**The FFA2 (GPR43) antagonist GLPG0974: opportunity to treat neutrophil-driven inflammation**

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### Introduction

Free fatty acids (FFA) have been shown to act as direct signalling molecules through activation of several GPCRs. FFA2 (also known as GPR43) is activated by short chain fatty acids (SCFAs) such as acetate, propionate or butyrate. FFA2 is mainly expressed on immune cells (neutrophils, monocytes, B lymphocytes), enterocytes, entero-endocrine cells and adipocytes. FFA2 has been shown to play a major role in SCFA-induced neutrophil activation and migration. Studies in FFA2 knockout mice suggest an important contribution of FFA2 in the development and control of inflammation.

### Pharmacology

**Target assay:** Human FFA2 was stably over-expressed in HEK293 cells (FA2-H6293). Membranes of these cells were used for a FFA2 (35S) GTPγS binding assay with acetate (1.5 mM) as agonist. Intracellular mobilization of calcium was determined in acetate-stimulated FA2-H6293.

**Functional assay:** Neutrophils were isolated from blood and migration was evaluated in a transwell system. Sodium acetate (1 mM) was used as chemotactic agent.

### Pharmacodynamic biomarker

Activation of CD11b

### Phase I studies

**Design and objectives**

- Randomized, double-blind, placebo-controlled, dose ranging studies
- Healthy male subjects (18-50 years)
- In each dose group, 6 volunteers received GLPG0974 and 2 received placebo
- First-in-human: single ascending dose study
  - 4 doses (10 to 250 mg, oral solution)
  - Multiple ascending dose study (MAD)
  - 4 doses (50 to 400 mg, daily, capsules)
- 14 days dosing
- Safety parameters
  - adverse events, ECG, vital signs, lab biochemistry & hematology
  - oral glucose tolerance (MAD)

**Pharmacodynamics:** inhibition of ex vivo activated CD11b on neutrophils

**Pharmacokinetics**

### Methods

**Pharmacology**

**Target assay:** Human FFA2 was stably over-expressed in HEK293 cells (FA2-H6293). Membranes of these cells were used for a FFA2 (35S) GTPγS binding assay with acetate (1.5 mM) as agonist. Intracellular mobilization of calcium was determined in acetate-stimulated FA2-H6293.

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### Pharmacodynamic biomarker

Activation of CD11b

### Phase I studies

**Safety**

GLPG0974 is well tolerated and safe at all doses, up to daily doses of 400 mg (14 days)

- no relevant treatment-emergent adverse events
- no relevant effects on lab safety parameters, ECGs and vital signs
- no clinically relevant changes in oral glucose tolerance test

### Pharmacokinetics

**Single ascending doses (oral solution)**

**Multiple ascending doses (capsules)**

### Pharmacodynamics

Inhibition of ex vivo activation of CD11b on neutrophils

### Conclusions

GLPG0974 is a potent and selective antagonist of FFA2, a GPCR activated by SCFA. The compound inhibits SCFA-induced activation and migration of neutrophils. In healthy volunteers, GLPG0974 exhibits a clean safety profile as well as good pharmacokinetic and pharmacodynamic properties.

GLPG0974 is the first FFA2 antagonist in clinical development. A Proof-of-Concept study is initiated to evaluate the safety and efficacy of GLPG0974 in patients with mild-to-moderate ulcerative colitis.

### References

2. Skoldt et al, Pharm Rev, 61, 405, 2009
6. Polancec et al, CYTO 2013: ISAC’s XXVIII Int. Congress, 2013, abstract

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