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 the currently approved dose in the US, Canada, Australia, and Hong Kong[1,2,3]
- In a phase 1 study (NCT02571036), 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 1 and phase 3 (INVICTUS; NCT03353753) clinical studies after radiologic disease progression on 150 mg QD. This regimen has been well tolerated with a similar safety profile as seen at 150 mg QD[4,5,6]
- 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 are metabolized via CYP3A4/5. Coadministration with strong CYP3A inhibitors (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 acid-reducing agents (such as pantoprazole, a proton pump inhibitor, PPI) due to its pH-dependent solubility. Gastric acid inhibition by acid-reducing agents may impact the dissolution of ripretinib and potentially impair 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

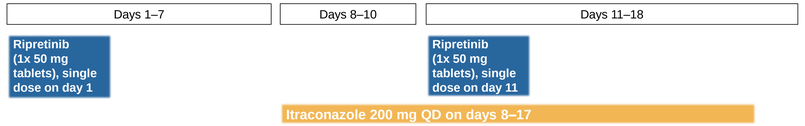
METHODS

- For each interaction, single doses of ripretinib were given before and concurrently with multiple doses of each perpetrator agent to healthy volunteers (**Figure 1**)

Figure 1. Study design

A) DDI with itraconazole

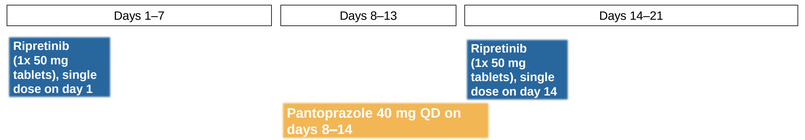
Fixed-sequence, single-dose study design: n = 20



PK samples were collected at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing on days 1 and 11

B) DDI with pantoprazole

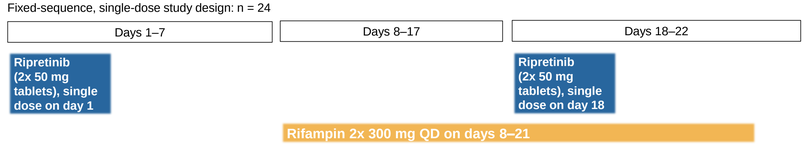
Fixed-sequence, single-dose study design: n = 25



PK samples were collected at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing on days 1 and 14

C) DDI with rifampin

Fixed-sequence, single-dose study design: n = 24



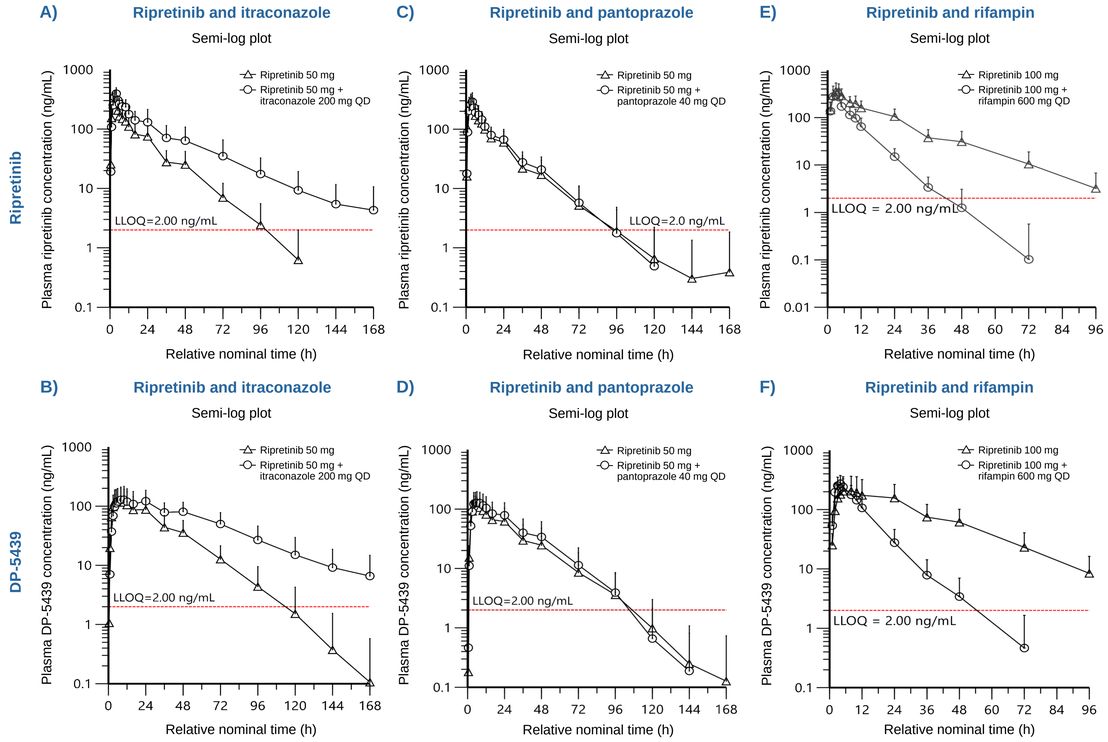
PK samples were collected at predose and 1, 2, 3, 4, 5, 8, 10, 12, 24, 36, 48, 72, and 96 hours after oral administration of ripretinib on days 1 and 18

