Effect of gastric acid reduction and strong CYP3A induction/inhibition on the pharmacokinetics of ripretinib, a switch control tyrosine kinase inhibitor

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INTRODUCTION

Ripretinib is a tyrosine kinase inhibitor indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor who have received prior treatment with 3 or more kinase inhibitors, including imatinib. The dose of 150 mg once daily (QD) is in the currently approved dose in the US, Canada, Australia, and Hong Kong.1

In a phase 1 study (NCT02711006), the maximum tolerated dose (MTD) was not reached with doses up to ripretinib 200 mg twice daily (BID). Dose escalation to ripretinib 150 mg BID is offered to patients in the phase 2 and phase 3 (NCT03593753) clinical studies after no disease progression on 150 mg QD. This regimen has been well tolerated with a similar safety profile as seen at 150 mg QD.2

steady-state pharmacokinetics (PK) exposure following ripretinib 150 mg BID were approximately 2-fold higher compared with ripretinib 150 mg QD.

Drug-drug interaction (DDI) effects with strong CYP3A inhibitors/inducers were expected because ripretinib and its active metabolite DP 5439 were metabolized via CYP3A4. Co-administration with strong CYP3A inhibition (e.g. Itraconazole) and inducers (e.g. Rifampin) may result in increased and decreased exposure to ripretinib, respectively.

Ripretinib may also be subject to a drug interaction with acidic reducing agents such as pantoprazole, a proton pump inhibitor (PPI) due to its pH-dependent solubility. Gastric acid reducing agents may impact the dissolution of ripretinib and potentially impact its absorption.

Here, we report the effect of Itraconazole, pantoprazole, and rifampin on the PK of ripretinib and its active metabolite DP 5439 in healthy subjects.

METHODS

For each treatment, single-doses of ripretinib were given and concurrently with multiple doses of each permutating agent to healthy volunteers (Figure 1).

Figure 1. Study design

A) DDI with Itraconazole

Fixed-dose, single-dose study n=20

• PK samples were collected in healthy volunteers (0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 36, 48, 72, 96, 144, and 168 hours after dosing on days 1 and 11)

B) DDI with pantoprazole

Fixed-dose, single-dose study n=20

• PK samples were collected in healthy volunteers (0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 36, 48, 72, 96, 144, and 168 hours after dosing on days 3 and 11)

C) DDI with rifampin

Fixed-dose, single-dose study n=20

• PK samples were collected in healthy volunteers (0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 36, 48, 72, 96, 144, and 168 hours after dosing on days 7 and 17)

• PK samples were analyzed to determine the concentration of ripretinib and its active metabolite DP 5439 in plasma by validated liquid chromatography with tandem mass spectrometry assays.

• PK parameters were calculated using Phoenix® WinNonlin® (Version 7.2 or higher). For the evaluation of DDI, an analysis of variance was performed using natural log-transformed data to model observed concentration (C0,inf) time under the concentration time curve from time zero to infinity (AUC0,inf) for ripretinib and DP 5439 with treatment (with or without Itraconazole, pantoprazole, or rifampin) as a fixed effect. The geometric mean ratio and 90% confidence intervals of Cmax, AUC0-24, and AUC0-∞ were calculated.

RESULTS

Figure 2. Mean plasma concentration-time profiles

A) Ripretinib and Itraconazole

Semi-log plot

B) Ripretinib and pantoprazole

Semi-log plot

C) Ripretinib and pantoprazole

Semi-log plot

D) DP 5439 and Itraconazole

Semi-log plot

E) DP 5439 and pantoprazole

Semi-log plot

F) DP 5439 and rifampin

Semi-log plot

CONCLUSIONS

• No dose adjustment is required when ripretinib is co-administered with a PPI or other gastric acid reducers and strong CYP3A inhibitors.

• Patients should be monitored more frequently for adverse reactions when a strong CYP3A inhibitor is co-administered with ripretinib.

• Decreased exposure of ripretinib may decrease ripretinib antitumor activity. Therefore, avoid concomitant use of ripretinib with strong CYP3A inducers.

• An analysis of pharmacokinetic data is ongoing to identify appropriate dose adjustment when concomitant use of strong CYP3A inducers is not avoidable.

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References


Figure 3. Forest plot summarizing the effect of coadministered drug in ripretinib and DP 5439 pharmacokinetics

Geometric least squares (LS) mean ratios for ripretinib AUC0–24 and AUC0–∞ were 100%, and 159%, respectively, when taken with Itraconazole, whereas the Cmax ratio was 106% (90% confidence interval [CI], 99%–112%). Similar ratios were noted for DP 5439 (98% and 158% for AUC0–24 and AUC0–∞, respectively, whereas the Cmax ratio was 157%).

The ratios of geometric LS mean and the corresponding 90% confidence interval for AUC0–24, AUC0–∞, and Cmax were each within the 80%–125% range for ripretinib with pantoprazole relative to ripretinib alone. Ratios of geometric LS mean for plasma DP 5439 AUC0–24, AUC0–∞, and Cmax were 131%, 110%, and 112%, respectively, for ripretinib with pantoprazole relative to ripretinib alone.

Ratios of geometric LS mean for plasma DP 5439 AUC0–24, AUC0–∞, and Cmax were 39%, 30%, and 62%, respectively, for ripretinib with rifampin relative to ripretinib alone. Ratios of geometric LS mean for plasma DP 5439 AUC0–24, AUC0–∞, and Cmax were 43%, 43%, and 137%, respectively, for ripretinib with rifampin relative to ripretinib alone.

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