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) (5). Biology of LPA in IPF:

- Increase in LPA levels in the bronchoalveolar lavage fluid (12),
- Elevation of LPA C22:4 in exhaled breath condensate (5),
- Increase of ATX levels in human fibrotic lung (12).

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 IC50 (nM)
C18:0 96
C18:1 117
C18:2 119
C18:3 112
C18:4 102
C20:4 93
C22:0 94

- Similar IC50 for different LPA species in human plasma (5).

PK/PD correlation in plasma

GLPG1690 concentration (ng/mL)

Dose  (µg/kg)

Healthy volunteers

D14: 24h post-dose 4.21 ± 0.39
D14: 4h post-dose 4.06 ± 0.30

FLORA

Week 4 24h post-dose 8.04 ± 0.32
Week 4 4h post-dose 7.74 ± 0.26

IPF patients

Week 12 24h post-dose 1000 ± 100
Week 12 4h post-dose 900 ± 100

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

Results - GLPG1690 PK at week 4

PK parameters

\[ \frac{C_{\text{max}}}{\text{mean}} (\mu g/mL) \]
\[ \frac{AUC_{\text{last}}}{\text{mean}} (\mu g h/mL) \]

Mean (SD) 8.06 (3.72) 8.4 (3.53)

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 (FHV)11
- 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


Disclosure

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