No Clinically Meaningful Drug Interaction Between Futibatinib and Digoxin, Rosuvastatin or Quinidine

Sabina Paglialunga[1], Aernout van Haarst[2], Ziv Machnes[3], Ling Gao[4], Ikuo Yamamiya[5], Amanda Long[4], Michelle Valentine[1] and Aram Oganesian[6]

1. Celerion, Tempe, AZ; 2. Celerion, Belfast, UK; 3. Celerion, Montreal, Canada; 4. Taiho Oncology, Princeton, NJ; 5. Taiho Pharmaceutical, Tsukuba, Japan; 6. Taiho Oncology, Pleasanton, CA.

BACKGROUND

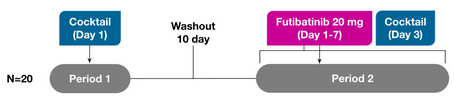
- Fibroblast growth factor receptor (FGFR) attenuation results in tumor growth inhibition and is an ideal target for oncologic treatment
- Futibatinib is a highly selective FGFR 1-4 tyrosine kinase inhibitor used to treat advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements [1]
- In vitro studies suggest that futibatinib is a substrate and inhibitor of P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP)
- Co-administration of futibatinib with itraconazole, a strong cytochrome P450 3A (CYP3A) inhibitor, resulted in a ~50% increase in futibatinib exposure, suggesting futibatinib is primarily metabolized by CYP3A [2]
- Itraconazole is also recognized as a P-gp and BCRP inhibitor [3], however the extent to which transporter inhibition contributed to the effect on futibatinib exposure remains to be elucidated
- Therefore, a drug-drug interaction (DDI) study with substrates of P-gp (digoxin) and BCRP (rosuvastatin) and a P-gp inhibitor (quinidine) was performed to investigate the effect of futibatinib on these drug transporters

METHODS

- An open-label, fixed-sequence, 2-part, 2-period DDI study (Figure 1)
  - **Part 1:** Drug cocktail = 0.25 mg Digoxin + 10 mg Rosuvastatin and 20 mg Futibatinib
  - **Part 2:** 20 mg Futibatinib and 200 mg Quinidine Sulfate
- 44 healthy volunteer participants (n=20 Part 1, n=24 Part 2)
- Plasma and urine (digoxin only) pharmacokinetic (PK) parameters were assessed with standard equivalence statistical analyses
- The geometric mean ratios (GMRs) and associated 90% confidence intervals (CIs) were estimated based on the least square means from the analysis of variance and bioequivalence limits were set at 80%–125%

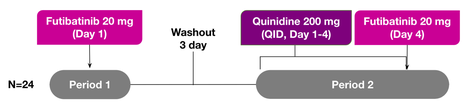
Figure 1: Transporter DDI Study Design

Part 1: Digoxin (P-gp substrate) + Rosuvastatin (BCRP substrate) Cocktail



Cocktail = Digoxin 0.25 mg + Rosuvastatin 10 mg

Part 2: Quinidine (P-gp inhibitor)



QID = four times daily

Table 1. Participant Demographics

Parameters	Part 1 (n=20)	Part 2 (n=24)	Total (n=44)
Age, years [median (range)]	37.5 (21–53)	49.0 (20–55)	39.5 (20–55)
Males / Females [n]	13 / 7	16 / 8	29 / 15
Race [n (%)]			
• Black or African American	1 (5)	1 (4)	2 (5)
• White	19 (95)	23 (96)	42 (95)
Ethnicity [n (%)]			
• Hispanic or Latino	14 (70)	19 (79)	33 (75)
• Not Hispanic or Latino	6 (30)	5 (21)	11 (25)
Body weight, kg [mean (SD)]	82.1 (14.80)	76.4 (13.03)	78.9 (13.98)
BMI, kg/m^2 [mean (SD)]	27.6 (2.42)	26.4 (3.61)	26.9 (3.15)

BMI, body mass index; SD, standard deviation.

