No Clinically Relevant Effect of Moderate Hepatic Impairment on the Pharmacokinetics of Lirafugratinib

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INTRODUCTION

- Lirafugratinib is a potent and highly selective fibroblast growth factor receptor-2 (FGFR2) inhibitor in clinical development for the treatment of *FGFR2*-altered cancers[1–3]
- In the Phase 1/2 ReFocus trial, lirafugratinib showed encouraging initial efficacy across multiple solid tumor types with various *FGFR2* alterations[2,3]
- The safety profile of lirafugratinib is differentiated by its minimal off-isoform toxicity[2,3]
- Nonclinical data indicated that lirafugratinib was a substrate of drug-metabolizing enzymes (DMEs) and efflux transporters in the liver[4]
- Hepatic impairment can significantly influence the activities of DMEs and transporters and, therefore, the pharmacokinetics (PK) of drugs that are substrates of DMEs and transporters[5,6]
- We conducted a Phase 1 trial to characterize the effect of moderate hepatic impairment on the PK of lirafugratinib and thereby inform dosing guidance for patients with impaired hepatic function

METHODS

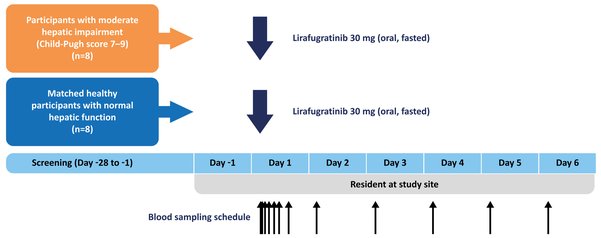
Trial design and objectives

- This Phase 1, open-label trial was conducted in participants with moderate hepatic impairment and matched healthy participants with normal hepatic function
- The primary objective was to compare the single-dose PK of lirafugratinib between participants with moderate hepatic impairment and participants with normal hepatic function
- The secondary objective was to evaluate the safety and tolerability of a single dose of lirafugratinib in these two participant groups

Eligibility and treatment

- Eligible participants were males and females 18–75 years of age, with a body mass index (BMI) of 18.0–40.0 kg/m^2 and body weight ≥45 kg, who either were nonsmokers or light smokers (≤10 cigarettes/week and able to abstain during the study)
  - For enrollment into the moderate hepatic impairment group, participants were required to have a Child–Pugh score of [7–9]
  - Participants with normal hepatic function were matched (1:1) to participants in the moderate hepatic impairment group based on sex, age (±10 years), BMI (±15%), and smoking status
- All participants received a single oral 30 mg dose of lirafugratinib on Day 1 after an overnight fasting of at least 10 hours (**Figure 1**)

Figure 1. Phase 1 study design



Assessments

- Blood samples 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
  - Plasma protein binding of lirafugratinib was assayed in 2- and 24-hour post-dose samples using equilibrium dialysis
  - Plasma concentrations of lirafugratinib were determined at all time points using a validated liquid chromatography–tandem mass spectrometry assay to estimate PK parameters
- Safety and tolerability assessments included reporting of adverse events (AEs), as graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0

Statistical analyses

- A sample size of 16 participants (eight with moderate hepatic impairment and eight with normal hepatic function) was planned based on practical considerations and US Food and Drug Administration guidance[6]
- Equilibrium dialysis data were used to calculate the lirafugratinib percent plasma protein binding and unbound fraction (f_u)
- Plasma PK parameters were estimated based on actual sampling times using non-compartmental methods in Phoenix™ WinNonlin® Version 8.3.4.295 (Certara, Princeton, NJ, USA)
  - Evaluated PK parameters included maximum observed plasma concentration (C_{max}) and area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration (AUC_{0-last}) or from time 0 extrapolated to infinity (AUC_{0-inf})
  - Unbound PK parameters (i.e., $C_{max,u}$, $AUC_{0-last,u}$, and $AUC_{0-inf,u}$) were also evaluated based on individual f_u estimates
- Log-transformed PK parameters were compared between groups using an analysis-of-variance model, including participant group as a fixed effect and participant as a random effect
  - PK effects were expressed as least-squares geometric mean ratios (LSGMRs) comparing participants with moderate hepatic impairment versus participants with normal hepatic function, with associated 90% confidence intervals (CIs)
- PK parameters were also summarized descriptively according to the NCI-Organ Dysfunction Working Group (NCI-ODWG) classification of hepatic function[7]

