Drug–Drug Interactions of Lirafugratinib

Xiaoyan Li*,[1] Helen Humphries,[2] Rishikesh Sawant,[1] Florence (Tianhui) Ramirez,[1] Kai Yu Jen,[1] Fabien Ricard,[1] Jinshan Shen[1]

[1]Relay Therapeutics, Cambridge, Massachusetts, USA; [2]Certara UK Ltd, Simcyp Division, Sheffield, United Kingdom
* Research completed while employed at Relay Therapeutics

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INTRODUCTION

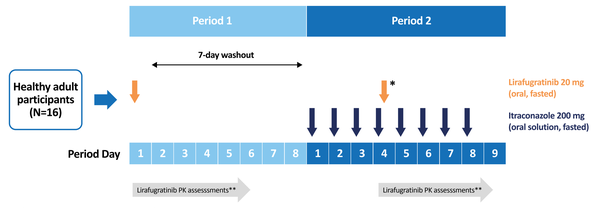
- Lirafugratinib, a potent and highly selective fibroblast growth factor receptor-2 (FGFR2) inhibitor,[1] has shown encouraging initial efficacy in patients with *FGFR2*-altered cancers[2,3]
  - The safety profile of lirafugratinib is differentiated by its minimal off-isoform toxicity[2,3]
  - In vitro data suggest that lirafugratinib is a substrate of cytochrome P450 (CYP)3A4, CYP2J2, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp)[4]
  - Lirafugratinib may also inhibit CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, P-gp, BCRP, organic anion transporting polypeptide (OATP)1B, and multidrug and toxin extrusion proteins (MATEs)[4]
- To assess the drug–drug interaction (DDI) potentials of lirafugratinib, we used an integrated approach that included a clinical DDI study and a physiologically based pharmacokinetic (PBPK) modeling and simulation

METHODS

Clinical DDI study

- A Phase 1, open-label, two-period, fixed sequence, crossover DDI study was conducted to evaluate the effect of itraconazole (strong CYP3A4 inhibitor) on the pharmacokinetics (PK) of lirafugratinib in healthy adults (**Figure 1**)
- In Period 1, participants received a single oral dose of lirafugratinib (20 mg), followed by a 7-day washout period. In Period 2, participants received itraconazole oral solution (200 mg) once daily (QD) for 8 days, with a single oral dose of lirafugratinib (20 mg) given ~60 minutes after itraconazole on Day 4 of the study period. Lirafugratinib PK assessments were conducted in both study periods for up to 120 hours after lirafugratinib dosing
- Plasma concentrations of lirafugratinib were determined using a validated liquid chromatography–tandem mass spectrometry assay. PK parameters were estimated using noncompartmental methods in Phoenix™ WinNonlin® Version 8.3.4.295 (Certara, Princeton, NJ, USA)
- The potential effect of itraconazole on log-transformed lirafugratinib PK parameters was assessed in linear mixed-effect models, including treatment as a fixed effect and participant as a random effect. PK effects were expressed as least-squares geometric mean ratios (LSGMRs) comparing lirafugratinib plus itraconazole (test) versus lirafugratinib alone (reference) with associated 90% confidence intervals (CIs)

Figure 1. Clinical DDI study design

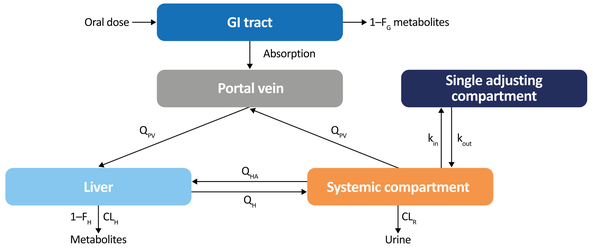


*Lirafugratinib was administered ~60 minutes after itraconazole on Period 2 Day 4.
**Blood samples for PK assessment were collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours post-dosing of lirafugratinib.
DDI, drug–drug interaction; PK, pharmacokinetic.

