Selective JAK1 Inhibition in the Treatment of Rheumatoid Arthritis: Proof of Concept with GLPG0634

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#2489
Disclaimer

- Galapagos sponsored the studies
- Abbott provided financial support to Galapagos for future scientific and clinical evaluation of GLPG0634
Cytokine signaling through JAK-STAT

- **Cytokines**
  - Interleukins (e.g. IL-6)
  - Interferons (IFNα, β)

- **Janus kinases (JAKs)**
  - JAK1 - IFN; IL-2, IL-4, IL-6
  - JAK2 - IL-6; EPO
  - JAK3 - IL-2, IL-4
  - TYK2 - IFN; IL-6

- **Signal Transducer and Activator of Transcription**
  - STAT1, 2, 3, 4, 5


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JAK1 selectivity over JAK2
GLPG0634 compared to tofacitinib and baricitinib

Profiling for JAK1 and JAK2 in human whole blood assay

- JAK1: IL-6/pSTAT1 vs. JAK2: GM-CSF/pSTAT5
- Internal GLPG head-to-head profiling vs. tofacitinib and baricitinib

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

GLP0634 is the most JAK1 selective clinical compound

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JAK1 selectivity confirmed in Phase I

JAK1 and JAK2 measured in whole blood from Phase I healthy volunteers

- JAK1 (IL-6/pSTAT1) compared to JAK2 (GM-CSF/pSTAT5)

GLPG0634 is a selective JAK1 inhibitor

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GLPG0634 Phase IIA
Proof of Concept in rheumatoid arthritis (RA)

- Randomized, double-blind, placebo-controlled study
  - Single center in Chisinau, Moldova
  - 36 RA patients with insufficient response to MTX
    - Add on: MTX continued, as needed with stable low-dose steroids/NSAIDs
  - 4 weeks oral treatment; once-daily vs twice daily
    - 200 mg QD vs 100 mg BID vs placebo
  - Patients on average had ≥6 years of RA and severe disease
    - Within each group, 11 of 12 were female; average age 49 years
    - All naïve to biologic agents, and most used NSAIDs, few steroids

Designed to give rapid evaluation of efficacy at high dose

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## Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=12</th>
<th>GLPG0634 100 mg BID n=12</th>
<th>GLPG0634 200 mg QD n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA diagnosis (years)</td>
<td>5.6</td>
<td>9.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Mean dose of steroids (&lt;10 mg/d)</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mean dose of NSAIDS</td>
<td>11</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Mean dose of MTX (mg/wk)</td>
<td>12.3</td>
<td>11.7</td>
<td>10.2</td>
</tr>
<tr>
<td>CRP at baseline (mg/L)</td>
<td>34.9</td>
<td>21.3</td>
<td>40.5</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.3</td>
<td>6.7</td>
<td>6.4</td>
</tr>
</tbody>
</table>
GLPG0634 efficacy: ACR20

- Achieved primary endpoint
- ACR20 scores at Day 28: 42-58% improvement over placebo

GLPG0634 is highly efficacious with rapid onset of action

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GLPG0634 efficacy: DAS28

GLPG0634 rapidly improves disease activity score

GLPG0634 is highly efficacious with rapid onset of action

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GLPG0634 efficacy: C-reactive protein

- GLPG0634 treatment induces a rapid and lasting decrease in serum CRP to near-normal levels.

GLPG0634 is highly efficacious with rapid onset of action.

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GLPG0634 efficacy
SJC and TJC

Swollen Joint Count

Tender Joint Count

% change from baseline

Time (days)

Placebo  100mg BID  200mg QD

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GLPG0634 efficacy
Other ACR components

% change from baseline

Time (days)

Pat GA

Pat Pain VAS

HAQ-DI

Placebo 100mg BID 200mg QD
GLPG0634 efficacy summary: week 4

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=12</th>
<th>100 mg BID n=12</th>
<th>GLPG0634 200 mg QD n=12</th>
<th>Pooled n=24</th>
<th>Pooled vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 (%)</td>
<td>33.3</td>
<td>91.7</td>
<td>75.0</td>
<td>83.3</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>DAS28 (change)</td>
<td>- 0.30</td>
<td>- 2.81</td>
<td>- 2.23</td>
<td>- 2.52</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>CRP (change, mg/L)</td>
<td>21.9</td>
<td>- 13.8</td>
<td>- 35.1</td>
<td>- 24.4</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

- High ACR20 scores
- High level of activity after only 4 weeks of treatment
- Statistical significance on ACR20, DAS28, CRP endpoints

Efficacy results among the best reported for kinase inhibitors in RA

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## GLPG0634 safety findings

<table>
<thead>
<tr>
<th>Any treatment-related AE</th>
<th>Placebo n=12</th>
<th>GLPG0634 100 mg BID n=12</th>
<th>GLPG0634 200 mg QD n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Asthenia (weakness)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia (abnormal taste)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Somnolence (drowsiness)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
GLPG0634 safety: selected lab data

- **Hemoglobin (g/dL)**
- **Platelets (giga/L)**
- **Neutrophils (giga/L)**
- **LDL (mmol/L)**

Graphs showing changes over time (Days) with different treatment groups:
- Placebo
- 100mg BID
- 200mg QD
GLPG0634 safety summary

- no SAEs on GLPG0634 treatment
- few patients reported treatment-emergent side-effects
- improvement of hemoglobin was observed
- no increase in LDL-cholesterol
- no treatment-induced effects on liver function tests (ALT, AST)
- modest decrease in neutrophils and platelets
- no effects on cardiovascular safety (incl. blood pressure)
Conclusions
Profile as compared to other JAK inhibitors

• First selective JAK1 inhibitor
• JAK1 selectivity makes a difference:
  ➢ High level of anti-inflammatory response after QD dosing
    ▪ Proof of Concept efficacy among the best reported
  ➢ Very encouraging safety
    ▪ JAK1 associated decrease in neutrophils
    ▪ Hb increase and platelets indicative of suppression of inflammation
    ▪ No increase in LDL
    ▪ No signals on ALT/AST, creatinine
Acknowledgements

- Professor Minodora Mazur and co-investigators
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- SGS who took care of the study oversight
- Colleagues at Galapagos

- All patients consenting to the study