RESULTS

Study participants

- The study enrolled 16 participants, including eight participants with moderate hepatic impairment (Child–Pugh score 7–9) and eight healthy participants with normal hepatic function, all of whom completed the study
- Participant demographic characteristics were similar between the two groups (**Table 1**)

Table 1. Participant characteristics (N=16)

	Moderate hepatic impairment (n=8)	Normal hepatic function (n=8)
Age, median (range), years	56.0 (36–63)	50.5 (36–63)
Male, n (%)	7 (87.5)	7 (87.5)
Ethnicity, n (%)		
Hispanic/Latino	6 (75.0)	6 (75.0)
Not Hispanic/Latino	2 (25.0)	2 (25.0)
Race, n (%)		
White	8 (100)	8 (100)
Weight, mean (SD), kg	90.1 (11.3)	87.4 (16.7)
BMI, mean (SD), kg/m^2	30.3 (2.8)	29.4 (4.2)
NCI-ODWG hepatic function classification, n (%)		
Normal hepatic function	1 (12.5)	8 (100)
Mild hepatic impairment	4 (50.0)	0
Moderate hepatic impairment	2 (25.0)	0
Severe hepatic impairment	1 (12.5)	0

BMI, body mass index; NCI-ODWG, National Cancer Institute-Organ Dysfunction Working Group; SD, standard deviation.

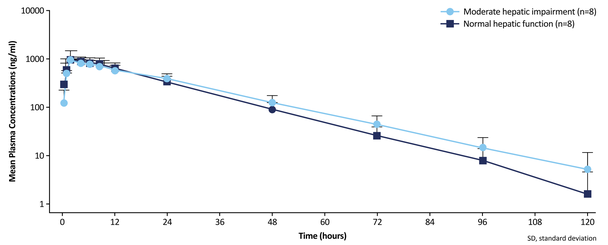
Lirafugratinib plasma protein binding

- Plasma protein binding at 2 and 24 hours post-dose for each participant was concentration-independent; therefore, the mean of the f_u estimates at the two time points was used for further analyses
- Plasma protein binding was high in both groups; f_u was slightly higher in participants with moderate hepatic impairment, with geometric mean (CV%) values of 0.000885 (18.6%) and 0.000665 (6.21%), respectively

Effect of moderate hepatic impairment on lirafugratinib PK

- Lirafugratinib exposures were similar between participants with moderate hepatic impairment and participants with normal hepatic function (**Figure 1**, **Table 2**)
  - LSGMRs (90% CIs) were 0.95 (0.68–1.31) for C_{max}, 1.04 (0.81–1.34) for AUC_{0-last}, and 1.05 (0.81–1.35) for AUC_{0-inf}

Figure 2. Mean (+SD) plasma concentrations of lirafugratinib in participants with moderate hepatic impairment or normal hepatic function after a single 30 mg dose



- The unbound lirafugratinib exposures were slightly higher in participants with moderate hepatic impairment than participants with normal hepatic function
  - LSGMRs (90% CIs) were 1.26 (0.94–1.68) for $C_{max,u}$, 1.39 (1.09–1.77) for $AUC_{0-last,u}$, and 1.39 (1.09–1.77) for $AUC_{0-inf,u}$
  - These slightly higher exposures in participants with moderate hepatic impairment are not expected to be clinically relevant

Table 2. Effect of moderate hepatic impairment on lirafugratinib total and unbound PK following a single 30 mg dose

