

SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARM) – A NEW TEMPTATION IN SPORTS. TYPES, MODE OF ACTION AND SIDE EFFECTS OF THEIR APPLICATION: REVIEW

Veselin Vasilev, Nikolay Boyadjiev
Medical University of Plovdiv, Bulgaria

ORCID

Veselin Vasilev <https://orcid.org/0000-0001-8887-6469>

Nikolay Boyadjiev <https://orcid.org/0000-0002-7125-3879>

ABSTRACT

The selective androgen receptor modulators (SARMs) are androgen receptor ligands that bind to androgen receptors on target cells and exhibit a more pronounced anabolic effect at the expense of the androgenic effect on the latter. The aim of the article is to explain what SARMs are and how they are connected with sports. We used over 300 articles for the last 20 years connected with SARMs. Recently, the interest in these new molecules and their use has grown significantly, including in sports, which has led to their listing on the WADA prohibited list. In recent years, a lot of data have been gathered, both on the mechanism of action of a number of steroidal and non-steroidal representatives of this class of substances and on the adverse side effects of their use, as the latter should be well-known to sports doctors and especially to amateurs practicing in their free time and willing to increase their muscle mass with a view to preventing any potential health risks.

Key words: SARMs, anabolic steroids, androgen receptor, ostarine, doping

INTRODUCTION

The selective androgen receptor modulators (SARMs) represent a new class of androgen receptor ligands that act similarly to anabolic steroids, but are selective in their effects, with anabolic predominance, and androgenic ones being relatively limited. This gives a number of advantages of SARM over the anabolic androgenic steroids, associated with avoiding some of the side effects of the latter, such as acne, liver damage, testicular atrophy, thickening of vocal cords, hair growth, menstrual disorders in women, etc. Therefore, they have potential use in patients with a number of diseases, such as amyotrophic lateral sclerosis (Lou Gherig's disease), dermatomyositis, osteoporosis, breast cancer, sarcopenia, various

types of cachexia, benign prostatic hyperplasia, and hypogonadism (Chen et al., 2005a; Zhang, Sui, 2013).

Due to the pronounced anabolic effect, the selective androgen receptor modulators are widely used in sports to improve physical performance and athletic achievements. However, since 2008, they have been included in the World Anti-Doping Agency (WADA) List of Prohibited Substances, falling under the category of "other anabolic agents" in Section S1.2 of this list (Thevis, Schaenzer, 2018).

Although there is currently no approved representative of SARMs as a drug, these preparations/substances can be purchased online, but a study of Van Wagoner et al., 2017 evidences that only 52% of the 44 products of-

ferred online and tested contained real SARMs (Van Wagoner et al., 2017). Moreover, they are also included as ingredients in some dietary supplements which poses a significant risk of their use in sports. In some cases, as a matter of fact, consumers are misled by masking the presence of SARM on the label, using a coded one instead of the trade name of the substance (for example, MK-2866 or GTx-024 is indicated as an ingredient, instead of Ostarine).

Some of the most widespread and used preparations of this group are Ostarine and Andarine (Geyer et al., 2014). To carry out doping-control in sports in order to prove the use of SARM, various screening methods (gas chromatography, liquid chromatography and mass spectrometry) are used to detect them or prove the presence of their metabolites in blood or urine (Thevis et al., 2008; Thevis et al., 2008; Thevis et al., 2011).

With regard to their chemical structure, SARMs can be divided into two main groups: steroidal and non-steroidal. The steroidal group of SARM representatives have been known since as early as the middle of the last century (Bhasin, Jasuja, 2009).

The steroidal types of SARMs are obtained

through structural changes in the molecule of testosterone. By removing the 19-methyl group, an increased anabolic effect of testosterone is achieved. Replacement of 7-alpha alkyl group reduces the interaction with the enzyme 5- α reductase and increases its tissue selectivity. Replacing the 17-alpha alkyl group increases the half-life of testosterone.

