Human safety, pharmacokinetics and pharmacodynamics of the GPR84 antagonist GLPG1205, a potential new approach to treat IBD


* Galapagos NV, Mechelen, Belgium; † Galapagos SASU, Romainville, France; # SGS Life Sciences Services, CPU, Antwerp, Belgium

Introduction

GPR84, a free fatty acid receptor

Medium chain free fatty acids (C10-C12)

\[ \text{neutrophil} \rightarrow \text{monocyte/macrophage} \rightarrow \text{Inflammatory response} \rightarrow \text{chemokines} \rightarrow \text{cytokine release} \]

GLPG1205:
- potent and selective antagonist of GPR84
- inhibits neutrophil and macrophage migration
- effective in DSS mouse IBD model:
  - decreases the disease activity index
  - reduces colonic neutrophil influx & MPO content
  - reduces histological colonic lesion score
- The first GPR84 antagonist to be evaluated in man

Methods

- Randomized, double-blind, placebo-controlled, dose ranging study
- Healthy male subjects (18-50 years)
- Single ascending dose (SAD)
  - 7 doses: 10 to 800 mg, oral suspension
  - Multiple ascending dose (MAD)
    - 3 doses: 50 to 200 mg daily, oral suspension
    - 14 days dosing
  - SAD & MAD: 6 subjects receiving GLPG1205 and 2 receiving placebo per dose
- Food effect & bioavailability: cross-over design
  - 1 dose: 100 mg, single dose, capsule
  - 12 subjects receiving GLPG1205
- Safety parameters
  - adverse events, ECG, vital signs, lab biochemistry & hematology
- Pharmacokinetics: samples were analyzed by LC-MS/MS
  - Pharmacodynamics: target engagement was assessed by a competitive radiometric displacement assay in whole blood.

Conclusions

GLPG1205, a potent and selective inhibitor of GPR84, is safe and well tolerated in healthy subjects up to 100 mg daily. It shows a favorable PK/PD profile, clearly demonstrating the ability of the compound to engage GPR84, a target which is implicated in several neutrophil- and macrophage-driven inflammatory conditions. At 100 mg once-daily, a sustained and extensive full 24-hour inhibition of GPR84 ligand binding was obtained. This dose regimen was therefore selected to explore GLPG1205’s therapeutic potential in a currently ongoing Proof of Concept study in patients with ulcerative colitis.

Safety

Treatment-emergent adverse events after multiple dosing considered at least possibly related to study drug occurring in ≥ 2 subjects at a given dose:

<table>
<thead>
<tr>
<th>TEAE incidence (%)</th>
<th>Placebo</th>
<th>GLPG1205</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled</td>
<td>50 mg, q.d.</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ocular/ocular pain</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Single doses up to 800 mg and multiple doses up to 100 mg q.d. for 14 days were safe and well tolerated.

Pharmacokinetics

- Rapid absorption (tmax: 2-4 h) and long terminal elimination half-life (~100 h)
- Steady state reached within 10 days, with an accumulation ratio of 5.4
- Dose-proportional PK, up to 100 mg once daily
- Capsule formulation shows similar exposure as oral suspension
- No food effect

Pharmacodynamics

Inhibition of ligand binding to GPR84

Acknowledgements


This work was partially supported by grant IWT-120550 from the Flemish Government.

Poster available online at: www.glpq.com
E-mail: rd@glpq.com