Background
Muscular degeneration or sarcopenia is a natural process which accelerates with age. It is characterised by a loss of skeletal muscle mass and function, which is at the origin of a general deterioration in physical condition. Muscle atrophy results from a reduction of fibre number and diameter. Obesity aggravates sarcopenia and impairs functional capacities. The aim of this study was to characterize a new semi-synthetic derivative of 20-hydroxyecdysone (BIO103) in vitro on myocytes and in vivo on various animal models designed to analyze the effects of high-fat diet, aging and muscle disuse.

Methods
Murine C2C12 cells were employed to evaluate the effects of BIO103 on protein synthesis (via ELISA measurements of pS6K levels) and on myostatin and atrogin gene expression (qRT/PCR). The oral bioavailability of BIO103 was determined in rats (n=3) who received a single dose of the compound either orally (50 mg/kg) or intravenously (5 mg/kg). Plasma concentrations were determined by HPLC-MS/MS at various time points and AUC were then calculated for each route of administration. In vivo, two animal models employing C57Bl6/J mice under high-fat diet (4424 kcal/kg; proteins 19.8%, lipids 23% and carbohydrates 39.5%) were used. The first one involved 12-week-old male (n=8) treated orally for 6 weeks with vehicle or BIO103 at 5 or 50 mg/kg/day. At completion of experiment, the soleus of each animal was weighed and then tested for protein content and myostatin, myogenin and MyoD gene expression (qRT/PCR). The second animal model compared old (22 months) versus adult (12 months) female mice treated orally for 14 weeks with either vehicle or 50 mg/kg/day of BIO103 (n=7-10). One week before the completion of the study, the animals were tested for functional activity in tto (maximal running velocity on treadmill) and their right hind limb was immobilized. At the end of the experiment, in situ tibialis anterior contractility parameters (maximal force and fatigue resistance) were recorded on both immobilized and active limbs. At euthanasia, plasma was collected and various muscles were weighed. IGF-1 plasma levels were determined by ELISA assay.

Results

Conclusion
BIO103, a new orally-available semi-synthetic derivative of 20-hydroxyecdysone, displayed both in vitro and in vivo anabolic properties, which translated into improved functional performance in old animals. These investigations demonstrate the potential of BIO103 in improving skeletal muscle quality in aging mammals, and warrant further studies towards its development as a drug candidate for the treatment of sarcopenia.

BIO103, a second-generation compound for the treatment of sarcopenia: from anabolic properties to the reversion of aging-related functional loss

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