PBPK model development, verification, and application

- A minimal PBPK model including separate compartments for the gastrointestinal tract and liver, along with a non-physiological single adjusting compartment, was developed using the population-based Simcyp™ PBPK Simulator version 21 (Certara) (**Figure 2**)
- The PBPK model integrated in vitro data and clinical PK data following single and multiple dosing of lirafugratinib 70 mg QD from the Phase 1/2 ReFocus trial in patients with *FGFR2*-altered cancers (NCT04526106)[2,3]
- The performance of the PBPK model was verified against clinical PK data from the ReFocus trial, including the full range of evaluated doses (20–100 mg once daily [QD] or twice daily [BID]), as well as clinical data from the DDI study in healthy adults
- The verified PBPK model was used to simulate DDI potentials between lirafugratinib (as the victim) and CYP3A4 inhibitors or inducers, and between lirafugratinib (as the perpetrator) and CYP or transporter substrates using in vitro K_I, Ind_{max} and $IndC_{50}$ values
- In an exploratory sensitivity analysis, the minimal PBPK model was expanded to a full PBPK model incorporating intestinal and liver passive permeability and P-gp efflux to simulate the effect on lirafugratinib PK following concurrent inhibitions of CYP3A4 and P-gp or inhibition of CYP3A4 alone by itraconazole or quinidine

Figure 2. Minimal PBPK model with a single adjusting compartment and advanced dissolution, absorption, and metabolism of lirafugratinib



CL_r, hepatic clearance; CL_R, renal clearance; F_G, fraction escaping first-pass metabolism in the gut; F_H, fraction escaping first-pass metabolism in the liver; GI, gastrointestinal; k_{in}, rate constant for drug transfer into the single adjusting compartment; k_{out}, rate constant for drug transfer out of the single adjusting compartment; PBPK, physiologically based pharmacokinetic; Q_H, blood flow in the liver; Q_{HA}, blood flow in the hepatic artery; Q_{PV}, blood flow in the portal vein.

RESULTS

Clinical DDI study

- Sixteen participants were enrolled and completed the study
- The median age was 32.5 years (range, 23–50); nine (56.3%) were female, 10 (62.5%) were Black or African American, and six (37.5%) were White
- Compared with lirafugratinib alone, coadministration of itraconazole led to a 26% increase in lirafugratinib C_{max} (LSGMR, 1.26; 90% CI, 1.16–1.37) and a 2-fold increase in the area under the plasma concentration–time curve from time 0 extrapolated to infinity (AUC_{0-inf}; LSGMR, 2.00; 90% CI, 1.91–2.09; **Table 1**)

Table 1. Effect of itraconazole on the PK of lirafugratinib (N=16)

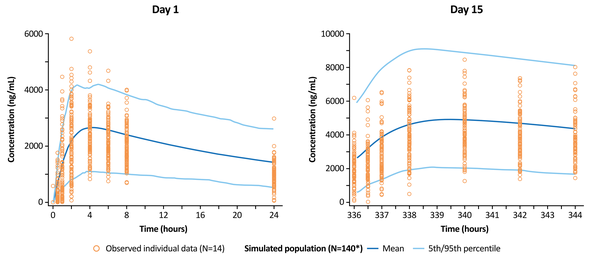
PK parameter	Treatment	LS geometric mean	Lirafugratinib plus itraconazole versus lirafugratinib alone	
			LSGMR	90% CI
C_{max} (ng/mL)	Lirafugratinib plus itraconazole	1365	1.26	1.16–1.37
	Lirafugratinib alone	1081		
AUC_{0-last} (h*ng/mL)	Lirafugratinib plus itraconazole	32663	1.98	1.90–2.07
	Lirafugratinib alone	16471		
AUC_{0-inf} (h*ng/mL)	Lirafugratinib plus itraconazole	33237	2.00	1.91–2.09
	Lirafugratinib alone	16644		

