowing the B-ring to avoid steric conflict with the side chain of W741 in AR and potentially explaining the agonist activity [23].

The hydantoin derivatives developed by the BMS group have an A-ring structure that is similar to that of bicalutamide. The cyano-nitro group of these molecules interact with Q711 and R752 [24-26]. The benzene ring or the naphthidyl group, together with the hydantoin ring overlaps the steroid plane, while the hydantoin rings forms a H-bond with N705. BMS-564929 binds AR with high affinity and high specificity. BMS-564929 demonstrated anabolic activity in the levator ani muscle and a high degree of tissue selectivity as indicated by a substantially higher ED<sub>50</sub> (Effective Dose for 50% of the population receiving the drug) for the prostate. Hydantoin derivatives are potent suppressors of LH. BMS-564929 is orally available in humans with a half-life of 8-14 hours. The prolonged

half-life of these ligands in rats may explain the lower dose needed to achieve pharmacological effects. Differences regarding in vivo activities of SARMs, that share similar binding affinity and in vitro activity, may be related to the differences in pharmacokinetics and drug exposure [27].

Hanada et al. [28] Pharmaceutical Co. reported a series of tetrahydroquinolinone derivatives as AR agonists for bone. Although these compounds displayed high AR affinity and strong agonist activity in prostate and levator ani, they demonstrated little selectivity between androgenic and anabolic tissues [27]. Significant in vivo pharmacological activity was only observed at high subcutaneous doses [27,28]. Ligand Pharmaceuticals developed LGD 2226 and LGD 2941, that are bicyclic 6 anilino quinolinone derivatives, showing anabolic activity on the levator ani muscle as well as on bone mass and strength, while having little effect on prostate size in a preclinical rodent model [29-31]. LGD 2226 was also shown to maintain male reproductive behavior in the castrated rodent model [30].

Scientists at Johnson and Johnson replaced the propionamide linker with cyclic elements such as the pyrazoles, benzimidazoles, indoles and cyclic propionanilide mimetics [31]. Merck scientists have developed a number of 4-azosteroidal derivatives and butanamides [32]. All the above mentioned SARMs belong to the so called "first generation SARMs". The mechanisms that contribute to the tissue specific transcriptional activation and selectivity of biologic effects of the SARMs remain poorly understood. Three general hypotheses have been proposed, although these hypotheses are not mutually exclusive.

- a) The coactivator hypothesis assumes that the repertoire of coregulator proteins that associate with the SARM-bound AR differs from that with testosterone-bound AR leading to transcriptional activation of a differentially regulated set of genes.
- b) The conformational hypothesis states that functional differences in ligand classes (agonist, antagonists and SARMs) are reflected into conformationally distinct states with distinct thermodynamic partitioning. Ligand binding induces specific conformational changes in the ligand binding domain, which could modulate surface topology and subsequent protein-protein interactions between the AR and other coregulators involved in genomic transcriptional activation or cytosolic proteins involved in non-genomic signalling. Differences in ligand-specific receptor conformation and protein-protein interactions could result in tissue-specific gene regulation, due to potential changes in interactions with the AR effectors, coregulators or transcriptional factors.
- c) The third hypothesis states that the tissue selectivity of SARMs could also be related to differences in their tissue distribution, potential interactions with 5-alpha reductase or

CYP19 aromatase or tissue specific expression of coregulators [33]. Testosterone actions in some androgenic tissues are amplified by its conversion to 5-alpha dihydro testosterone [34]. Nonsteroidal SARMS do not serve as a substrate for 5-alpha reductase. Tissue selectivity of SARMS might be related to tissue specific expression of coregulatory proteins. Similarly, some differences of the action of SARM of testosterone could be related to the inability of nonsteroidal SARMS to undergo aromatization.

### Preclinical and early clinical trials with SARMS

A large number of candidate SARMS have undergone preclinical proof of concept and toxicology studies and have made it into phase 1 and phase 2 clinical trials [29,35]. These compounds are being positioned for early efficacy trials for osteoporosis, frailty, cancer cachexia and aging-associated fundamental limitations. The use of SARMS for the treatment of androgen deficiency in men has been proposed. However, the relative advantages of SARMS over testosterone for this indication are not readily apparent. Many biological features of testosterone, especially its effects on libido and behavior, bone and plasma lipids require its aromatization to estrogen. Because the currently SARMS are neither aromatized nor 5-alpha reduced, these compounds would face an uphill regulatory bar for FDA approval, as they would be required to show efficacy and safety in many more domains of androgen action, than has been required of testosterone formulations.

