Navigating the Potential of Receptor Modulators Through GSK-2881078

Overview

GlaxoSmithKline (GSK) 2881078 is a member of the class of selective androgen receptor modulators (SARMs). This class has been proposed to be very promising both for medical application, but also for performance enhancement in athletes. Unlike classical steroids, SARMs have few side effects, but still retain anabolic activity. This is because they don`t effect each tissue like a androgen would do, instead they selectively address some tissues more and some only in very small amount. Hence the word “selective” in their name. An appropriately selective SARM has the potential to be given to postmenopausal women without inducing hirsutism or virilization, which both occur with steroidal androgen receptor modulators. They also have good transdermal and oral bioavailability which enables easier administration.

SARMs have been studied as possible therapies for many conditions, including osteoporosis, Alzheimer’s disease, breast cancer, stress urinary incontinence (SUI), prostate cancer (PCa), benign prostatic hyperplasia (BPH), male contraception, hypogonadism, Duchenne muscular dystrophy (DMD), and sarcopenia/muscle wasting/cancer cachexia. While there are no indications for SARMs currently approved by the Food and Drug Administration (FDA), many potential applications are still being explored, and results are promising.[1]

In Vitro Studies

The effective concentration of GSK-2881078 that was needed to activate the androgen receptor was compared to 2 other SARMs, namely RAD-140 and GLPG0492. It was found that RAD-140 was the most potent SARM, followed by GSK-2881078 (concentration needed to be at $4 \cdot 10^{-9}$ M higher compared to RAD-140 $1.7 \cdot 10^{-9}$ M) and then GLPG0492 ($1.24 \cdot 10^{-8}$ M).[2]

A study evaluated the metabolites forming from GSK-2881078 were produced by cleaving the alkyl chains at the nitrogen atom and a methoxylation at the aromatic system. This study also evaluated & established analytic procedures to confirm levels of GSK-2881078 for anti- doping purposes. [3]

A further study has found additional chromatographic methods to detect GSK-2881078 in urine.[4] Two additional studies have elucidated the metabolites of GSK-2881078 using horse liver microsomes, which did not yield any additional information for the

purpose of this review.[5]