DDI = drug-drug interaction; PK = pharmacokinetics, QD = once daily.

- 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 7.0 or higher). For the evaluation of DDI, an analysis of variance was performed using natural log-transformed data for maximum observed concentration (C_{max}), area under the concentration-time curve from time zero to time t (AUC_{0-t}), and area under the concentration-time curve from 0 to infinity (AUC_{inf}) for ripretinib and DP-5439, with treatment (ripretinib with or without itraconazole, pantoprazole, or rifampin) as a fixed effect. The geometric mean ratios and corresponding 90% confidence intervals of C_{max}, AUC_{0-t}, and AUC_{inf} were calculated

RESULTS

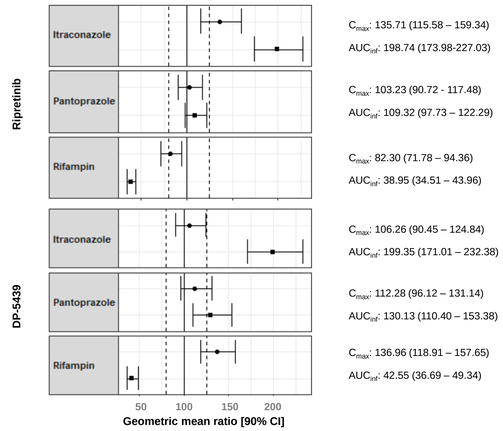
Figure 2. Mean plasma concentration-time profiles



LLOQ = lower limit of quantitation; QD = once daily.

- Exposure to ripretinib and its active metabolite DP-5439 was increased when co-administered with a strong CYP3A inhibitor (itraconazole)
- There was no DDI between ripretinib and a proton pump inhibitor (pantoprazole)
- Exposure to ripretinib and its active metabolite DP-5439 was decreased when co-administered with a strong CYP3A inducer (rifampin)

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



Dashed lines represent the 80-125% range
AUC_{inf} = area under the concentration-time curve from 0 to infinity; CI, confidence interval; C_{max} = maximum concentration.

- Geometric least-squares (LS) mean ratios for ripretinib AUC_{0-t} and AUC_{inf} were 198% and 199%, respectively, when taken with itraconazole, whereas the C_{max} ratio was approximately 136%. Similar ratios were noted for DP-5439 (194% and 199% for AUC_{0-t} and AUC_{inf}, respectively, whereas the C_{max} ratio was 106%)
- The ratios of geometric LS mean and the corresponding 90% confidence interval for AUC_{0-t}, AUC_{inf}, and C_{max} were each within the 80%–125% range for ripretinib with pantoprazole relative to ripretinib alone. Ratios of geometric LS means for plasma DP-5439 AUC_{0-t}, AUC_{inf}, and C_{max} were 131%, 130%, and 112%, respectively, for ripretinib with pantoprazole relative to ripretinib alone
- Ratios of geometric LS means for plasma ripretinib AUC_{0-t}, AUC_{inf}, and C_{max} were 39%, 39%, and 82%, respectively, for ripretinib with rifampin relative to ripretinib alone. Ratios of geometric LS means for plasma DP-5439 AUC_{0-t}, AUC_{inf}, and C_{max} were 43%, 43%, and 137%, respectively, for ripretinib with rifampin relative to ripretinib alone

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 physiologically based PK modeling is ongoing to identify appropriate dose adjustment when concomitant use of strong CYP3A inducers is not avoidable

Presented at the AACR Virtual Annual Meeting 2021, April 10–15

References

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Acknowledgments

We would like to thank the patients, their families, and caregivers, the investigators, and the investigational site staff of this study. This study was sponsored by Deciphera Pharmaceuticals, LLC (Waltham, MA). Medical writing and editorial support were provided by Helen Rodgers, PhD, of AlphaBioCom, LLC (King of Prussia, PA), and was funded by Deciphera Pharmaceuticals, LLC.