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A1649

Pharmacodynamics and Pharmacokinetics of the Autotaxin Inhibitor GLPG1690 in the FLORA Trial: A Randomized, Placebo-Controlled, Double Blind Phase IIa Clinical Trial of 12 Weeks in Individuals with Idiopathic Pulmonary Fibrosis

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive respiratory disease with median survival of 2-5 years after diagnosis.

GLPG1690 is a novel, potent, and selective small-molecule autotaxin (ATX) inhibitor (Fig.1). ATX is the main enzyme responsible for the production of lysophosphatidic acid (LPA) in blood.

LPA signals through multiple receptors, controlling a range of cell activities like migration, proliferation and survival (Fig.2) [1].

Biology of LPA in IPF:
- increase in LPA levels in the bronchoalveolar lavage fluid [2],
- elevation of LPA C22:4 in exhaled breath condensate [3],
- increase of ATX levels in human fibrotic lung [4].

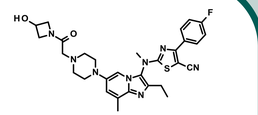

Figure 1. GLPG1690 chemical structure

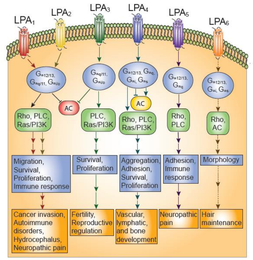

Figure 2. LPA signaling

Objectives

- Evaluate the pharmacodynamic (PD) effects of GLPG1690 in IPF patients using plasma LPA C18:2 levels as target engagement biomarker
- Evaluate the pharmacokinetics (PK) of GLPG1690
- Investigate PK and PD correlation

Methods

- Randomized, double-blind, placebo-controlled (FLORA;NCT02738801)
- Subjects with IPF (≥40 years; non-smokers; not on pirfenidone or nintedanib treatment) with a centrally confirmed diagnosis

- PD: Plasma LPA C18:2 by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS)
- GLPG1690 plasma concentration by LC-MS/MS
- *Ex vivo* plasma assay: dose response of GLPG1690 incubated for 2h in human plasma and assessment on effects on levels of different LPA species by LC-MS/MS

Results - *Ex vivo* plasma assay

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

- Similar IC_{50} for different LPA species in human plasma [5]

Results - Pharmacodynamics

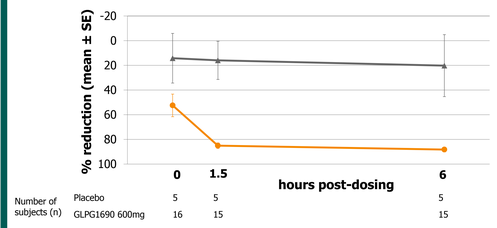

Figure 3. Mean±SE plasma LPA C18:2 % reduction at week 4

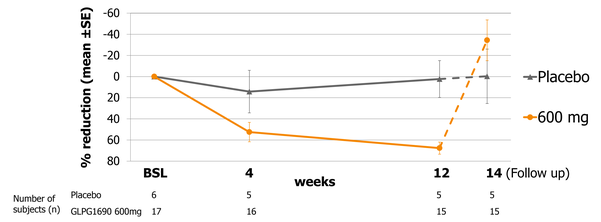

Figure 4. Mean±SE pre-dose plasma LPA C18:2 % reduction over the study

Mean % reduction (± SE)	Week 4 0h	Week 4 1.5h	Week 4 6h	Week 12 0h	Follow up week 14
Placebo	14 ± 20	16 ± 15	20 ± 25	2 ± 17	0 ± 26
GLPG1690	52 ± 9	85 ± 2	88 ± 2	68 ± 6	-34 ± 19

- > 80% reduction of plasma LPA C18:2 post-dosing
- Sustained PD effect over 12 weeks: 52 and 68% reduction of LPA at pre-dose at 4 and 12 weeks, respectively
- Reversibility of the effect at 2 weeks post-treatment (see dotted lines in Fig. 4)

Results - GLPG1690 PK at week 4

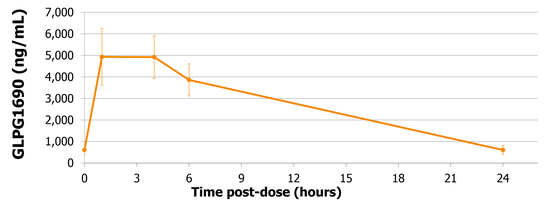

Figure 5. Mean ± SE GLPG1690 plasma profile at Week 4

PK parameters	C_{max} (µg/mL)	t_{max} (h) [1]	AUC $_{0-T}$ (µg.h/mL)
Mean (CV%)	6.06 (81.2)	4 (1.5-6)	55.6 (83.9)

[1] Median (range) for t_{max}
24h datapoint = predose assuming steady state

PK /PD correlation in plasma

Study	Time point	GLPG1690 concentration		LPA C18:2 % reduction
		nM	ng/mL	
FiH [5] Healthy volunteers	D14- 24h post-dose	421	249	66
	D14-6h post-dose	6506	3830	83
FLORA IPF patients	Week 4 0h post-dose	1020	604	52
	Week 12 0h post-dose	1698	1000	68
	Week 4 6h post-dose	6557	3860	88

- Similar PK/PD profile in healthy and IPF subjects
- PK/PD modelling under evaluation

Conclusions

Results from this Phase IIa trial in IPF subjects indicate that GLPG1690, a small molecule inhibitor of autotaxin:
- Induced a fast and sustained reduction of plasma LPA C18:2, indicative for target engagement
- Presented a similar PK/PD profile in IPF and healthy subjects (FiH)[5]

PK profile and sustainable PD effect support once-daily dosing

More data @ ATS

Pr T. M. Maher (A2436) & Dr. B. Mignot (A5928) oral presentations

Next steps

Evaluate GLPG1690 in the ISABELA Phase 3 program in patients with idiopathic pulmonary fibrosis

References

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Disclosure

All authors are employees of Galapagos or employees of Fidelta, a subsidiary of Galapagos, at the time of the study.

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