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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 lysophosphatidic acid (LPA). LPA 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. This prompted us to evaluate GLPG1690, a potent ATX inhibitor that has successfully completed Phase 1 evaluation, in an *in vivo* model for idiopathic pulmonary fibrosis (IPF).

Aims and Objectives

To characterize GLPG1690, a novel ATX inhibitor

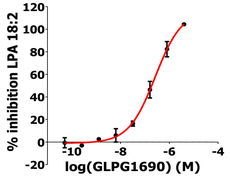
- *in vitro* pharmacological profile
- mouse PK/PD
- efficacy in mouse bleomycin model for IPF
- binding mode in human ATX

In vitro pharmacological profile

A) *In vitro* LPC assay

Source	GLPG1690 inhibition
mATX	IC_{50}=224 nM
hATX	IC_{50}=131 nM
hATX	K_i =14.7 nM (competitive)

B) *Ex vivo* human plasma LPA assay (LC/MS)



LPA species	GLPG1690 IC_{50} value (nM)
C14:0	96
C16:0	117
C18:1	115
C18:2	112
C18:3	102
C22:6	94
C20:4	93

Fig. 1 A) GLPG1690 was shown to be a potent competitive inhibitor of mouse and human ATX in biochemical assays.
B) Similar potency was observed *ex vivo* in human plasma for all investigated LPA species

Mouse PK/PD model

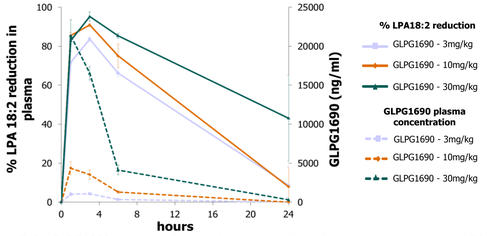
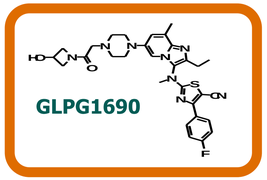


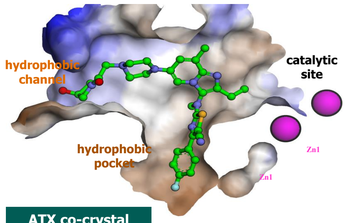
Fig. 2 In GLPG1690-treated mice, an inverse relationship was shown between LPA and GLPG1690 plasma levels reflecting *in vivo* target engagement.

Methods

- Biochemical potency was assessed using human and mouse recombinant ATX using lysophosphatidylcholine (LPC) as substrate and measuring choline formed (with choline oxidase and peroxidase successively)
- *Ex vivo* potency was determined in human plasma by measuring LPA levels (by LC-MS/MS) after incubation with GLPG1690
- Plasma LPA levels of GLPG1690-treated animals were used as PD marker.
- In the mouse bleomycin model, lung fibrosis was induced in C57Bl/6 male mice by intranasal administration of bleomycin (30 µg /50 µL/ mouse). In prophylactic setting, GLPG1690 (10 and 30 mg/kg, bid, p.o.) and pirfenidone (50 mg/kg, bid, p.o.) were dosed for 21 days. In therapeutic setting GLPG1690 (30 mg/kg, bid, p.o.), pirfenidone (50 mg/kg, bid, p.o.) and nintedanib (60 mg/kg, qd, p.o.) were dosed from day 7 to 21. The Ashcroft score and collagen content (quantified by immuno-histochemical staining) were used as measure for efficacy. Reduction in LPA levels in bronchoalveolar lavage fluid (BALF) was used as measure for target engagement in a relevant matrix.
- Binding mode was determined by co-crystallization of GLPG1690 with hATX

GLPG1690 Binding mode





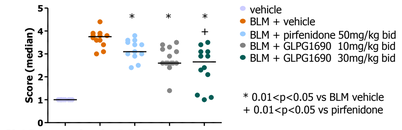
ATX co-crystal structure with GLPG1690

Fig. 3 Chemical structure of GLPG1690 and co-crystal structure of GLPG1690 with human ATX showing the unique binding mode of GLPG1690 occupying both hydrophobic pocket and hydrophobic channel

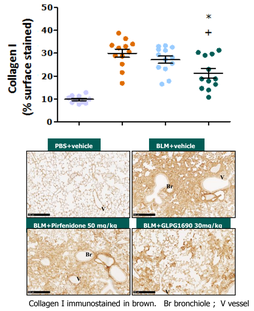
Mouse bleomycin-induced lung fibrosis model

Prophylactic setting

A) Matsuse modification of Ashcroft score



B) Collagen content



C) LPA species in BALF

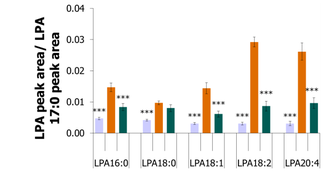
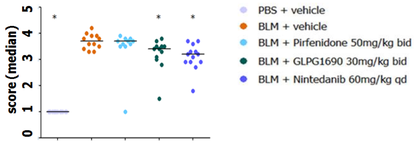


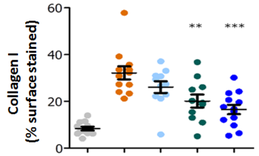
Fig. 4 In a prophylactic mouse bleomycin-induced lung fibrosis model, GLPG1690 dosed orally at 30 mg/kg bid was superior to oral pirfenidone (50 mg/kg bid) on both Ashcroft score (**A**) and collagen content (**B**). At 10 mg/kg bid, GLPG1690 already reduced fibrosis to a similar extent as pirfenidone (**A**). An increase of various LPA species (C16:0; C18:0; C18:1; C18:2; C20:4; C22:5 and C22:6) was observed in BALF of bleomycin-treated animals. This increase was reduced by GLPG1690 treatment for short LPA species (C16 to C20) (**C**) but not for longer species (C22:5 and C22:6) (data not shown), suggesting the involvement of a different enzyme for the production of those longer LPA species.
In therapeutic setting, GLPG1690 dosed orally at 30 mg/kg bid was superior to oral pirfenidone (50 mg/kg bid) and similar to nintedanib on both Ashcroft score and collagen content readouts (**D** and **E**)

Therapeutic setting

D) Matsuse modification of Ashcroft score



E) Collagen content



*p<0.05 and ** p<0.01 and *** p<0.001 vs BLM vehicle

Conclusions

GLPG1690 is a potent and selective ATX inhibitor with a solid PK/PD correlation in mice and displayed strong efficacy in a preclinical model for IPF. Data suggest that not all LPA species are impacted to the same extent by GLPG1690 treatment in the IPF model. Overall, a pronounced impact on different disease-relevant readouts support IPF as a novel therapeutic indication for this target. Taking this information in combination with results from a phase 1 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 (FLORA; NCT02738801).

Disclosure

All authors are employees of Galapagos or employees of Fidelta a subsidary of Galapagos

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