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Favorable human safety, pharmacokinetics and pharmacodynamics of the autotaxin inhibitor GLPG1690, a potential new treatment in IPF

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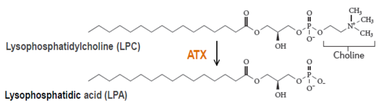
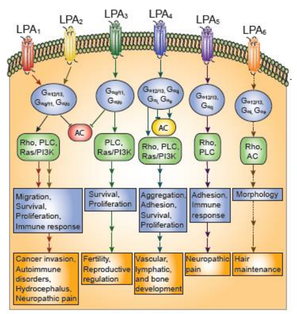
Introduction

Autotaxin (ATX)[1,2,3]

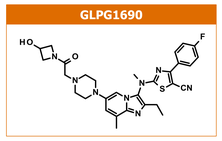
- secreted lysophospholipase
- central role in the production of bioactive lysophosphatidic acid (LPA)
- LPA signals through multiple LPA receptors, controlling a range of cell activities like migration, proliferation and survival





GLPG1690[4,5]

- potent and selective inhibitor of ATX
- reduces plasma LPA *ex vivo* and *in vivo*
- effective in mouse models:
  - tobacco smoke model (predictive for COPD)
  - bleomycin model (predictive for IPF)
- first ATX inhibitor evaluated in man



1. Aoki et al, Biochim Biophys Acta 1781, 513, 2008
2. Yung et al, J Lipid Res 55, 1192, 2014
3. Stoddard and Chun, Biomol Ther 23, 1, 2015
4. Blanqué et al, ERS meeting, Amsterdam 2015
5. Heckmann et al, FASEB meeting, Banff 2015

Objectives

The primary objective of this study was to evaluate the safety, tolerability pharmacokinetics (PK) and pharmacodynamics (PD) of GLPG1690 in healthy male subjects.

Methods

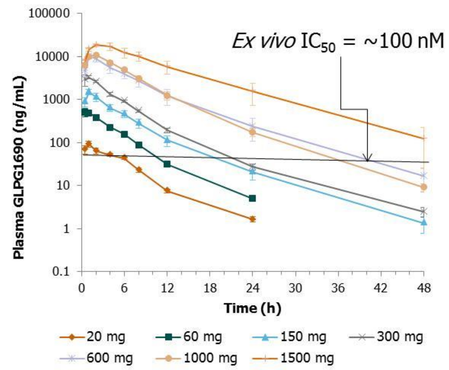
- Randomized, double-blind, placebo-controlled, single center, dose ranging study
- Healthy male subjects (18-50 years)
- In each dose group, 6 subjects received GLPG1690 and 2 received placebo
- Single ascending dose part (SAD)
  - 7 dose levels: 20 to 1500 mg, oral suspension, fed conditions
- Multiple ascending dose part (MAD)
  - 3 doses/regimen: 150 mg b.i.d., 600 and 1000 mg q.d., oral suspension, fed conditions
  - 14 days dosing
- Safety parameters
  - adverse events, ECG, vital signs, laboratory biochemistry/hematology and urinalysis
- Pharmacokinetics: GLPG1690 plasma and urine concentrations were determined by LC-MS/MS
- Pharmacodynamics: plasma LPA18:2 levels quantified by LC-MS/MS

Results – Safety

- Single ascending oral doses up to 1500 mg and repeated doses up to 1000 mg q.d. for 14 days were safe and well tolerated
- There were no clinically relevant findings in ECGs, vital signs, physical exam and laboratory parameters

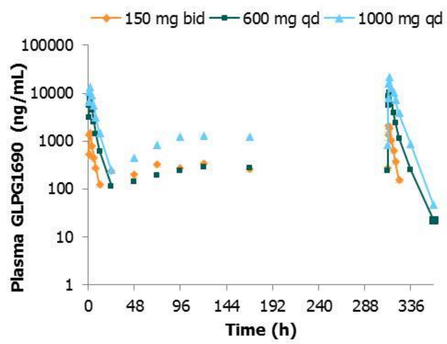
Results – Pharmacokinetics

Single Ascending Dose part



- Rapid absorption and elimination half life of ~5 h
- Approximate dose-proportional increase in exposure
- 60 mg dose is first dose with plasma concentrations durable above the *ex vivo* LPA IC_{50} (100 nM)

Multiple Ascending Dose part

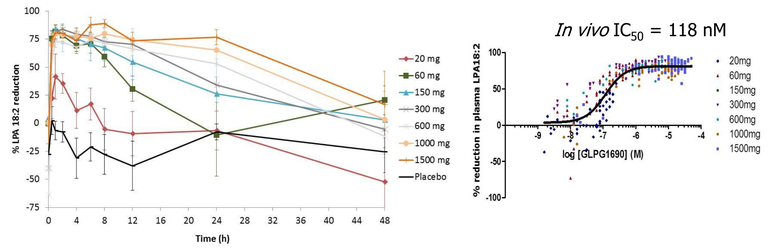


- Similar PK profile as in SAD, steady state reached after 4 days
- Accumulation ratio of up to 1.7 fold, leading to minor accumulation over 14 days
- Urinary excretion of unchanged GLPG1690 less than 1%

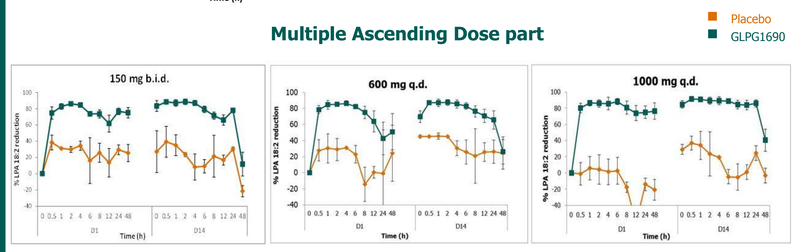
Results – Pharmacodynamics

Dose-dependent reduction of LPA18:2 in plasma from healthy volunteers by GLPG1690

Single Ascending Dose part



Multiple Ascending Dose part



- Dose/regimen-dependent reduction of plasma LPA18:2
- *In vivo* IC_{50} for reduction LPA18:2 is 118 nM, in line with *ex vivo* IC_{50}
- Maximum reduction around 85-90%
- At steady state, continuous reduction of LPA18:2 of >60% from 0-24 h achieved with all three dose regimens evaluated

Next step: exploratory Phase 2a in IPF patients

- Randomized, double blind, parallel group, placebo-controlled
- 24 subjects with IPF will receive oral doses of 600 mg GLPG1690 for 12 weeks
- Primary endpoints: safety, tolerability, PK and PD
- Exploratory endpoints: LPA in BALF, disease biomarkers in serum, imaging (HRCT), pulmonary function testing (spirometry), quality of life (SGRQ)

Conclusions

- Single ascending oral doses of GLPG1690 up to 1500 mg and multiple ascending doses up to 1000 mg q.d. administered for 14 days were generally safe and well tolerated in healthy male subjects
- Favorable PK/PD profile, clearly demonstrating the ability to reduce plasma LPA18:2 levels via inhibition of ATX
- Exploratory Phase 2a study with GLPG1690 in IPF patients ongoing (FLORA; NCT02738801)

Disclosure

All authors are employees of Galapagos or employee of Fidelta, a subsidary of Galapagos, except L. Gheyle who is employed by SGS

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