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

PBPK model development and verification

- The PBPK model sufficiently captured the observed concentration–time data in patients who received lirafugratinib 70 mg QD in the ReFocus trial (**Figure 3**)
- The predicted concentration–time data were also comparable to the clinical data for the other QD and BID doses tested in the ReFocus trial (data not shown)
- Predicted C_{max} and AUC_{0-inf} geometric mean ratios (GMRs) for lirafugratinib with versus without itraconazole were consistent with data from the clinical DDI study (**Table 2**), verifying the value for the fraction of drug metabolized by CYP3A4 (fm_{CYP3A4}) used in the PBPK model (0.46)

Figure 3. Observed and model-predicted plasma concentration–time profiles on Day 1 and Day 15 for patients who received lirafugratinib 70 mg QD in the ReFocus trial



*The simulated data represent ten trials of 14 patients, with sex and age ranges matched to those who received lirafugratinib 70 mg QD in the ReFocus trial.

Table 2. Observed and PBPK model-predicted DDI effects of itraconazole on the PK of a single dose of lirafugratinib 20 mg

PK parameter	Treatment	Observed		Predicted	
		Geometric mean (CV%)	GMR (90% CI)	Geometric mean (CV%)	GMR (90% CI)
C_{max} (ng/mL)	Lirafugratinib plus itraconazole	1370 (22%)	1.26 (1.16–1.37)	1000 (34%)	1.13 (1.13–1.14)
	Lirafugratinib alone	1080 (18%)		883 (33%)	
AUC_{0-inf} (h*ng/mL)	Lirafugratinib plus itraconazole	33,200 (30%)	2.00 (1.91–2.09)	40,761 (67%)	2.04 (1.98–2.11)
	Lirafugratinib alone	16,600 (26%)		19,967 (57%)	

*The simulated data represent ten trials of 16 participants, with sex and age range matched to participants in the clinical DDI study, for a single 20 mg dose of lirafugratinib with or without coadministration of itraconazole.
AUC_{0-inf}, area under the plasma concentration–time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetics.

PBPK model application: DDI simulations

- Victim DDI simulations from the PBPK model indicated no clinically relevant DDIs between lirafugratinib and cimetidine (weak CYP3A4 inhibitor) (**Table 3**)
- Lirafugratinib AUC_{0-inf} was predicted to increase by 66% with erythromycin (moderate CYP3A4 inhibitor), and decrease by 57% with efavirenz (moderate CYP3A4 inducer) and 75% with rifampicin (strong CYP3A4 inducer)
- Perpetrator DDI simulations predicted no clinically relevant DDIs between lirafugratinib and substrates of various CYP enzymes, including CYP2B6 (bupropion), CYP2C8 (repaglinide), CYP2C9 (tolbutamide), CYP2C19 (omeprazole), CYP2D6 (desipramine), and CYP3A4 (midazolam) (**Table 4**)
- Similarly, no clinically relevant DDIs were predicted between lirafugratinib and substrates of the transporters P-gp (digoxin), organic anion transporting polypeptide-1B (rosuvastatin) and MATEs (metformin), whereas a weak-to-moderate DDI was predicted for BCRP (rosuvastatin)

Exploratory sensitivity analysis to assess DDI mediated by P-gp

- Concurrent inhibitions of CYP3A4 and P-gp inhibition only marginally increased the predicted AUC_{0-inf} GMR for lirafugratinib (<15%) as compared with inhibition of CYP3A4 alone by itraconazole or quinidine
  - For itraconazole, GMRs were increased by 9% for both C_{max} (1.21-fold vs. 1.11-fold, respectively) and AUC_{0-inf} (1.95-fold vs. 1.79-fold)
  - For quinidine, GMRs were increased by 13% for C_{max} (1.18-fold vs. 1.04-fold) and 12% for AUC_{0-inf} (1.18-fold vs. 1.05-fold)

Table 3. Model-predicted DDI effects between lirafugratinib (as the victim) and CYP3A4 inhibitors or inducers (N=100*)

