GLPG0634, The First Selective JAK1 Inhibitor, Shows Strong Activity In The Mouse DSS-Induced Colitis Model

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Background
GLPG0634 is a JAK1 inhibitor with high selectivity for JAK1 over JAK2 in human whole blood (about 30-fold) and over JAK3 and TYK2 in biochemical assays. The pan-JAK inhibitor tofacitinib has shown long-term efficacy in rheumatoid arthritis (RA) and in ulcerative colitis, but also safety issues related to JAK2. GLPG0634 showed a favorable safety and efficacy profile in two small 4-week Phase 2A studies in RA patients and is being evaluated as treatment for Crohn’s disease (CD) in a Phase 2 study. Here, we report the strong efficacy of GLPG0634 in a mouse DSS-induced colitis model.

Conclusions
Oral administration of the selective JAK1 inhibitor GLPG0634 in DSS-treated mice demonstrates that inhibition of JAK1 only is sufficient for achieving strong efficacy in this pre-clinical mouse model, with protection against colitis at both the macroscopic (signs and symptoms) and tissue level (histology), and lowering of serum inflammation marker levels. This effect is correlated to the inhibition of STAT3 phosphorylation in the inflamed colon.

These data suggest that GLPG0634 may be beneficial for treating patients with inflammatory bowel disease and support its testing in a clinical study in CD.

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Methods
- Chronic colitis induction in Balb/c mice: 4% dextran sodium sulfate (DSS) in drinking water in 3 successive periods
- GLPG0634 treatment: 10 and 30 mg/kg GLPG0634 QD orally for 16 days
- Disease score: daily assessment of weight loss, rectal bleeding, and stool consistency; all scores added gives the Disease Activity Index score (DAI).
- Histological scoring: evaluation of severity and extent of inflammation and epithelial damage
- JAK/STAT target engagement in colon tissue was evaluated by measuring STAT phosphorylation, using immunohistochemistry (IHC) and the 5-Plex STAT kit on Luminex for confirmation
- Serum proteins were quantified by Luminex multi-analyte technology
- GLPG0634 concentrations in plasma were measured by LC-MS/MS

Results
GLPG0634 decreases the DAI score in a dose-dependent fashion

GLPG0634 reduces the histology lesion score

GLPG0634 prevents DSS-induced STAT3 phosphorylation in the colon

GLPG0634 prevents the increase of serum inflammation markers (CRP, IL-1β) and chemoattractants (KC/GROα and MIP-2)

GLPG0634 plasma concentration-time plot in DSS-treated mice

Conclusions
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