Exploration of GLPG0634, the first selective JAK1 inhibitor, in Inflammatory Bowel Disease is supported by early clinical results and mouse DSS-colitis data

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Janus kinases (JAKs) signal for cytokines and growth factors

- 4 types of JAKs signal for interferons, many interleukins and growth factors
  - JAK1: IFN; IL2, IL6, IL7, IL15, IL21, …
  - JAK2: EPO, TPO, GH; IL6, …
  - JAK3: IL2, IL4, IL7, IL15, IL21, …
  - TYK2: IFN; IL12, IL23

- Typically two JAKs combine to phosphorylate STATs* for signal progression to cell nucleus

* signal transducer and activator of transcription
Selectivity in JAK inhibition makes a difference

Cytokine receptors sharing the $\gamma_c$-chain

Homodimeric cytokine receptors

Cytokine receptors sharing IL-12R$\beta_1$ subunit

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<th>IL-2</th>
<th>IL-6</th>
<th>Erythropoietin</th>
<th>IFN</th>
<th>IL-12, IL-23</th>
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Jak1 inhibitor: +
Jak2 inhibitor: -
Jak3 inhibitor: +
Tyk2 inhibitor: -

Courtesy: Dr. John J. O'Shea, NIH, Bethesda
Selective JAK1 inhibition

- JAK1 inhibition suppresses signaling for (pro)inflammatory cytokines
- JAK2 inhibition (also) suppresses EPO, TPO, GH signaling
  - Risks of inducing anemia
GLPG0634: a selective JAK1 inhibitor

• Highly selective inhibitor of Janus kinase 1 (JAK1)
  ➢ Biochemical IC50 ~ 10 nM
  ➢ >50-fold selective over non-JAK kinases and JAK3
    ▪ 30-fold for FLT3/4
  ➢ 30-fold selective over JAK2 in human whole blood
    ▪ no anemia induced

• Oral treatment with opportunity for once-daily dosing
• Novel mode of action for potential treatment of IBD
• Shown safe and effective in short-term studies in rheumatoid arthritis
GLPG0634 *in vitro* pharmacology

High selectivity for JAK1 over JAK2

- Highly selective for JAK3 and TYK2 in biochemical assays
- Pharmacology profiling in human whole blood
  - JAK1: IL-6 induced pSTAT1 in CD4+ cells (GLPG0634 IC$_{50}$ ~ 600 nM)
  - JAK2: GM-CSF induced pSTAT5 in CD34+ cells (GLPG0634 IC$_{50}$ ~ 17.5 µM)

Selectivity for JAK1 over JAK2 (ratio IC$_{50}$ values)

Early clinical evaluation of GLPG0634

- Healthy volunteers dosed up to 450 mg QD for 10 days
- RA patients dosed up to 300 mg QD for 4 weeks

- Well tolerated and safe – no MTD reached
  - No anemia, no effects on LFTs or lipids

- Good oral pharmacokinetics – similar in patients and healthy volunteers
  - Consistent with once-daily dosing

- Pharmacodynamics in healthy volunteers confirms JAK1 selectivity
High-level JAK1 inhibition in humans
No JAK2 inhibition up to high doses

- Healthy volunteers taking oral 300mg GLPG0634 once-daily
- Well tolerated with no changes in hematology, including reticulocytes

F. Namour et al., ACR2013, abstract 1795
4-weeks of GLPG0634 in rheumatoid arthritis improves disease and suppresses inflammation

- 4 weeks GLPG0634 as 100 mg BID or 200 mg QD
  - Generally well tolerated and safe; no significant findings
  - Dose range (30-75-150-300 mg QD) in subsequent 4-week study showed similar effects overall for doses ≥ 75 mg QD

F. Vanhouette et al., ACR2012, abstract 2489
JAK inhibition: therapeutic opportunity in IBD

- **Rationale:**
  Cytokines that depend on JAK signaling play a key role in both UC and Crohn’s disease

- **Current clinical experience: tofacitinib**
  - inhibits JAK3>JAK1>JAK2
  - low Hb/anemia dose-limiting in early clinical exploration (RA)\(^1\)
  - effective in Phase 2 study in UC\(^2\), not (yet) in initial exploration in Crohn’s\(^3\)

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GLPG0634 dose-dependently improves DSS-induced chronic colitis in mice

Graph showing the disease activity index over days for different treatments:
- H2O intact
- 4% DSS
- 10 mg/kg GLPG0634
- 30 mg/kg GLPG0634

Balb/c mice treatment:
- DSS 4%
- H2O
- DSS 4%
- H2O
- DSS 4%

GLPG0634 once-daily oral treatment
GLPG0634 improves DSS-inflammation

- GLPG0634 treatment controls serum inflammation markers (CRP, IL-1β) and chemo-attractants (CXCL1, CXCL2)
JAK1 inhibition improves DSS-inflammation

- Anti-inflammatory effects of GLPG0634 are associated with suppression of STAT3 phosphorylation
- Plasma exposures are around the IC₅₀ for JAK1 inhibition but remain well below the IC₅₀ for JAK2
Summary and Conclusions

- GLPG0634 is a potent and selective inhibitor of JAK1
- In Phase 1 clinical evaluations, once-daily oral GLPG0634 showed a good tolerability, safety and PK, and inhibition of JAK1 but not JAK2
- 4-week studies in patients with rheumatoid arthritis have confirmed a good safety and have demonstrated anti-inflammatory efficacy
- Once-daily treatment with GLPG0634 shows convincing efficacy in the mouse DSS-induced colitis model
- By inhibition of JAK1 but not JAK2, unwanted effects such as anemia may be prevented – this may be of particular importance in IBD patients with IBD, who frequently experience fecal blood loss
Ongoing study in Crohn’s disease

- These early data support a currently ongoing multi-center evaluation of GLPG0634 treatment in patients with Crohn’s disease
  - 180 patients with moderate to severe Crohn’s disease (CDAI: 220 – 450)
  - Two-part study: 10 weeks induction (Part 1) and 10 weeks follow-up (Part 2)
    - Re-randomization Part 2; placebo non-responders to receive 100 mg GLPG0634 QD
  - Efficacy, safety, tolerability, pharmacokinetics over 20 weeks
  - Primary endpoint at week 10: CDAI <150.
    - Secondary: CDAI decrease >100, SES-CD <4 or 50% reduction in SES-CD

![Graph showing placebo and GLPG0634 treatments over 20 weeks]
Acknowledgements

- All clinical trial participants, patients and healthy volunteers
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