The first non-steroidal SARMs were presented in 1998 and since then there has been a growing list of substances of this group, some of which are drug candidates and many of them are currently under clinical trials (Chen et al., 2005a). Non-steroidal SARMs are grouped into different classes: aryl propionamide analogues, bicyclic hydantoin analogues, quinolones, tetrahydroquinoline analogues, butanamides, benzimidazoles. The first discovered class is that of aryl propionamides. The number of representatives of the different classes is constantly increasing.

Narayanan et al., 2008 and Bhasin, Jasuja, 2009 and Jasuja et al., 2012 represent very adequately the chemical structure of the two main groups of SARMs (Bhasin, Jasuja, 2009; Jasuja et al., 2012; Narayanan et al., 2008) (Table 1) and (Table 2).

Table 1. Structure of steroidal representatives of SARM

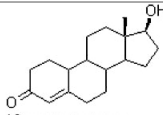
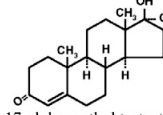
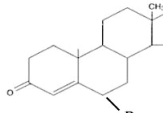
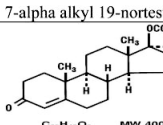
Structure:Activity Relationship	Compounds	Chemical Structure
Removing 19 methyl increases anabolic activity	19-nor testosterone (nandrolone) series of compounds	 19-nortestosterone
17-alpha alkyl substitutions retard first-pass presystemic metabolism	Many orally active steroidal androgens have 17-alpha alkyl substitutions	 17-alpha methyl testosterone
7-alpha alkyl substitutions increase anabolic activity	7-alpha-methyl-19-nortestosterone	 7-alpha alkyl 19-nortestosterone
Esterification of 17-beta hydroxyl group increases hydrophobicity and extends duration of in vivo action	Testosterone enanthate, cypionate, and undecanoate	 Testosterone enanthate

Table 2. Structure of non-steroidal representatives of SARM

Chemotype	Structure	Examples
Aryl-propionamide analogs		Ostarine, andarine
Bicyclic hydantoin analogs		BMS-564929
Quinolinones		LGD-2226, LGD-2941
Tetrahydroquinoline analogs		Kanem Pharmaceuticals, S-40503
Benzimidazoles		Johnson and Johnson's benzimidazole derivative
Butanamides		Merck SARM based on butanamide scaffold

MATERIALS AND METHODS

Inclusion criteria

The aim of this review is to make it clear for all sportsmen (professional or amateur) what to expect from SARMs (which are the different types and what is their mechanism of action) and to present the adverse side effects and possible risks of their usage. Firstly, for an article to be included in our review it had to be connected with SARMs. Secondly, we used only the articles which provided information about SARMs in general, their role in sports (different methods to detect them in doping control), their mechanism of action and their adverse side effects no matter in animals or in people. The articles used were available in English and were open access.

Data sources

We examined over 300 articles connected with SARMs for the period 1998 - 2020 years to collect the needed information for this review. Studies were identified by searching electronic databases. The search was applied to ScienceDirect, PubMed, Elsevier, Google

Scholar. We used the following search terms in the different databases: - selective androgen receptor modulators, SARMs, selective androgen receptor modulators - rats. There was no restriction connected with the representative of SARMs used. Also, there were no restrictions for the type of the experiment performed with SARMs.

Exclusion criteria

There were a lot of articles connected with SARMs which we did not include in our review. The main reason for them not to be included is that they do not provide the type of information we were looking for. They give detailed information about the chemical structure and development of SARMs and the process of their synthesis and discovery. As we already explained this is not the focus of our review and such articles were considered irrelevant by us. The review is based on 32 articles.

RESULTS

SARMs perform their effects after the ligand binds to the androgen receptor (AR) (Figure 1) by genomic mechanism. AR is coded

by a gene that is located on the X chromosome (Narayanan et al., 2018). AP is a transcription factor and consists of three main domains: N-terminal domain (NTD) which modulates the transcription activation; DNA-binding domain (DBD) which binds to androgen response elements of DNA; C-terminal ligand-binding domain (LBD). There is also a hinge region between DBD and LBD (Gao, 2010).