While the FDA regulatory pathway for the approval of drugs for osteoporosis has been well delineated, because of precedence set by previously approved drugs, the pathway for approval of function promoting anabolic therapies has not been clearly established. Efforts are underway to generate a consensus around indications, efficacy outcomes in pivotal trials, and minimal clinically important differences in key effective outcomes. These efforts should facilitate efficacy trials of candidate molecules. There are 2 types of administering SARMS: orally or in injectable dosages. Well known SARMS are LGD-4033, Ostarine (MK-2866), S4 (Andarine), RAD 140, Cardarine (GW 501516) and SR9009. The last two preparations are usually grouped with SARMS, but are not the same and are used as endurance supplements. SARMS have been prohibited by the World Anti-Doping Agency (WADA) since 2008. SARMS have the potential to be misused for performance enhancement in sport due to their anabolic properties, as well as their ability to stimulate androgen receptors in muscle and bone. They are currently prohibited at all times in the category of "other anabolic agents" under section S1,2 of the WADA Prohibited List [36]. Full clinical FDA approval for human consumption as prescription drugs has not yet been accomplished for any of the SARMS until now.

### Ligandrol (LGD-4033)

Ligandrol is a SARM discovered by Ligand Pharmaceuticals and currently under licensed development by Viking Therapeutics

[37]. There has been a lot of research into the efficacy of SARMS, but very little published research to date on LGD-4033. Ligandrol has exhibited desirable in vivo efficacy on skeletal muscle and bone measurements in animal models of disease. There is only one published study on the effects of LGD-4033 in humans, as well as phase B1 clinical trial results. A 2010 phase 1 clinical trial was the first study in humans of LGD-4033 and evaluated the safety, tolerability and pharmacokinetic profiles of the molecule in a single escalating dose, double-blind, placebo-controlled study in 48 healthy volunteers [38].

In 2013, Bhasia et al. [36] conducted a rigorous 3-week placebo-controlled study of 76 healthy men (21-50 years), that looked at the safety and tolerability of LGD-4033. During this study participants were randomized to placebo, 0, 1.0, 3 or 1mg LGD-4033 for 21 days. The study evaluated the safety, tolerability, pharmacokinetics and the effects of ascending doses of LGD-4033 on lean body mass, muscle strength, stair climbing power and sex hormones [39]. The sample size was still small and the study was not based on considerations of effect sizes, as the study's primary aim was to establish safety and tolerability, rather than efficacy. Similarly, the 3-week study duration was not designed to demonstrate maximal effects on muscle mass and strength. Therefore larger and longer studies are needed to assess the efficacy of LGD-4033. Furthermore the study was supported by Ligand Pharmaceuticals, who developed LGD-4033.

Ligandrol showed a dose-dependent suppression of total testosterone from baseline to 21 days, rather than an increase. Ligandrol did not result in fat loss in this study. It promoted muscle growth, but the evidence is very early weak evidence at this stage. There was an increase in lean body mass, that was dose-related. The mechanisms by which androgens increase muscle mass remain incompletely understood. However, the increase in strength measured by stair climbing speed and power also showed improvement, but not enough to be statistically significant. With a larger sample size and or longer study, it is possible that this effect may be demonstrated. LGD-4033 displayed an immediate effect on hormones in the body from the time it was taken. The research showed gains in lean muscle mass within the 21 days of the study. Adverse effects were not noted. LGD-4033 displayed a prolonged elimination half-life of 24-36 hours. Upon discontinuation of LGD-4033 the hormone levels returned to baseline by day 56 [39]. There is just not enough research to show the efficacy of Ligandrol at this stage, despite it was safe and well tolerated at all doses administered.

### Ostarine (MK-2866, Enobosarm)

Merck presented the results of a phase 2 clinical trial evaluating Ostarine (MK-2866), an investigational SARM in patients with cancer induced muscle loss, also known as cancer cachexia at the Endocrine Society Annual Meeting in Washington in 2009 [40]. In this study 159 cancer patients with non-small cell lung cancer,

colorectal cancer, non-Hodgkins lymphoma, chronic lymphocytic leukemia or breast cancer were randomized. Participants received placebo, 1mg or 3mg Ostarine daily for 16 weeks. Average weight loss prior to entry was 8,8 percent and patients were allowed to receive standard chemotherapy during the trial. The drop-out rate during the trial was 33%.

Ostarine treatment led to statistically significant increases in lean body mass (LBM) and improvement in muscle performance measured by stair climbing in patients with cancer cachexia compared to baseline in both the Ostarine 1mg and 3mg cohorts. In the study Ostarine met the primary endpoint of LBM measured by DEXA (dual energy x-ray absorptiometry) scan, by demonstrating significant increases in LBM compared to baseline in both the Ostarine 1mg and 3mg treatment was 0,1kg ( $p=0,874$  compared to baseline, 1,5kg ( $p=0,001$ ) and 1,3 kg ( $p=0,0045$ ) at the end of the 16 week trial.

