Abstract CT125

Evaluation of Potential Drug–Drug Interactions Between Futibatinib and CYP3A Inhibitors/Inducers, CYP3A Substrates, or Proton Pump Inhibitors

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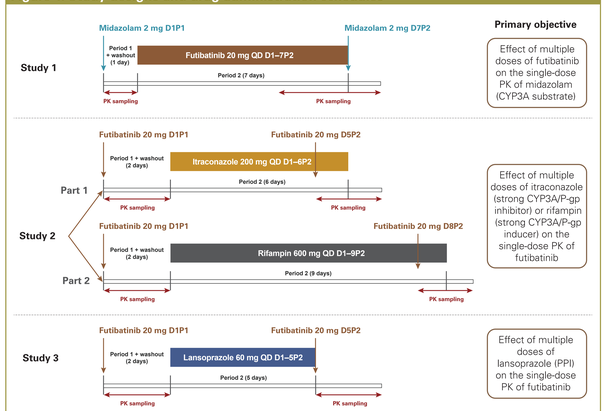
Background

- Futibatinib is an oral, highly selective, and irreversible fibroblast growth factor receptor (FGFR) 1–4 inhibitor with clinical activity in patients with advanced *FGFR*-aberrant tumors[1–4]
  - The recommended phase 2 dose, futibatinib 20 mg once daily (QD), demonstrated promising efficacy and tolerability in previously treated patients with intrahepatic cholangiocarcinoma harboring *FGFR2* fusions/rearrangements (interim results from FOENIX-CCA2)[4]
- In vitro experiments (data on file) showed that futibatinib
  - Was predominantly metabolized by cytochrome p450 3A (CYP3A; hepatic microsomes)
  - Exhibited time-dependent inhibition toward CYP3A (hepatic microsomes)
  - Is a likely substrate of the drug transporter P-glycoprotein (P-gp; overexpressing cell line)
- In vitro, futibatinib's solubility decreased as pH increased (data on file)
  - Changes in gastric pH (induced by proton pump inhibitors [PPIs])[5] may potentially affect futibatinib absorption and pharmacokinetics (PK)
- Three phase 1 studies were performed in healthy adult volunteers to evaluate potential drug–drug interactions (DDIs) of futibatinib with midazolam (CYP3A substrate), itraconazole (CYP3A/P-gp inhibitor), rifampin (CYP3A/P-gp inducer), and lansoprazole (PPI; **Figure 1**)[6–8]

Methods

- All 3 phase 1 studies were open-label, fixed-sequence, 2-period cross-over studies with a 1- or 2-day washout period between each dosing period
  - All studies were conducted in healthy adult nonsmokers aged 18–55 years
- The drug dosing and administration schedule for each study is shown in **Figure 1**
  - Plasma PK samples were collected before through 24 h after midazolam dosing (study 1) or before through 48 h after futibatinib dosing (studies 2 and 3)
- PK parameters were calculated using a noncompartmental method (Phoenix® WinNonlin® v.7.0) and included the following:
  - Area under the concentration–time curve from time 0 to the last observed/measured nonzero concentration (AUC_{0-t}), or from time 0 extrapolated to infinity (AUC_{0-inf}), and maximum observed concentration (C_{max}), time to C_{max} (T_{max}), and first-order terminal elimination half-life ($T_{1/2}$)
- A linear mixed-effect analysis of variance (ANOVA) model was used to compare C_{max}, AUC_{0-inf}, and AUC_{0-t} between drugs administered alone or in combination with other agents

Figure 1. Study designs and drug administration schedules



CYP3A, cytochrome p450 3A; D, day; P, period; P-gp: P-glycoprotein; PK, pharmacokinetics; PPI, proton pump inhibitor; QD, once daily.