AR is located in the cytosol of the cell because its ligands are liposoluble and can go through the cell membrane. After the ligand binds to the receptor, initially, conformational

changes in the receptor occur. The heat shock proteins and chaperons associated with it are released. Then, the obtained complex moves to the cell nucleus. There, an interaction with the nuclear DNA occurs. Thus, AR may activate target genes that are involved in the regulation of a number of physiological processes. However, its transcriptional activity may be affected by proteins known as co-regulators. They are divided into co-activators which increase transcriptional activity, and co-repressors which decrease it.

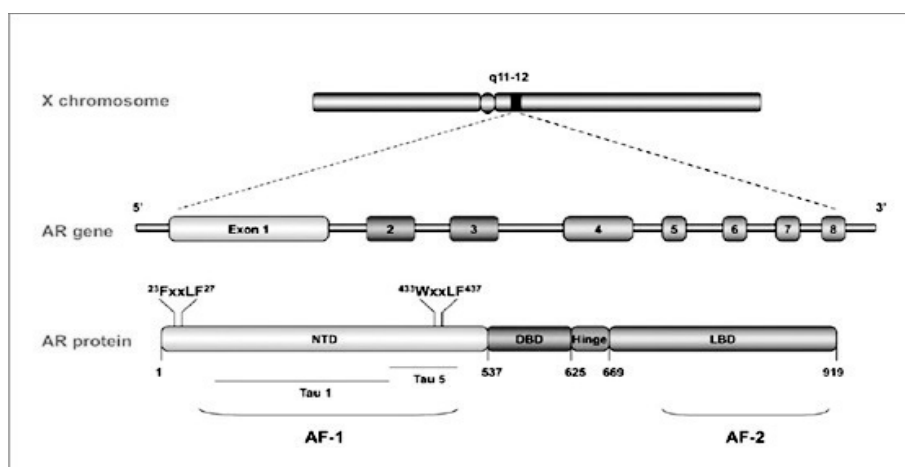


Figure 1. Diagram of the domains of the androgen receptor (AR) and of the gene which encodes it (after Lonergan P.E. & Tindall D.J.) (Lonergan, Tindall, 2011)

The mechanisms by which tissue selectivity of SARM is achieved are not fully understood, but there are different hypotheses. Testosterone and anabolic androgenic steroids (AAS), under the action of the enzyme 5- α reductase, are converted into dihydrotestosterone (DHT) and other metabolites, which have greater biological activity and more pronounced effects on the genitals. SARMS are not susceptible to the action of this enzyme which helps to demonstrate their tissue selectivity (Gao et al., 2004). Another enzyme whose action is associated with side effects when taking AAS or testosterone is aromatase. It converts androgens into female sex hormones (estrogens), which

are also responsible for the abovementioned side effects. Non-steroidal representatives of SARM are not susceptible to the action of this enzyme as well (Bhasin, 2015).

The mechanisms of tissue selectivity of SARM are performed regardless of their pharmacokinetic profile (Vajda et al., 2009). For example, the local tissue concentration of LGD-3303 was found to be higher in the prostate than in the muscles, despite the greater SARM in the muscles. The interaction of the androgen receptor with the various co-activators and co-suppressors is very essential. When DHT, testosterone or AAS bind to AR, the induced conformational change of the re-

ceptor leads to interaction with some co-regulators, and when binding SARMs to AR, the conformational change and co-activators with which AR interacts, are others (Narayanan et al. 2008; Narayanan et al., 2018). Similar data are presented by Furuya K. et al., who found that in an osteopenic model in female rats, after binding to AR, DHT caused the receptor to interact with the co-regulators TIF2, SRC1, β -catenin, NCoA3, gelsolin and PROX1 (Furuya et al., 2013). After S-101479 is bound to AR, the selection of co-regulators is different, and the receptor interacts only with the co-regulators gelsolin and PROX1, which is sufficient for the performance of tissue selectivity. More than 200 co-regulators are known to activate or suppress various target genes.

After binding to AR, DHT and SARM increase the phosphorylating activity of various kinases (Bhasin, Jasuja, 2009). For example, a non-steroidal SARM representative of the aryl propionamide class mediates its effects through the kinase pathways: MEK, ERK, p38 MAPK and others. While DHT uses the kinase pathways: PI3K, PKC, ERK and others (Narayanan et al., 2008). This shows that the two groups of ligands use different signalling pathways.