The study also met the secondary endpoint of muscle function as measured by a 12 step stair climbing test measuring speed and calculating power with each Ostarine treatment arm demonstrating a statistically significant average decrease in time to completion and average percentage increase in power exerted. The change from baseline in stair climb power in the placebo, 1mg, and 3mg treatment groups was 0,23 Watts ( $p=0,66$ , compared to baseline) 8,4Watts ( $p=0,002$ ) and 10,1 Watts ( $p=0,001$ ), respectively. A critical appraisal results in the same critics, as depicted for the Ligandrol results. Ostarine is also known as Enobosarm and S-22 SARM by various licensing contracts in the body building world.

Ostarine had already shown significant improvement in the ability of healthy, elderly men and women to climb stairs in a phase 2A study in 2007. Elderly men and women improved climbing stairs in speed and power, accompanied by significant increases in LBM and decreases in fat mass after only 86 days [41]. Enobosarm (GTx-024, Ostarine and S-22) is the most well characterized clinically and has consistently demonstrated increases in LBM and better physical function across several populations, along with a lower hazard ratio for survival in cancer patients. Enobosarm was evaluated in the POWER 1 (Prevention and Treatment of Muscle Wasting in Patients with Cancer) and in the POWER 2 trial. These are the first phase 3 trials for a SARM. Full results from these studies will soon be published and will guide the development of future anabolic trials [42].

### Andarine (S4)

Andarine (S4) was studied in 120 ovariectomized rats for 120 days. The study found that treatment with S4 (Andarine) was beneficial to maintain cortical bone content and whole body and trabecular bone mineral density (BMD) measured by DEXA scan. The S4 treatment also decreased body fat and increased body strength in these animals. It was further disclosed by this study that S4 had the ability to reduce the incidence of fractures via minimizing the incidence of falls, through increased muscle

strength and through direct effects on bone, as compared to current therapies that are primarily antiresorptive in nature. The study also found that dosages of S4 were effective to increase LBM and reduce body fat in intact and ovariectomized rats. It was also revealed that Andarine provides the unique potential to prevent bone resorption, increase skeletal muscle mass and strength positions and promotes bone anabolism, that makes it a possible new alternative for the treatment of osteoporosis [43]. To date there are no clinical human studies of Andarine in osteoporosis. Andarine has a half-life of 4-6 hours and is prized for weight loss and building and repair of muscle as a muscle boosting supplement in the fitness community.

### RAD 140 (Testolone)

RAD 140 is a SARM that stimulates muscle weight increases at a lower dose than that required to stimulate prostate weight. It results in the expected lowering of lipids (LDL, HDL, triglycerides), without elevation of liver enzyme transaminase levels. RAD 140 has excellent pharmacokinetic properties and is a potent anabolic [44]. RAD 140 is a potent AR agonist in breast cancer cells with a distinct mechanism of action, including the AR-mediated repression of estrogen receptor 1 (ESR1). It inhibits the growth of multiple AR/ER+ breast cancer PDX (patient-derived xenograft) models as a single agent, and in combination with palbociclib. These preclinical data present support for further investigation of RAD 140 in AR/ER+ breast cancer patients [45].

In addition, RAD 140 demonstrated initial preclinical efficacy of a SARM in neuroprotective actions relevant to Alzheimer's disease and related neurodegenerative disease. In cultured hippocampal neurons, RAD 140 was as effective as testosterone in reducing cell death by apoptotic insults. RAD 140 neuroprotection was dependent on MAPK (mitogen-activated-protein) kinase signalling, as evidenced by elevation of ERK (extracellular-signal-regulated kinase) phosphorylation and inhibition of protection by the MAPK kinase inhibitor UO 126. Importantly, RAD 140 was also neuroprotective in vivo, using the rat kainate lesion model in experiments with gonadectomized adult rats. RAD 140 was shown to inhibit peripheral tissue specific androgen action, that largely spared prostate, neural efficacy as demonstrated by activation of androgenic gene regulation effects and neuroprotection of hippocampal neurons against cell death caused by systemic administration of the excitotoxin kainate [46]. There are no clinical human studies of RAD 140 until now.

In the fitness community Testolone is seen as one of the latest additions to the line of SARMS. Testolone is developed by Radius Health Company. The increase in LBM and fat loss are highly appreciated, as its androgenic-anabolic ratio of 90:1, compared to testosterone. Recommended dosages of Testolone vary from 20-30 mg once daily and it is used in cycles of 12-14 weeks duration. Because Testolone does not interact with the aromatase enzyme and is not liver toxic, no adverse effects are claimed. The half-life of Testolone is estimated 12-18 hours.

