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

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Outline

- Target background
- GLPG1690 pharmacology
- GLPG1690 first-in-human data: safety, PK and PD
  - single ascending dose
  - multiple ascending dose
- Conclusions
**Autotaxin (ATX)**

**Target background**

- Also known as ENPP2, secreted enzyme
- Converts LPC to the bioactive lipid mediator LPA
- “LPA” covers a family of related molecules (i.e. LPA 18:2, LPA 20:4)
- ATX is main source of LPA in blood
LPA signalling

- LPA acts through at least six distinct G-protein-coupled receptors (LPA$_{1-6}$)
- Studies with KO of LPA receptors indicate a role in
  - bone development
  - fertility/reproduction
  - neurogenesis
  - formation of blood- and lymphatic vessels

Stoddard and Chun, 2015
‘1690 *in vitro* activity

*In vitro* LPC assay

<table>
<thead>
<tr>
<th>Source</th>
<th>Inhibition by ‘1690</th>
</tr>
</thead>
<tbody>
<tr>
<td>mATX</td>
<td>IC$_{50}$=224 nM</td>
</tr>
<tr>
<td>hATX</td>
<td>IC$_{50}$=131 nM</td>
</tr>
<tr>
<td>hATX</td>
<td>K$_i$=14.7 nM (competitive)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>LPA species</th>
<th>‘1690 IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C14:0</td>
<td>96</td>
</tr>
<tr>
<td>C16:0</td>
<td>117</td>
</tr>
<tr>
<td>C18:1</td>
<td>115</td>
</tr>
<tr>
<td>C18:2</td>
<td>112</td>
</tr>
<tr>
<td>C18:3</td>
<td>102</td>
</tr>
<tr>
<td>C20:4</td>
<td>93</td>
</tr>
<tr>
<td>C22:6</td>
<td>94</td>
</tr>
</tbody>
</table>

- Similar biochemical potency for mouse and human ATX
- Release of LPA species observed in plasma incubated at 37 °C
- When co-incubated with ‘1690, inhibition of LPA release
  - similar IC$_{50}$ for all LPA species
"1690 *in vivo* activity

PK/PD model in mouse

"1690 at ≥ 3 mg/kg in mice causes sustained reduction in plasma LPA levels
‘1690 *in vivo* activity

11-day prophylactic mouse tobacco smoke model

Cell count in BALF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Exposure</th>
<th>Vehicle</th>
<th>GLPG1690</th>
<th>Dex</th>
<th>Rof</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS + vehicle</td>
<td>TS</td>
<td>47%</td>
<td>51%</td>
<td>-5%</td>
<td>47%</td>
</tr>
<tr>
<td>TS + ‘1690 5 mg/kg bid</td>
<td>TS</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>TS + ‘1690 10 mg/kg bid</td>
<td>TS</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>TS + dexamethasone 0.3 mg/kg bid</td>
<td>TS</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>TS + roflumilast 5 mg/kg qd</td>
<td>TS</td>
<td>***</td>
<td>***</td>
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</tr>
</tbody>
</table>

‘1690 significantly reduced the total cells in BALF to a similar extent as roflumilast

See poster discussion session
PA2129
Monday, Sept 28
(Blanqué et al)
‘1690 in vivo activity
21-day prophylactic mouse bleomycin model

Ashcroft fibrotic score

Collagen content

‘1690 at 30 mg/kg bid significantly superior to pirfenidone on the Ashcroft fibrotic score and on collagen content
‘1690: First-in-Human
Objectives/design

- Randomized, double-blind, placebo-controlled, single center
- Healthy male subjects (18-50 years)
- In each dose group: 6 on active and 2 on placebo, oral suspension
- Part 1: single ascending dose (SAD)
  - 20 up to 1500 mg
- Part 2: multiple ascending dose (MAD)
  - 150 mg bid - 600 mg qd - 1000 mg qd for 14 days
- Objectives
  - safety and tolerability
  - pharmacokinetic profile
  - pharmacodynamics: effects on plasma LPA 18:2
‘1690: SAD
Plasma profile (mean ± SEM)

Ex vivo IC$_{50}$ = ~100 nM

- Safety: well-tolerated up to highest dose (1500 mg)
- PK: dose proportional; t$_{1/2}$ ~5 h
- Plasma levels above *ex vivo* IC$_{50}$ for LPA 18:2 reduction as of dose of 60 mg
Dose-dependent reduction observed in plasma LPA 18:2
‘1690 SAD
PK/PD relationship

IC$_{50}$=118 nM

_In vivo_ IC$_{50}$ for inhibition of LPA 18:2 is in accordance with _ex vivo_ IC$_{50}$
‘1690: MAD
Plasma profile (mean ± SEM)

- Mild AEs reported: GI disturbances, dry mouth and headache
- No clinically relevant findings in ECGs, vital signs, physical exam, lab parameters
- Multiple dose PK profile and exposure consistent with single dose data
- Minor accumulation (ratio of ~1.7) to steady state
• Dose/regimen-dependent reduction in plasma LPA 18:2
• Maximum inhibition of LPA 18:2 around 85-90%
• At steady state continuous inhibition of LPA of >60% from 0 to 24h
• Transient effect: LPA levels return to baseline 36 - 48h post-last dosing
Conclusions
GLPG1690

- Potent and selective inhibitor of autotaxin
- Reduces plasma LPA levels *ex vivo* and *in vivo*
- Favorable safety profile, good plasma PK and solid PD response indicating target engagement in healthy volunteers
- Galapagos is currently preparing for an exploratory Ph2a study in IPF patients
  - stronger validation of ATX/LPA pathway in IPF
  - ongoing collaboration with professor Hiemstra (LUMC, Leiden, NL) to strengthen the link with COPD
Acknowledgment