GLPG0634, a selective JAK1 inhibitor, confirms its low liability for drug-drug interactions

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Background: GLPG0634 is an orally-available, selective Janus kinase 1 (JAK1) inhibitor. Less selective JAK inhibitors have shown long-term efficacy in treating RA but also dose-limiting side effects. Selective inhibition of JAK1 may combine improved safety and clinical efficacy profiles, as well as rapid onset of action. GLPG0634 showed encouraging safety and efficacy results in early clinical studies treating RA patients for 4 weeks and favorable once-daily oral pharmacokinetics. Its effects in humans are supported by high concentrations of an active metabolite.

Objectives: Explore potential drug-drug interactions in vitro and in humans.

Methods: In vitro experiments were conducted to identify the enzymes involved in GLPG0634’s metabolism [cytochrome P450 (CYP450) and carboxylesterases (CES)] and the interaction potential of GLPG0634 and its main metabolite. Inhibition or induction of drug-metabolizing enzymes [CYP450, uridine glucuronyltransferases (UGT)] and key drug transporters (Pgp, BCRP, BSEP, OATs, OCTs, OATP1B1 and OATP1B3) was studied using human microsomes, cell systems or recombinant enzymes with reference substrates as suitable. An open-label study in healthy subjects was conducted to confirm the conclusion on interaction potential by evaluating the effects of GLPG0634 co-administration on a sensitive CYP3A4 substrate, midazolam. The oral pharmacokinetics of midazolam was assessed over 24 hours following a single dose of 2 mg prior to and after once daily dosing of 200 mg GLPG0634 for 7 days. Standard safety assessments were performed throughout the study duration.

Results: In vitro studies showed that the GLPG0634 metabolism is not CYP450 dependent and is mediated by CES. Its major metabolite is produced by CES2 for 70% of metabolite formed and by CES1 for 6%. In vitro, GLPG0634 and its main metabolite do not induce CYP1A2, CYP2B6 and CYP3A4 at concentrations well in excess of the peak concentration (Cmax) in patients administered a 200 mg daily dose of GLPG0634. The IC50 for inhibition of each of the CYPs tested is at least 20-fold above clinical Cmax and inhibition of UGT1A1 and UGT2B7 showed IC50 values at least 18- and 7-fold above the Cmax for GLPG0634 and its main metabolite. Drug transporters are not inhibited by GLPG0634 and its metabolite, except minor effects on OCT2. The IC50 for OCT2 inhibition are 2.6- and 6.2-fold over the Cmax values of GLPG0634 and its metabolite, respectively, after a daily dose of 200 mg, while IC50 margins of at least 18- and 5-fold were observed for all other transporters. In healthy subjects, there was no difference in the plasma midazolam pharmacokinetic profile with and without GLPG0634. Adjusted geometric ratios for midazolam plus GLPG0634 were 99.3% [87.6-112.5%] and 105.4% [94.8-117.3%] for Cmax and AUC, respectively, well within the no effect boundary guidelines (80-125%). There was no difference in the pharmacokinetics of GLPG0634 following co-administration with midazolam. GLPG0634 was safe and well tolerated.

Conclusions: The clinical data show a lack of relevant drug interactions by GLPG0634 with CYP3A4 substrates, either through inhibition or induction of CYP3A4 activity in humans. Combined with the in vitro data on CYP450s, UGTs and key drug transporters, the current data support that GLPG0634 presents a low risk of PK interference with drugs concomitantly administered to patients.

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