RESULTS

Part 1: Futibatinib Had Minimal Effects on the Digoxin + Rosuvastatin Cocktail Drug Exposures

Figure 2. Plasma Digoxin Concentration Time Profile and Urine Digoxin Accumulation

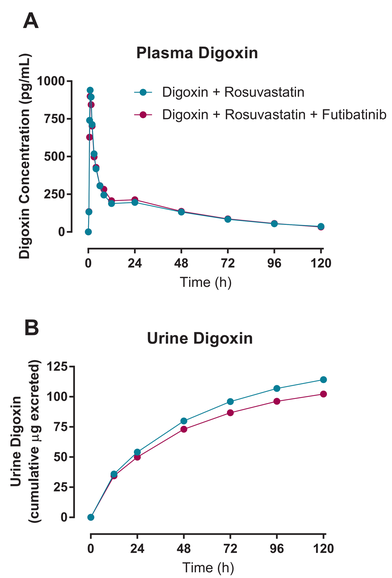


Figure 3. Plasma Rosuvastatin Concentration Time Profile

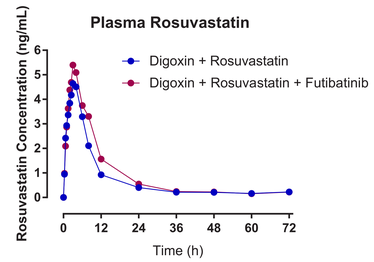


Table 2. Digoxin and Rosuvastatin PK Parameters Without or With Futibatinib

PK Parameter	Digoxin + Rosuvastatin	Digoxin + Rosuvastatin + Futibatinib	GMR[1], % (90% CI)
Plasma Digoxin			
AUC_{0-120}, pg*hr/mL	15,640 (26.0)	16,240 (29.3)	103.9 (94.5–114.2)
AUC_{inf}, pg*hr/mL	17,670 (26.6)	17,950 (29.9)[a]	100.2 (90.8–110.5)
C_{max}, pg/mL	1003 (38.0)	953.3 (45.1)	95.1 (81.1–111.5)
Urine Digoxin			
Cumulative Ae, ug	114.2 (20.8)	102.2 (24.9)	-
CLr, L/hr	7.31 (1.33)	6.49 (1.99)	87.1 (80.8–93.9)
Plasma Rosuvastatin			
AUC_{0-72}, ng*hr/mL	45.9 (53.4)[a]	53.9 (54.8)	118.8 (107.9–130.7)
AUC_{inf}, ng*hr/mL	46.9 (56.7)[b]	54.7 (56.4)	113.5 (102.6–125.5)
C_{max}, ng/mL	4.4 (61.4)	4.8 (65.5)	110.2 (97.3–124.8)

Data presented as geometric mean (geometric CV%) for C_{max} and AUC; arithmetic mean (SD) for urine parameters. [1]Only participants for whom PK parameters were determined for both period 1 and period 2 were included in the comparison. [a]Data available for 19 participants. [b]Data available for 18 participants. Ae, amount excreted; AUC, area under the concentration vtime curve; C_{max}, maximal concentration; CLr, renal clearance; CV, coefficient of variation; SD, standard deviation.

Part 2: No Clinically Relevant Increase in Futibatinib Following Quinidine Co-administration

Figure 4. Plasma Futibatinib Concentration Time Profile

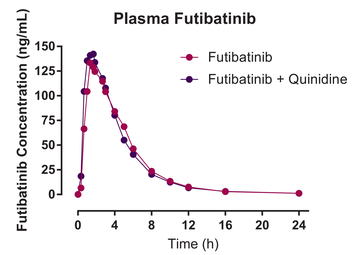


Table 3. Futibatinib PK Parameters Alone and With Quinidine

PK Parameter	Futibatinib (n = 24)	Futibatinib + Quinidine (n = 15)	GMR[1], % (90% CI)
AUC_{0-24}, pg*hr/mL	579.5 (66.1)	622.8 (41.4)	116.4 (95.4–142.1)
AUC_{inf}, pg*hr/mL	581.5 (66.3)	627.0 (41.6)	117.0 (96.0–142.7)
C_{max}, pg/mL	151.4 (53.5)	161.1 (48.4)	108.0 (90.9–128.3)

Data presented as geometric mean (geometric CV%) for C_{max} and AUC. [1] Only participants for whom PK parameters were determined for both period 1 and period 2 were included in the comparison. AUC, area under the concentration time curve; C_{max}, maximal concentration; CV, coefficient of variation; SD, standard deviation.