The conformational change caused by the classical agonists of AR (testosterone or AAS) favours the classical intramolecular N-terminal/C-terminal interaction (N/C interaction). This interaction is essential for the selection of certain co-regulators, for the transcriptional activity of AR and for the modulation of target genes. In the synthesis of SARM, the aim is to bring about a conformational change which does not stimulate this N-terminal/C-terminal interaction (N/C interaction). This would lead to the manifestation of the desired tissue selectivity by selecting other co-regulators and activating other target genes (Sathya et al., 2003). Antagonizing the N-terminal/C-ter-

minial interaction (N/C interaction) leads to incomplete activation of the receptor, and to implement the effects on the prostate and seminal vesicles, it is necessary to fully activate AR (Schmidt et al., 2010). Through this mode of action, the representative of SARM TFM-4AS-1 exhibits anabolic effects in osseous and muscular tissue, without performing activity in the prostate (Schmidt et al., 2009).

SARM can also modulate the activity of the androgen receptors by inhibiting their transport to the cell nucleus (Roy et al., 2001). To implement their effects, SARM modulate AR in the muscular satellite cells (the stem cells of the striated muscles). Dubois et al., 2015 prove that anabolic effects are manifested in the other muscular cells as well (Dubois et al., 2015).

The established mechanisms of action of SARM make them an attractive future option in the treatment of a great number of diseases, such as osteoporosis, cachexia, sarcopenia, benign prostatic hyperplasia, neurological diseases with cognitive deficits, hypogonadism, sexual dysfunction, breast cancer and for the effective contraception in men. It should be considered, however, that their use, including by athletes, is also associated with a number of adverse side effects (Geyer et al., 2014). However, most of them are of low frequency and manageable. The most common ones are related to elevated liver enzymes and changes in various lipid fractions. There are still insufficient data on what the side effects of SARM would be in their long-term use. However, SARMs are thought to be far more sparing than AAS. AAS provoke responses from the body which very often significantly reduce the quality of life. Some of them can even be fatal.

What are references to date on the side effects of the use of SARM in healthy people and in experimental models in humans and animals?

For example, healthy men taking LGD-

4033 for 21 days were found to have decreased plasma levels of the sex hormone binding globulin (SHBG), triglycerides, HDL, FSH (Basaria et al., 2013). The changes found were manageable, with lipid and hormone concentrations returning to normal after discontinuation of the intake of LGD-4033.

Administration for 2 weeks of the selective modulator C-6 in intact rats caused a decrease in gonadotropic hormone and serum testosterone levels, and after ten weeks a suppression of spermatogenesis (Chen et al., 2005b).

In a postmenopausal model of osteoporosis in female rats, Ostarine was found to cause uterine weight gain and increased plasma phosphorus concentration (Hoffmann et al., 2019).

Adverse reactions observed in the use of Ostarine in humans include febrile neutropenia, pneumonia and progression of the malignant disease in patients who have it (Dobs et al., 2013).

In a large-scale experiment with women who suffer from sarcopenia, it was found that the intake of MK-0773 does not cause androgenization, but in some of the respondents, there is, albeit transient, an increase in transaminase liver enzymes (Papanicolaou et al., 2013).

Another study of healthy men and women in postmenopausal age found that the administration of GSK2881078 caused a decrease in HDL and SHBG. In women, these effects have occurred even at lower doses than in men. One woman was reported to have a rash, and two men were found to have elevated creatine phosphokinase levels after physical exercise (Clark et al., 2017).

The selective modulator RAD140, in various in vivo and in vitro models, was found to cause decreased appetite and weight, elevated liver enzymes ASAT and ALAT, as well as hypophosphatemia (Hamilton et al., 2019).

After the application of the new representative of SARM - PF-06260414 in healthy people

of different ethnics (Japanese and people from countries more to the West), the tolerance of the preparation is good, but there are slight adverse effects, such as headache and increased ALAT (Bhattacharya et al., 2016).

