**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 FGFR2/3+ tumors. 1–4
- The recommended phase 2 dose, futibatinib 20 mg once daily (QD), demonstrated promising efficacy and tolerability in previously treated patients with metastatic colorectal cancer harboring FGFR2/3 fusion/amplifications. (Clinical trial results from FODIN-C2A2.)
- 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)
- It is likely substrate of the drug transporter P-glycoprotein (P-gp; overexpressing cell line)
- In vivo, futibatinib’s solubility decreased as pH increased on data file
- Changes in gastric pH (induced by proton pump inhibitors [PPIs]) may potentially affect futibatinib absorption and pharmacokinetics (PK)
- A linear mixed-effect analysis of variance (ANOVA) model was used to compare Cmax, CYP3A, cytochrome p450 3A; D, day; P, period; P-gp: P-glycoprotein; PK, pharmacokinetics; PPI, proton pump inhibitor; QD, once daily.

**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.

**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 midazolam were reached within 4 days of OD-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 (AUC0–t, 96%; AUC0–inf, 99%; Cmax, 99%, Table 1).
  - As earlier midazolam concentrations higher than midazolam administered alone (median difference, −0.17 h; 90% CI, −0.63 to 0.30 h; P = 0.825), this change was not clinically significant.
  - Both agents were well tolerated, no deaths, serious adverse events (SAEs), or AE-related discontinuations were reported.
- All phase 1 studies were performed in healthy adult volunteers to evaluate potential drug–drug interactions (DDIs) of futibatinib with molecular CYP3A substrates, micromolar CYP3A4 inhibitor, (herpes) CYP3A4 inducer, and lossanoprazole (PPI). Figure 1).

**Study 2: Effect of coadministration of itraconazole (strong CYP3A/P-gp inhibitor) or rifampin (strong CYP3A/P-gp inducer) on futibatinib PK on futibatinib PK**
- Forty participants were enrolled; 20 received futibatinib and itraconazole, and 20 received futibatinib and rifampin.
- Twenty-four participants were enrolled, received treatment, and completed the study.
- Coadministration of futibatinib and midazolam resulted in the following:
  - A statistically significant increase in midazolam plasma exposure relative to midazolam administered alone (AUC0–t, 122.2–162.4) 344.4 954.9 36.1
  - AUC0–inf, 990.7 941.6 105.2 (95.3–116.3)
  - Cmax, 983.3 934.0 105.3 (95.3–116.3)
- No statistically or clinically significant changes in midazolam plasma exposure relative to midazolam administered alone (AUC0–t, AUC0–inf, Cmax).
- In patients with history of renal impairment, the majority being grade 1 in severity, no grade 3 or 4 AEs were reported.

**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 administered alone (Figure 4).
- Overall, 8 patients (40%) experienced AEs, the majority being grade 1 in severity; no grade 3 or 4 AEs were reported.

**Conclusions**
- These results indicate that futibatinib is not expected to affect the exposure of concomitant medications metabolized on CYP3A, the most common drug metabolism pathway.
- Coadministration should be avoided with itraconazole, the strongest CYP3A4 inhibitors, or rifampin, the strongest CYP3A4 inducers, which may result in clinically significant DDIs that were observed with trastuzumab and radiotherapy.
- However, the c-2-fold increase in plasma futibatinib exposures in the presence of trastuzumab versus when administered alone suggests that futibatinib is not a sensitive CYP3A4/P-gp substrate.
- Futibatinib can be concomitantly administered with PPIs with no clinically relevant impact on futibatinib exposure.

**Table 1. Comparison of midazolam PK with or without itraconazole or rifampin**

<table>
<thead>
<tr>
<th>CYP3A/P-gp Inhibitor</th>
<th>AUC0–t, ng·h/mL</th>
<th>AUC0–inf, ng·h/mL</th>
<th>Cmax, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>304.0</td>
<td>908.7</td>
<td>36.1</td>
</tr>
<tr>
<td>Rifampin</td>
<td>304.0</td>
<td>908.7</td>
<td>36.1</td>
</tr>
</tbody>
</table>

**Table 2. Comparison of futibatinib PK with or without lansoprazole**

<table>
<thead>
<tr>
<th>CYP3A/P-gp Inhibitor</th>
<th>AUC0–t, ng·h/mL</th>
<th>AUC0–inf, ng·h/mL</th>
<th>Cmax, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole</td>
<td>105.3</td>
<td>994.9</td>
<td>105.3</td>
</tr>
</tbody>
</table>