THE FFA2 ANTAGONIST GLPG0974: OPPORTUNITY TO TREAT NEUTROPHIL-DRIVEN INFLAMMATION

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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.

Methods

Pharmacology

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

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

Whole blood was primed by TNFα and cytochalasin B, and stimulated with acetate (10 mM). Immunophenotyping of whole blood samples was performed using fluorochrome-labeled antibodies for CD16, CD45 and CD11b [AE] and analysed by flow cytometry.

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
- 14 days dosing
- Safety parameters
  - adverse events, ECG, vital signs, lab biochemistry & hematology
  - oral glucose tolerance

Pharmacokinetics

Single ascending doses (oral solution) Multiple ascending doses (capsules)

Pharmacodynamics

Inhibition of ex vivo activation of CD11b on neutrophils

References

2. Stoubart et al, Pharm Rev, 60, 405, 2008
6. Polancec et al, CYTO 2013: DAC's XXVIII Int. Congress, 2013; Abstract

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