

Introduction

GLPG0634 is an orally-available, selective Janus kinase 1 (JAK1) inhibitor. Selective inhibition of JAK1 may combine favorable safety and clinical efficacy profiles with rapid onset of action.

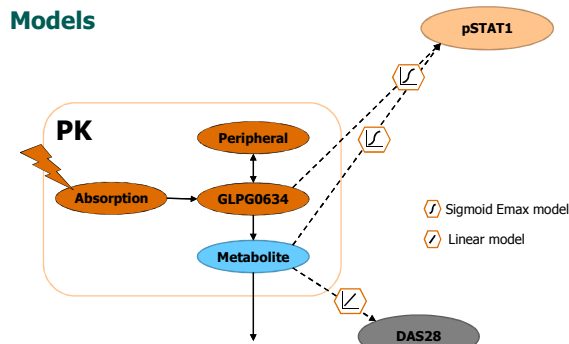
GLPG0634 showed encouraging PD, safety and efficacy in early clinical studies treating RA patients for 4 weeks studies^{1,2}.

Here the contribution of exposure-response (E-R) modelling and simulation to support GLPG0634 dose selection for Phase 2B studies is presented.

Methods

- Population predicted and individual responses to treatment were investigated on the basis of simulated exposures to GLPG0634 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
- The DAS28 E-R model was used to predict the improvement of the clinical response following 12 weeks of GLPG0634 treatment.

Models



PK model: The pharmacokinetics of GLPG0634 and its main metabolite were adequately described by an integrated model with two- and one-compartmental disposition, respectively.

pSTAT1 biomarker: The percentage of pSTAT1 inhibition was adequately described by a combined direct-response model of predicted GLPG0634 (P) and metabolite (M) plasma concentration. The drug effect on pSTAT1 inhibition was implemented as a sigmoid Emax model:

$$pSTAT1 = pSTAT1_{BL} \cdot \left(1 - \frac{C_{0,P} + C_{0,M}}{1 + C_{0,P} + C_{0,M}} \right) + \varepsilon_{pSTAT1}, C_{0,x} = \left(\frac{C_x}{EC_{50,x}} \right)^H, x \in \{P, M\}$$

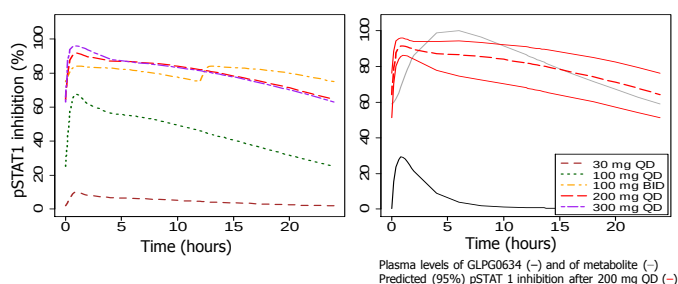
DAS28 clinical response: The DAS28 change from baseline (DAS28_{CFB}) was adequately described by a regression model depending on individual predicted steady state metabolite exposure (AUC_{M,24 hr}). The drug effect on DAS28 response was implemented as a linear function of the predicted exposure with an exponential onset of response. The placebo response was found to follow the same parametric time course:

$$DAS28_{CFB} = -DAS28_{BL} \cdot (SLP_M \cdot AUC_{M,24 hr} + pbo_i) \cdot (1 - \exp(-keff \cdot t)) + \varepsilon$$

ε : residual (unexplained) variability

Simulated biomarker (pSTAT1) response Healthy subjects

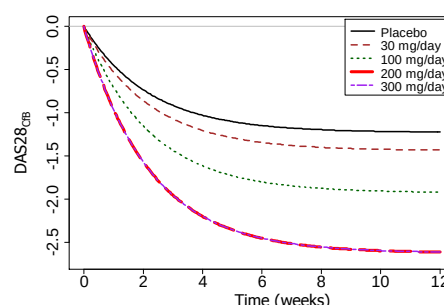
Dose	Mean (95%CI)	%pSTAT1 inhibition Minimum (95%CI)	%pSTAT1 inhibition Maximum (95%CI)
30 mg QD	4.78 (1.06; 14.1)	1.86 (0.242; 7.32)	10.2 (2.14; 38.6)
100 mg QD	45.1 (31.5; 56.0)	25.2 (13.7; 38.3)	67.8 (53.4; 82.8)
100 mg BID	80.7 (65.1; 91.3)	75.0 (55.8; 88.0)	84.6 (75.3; 94.1)
200 mg QD	80.0 (63.3; 90.6)	64.3 (47.2; 79.2)	91.9 (85.1; 97.4)
300 mg QD	80.1 (63.4; 90.4)	63.1 (45.7; 78.9)	96.0 (90.6; 99.1)



- At 200 mg QD, the steady state pSTAT1 inhibition was predicted to be within 64.3% (predose) and 91.9% (at C_{max}) with no relevant increase in PD response at higher doses
- While inhibition is maximal at the peak of GLPG0634, the sustained inhibition correlates with the long-lasting metabolite exposure

Simulated clinical (DAS28) response RA patients

Dose	Observed mean DAS28 _{CFB} (95%) Week 4	Predicted DAS28 _{CFB} Week 4	Predicted DAS28 _{CFB} Week 12
placebo	-0.854 (-1.25, -0.460)	-1.03	-1.23
30 mg QD	-1.08 (-1.59, -0.560)	-1.21	-1.43
100 mg QD	No data	-1.62	-1.92
200 mg QD/100 mg BID	-2.23 (-2.62, -1.84)	-2.20	-2.61
300 mg QD	-2.25 (-2.73, -1.76)	-2.20	-2.61



- At 200 mg QD, the DAS28_{CFB} was predicted to decline by 2.2 and 2.6 at week 4 and 12 with no improvement in DAS28 response at higher dose
- Steady state response is reached between 8 and 12 weeks

Conclusions

- Current modeling and simulation show that both GLPG0634 and its main metabolite contribute to pSTAT1 biomarker response, as reflected in pSTAT1 biomarker response.
- Simulations of the pSTAT1 and DAS28 dose-response relation suggest that the efficacy is favorable up to a daily dose of 200 mg GLPG0634, above which no further improvement is gained. 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.