In vivo effects of Sarconeos (API BIO101) on a mouse model of severe spinal muscular atrophy

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Introduction

Spinal Muscular Atrophy (SMA) is an autosomal recessive neurodegenerative disease characterized by the loss of spinal cord motor neurons and progressive muscular atrophy, due to insufficient level of Survival of Motor Neuron (SMN) protein (Crawford and Pardo, 1996; Lefebvre et al, 2000). SMA is now defined as a non-cell autonomous disease, involving numerous tissues and cell-types, including skeletal muscles (Tony Frugier et al, 2001).

Sarconeos is a first-in-class drug candidate based on the activation of the MAS receptor (major player of the renin-angiotensin system) which demonstrated meaningful activity in animal models of muscular dystrophies. Sarconeos is being tested in severe SMA as a non-cell autonomous disease, involving numerous tissues and cell-types, including skeletal muscles (Tony Frugier et al, 2001).

In SMA-like mouse models, it has been shown that NMDA receptor activation and partial inactivation of IGF-1R result in lifespan and motor functions improvement, motor-neurons protection and SMN overexpression in the spinal cord by activating the AKT/ERK pathway and inhibiting the ERK5/1 pathway (Branchu et al, 2013; Biondi et al, 2015). In this context, using BIO101 administration could improve the neuromuscular functions in SMA by stimulating muscular anabolism and increasing SMN expression through the activation of the PI3K/AKT pathway via the MAS receptor.

Severe SMA-like mouse model

- Smn<sup>Δ7</sup>;huSMN2<sup>−/+</sup> (Hsieh-Li et al, 2000).
- Mean survival of 12 days post-natal (P12).
- 50% loss of spinal motor neurons.
- Severe motor neuron and atrophy.

![Severe SMA-like mouse model](image)

Results

2. Tissue effects

- In muscles: Plantaris
  - Figure 2: Effect of BIO101 chronic treatment on muscular phenotype in SMA-like mice. (A) Haematoxylin-eosin staining, (B) quantification of the cross-sectional area and (C) cross-sectional area variability analysis of myofibers in the Plantaris of vehicle treated control mice and VH- or BIO101-treated SMA-like mice at P11 (n=4 in each group, *p<0.05).
  - BIO101 limits the muscular atrophy, and restores the myofiber size variability in the fast-twitch extensor plantaris of SMA-like mice. Similar results are also found in the fast-twitch extensor Tibialis and the slow-twitch extensor Soleus.

- In lumbar motor neurons
  - Figure 5: Effect of BIO101 on AKT and ERK pathways and on SMN expression in SMA-like mice. (A) Western blot analysis and (B) quantification of AKT phosphorylation, (C) ERK phosphorylation and (D) SMN expression in the lumbar spinal cord of vehicle-treated control mice and VH- or BIO101-treated SMA-like mice at P11 (n=4 in each group for AKT and ERK pathways, n=4 in each group for SMN expression).
  - BIO101 induces an activation of PI3K-AKT signaling pathway and an inhibition of ERK signaling pathway without having any effect on SMN expression in the lumbar spinal cord of SMA-like mice.

![Results](image)

Conclusions

![BIO101 effects](image)

BIO101 effects are SMN expression-independent

BIO101, for which Orphan Disease Designation has been granted in Duchenne Muscular Dystrophy, could be considered as a key molecule for a new therapeutic strategy in combination with gene therapies for SMA patients.

Bibliography