SARCONEOS, a drug candidate in clinical development for sarcopenia, demonstrates sharp functional improvement and anti-fibrotic properties in an animal model of Duchenne muscular dystrophy

Abstract

Duchenne muscular dystrophy (DMD), an inherited muscular disease, characterized by progressive muscle weakness and cardiac impairment, leading to premature death. DMD is caused by an absence of dystrophin. Muscles undergo repeated cycles of necrosis/regeneration and are replaced by connective and adipose tissues. Glucocorticoids and support therapy are the current standard of care leaving many patients with an unmet medical need.

About Sarconeos: Sarconeos is a first-in-class drug candidate based on the activation of the MAS receptor (major player of the renin-angiotensin system), restoring muscular anabolism, inhibiting myostatin, that had demonstrated meaningful activity in animal models of muscular dystrophies. Sarconeos is developed for the treatment of sarcopenia, an age-related degeneration of skeletal muscles, leading to loss of mobility in elderly people. In a Phase I clinical trial (SARA-PK), Sarconeos showed favourable pharmacokinetics and pharmacodynamics profiles. It is currently entering a clinical Phase 2b trial named SARA-INT. BIO101 is the active principal ingredient of Sarconeos.

Methods

12-week-old C57BL10 and C57BL10 mdx male mice were treated orally for 8 weeks with either vehicle, BIO101 or BIO103 (at 50 mg/kg/day) under normal diet. Exercise tolerance test: the animals from all groups were subcutaneously injected with exercise endurance test; and maximal running distance was recorded at the completion of the experiment (after 8 weeks of treatment). The running test consists of 2 minutes of warm-up session in which the speed of the treadmill is increased from 0 to 20 cm/s. Then, the speed is increased by 5 cm/s every 10 minutes.

Muscle force measurement: all biopsies were excised immediately after euthanasia, and the force generated by each muscle was measured using an isometric force transducer (model SF100, San Diego, CA, USA) connected to a data acquisition system (Cortex Instruments, Varese, Italy). Protein expression: protein expression of Col1a1 was evaluated by Western blot analysis. Proteins were extracted from gastrocnemius muscle. Protein expression was revealed by chemiluminescence and quantified by densitometry after normalization against GAPDH.

Results

Introduction

About DMD: DMD is a X-linked inherited muscular disease, characterized by progressive muscle weakness and cardiomyopathy, leading to premature death. DMD is caused by an absence of dystrophin. Muscles undergo repeated cycles of necrosis/regeneration and are replaced by connective and adipose tissues. Glucocorticoids and support therapy are the current standard of care leaving many patients with an unmet medical need.

Mizner et al. find that mdx mice exhibited a significant reduction in muscle mass compared to wild-type mice. In this study, they observed a significant decrease in muscle mass in mdx mice when compared to wild-type mice. The decrease in muscle mass was accompanied by an increase in adipose tissue, as evidenced by histological analysis of the gastrocnemius muscle. In addition, they observed a significant decrease in muscle fiber size and an increase in fibrosis, as determined by Masson's trichrome staining.

Histochemistry analysis of the gastrocnemius muscle showed a significant decrease in muscle fiber size and an increase in fibrosis, as determined by Masson's trichrome staining.