## Cardarine(GW 501516) and SR 9009 (Stenabolic)

These two preparations are usually grouped with the SARMs in the fitness community, but are not the same. Cardarine is used as an enhancing running endurance supplement. Cardarine is not a SARM, but a peroxisome proliferative activated receptor-omega agonist (PPAR-omega), that increases PPAR-omega, and regulates muscle metabolism and reprograms muscle fibre types to enhance running training endurance. While training alone increases the exhaustive running performance Cardarine treatment enhances running endurance and the proportion of succinate dehydrogenase(SDH)-positive muscle fibres in both trained and untrained mice. It appeared while training increases energy availability by promoting protein catabolism and gluconeogenesis, Cardarine enhances specific consumption of fatty acids and reduces glucose utilisation [47]. In the fitness community Cardarine is regarded as "king of the gym". Half-life is between 16-24 hours and it should be taken at 10 mg once a day or twice daily. It is claimed to be useful in conjunction with anabolics and stimulants of any kind without adverse reactions in 12-14 week cycles.

SR 9009 (Stenabolic) is a REV-ERB (revised-viral nuclear erythroblastosis receptors) agonist, that can modulate the expressions of circadian core clock proteins and therefore help to modulate the circadian rhythm. Modulation of the REV-ERB activity by synthetic agonists e.g., SR 9009 SR 9011 alters the expression of genes involved in lipid and glucose metabolism and, therefore plays an important role in maintaining the energy homeostasis. Effects of SR9009 and SR9011 in animal studies are increased basal oxygen consumption, decreased lipogenesis, cholesterol and bile acid synthesis in the liver, increased mitochondrial content, glucose and fatty oxidation in the skeletal muscle and decreased lipid storage in the white adipose tissue. The observed increase in energy expenditure and decrease in fat mass make the REV-ERB agonists promising drug candidates for the treatment of several metabolic disorders. They are also attractive for performance enhancement by athletes. Such use can be classified as doping [48].

SR9009 (Stenabolic) has been developed by Scripps Research by the team of Prof. Thomas Burris. Stenabolic is taken orally as a metabolism enhancer in the fitness community. It is believed to have results similar to Cardarine, but with considerable more extra benefits. It is recommended as a very good addition to any steroid (Anavar or Trembolone) or SARMs cycle, especially when used together with Cardarine. The half-life is short, 30-60 minutes, so the dose should be spaced through the day e.g., 10 mg 4-6 times daily. Again no adverse effects are reported.

### Illicit use of SARMs

Recently, the FDA issued a consumer warning letter against supplement-like bodybuilding products, that contain SARMs. The FDA warning came on the heels of warning letters sent to three companies, that market products containing the ingredients. FDA had this to say about the offending products distributed by Infantry

Labs LLC, Iron Mag Labs and Panther Sports Nutrition: "Although the products identified in the warning letters are marketed and labeled as dietary supplements, they are not dietary supplements. The products are unapproved drugs, that have not been reviewed by the FDA for safety and effectiveness" [49]. FDA told consumers among the dangers associated with SARMs are liver toxicity and the potential to increase the risk of heart attack and stroke. But the agency said the long-term effects of these substances are unknown. However, these FDA health risk statements can not be supported by the few small clinical human phase 1 and 2 SARMs studies performed and the ongoing POWER trials. Furthermore, the FDA did not mention that Ostarine and Ligandrol have previously been investigated as new drugs, which makes them ineligible for use as dietary supplements.

Nevertheless, as clinical research of SARMs is slow, we are now in the wonderful situation the real world clinical SARMs experience is now represented by the fitness and body building world. It is estimated that there are between 2 and 4 million young people in the U.S. alone, who have used performance-enhancing drugs sometime in their life. There are thousands of internet sites offering SARMs in and outside the U.S [50]. So the magnitude of the problem is completely unknown, if there is any problem at all. In general, these young people are very concerned about their health and "looks" and have the good right of their own responsibility.

A recent JAMA publication found that the chemical analysis of 44 products sold via the internet as SARMs revealed, that only 52% contained SARMs and another 39% contained another unapproved drug. In addition, 25% of products contained substances not listed on the label, 9 percent did not contain an active substance and 59% contained substance amounts, that differed from the label [50]. Although these figures must be frightening, there is no registered SARMs epidemic at the U.S. emergency rooms. At present the biggest problems are the "loopholes" in the FDA regulation of dietary supplements.

### Conclusion

The SARMs were discovered in the late 1990's. Clinical development is slow. Few human phase 1 and 2 clinical studies are available. Results of the phase 3 POWER trials, studying SARMs in wasting, are awaiting and will guide the development of future anabolic trials. Until now no SARM has received FDA approval. Due to "loopholes" in the FDA regulations the SARMs are widespread used as dietary supplements in the fitness community and body building world. This results in the wonderful situation the clinical experience with SARMs is represented by illicit SARMs use and not by clinical science

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