Futibatinib Was Well Tolerated in Healthy Adult Participants When Administered With and Without Digoxin and Rosuvastatin or Quinidine

- In Part 1, the most common adverse event (AE) was diarrhea, reported by 80% of participants. All diarrhea events resolved without the need for dose modifications
- Hyperphosphatemia, a known on-target AE of FGFR inhibitors [4,5], was experienced by 75% of subjects yet was reversible upon completion of futibatinib dosing
- In Part 2, nine participants discontinued treatment due to prolonged ECG QT following quinidine administration in Period 1
- These AEs were considered related to quinidine treatment, and all resolved upon discontinuation. Quinidine, an anti-malaria drug, is also a substrate of cardiac channels known to lengthen the QT internal on an ECG [6]

Table 4. Most Frequent Treatment Emergent AEs (TEAEs) in Part 1 and Part 2

Adverse Events	Part 1*		Part 2*	
TEAEs, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any TEAE	19 (95)	4 (20)	15 (63)	9 (38)
Diarrhea	16 (80)	4 (20)	3 (13)	0
Blood phosphorus increased	15 (75)	0	0	0
Abdominal pain	6 (30)	0	1 (4)	0
Dry mouth	5 (25)	0	0	0
Abdominal discomfort	4 (20)	0	0	0
Constipation	4 (20)	0	0	0
Nausea	3 (15)	0	2 (8)	0
Back pain	3 (15)	0	0	0
Dysuria	3 (15)	0	0	0
ECG QT prolonged	0	0	9 (38)	9 (38)

*TEAEs reported in at least three participants in either part of the study. ECG, electrocardiogram.

CONCLUSION

- Futibatinib had no impact on plasma and urine digoxin (a P-gp substrate) exposure and no clinically relevant effect on plasma rosuvastatin (a BCRP substrate) exposure, suggesting lack of clinically meaningful effects on these drug transporters
- Co-administration with quinidine (a P-gp inhibitor) revealed that the contribution of P-gp to futibatinib absorption appeared to be negligible, and clinical perpetrators of P-gp are unlikely to have a clinically meaningful effect on the bioavailability of futibatinib
- Futibatinib, when administered either alone or with digoxin + rosuvastatin or quinidine, was safe and well tolerated in healthy adult subjects
- Altogether, these findings support the concomitant administration of futibatinib with other drugs that are P-gp and BCRP substrates and/or P-gp inhibitors

REFERENCES

1. U.S. Food and Drug Administration (FDA). LYTGOBI® (futibatinib) tablets, for oral use. US prescribing information. Updated September 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214801Orig1s000lbledt.pdf
2. Yamamiya I, et al. Evaluation of the cytochrome P450 3A and P-glycoprotein drug-drug interaction potential of futibatinib. Clin Pharmacol Drug Dev. 2023;12:966-978.
3. International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH). Drug Interaction Studies M12. Updated May 2024. https://database.ich.org/sites/default/files/ICH_M12_Step4_Guideline_2024_0521_0.pdf
4. Kommalapati A, et al. FGFR inhibitors in oncology: insight on the management of toxicities in clinical practice. Cancers (Basel). 2021;13:2968.
5. Meric-Bernstam F, et al. Safety Profile and Adverse Event Management for Futibatinib, an Irreversible FGFR1–4 Inhibitor: Pooled Safety analysis of 469 patients. Clin Cancer Res. 2024; Epub ahead of print.
6. Wiśniowska B, et al. Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect - comprehensive overview of clinical trials. BMC Pharmacol Toxicol. 2016;17:12.

Sabina Paglialunga, PhD
Senior Director, Scientific Affairs
sabina.paglialunga@celerion.com

Acknowledgments: The authors thank the participants who took part in the trial, as well as the Celerion research staff who assisted this study.

Disclosures: This study was funded by Taiho Oncology, Inc.

Read the Full Paper:
Long A, Yamamiya I, Valentine M, et al. A phase I drug–drug interaction study to assess the effect of futibatinib on P-gp and BCRP substrates and of P-gp inhibition on the pharmacokinetics of futibatinib. Clin Transl Sci. 2024;17:e70012. doi:10.1111/cts.70012