CONCLUSION

There are still insufficient data in literature on the effects of SARM when used in combination with physical exercise. Studies are needed in this aspect to determine possible side effects, to establish whether SARM will enhance the effects of the training itself, or just the opposite – will have an antagonistic effect on some of them.

Despite the described side effects of their use, the selective androgen receptor modulators are a promising alternative for their inclusion in the treatment of a number of diseases, although among them there is still no officially approved drug. They could be used as a replacement therapy instead of androgens and would improve the quality of life of patients.

SARMs also have a number of advantages over testosterone and AAS, as they exhibit tissue selectivity, which allows them to have poorly expressed or no androgenic effects, and at the same time to have similar or even more pronounced anabolic effects in comparison to testosterone and AAS. For example, selective modulators S-1 and S-4 do not decrease the plasma concentrations of FSH and LH in castrated rats, and have lower androgenic activity than testosterone propionate, but their anabolic effects are similar or even better than the ones thereof (Yin et al., 2003).

Of all selective androgen receptor modulators, Ostarine is the representative which is the most advanced in clinical trials. However, given that this group of substances is on the WADA prohibited list, SARM should not be used by athletes, even more so that a further in-depth research with the different represen-

tatives is required to clarify the mechanisms of their action, as well as any previously unreported side effects. Furthermore, there is lack of data regarding the interaction of SARMs with alcohol or drugs and their long-term effects.

SARMs are a new class of molecules which can contribute to the treatment process of various types of diseases. This is possible due to their very strong anabolic effect and weak androgenic one. They are also appropriate for increasing the physical working capacity and their use is prohibited in sports. This is the reason every sportsman whether professional or amateur should be familiar with them.

REFERENCES

- Basaria, S., Collins, L., Dillon, E.L., Orwoll, K., Storer, T.W., Miciek, R., Ulloor, J., Zhang, A., Eder, R., Zientek, H., Gordon, G., Kazmi, S., Sheffield-Moore, M., Bhasin, S. (2013). The Safety, Pharmacokinetics, and effects of LGD-4033, a novel nonsteroidal oral, selective androgen receptor modulator in healthy young men. *The Journal of Gerontology: Series A*, 68 (1), 87–95.
- Bhasin, S. (2015). Selective androgen receptor modulators as function promoting therapies. *The Journal of Frailty & Aging*, 4(3): 121–122.
- Bhasin, S., Jasuja, R. (2009). Selective androgen receptor modulators (SARMs) as function promoting therapies. *Current Opinion in Clinical Nutrition & Metabolic Care*, 12(3): 232–240.
- Bhattacharya, I., Tarabar, S., Liang, Y., Pradhan, V., Owens, J., Oemar, B. (2016). Safety, pharmacokinetic, and pharmacodynamic evaluation after single and multiple ascending doses of a novel selective androgen receptor modulator in healthy subjects. *Clinical Therapeutics*, 38(6): 1401-1416.
- Chen, J., Kim, J., Dalton, J. (2005a). Discovery and therapeutic promise of selective androgen receptor modulators. *Molecular Interventions*, 5(3): 173-188.
- Chen, J., Hwang, D.J., Bohl, C.E., Miller, D.D., Dalton, J.T. (2005b). A selective androgen receptor modulator for hormonal male contraception. *Journal of Pharmacology and Experimental Therapeutics*, 312 (2): 546-553.
- Clark, R.V., Walker, A.C., Andrews, S., Turnbull, P., Wald, J.A., Magee, M.H. (2017). Safety, pharmacokinetics and pharmacological effects of the selective androgen receptor modulator, GSK2881078, in healthy men and postmenopausal women. *British Journal of Clinical Pharmacology*, 83(10): 2179-2194.
- Dobs, A.S., Boccia, R.V., Croot, C.C., Gabrail, N.Y., Dalton, J.T., Hancock, M.L., Johnston, M.A., Steiner, M.S. (2013). Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. *The Lancet Oncology*, 14(4):335-45.
- Dubois, V., Simitsidellis, I., Laurent, M.R., Jardi, F., Saunders, P.T., Vanderschueren, D., Claessens, F. (2015). Enobosarm (GTx-024) modulates adult skeletal muscle mass independently of the androgen receptor in the satellite cell lineage. *Endocrinology*, 156(12): 4522-4533.
- Furuya, K., Yamamoto, N., Ohyabu, Y., Morikyu, T., Ishige, H., Albers, M., Endo, Y. (2013). Mechanism of the tissue-specific action of the selective androgen receptor modulator S-101479. *Biological and Pharmaceutical Bulletin*, 36(3): 442-451.
- Gao, W. (2010). Androgen receptor as a therapeutic target. *Advanced Drug Delivery Reviews*, 62(13): 1277-1284.
- Gao, W., Kearbey, J.D., Nair, V.A., Chung, K., Parlow, A.F., Miller, D. D., Dalton, J. T. (2004). Comparison of the pharmacological effects of a novel selective androgen receptor modulator, the 5 α -reductase inhibitor fi-

