Dose selection of filgotinib (GLPG0634), a selective JAK1 inhibitor, for rheumatoid arthritis Phase 2B studies: PK/ PD modeling of pSTAT1 biomarker and DAS28 clinical response

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Introduction
Filgotinib (GLPG0634) is an oral selective Janus kinase 1 (JAK1) inhibitor. Selective inhibition of JAK1 may combine favorable safety and clinical efficacy profiles with rapid onset of action.

Filgotinib showed encouraging PD, safety and efficacy in early clinical studies treating RA patients for 4 weeks1,2. This study presents the contribution of exposure-response (E-R) modelling and simulation that supported the dose selection for filgotinib’s Phase 2B studies.

Methods

• Population predicted and individual responses to treatment were investigated on the basis of simulated exposures to filgotinib and its main metabolite.

• Non-linear mixed effects E-R models were built to describe the proportion of cells showing phosphorylation of STAT1 (p-STAT1) following activation with IL-6 in healthy subjects (JAK1 activity) and DAS28 improvement from baseline in RA patients treated for 4 weeks.

• The pSTAT1 response over 24 h at steady state and the contribution of the active metabolite to the biomarker response were predicted for a male bodyweight of 75 kg.

• The DAS28 E-R model was used to predict the improvement of the clinical response following 12 weeks of filgotinib treatment.

pSTAT1 biomarker: The percentage of pSTAT1 inhibition was adequately described by a combined direct-response model of predicted Filgotinib (F) and metabolite (M) plasma concentration. The drug effect on pSTAT1 inhibition was implemented as a sigmoid EMAX model:

\[
\text{pSTAT1} = \text{pSTAT1}_{\text{max}} \times \frac{C_F}{C_F + EC_{50}^{\text{F}}} + \text{pSTAT1}_{\text{Cmax}}\times \frac{C_M}{C_M + EC_{50}^{\text{M}}} + \epsilon
\]

DAS28 clinical response: The DAS28 change from baseline (DAS28B) was adequately described by a regression model depending on individual predicted steady state metabolite exposure (ADU_M, 24 h). The drug effect on DAS28 response was implemented as a linear function of the predicted exposure with an exponential onset of response. The placebo response was found to follow the same parametric time course:

\[
\text{DAS28}_{\text{CR}} = -DAS28_{\text{B}}\times \left(\frac{1}{1+e^{-(F\text{C}_{\text{max}}) + e\text{r}}}\right) + e_r
\]

Covariates model: Continuous covariates (age, bodyweight) were included in the PK and exposure-response models as power functions, while binary covariates (gender, patient status) entered as factors:

\[
\text{pSTAT1}_{\text{P}} = \text{pSTAT1}_{\text{P,POP}}\times \left(\frac{C_M}{\text{median}}\right)^{\text{exponent, pSTAT1}_{\text{P}}} + (1-x_{\text{C0}}, \text{pSTAT1}_{\text{P}})
\]

PK model: The pharmacokinetics of filgotinib and its main metabolite were adequately described by an integrated model with two- and one-compartmental disposition, respectively. Gender and patient status as significant covariates were included in the PK model.

Models

Simulated biomarker (pSTAT1) response

Healthy subjects

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean (95%CI)</th>
<th>Minimum (95%CI)</th>
<th>Maximum (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg OD</td>
<td>4.78 (1.06; 14.1)</td>
<td>1.86 (0.242; 7.32)</td>
<td>10.2 (1.14; 38.6)</td>
</tr>
<tr>
<td>100 mg BD</td>
<td>45.1 (13.5; 63.6)</td>
<td>25.2 (13.7; 38.8)</td>
<td>67.0 (51.4; 82.8)</td>
</tr>
<tr>
<td>300 mg QD</td>
<td>80.7 (63.3; 91.3)</td>
<td>75.9 (55.8; 88.0)</td>
<td>84.6 (75.3; 94.1)</td>
</tr>
<tr>
<td>200 mg QD</td>
<td>80.0 (63.3; 90.6)</td>
<td>64.3 (42.7; 79.2)</td>
<td>91.9 (61.5; 97.9)</td>
</tr>
<tr>
<td>300 mg QD</td>
<td>80.1 (63.5; 90.4)</td>
<td>63.1 (45.7; 78.9)</td>
<td>90.6 (69.0; 99.1)</td>
</tr>
</tbody>
</table>

Simulated clinical (DAS28) response

RA patients

<table>
<thead>
<tr>
<th>Dose</th>
<th>Observed DAS28 (95%)</th>
<th>Predicted DAS28 (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>-0.86 (-1.25, -0.46)</td>
<td>-1.09 (-1.23</td>
</tr>
<tr>
<td>30 mg OD</td>
<td>-1.28 (-1.59, -0.96)</td>
<td>-1.21 (-1.43</td>
</tr>
<tr>
<td>100 mg BD</td>
<td>30 mg OD</td>
<td>-1.23 (-1.52, -0.94)</td>
</tr>
<tr>
<td>200 mg QD/100 mg BD</td>
<td>-2.33 (-1.82, -1.84)</td>
<td>-2.30 (-2.61, -2.06)</td>
</tr>
<tr>
<td>200 mg QD</td>
<td>-2.25 (-1.73, -1.76)</td>
<td>-2.20 (-2.61, -1.86)</td>
</tr>
</tbody>
</table>

At 200 mg OD, the steady state pSTAT1 inhibition was predicted to be within 64% (prior to dosing) and 91.9% (at Cmax) with no relevant increase in the PD response at higher doses.

While inhibition is maximal at Cmax of filgotinib, the sustained pSTAT1 inhibition correlates with the long-lasting metabolite exposure.

Conclusions
• Current modeling and simulation showed that both filgotinib and its main metabolite contribute to pSTAT1 biomarker response, as reflected in pSTAT1 dose-response relation.
• Simulations of the pSTAT1 and DAS28 dose-response relation suggest that maximum efficacy is achieved at a daily dose of 200mg filgotinib, above which no further improvement is gained. The clinical response is in the range of that observed with registered biological DMARDs.
• A daily dose range from 50 to 200 mg is currently being tested in the DARWIN Phase 2B program.

Simulated biomarker (pSTAT1) response

Healthy subjects

At 200 mg OD, the steady state pSTAT1 inhibition was predicted to be within 64% (prior to dosing) and 91.9% (at Cmax) with no relevant increase in the PD response at higher doses.

While inhibition is maximal at Cmax of filgotinib, the sustained pSTAT1 inhibition correlates with the long-lasting metabolite exposure.

No covariates were included in the biomarker model.

At 200 mg OD, the DAS28B was predicted to decline by 2.2 and 2.6 at week 4 and 12 with no improvement in DAS28 response at higher doses.

Steady state response is reached between 8 and 12 weeks.

No covariates were included in the DAS28 model.

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