Perpetrator drug	GMR (90% CI)	
	C_{max} (ng/mL)	AUC_{0-inf} (h*ng/mL)
Cimetidine (weak CYP3A4 inhibitor)	1.04 (1.04–1.04)	1.08 (1.08–1.09)
Erythromycin (moderate CYP3A4 inhibitor)	1.13 (1.12–1.14)	1.66 (1.61–1.71)
Efavirenz (moderate CYP3A4 inducer)	0.85 (0.84–0.86)	0.43 (0.40–0.45)
Rifampicin (strong CYP3A4 inducer)	0.65 (0.62–0.68)	0.25 (0.23–0.27)

*The simulated data represent ten trials of 10 participants, with sex and age range matched to patients in the ReFocus trial, who received a single 70 mg dose of lirafugratinib with or without coadministration of perpetrator drugs.
AUC_{0-inf}, area under the plasma concentration–time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CYP, cytochrome P450; GMR, geometric mean ratio.

Table 4. Model-predicted DDI effects between lirafugratinib (as the perpetrator*) and CYP or transporter substrates (N=100)**

Perpetrator drug	GMR (90% CI)	
	C_{max} (ng/mL)	AUC_{0-inf} (h*ng/mL)
Bupropion (CYP2B6 substrate)	1.01 (1.00–1.01)	1.00 (1.00–1.00)
Repaglinide (CYP2C8 substrate)	1.04 (1.04–1.05)	1.05 (1.04–1.05)
Tolbutamide (CYP2C9 substrate)	1.01 (1.01–1.01)	1.01 (1.01–1.01)
Omeprazole (CYP2C19 substrate)	1.04 (1.03–1.05)	1.05 (1.04–1.05)
Desipramine (CYP2D6 substrate)	1.03 (1.02–1.03)	1.03 (1.03–1.04)
Midazolam (CYP3A4 substrate)	1.18 (1.17–1.20)	1.19 (1.18–1.21)
Digoxin (P-gp substrate)	1.19 (1.17–1.20)	1.07 (1.06–1.08)
Rosuvastatin (BCRP substrate)	2.58 (2.47–2.70)	1.47 (1.44–1.51)
Rosuvastatin (OATP1B substrate)	1.02 (1.02–1.02)	1.02 (1.01–1.02)
Metformin (MATEs substrate)***	1.03 (NA)	1.03 (NA)

*The simulations were based on lirafugratinib enzyme competitive inhibition constants (Kis) established in vitro.
**The simulated data represent ten trials of 10 participants, with sex and age range matched to patients in the ReFocus trial, for single doses of victim drugs with or without coadministration of lirafugratinib 70 mg QD under steady-state conditions.
***The simulation of n=1 was conducted for a representative male participant with cancer, aged 68, due to the intensive computational time needed to run complex PBPK models of lirafugratinib and metformin.
AUC_{0-inf}, area under the plasma concentration–time curve from time 0 extrapolated to infinity; BCRP, breast cancer resistance protein; CI, confidence interval; C_{max}, maximum observed plasma concentration; CYP, cytochrome P450; DDI, drug–drug interaction; GMR, geometric mean ratio; MATE, multidrug and toxin extrusion protein; NA, not applicable; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; QD, once daily.

CONCLUSIONS

- Lirafugratinib C_{max} and AUC_{0-inf} were increased 1.26- and 2.00-fold, respectively, by coadministration of itraconazole in a clinical DDI study
- Based on PBPK modeling and simulation, weak CYP3A4 inhibitors are unlikely to have a clinically relevant effect on lirafugratinib exposure, whereas moderate or strong CYP3A4 inhibitors and inducers may have a weak-to-moderate effect
- Lirafugratinib is not expected to have a clinically relevant effect on the exposures of substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, P-gp, OATP1B and MATEs. In contrast, a weak-to-moderate effect is expected on the exposures of BCRP substrates. Modulation of P-gp activity is unlikely to affect lirafugratinib exposures significantly
- The assessment of DDI potentials of lirafugratinib using an integrated approach will inform its dosing with concomitant medications in patients with *FGFR2*-altered cancers

References

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