- nasteride, and the antiandrogen hydroxyflutamide in intact rats: New approach for benign prostate hyperplasia. *Endocrinology*, 145(12): 5420–5428.
- Geyer, H., Schänzer, W., Thevis, M. (2014). Anabolic agents: recent strategies for their detection and protection from inadvertent doping. *British Journal of Sports Medicine*, 48: 820–826.
- Hamilton, E., Vidula, N., Ma, C., LoRusso, P., Bagley, R.G., Yu, Z., Annett, M., Weitzman, A., Conlan, M.G., Weise, A. (2019). Phase I dose escalation study of a selective androgen receptor modulator RAD140 in estrogen receptor positive (ER+), HER2 negative (HER2-) breast cancer (BC). *Annals of Oncology*, 30, (Suppl. 5): v123.
- Hoffmann, D.B., Komrakova, M., Pflug, S. et al. (2019). Evaluation of ostarine as a selective androgen receptor modulator in a rat model of postmenopausal osteoporosis. *Journal of Bone and Mineral Metabolism*, 37: 243.
- Jasuja, R., Zacharov, M., Bhasin, S. (2012). The state-of-the-art in the development of selective androgen receptor modulators. in Nieschlag, E. (Ed.) *Testosterone: Action, Deficiency, Substitution* (2012). Cambridge University press, Cambridge Core, pp. 459 - 469.
- Lonergan, P.E., Tindall, D.J. (2011). Androgen receptor signaling in prostate cancer development and progression. *Journal of Carcinogenesis*, 10: 20.
- Narayanan, R., Coss, C.C., Yepuru, M., Kearbey, J.D., Miller, D.D., Dalton, J.T. (2008). Steroidal androgens and nonsteroidal, tissue-selective androgen receptor modulator, S-22, regulate androgen receptor function through distinct genomic and nongenomic signaling pathways. *Molecular Endocrinology*, (22)11: 2448–2465.
- Narayanan, R., Coss, C.C., Dalton, J.T. (2018). Development of selective androgen receptor modulators. *Molecular and Cellular Endocrinology*, 465: 134–142.
- Papanicolaou, D., Ather, S., Zhu, H., Zhou, Y., Lutkiewicz, J., Scott, B., Chandler, J. (2013). A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. *The Journal of Nutrition, Health & Aging*, 17(6): 533–543.
- Roy, A.K., Tyagi, R.K., Song, C.S., Lavrovsky, Y., Ahn, S.C., Oh, T., Chatterjee, B. (2001). Androgen receptor: Structural domains and functional dynamics after ligand-receptor interaction. *Annals of the New York Academy*, (949)1: 44–57.
- Sathya, G., Chang, C.Y., Kazmin, D., Cook, C.E., McDonnell, D.P. (2003). Pharmacological uncoupling of androgen receptor-mediated prostate cancer cell proliferation and prostate-specific antigen secretion. *Cancer Research*, 63: 8029–8036.
- Schmidt, A., Harada, S., Kimmel, D.B., Bai, C., Chen, F., Rutledge, S.J., Vogel, R., Scafonas, A., Gentile, M., Nantermet, P., Witmer, S., Pennypacker, B., Masarachia, P., Sahoo, S.P., Kim, Y., Meissner, R.S., Hartman, G.D., Duggan, M.E., Rodan, G.A., Towler, D.A., Ray, W.J. (2009). Identification of anabolic selective androgen receptor modulators with reduced activities in reproductive tissues and sebaceous glands. *The Journal of Biological Chemistry*, 284(52): 36367–36376
- Schmidt, A., Kimmel, D.B., Bai C., Scafonas, A., Rutledge, S.J., Vogel, R.L., Witmer, S., Chen, F., Nantermet, P.V., Kasparcova, V., Leu, C., Zhang, H., Dugga, M.E., Gentile, M. A., Hodor, P., Pennypacker, B., Masarachia, P., Opas, E.E., Adamski, S.A., Cusick, T.E., Wang, J., Mitchell, H.J., Kim, Y., Prueksaritont, T., Perkins, J.J., Meissner, R.S., Hartman, G.D., Freedman, L.P., Harada, S., Ray, W.J. (2010). Discovery of the Selective An-

