Pharmacological profile and efficacy of GLPG1690, a novel autotaxin inhibitor for the treatment of idiopathic pulmonary fibrosis

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Introduction

Autotaxin (ATX), a secreted lysophospholipase, plays a central role in the production of the bioactive lipid lysophosphatidylcholine (LPC). LPC signals through multiple LPA receptors to control a range of cell activities (migration, contraction, survival...). Several reports suggest a role for LPA in the pathogenesis of lung fibrosis in human. To support this, we aimed to evaluate GLPG1690, a potent ATX inhibitor that has successfully completed Phase 1 evaluation, in an in vitro model for idiopathic pulmonary fibrosis (IPF).

In vitro pharmacological profile

- GLPG1690 was shown to be a potent competitive inhibitor of mouse and human ATX in biochemical assays.
- This was confirmed with GLPG1690 treated mice, where an inverse relationship was observed between LPA and ATX levels suggesting a correlation of ATX to LPA levels in vitro.

Mouse bleomycin-induced lung fibrosis model

- This model is a well-established preclinical model for IPF pharmacology.
- GLPG1690 dose-dependently reduced lung fibrosis in both mouse and human LPA species.

GLPG1690 Binding mode

- GLPG1690 displays a unique binding mode with both hydrophobic pocket and hydrophilic channel.

GLPG1690 Binding mode

- GLPG1690 shows a potent and selective ATX inhibitor with a solid PD/PK correlation in mice and displayed strong efficacy in a preclinical model for IPF. Data suggest that both LPA species are impacted to the same extent by GLPG1690 treatment in the PD/PK model. Overall, a pronounced impact on different disease-relevant readouts support GLPG1690 as a novel therapeutic indication for this target. Taking this information into consideration with results from a phase 1a study in healthy subjects showing an excellent safety profile, good pharmacokinetics and a solid LPA biomarker response, Galapagos has decided to initiate an exploratory phase 2a study in IPF patients (FLAIR-PICT0738001).

Conclusions

- GLPG1690 is a novel autotaxin inhibitor for the treatment of IPF.

Disclosure

All authors are employees of Galapagos or employees of Fidelta a subsidiary of Galapagos.