Results

Study 1: Effect of futibatinib on PK of midazolam (CYP3A substrate)

- Twenty-four participants were enrolled, received treatment, and completed the study
- Steady-state plasma concentrations of futibatinib were reached within 4 days of QD dosing
- Coadministration of futibatinib and midazolam resulted in the following:
  - Midazolam plasma concentrations that were comparable to those observed with midazolam alone (**Figure 2**; **Supplementary Table S1**)
  - No clinically significant changes in midazolam plasma exposure relative to midazolam administered alone (AUC_{0-t}, –9%; AUC_{0-inf}, –9%; C_{max}, –5%; **Table 1**)
  - An earlier midazolam T_{max} versus midazolam alone (median difference, –0.17 h; *P*=0.0013), but this change was not clinically significant
- Both agents were well tolerated; no deaths, serious adverse events (AEs), or AE-related discontinuations were reported
  - 42% of participants experienced ≥1 treatment-emergent AE
  - All events were mild (grade 1) except for 1 grade 2 event of abdominal pain

Figure 2. Mean plasma concentration–time profile of midazolam administered with or without futibatinib

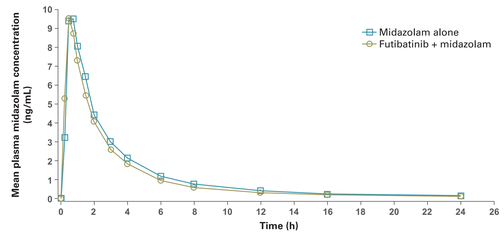


Table 1. Comparison of midazolam PK with or without futibatinib

	Geometric LS means		Futibatinib + midazolam/ midazolam GMR (90% CI), %
	Futibatinib + midazolam (n=24)	Midazolam (n=24)	
C_{max}, ng/mL	9.41	9.95	94.56 (84.35–106.01)
AUC_{0-t}, ng·h/mL	24.64	27.04	91.13 (80.06–103.74)
AUC_{0-inf}, ng·h/mL	25.80	28.31	91.13 (80.16–103.59)

AUC_{0-t}, area under the plasma concentration–time curve from time 0 to time of last measured nonzero concentration; AUC_{0-inf}, area under the plasma concentration–time curve from time 0 extrapolated to infinity; C_{max}, maximum plasma concentration; CI, confidence interval; GMR, geometric mean ratio; LS, least squares; PK, pharmacokinetics.

Study 2: Effect of coadministration of itraconazole (strong CYP3A/P-gp inhibitor) or rifampin (strong CYP3A/P-gp inducer) on futibatinib PK

- Forty participants were enrolled; 20 received futibatinib and itraconazole, and 20 received futibatinib and rifampin
  - All 40 participants completed the study
- Coadministration of futibatinib and itraconazole resulted in the following:
  - Higher peak plasma futibatinib concentrations than with futibatinib alone, but with no alteration of the elimination phase (**Figure 3A**; **Supplementary Table S2**)
  - Statistically significant increases in futibatinib plasma exposure relative to futibatinib administered alone (AUC_{0-t} and AUC_{0-inf}, +41% each; C_{max}, +51%; **Table 2**)
  - A significantly earlier futibatinib T_{max} than with futibatinib administered alone (median difference, –0.72 h; *P*=0.0071)
- Coadministration of futibatinib and rifampin resulted in the following:
  - Lower mean plasma concentrations of futibatinib at all time points than with futibatinib administered alone (**Figure 3B**; **Supplementary Table S3**)
  - Statistically significant decreases in futibatinib plasma exposure compared with futibatinib alone (AUC_{0-t} and AUC_{0-inf}, –64% each; C_{max}, –53%)
- No serious AEs, deaths, or discontinuations were reported in the study
  - Nineteen patients (48%) experienced AEs, mostly grade 1 in severity; no grade 3 or 4 AEs were reported

Figure 3. Mean plasma concentration–time profiles of futibatinib administered with or without itraconazole (A) or rifampin (B)