drogen Receptor Modulator MK-0773 Using a Rational Development Strategy Based on Differential Transcriptional Requirements for Androgenic Anabolism Versus Reproductive Physiology. *The Journal of Biological Chemistry*, 285(22): 17054-17064.

Thevis, M., Kohler, M., Schlörer, N., Fußhöller, G., Schänzer, W. (2008). Screening for Two Selective Androgen Receptor Modulators Using Gas Chromatography-Mass Spectrometry in Doping Control Analysis. *European Journal of Mass Spectrometry (Chichester)*, 14(3):153-161.

Thevis, M., Kohler, M., Thomas, A., Schlörer, N., Schänzer, W. (2008). Doping control analysis of tricyclic tetrahydroquinoline-derived selective androgen receptor modulators using liquid chromatography/electrospray ionization tandem mass spectrometry. *Rapid Communication in Mass Spectrometry*, 22(16): 2471-1278.

Thevis, M., Thomas, A., Möller, I., Geyer, H., Dalton, J.T., Schänzer, W. (2011). Mass spectrometric characterization of urinary metabolites of the selective androgen receptor modulator S-22 to identify potential targets for routine doping controls. *Rapid Communications in Mass Spectrometry*, 25(15): 2187-2195.

Thevis, M., Schänzer, W. (2018). De-

tection of SARMs in doping control analysis. *Molecular and Cellular Endocrinology*, 464, 34-45.

Vajda, E.G., López, F.J., Rix, P., Hill, R., Chen, Y., Lee, K., O'Brien, Z., Chang, W.Y., Meglasson, M.D., Lee, Y. (2009). Pharmacokinetics and pharmacodynamics of LGD-3303 [9-Chloro-2-ethyl-1-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrrolo-[3,2-f]quinolin-7(6H)-one], an orally available nonsteroidal-selective androgen receptor modulator. *Journal of Pharmacology and Experimental Therapeutics*, 328(2): 663-670.

Van Wagoner, R., Eichner, A., Bhasin, S., Deuster, P., Eichner, D. (2017). Chemical composition and labeling of substances marketed as selective androgen receptor modulators and sold via the internet. *JAMA*, 318(20): 2004-2010.

Yin, D., Gao, W., Kearbey, J.D., Xu, H., Chung, K., He, Y., Marhefka, C.A., Veverka, K.A., Miller, D.D., Dalton, J.T. (2003). Pharmacodynamics of selective androgen receptor modulators. *Journal of Pharmacology and Experimental Therapeutics*, 304 (3): 1334-1340.

Zhang, X., Sui, Z. (2013). Deciphering the selective androgen receptor modulators paradigm. *Expert Opinion on Drug Discovery*, 8(2): 191-218.

Corresponding author:

Dr. Veselin Vasilev
Physiology department
Medical University of Plovdiv
15A Vasil Aprilov blvd.
Plovdiv 4000, Bulgaria
E-mail: v_vasilev1892@abv.bg