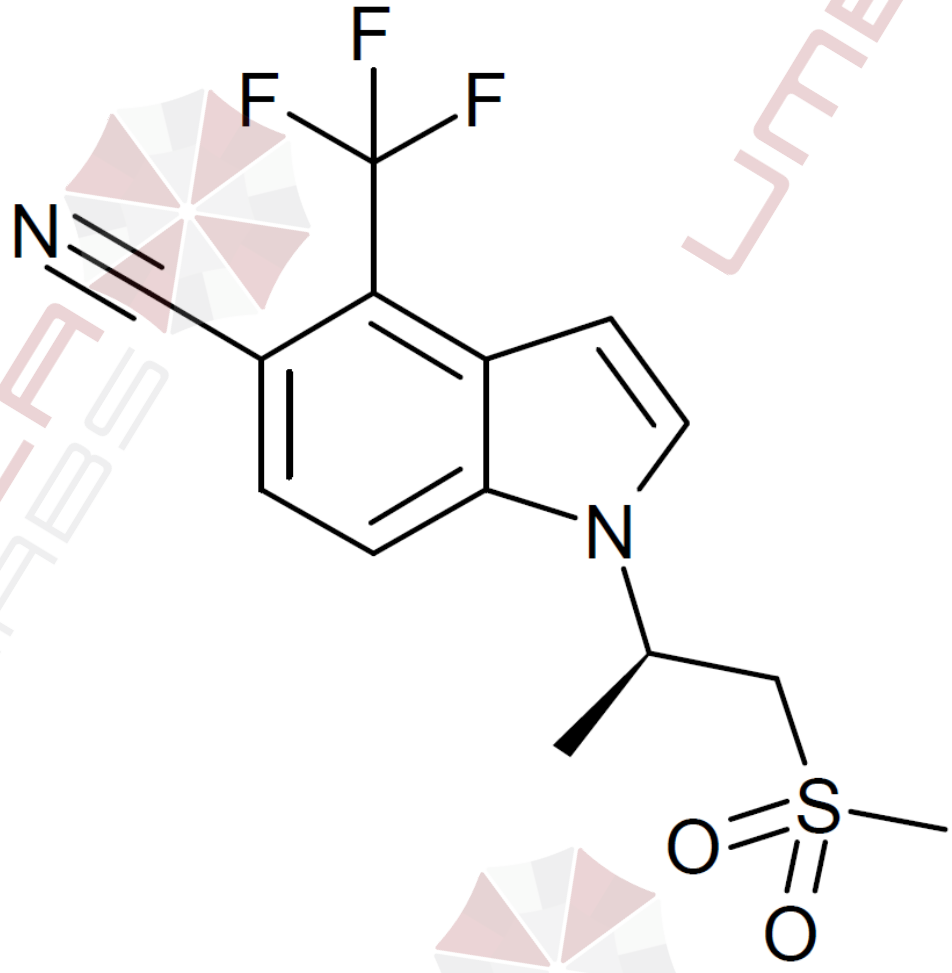
Clinical trials

GSK-2881078 in particular has already been used in clinical trials, therefore evidence for potentially beneficial effects in humans use is very good.

The first human study was conducted on about 100 volunteers in 2017. Doses used varied between 0,05 mg and 0,75 mg. [6] No significant effects on vital signs, electrocardiograms, cardiac telemetry or standard clinical laboratory studies were observed. A dose–response effect was observed on lowering both high-density lipoprotein (HDL) and sex hormone- binding globulin (SHBG). Drug-related adverse events (AEs) were mild. Effects on muscle mass and performance were not measured, since this was a phase I trial.

A follow-up study in 2018 measured the effects of a daily dose of GSK-2881078 (either 0,75 mg or 1,5 mg) on 93 subjects over the age of 50.[7] They found GSK-2881078 has a long elimination half-life, with around 150 hours (~6 days) depending on the dose. Compared with placebo, there was a greater lean mass gain across all doses of GSK-2881078, while increasing the dosage from 1.5 mg to 4 mg did not significantly lead to better results in this study.

GSK-2881078 was generally well tolerated across all doses for up to 56 days, with no serious adverse events reported and no symptomatic or hormonal evidence of virilization in females reported. Potentially clinically significant changes were observed in subjects dosed with GSK-2881078 in liver function tests,



lipids, and testosterone. All male subjects dosed with GSK-2881078 displayed reversible reductions in total testosterone, as would be expected from androgenic compounds. In the healthy aged volunteers studied, maximal mean change in lean body mass approached 1,76 kg in males and 3,39 kg in females after 8 weeks of treatment. This also showed that females apparently react more sensitively to GSK-2881078, which could be explained by their naturally lower androgen levels.

A study from 2023 investigated the effects of GSK-2881078 in chronic obstructive pulmonary disease, a serious condition with a high prevalence in long-term smokers.[8] 97 patients with COPD received GSK-2881078 in either 1 mg (women) or 2 mg (men) daily for 13 weeks. The lower dose for women was likely chosen due to the increased effect of GSK-2881078 on females found in previous studies. Here, both males and females showed similar increases in lean body mass of 2,1 kg and a varying increase in strength, which was statistically significant in men, but not in women. Quality of life was also assessed using various questionnaires, but did not increase significantly overall. Reversible reductions in high- density lipoprotein-cholesterol and transient elevations in liver enzymes were the main treatment-related safety findings.

Conclusion

Although there are only few studies specifically focusing on GSK-2881078 at this moment, it seems quite clear this compound is able to promote muscle growth in men and women, with a

stronger effect observed in women when using doses between 1 mg and 5 mg daily.

Studies were mostly carried out in older patients with pre-existing conditions, so it is not clear if the reported gains in lean mass would translate to young and trained individuals completely. There is good reason to believe that young individuals will increase muscle mass when using GSK-2881078 in a recreational setting and that female athletes will profit more than males, if dosing is equal. Adverse effects seem minor, although long time use should be monitored by measuring liver function, since the drug did show an effect on liver enzymes in some cases.

GSK-2881078 also seems promising in patients suffering from wasting syndromes, which leads to a decreased muscle mass. Such condition often affects people with chronic diseases, such as COPD and cancer. At the same time, individuals over 50 years of age may profit from intake GSK-2881078 to decrease age related muscle loss, while avoiding side effects like prostate hyperplasia in men and increased body hair growth in females.

Another potential big field of applications is Osteoporosis, a condition affecting dozens of million people in USA alone, mostly post-menopausal women. SARMs have demonstrated the ability to promote new bone growth and increase bone strength in animal models, while no studies have been conducted specifically on the effect of GSK-2881078.

Since the last study on GSK 2881078 was conducted in 2023 and showed good results, it is likely further clinical trials will be continued in the short to medium term future.

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