PK parameter	Group	LS geometric mean	Moderate hepatic impairment vs. normal hepatic function	
			LSGMR	90% CI
C_{max} (ng/mL)	Moderate hepatic impairment (n=8)	986	0.95	0.68–1.31
	Normal hepatic function (n=8)	1044		
AUC_{0-last} (h*ng/mL)	Moderate hepatic impairment (n=8)	21303	1.04	0.81–1.34
	Normal hepatic function (n=8)	20445		
AUC_{0-inf} (h*ng/mL)	Moderate hepatic impairment (n=8)	21562	1.05	0.81–1.35
	Normal hepatic function (n=8)	20607		
$C_{max,u}$ (ng/mL)	Moderate hepatic impairment (n=8)	0.873	1.26	0.94–1.68
	Normal hepatic function (n=8)	0.694		
$AUC_{0-last,u}$ (h*ng/mL)	Moderate hepatic impairment (n=8)	18.8	1.39	1.09–1.77
	Normal hepatic function (n=8)	13.6		
$AUC_{0-inf,u}$ (h*ng/mL)	Moderate hepatic impairment (n=8)	19.1	1.39	1.09–1.77
	Normal hepatic function (n=8)	13.7		

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

Lirafugratinib PK, according to NCI-ODWG classification of hepatic function

- Of the eight participants with moderate hepatic impairment based on Child–Pugh score, NCI-ODWG hepatic function classification was normal in one participant, mildly impaired in four, moderately impaired in two, and severely impaired in one (**Table 1**)
- All participants with normal hepatic function also had normal hepatic function per NCI-ODWG criteria
- There did not appear to be any notable differences in lirafugratinib PK according to NCI-ODWG classification of hepatic function (**Table 3**)

Table 3. Geometric mean (%CV) total and unbound lirafugratinib PK parameters after a single 30 mg dose according to NCI-ODWG classification of hepatic function (N=16)

	Normal hepatic function (n=9)	Mild hepatic impairment (n=4)	Moderate hepatic impairment (n=2)	Severe hepatic impairment (n=1)
C_{max} (ng/mL)	1047 (32.8)	1183 (39.0)	909 (34.3)	519 (NA)
AUC_{0-last} (h*ng/mL)	21030 (26.8)	23839 (34.6)	17358 (31.5)	16535 (NA)
AUC_{0-inf} (h*ng/mL)	21197 (26.7)	24130 (34.1)	17520 (31.7)	16898 (NA)
$C_{max,u}$ (ng/mL)	0.706 (35.3)	0.974 (35.1)	0.819 (37.7)	0.686 (NA)
$AUC_{0-last,u}$ (h*ng/mL)	14.2 (30.4)	19.6 (31.0)	15.6 (34.6)	21.9 (NA)
$AUC_{0-inf,u}$ (h*ng/mL)	14.3 (30.3)	19.9 (30.3)	15.7 (34.8)	22.3 (NA)

%CV, geometric percent coefficient of variance; AUC_{0-inf}, area under the plasma concentration–time curve time 0 extrapolated to infinity; $AUC_{0-last,u}$, unbound AUC_{0-last}; $AUC_{0-inf,u}$, area under the plasma concentration–time curve time 0 to the time of the last quantifiable concentration; $AUC_{0-inf,u}$, unbound AUC_{0-inf}; C_{max}, maximum observed plasma concentration; $C_{max,u}$, unbound C_{max}; NA, not applicable; NCI-ODWG, National Cancer Institute-Organ Dysfunction Working Group.

Safety and tolerability

- Treatment-emergent AEs were reported for no participants with moderate hepatic impairment and one participant (12.5%) with normal hepatic function (grade 1 headache)
- There were no deaths, serious AEs, or AEs leading to study discontinuation

CONCLUSIONS

- Lirafugratinib PK were similar between participants with moderate hepatic impairment and matched healthy participants with normal hepatic function
- A single 30 mg dose of lirafugratinib was well tolerated in participants with moderate hepatic impairment and in those with normal hepatic function
- These data indicate that no dose adjustment of lirafugratinib would be needed in patients with moderate hepatic impairment

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