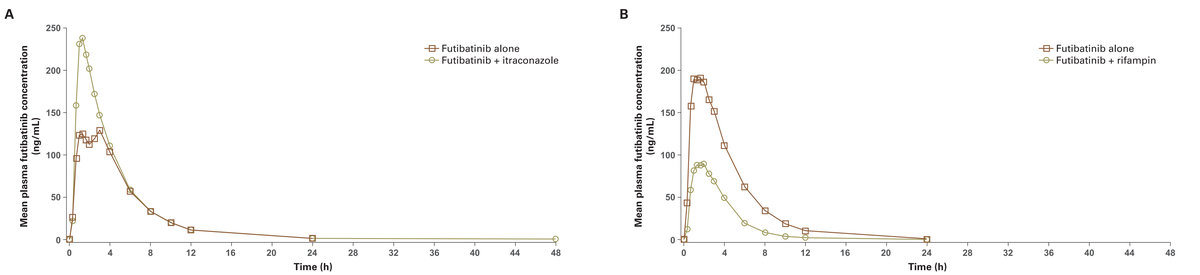


Table 2. Comparison of futibatinib PK with or without itraconazole or rifampin

	Itraconazole			Rifampin		
	Geometric LS means			Geometric LS means		
	Futibatinib + itraconazole (n=20)	Futibatinib (n=20)	Futibatinib + itraconazole/ futibatinib GMR (90% CI), %	Futibatinib + rifampin (n=20)	Futibatinib (n=20)	Futibatinib + rifampin/ futibatinib GMR (90% CI), %
C_{max}, ng/mL	253.1	167.3	151.3 (127.6–179.3)	105.0	222.4	47.2 (41.1–54.3)
AUC_{0-t}, ng·h/mL	950.7	673.9	141.1 (122.4–162.6)	340.6	946.7	36.0 (30.5–42.4)
AUC_{0-inf}, ng·h/mL	956.5	679.0	140.9 (122.2–162.4)	344.4	954.9	36.1 (30.5–42.6)

AUC_{0-t}, area under the plasma concentration–time curve from time 0 to time of last measured nonzero concentration; AUC_{0-inf}, area under the plasma concentration–time curve from time 0 extrapolated to infinity; C_{max}, maximum plasma concentration; CI, confidence interval; GMR, geometric mean ratio; LS, least squares; PK, pharmacokinetics.

Study 3: Effect of coadministration of lansoprazole (PPI) on futibatinib PK

- Overall, 20 participants were enrolled and treated; all 20 completed the study
- Coadministration of futibatinib and lansoprazole resulted in the following:
  - Plasma futibatinib concentrations that were comparable to those observed with futibatinib alone (**Figure 4**; **Supplementary Table S4**)
  - No statistically or clinically significant changes in futibatinib plasma exposure relative to futibatinib administered alone (AUC_{0-t} +5%, AUC_{0-inf} +5%; C_{max} +8%; **Table 3**)
  - Marginal, nonsignificant changes in T_{max} (median difference, –0.02 h)
- No serious AEs, deaths, or discontinuations were reported
  - Overall, 8 patients (40%) experienced AEs, the majority being grade 1 in severity; no grade 3 or 4 AEs were reported

Figure 4. Mean plasma concentration–time profile of futibatinib administered with or without lansoprazole

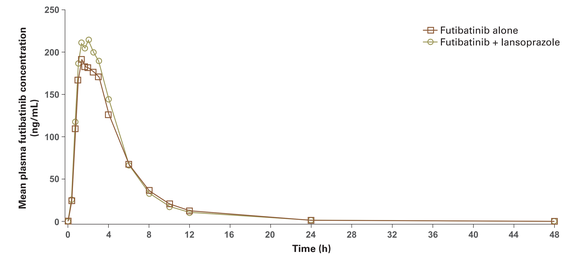


Table 3. Comparison of futibatinib PK with or without lansoprazole

	Geometric LS means		Futibatinib + lansoprazole/ futibatinib GMR (90% CI), %
	Futibatinib + lansoprazole (n=20)	Futibatinib (n=20)	
C_{max}, ng/mL	234.3	216.1	108.4 (97.7–120.2)
AUC_{0-t}, ng·h/mL	983.3	934.0	105.3 (95.3–116.3)
AUC_{0-inf}, ng·h/mL	990.7	941.6	105.2 (95.3–116.2)

AUC_{0-t}, area under the plasma concentration–time curve from time 0 to time of last measured nonzero concentration; AUC_{0-inf}, area under the plasma concentration–time curve from time 0 extrapolated to infinity; C_{max}, maximum plasma concentration; CI, confidence interval; GMR, geometric mean ratio; LS, least squares; PK, pharmacokinetics.

Conclusions

- These results indicate that futibatinib is not expected to affect the exposure of concomitant medications metabolized via CYP3A, the most common drug metabolism pathway
- Caution should be exercised when coadministering strong CYP3A inducers or inhibitors with futibatinib because significant DDIs were observed with itraconazole and rifampin
  - However, the <2-fold increase in plasma futibatinib exposures in the presence of itraconazole versus when administered alone suggests that futibatinib is not a sensitive CYP3A/P-gp substrate
- Futibatinib can be concomitantly administered with PPIs with no clinically relevant impact on futibatinib exposure

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