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


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Introduction

GPR84, a free fatty acid receptor

- Mediates free fatty acid (C16:0) chemotaxis
- Increases inflammatory response
- Increases 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 colon lesion score
- The first GPR84 antagonist to be evaluated in man

4. Dupont et al, UEGW 2014, oral presentation #OP183

Objectives

- Evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of GLPG1205 in healthy male subjects
- Identify a dose for subsequent Proof of Concept studies in inflammatory bowel disease.

Acknowledgements

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Methods

- Randomized, double-blind, placebo-controlled, dose-ranging study
- Healthy male subjects (18-50 years)
- In each dose group, 6 volunteers received GLPG1205 and 2 received placebo
- Single ascending dose part (SAD)
  - 7 doses: 10 to 800 mg, oral suspension
  - Multiple ascending dose part (MAD)
  - 3 doses: 50 to 200 mg daily, oral suspension
- 14 days dosing
- Safety parameters
  - Adverse events, ECG, vital signs, lab biochemistry & hematology and urinalysis
- Pharmacokinetics: samples were analyzed by LC-MS/MS
- Pharmacodynamics: target engagement was assessed by a competitive radiometric displacement assay in whole blood.

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>
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<tbody>
<tr>
<td>Preferred term</td>
<td>Pooled</td>
<td>50 mg, q.d.</td>
</tr>
<tr>
<td></td>
<td>N=6</td>
<td>N=6</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>Oropharyngeal 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 ascending doses up to 800 mg and up to 100 mg q.d. were safe and well tolerated.

No vital sign or ECG abnormalities were reported during the study.

The only noteworthy laboratory abnormalities were signs compatible with dehydration in subjects experiencing moderate to severe headache at 200 mg.

Pharmacokinetics

- GLPG1205 is rapidly absorbed, extensively metabolized and eliminated via the liver.
- Penetration into the brain and central nervous system is low.
- Mean elimination half-life is approximately 8 hours.

Pharmacodynamics

Inhibition of ligand binding to GPR84

Inflammatory response

- GLPG1205, a potent and selective inhibitor of GPR84, is safe and well tolerated in healthy volunteers 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. The compound will be evaluated in Proof of Concept studies in patients with IBD.

Conclusions

GLPG1205, a potent and selective inhibitor of GPR84, is safe and well tolerated in healthy volunteers 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. The compound will be evaluated in Proof of Concept studies in patients with IBD.