Effect of Rivoceranib Administered as 200 mg Once Daily on the Pharmacokinetics of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 Substrates

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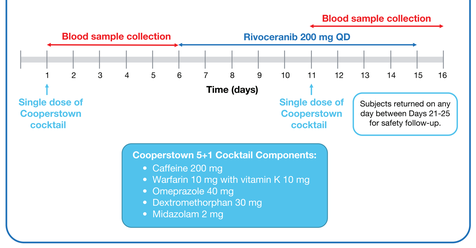
BACKGROUND

- Rivoceranib is a selective vascular endothelial growth factor receptor tyrosine kinase inhibitor with potent antitumor activity.
- In the phase 3 CARES-310 trial, rivoceranib in combination with camrelizumab significantly improved median progression-free survival and significantly extended median overall survival for the treatment of patients with unresectable hepatocellular carcinoma (uHCC) versus sorafenib[1].
- The purpose of this study is to evaluate the effect of rivoceranib on the pharmacokinetics (PK) of various cytochrome P450 (CYP) substrates in healthy subjects following administration of rivoceranib 200 mg once daily (QD), which is similar to the proposed rivoceranib dosing regimen (250 mg QD) in combination with camrelizumab for the treatment of uHCC.

STUDY DESIGN

- This open-label, fixed-sequence, crossover drug-drug interaction phase 1 study evaluated the impact of multiple oral doses of rivoceranib 200 mg QD on the PK of single oral doses of CYP enzyme substrates included in the Cooperstown 5+1 cocktail (caffeine 200 mg [CYP1A2 substrate], warfarin 10 mg [CYP2C9 substrate]/vitamin K 10 mg, omeprazole 40 mg [CYP2C19 substrate], dextromethorphan 30 mg [CYP2D6 substrate], and midazolam 2 mg [CYP3A4/5 substrate][2] (**Figure 1**).

Figure 1: Study design



METHODS

- Pharmacokinetic Sampling and Analyses
  - For probe substrate drugs, serial venous blood samples with a volume of 6 mL were collected at the following times on Days 1 and 11: pre-dose and 0.25 hours (h), 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 48 h, 72 h, 96 h, and 120 h post-dose.
  - Blood sample for analysis of rivoceranib concentration was collected on Day 11 pre-dose.
  - The plasma concentrations of rivoceranib, probe substrates, and their metabolites were measured using validated liquid chromatography tandem mass spectrometry (LC–MS/MS) methods.
- Statistical Analysis
  - PK parameters for the CYP probe substrates and metabolites were estimated using noncompartmental methods in Phoenix WinNonlin version 6.4 (Pharsight, A Certara Company, St. Louis, MO).
  - Statistical analyses were conducted using SAS Software version 9.4 or later (SAS Institute, Inc., Cary, NC). A linear mixed-effects model was used to evaluate the effect of rivoceranib on the PK of each probe drug; geometric mean ratio (GMR) and 90% confidence interval (CI) were estimated for the primary PK parameters of cocktail (C_{max}, AUC_{0-t}, AUC_{0-inf}) in combination with rivoceranib versus cocktail alone.
- Safety and tolerability were assessed by monitoring of treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs.

RESULTS

- **Table 2** presents the probe drug PK parameters and the GMR with 90% CI for the change in C_{max}, AUC_{0-t} and AUC_{0-inf} of the CYP probe substrates and metabolites in the presence or absence of rivoceranib.
  - Coadministration of rivoceranib 200 mg QD decreased caffeine AUC_{0-inf} by 18% and C_{max} by 7%, increased S-warfarin AUC_{0-inf} by 1.35-fold and C_{max} by 1.05-fold, increased omeprazole AUC_{0-inf} by 2.06-fold and C_{max} by 1.64-fold, increased dextromethorphan AUC_{0-inf} by 2.67-fold and C_{max} by 1.90-fold, and increased midazolam AUC_{0-inf} by 1.44-fold and C_{max} by 1.15-fold.
  - Coadministration of rivoceranib 200 mg QD has minimal effect on the exposures (GMRs of C_{max}, AUCs ranged from 0.81 to 1.26) of metabolites for all probe substrates.
- **Figure 2** presents the mean plasma concentration-versus-time profiles of CYP probe substrates and their metabolites in the presence or absence of rivoceranib.
- The mean pre-dose plasma concentration of rivoceranib on Day 11 was 78.4 ng/mL (minimum 5.95 ng/mL, maximum 141 ng/mL), demonstrating the presence of rivoceranib in all subjects prior to administration of Cooperstown cocktail + rivoceranib.
- Eight subjects (8/18, 44.4%) experienced a total of 14 TEAEs (1 TEAE from Cooperstown cocktail alone, 13 TEAEs from Cooperstown cocktail + rivoceranib). The most common TEAEs were panic attack (5/18, 27.8%) and headache (3/18, 16.7%). All TEAEs were mild in severity except 1 TEAE of moderate severity.

Table 1: Demographics and baseline characteristics

Characteristic	Overall (N=18)
Median age, years (min, max)	34.5 (23.0, 45.0)
Median height, meters (min, max)	1.7 (1.5, 1.8)
Median weight, kg (min, max)	70.3 (46.2, 85.4)
Median BMI, kg/m^2 (min, max)	24.4 (21.2, 28.1)
Male sex, n (%)	10 (55.6)
Race, n (%)	
American Indian or Alaska Native	0
Asian	1 (5.6)
Black or African American	2 (11.1)
Native Hawaiian or Other Pacific Islander	1 (5.6)
White	13 (72.2)
Other	1 (5.6)
Ethnicity, n (%)	
Hispanic or Latino	7 (38.9)
Not Hispanic or Latino	11 (61.1)

BMI, body mass index.

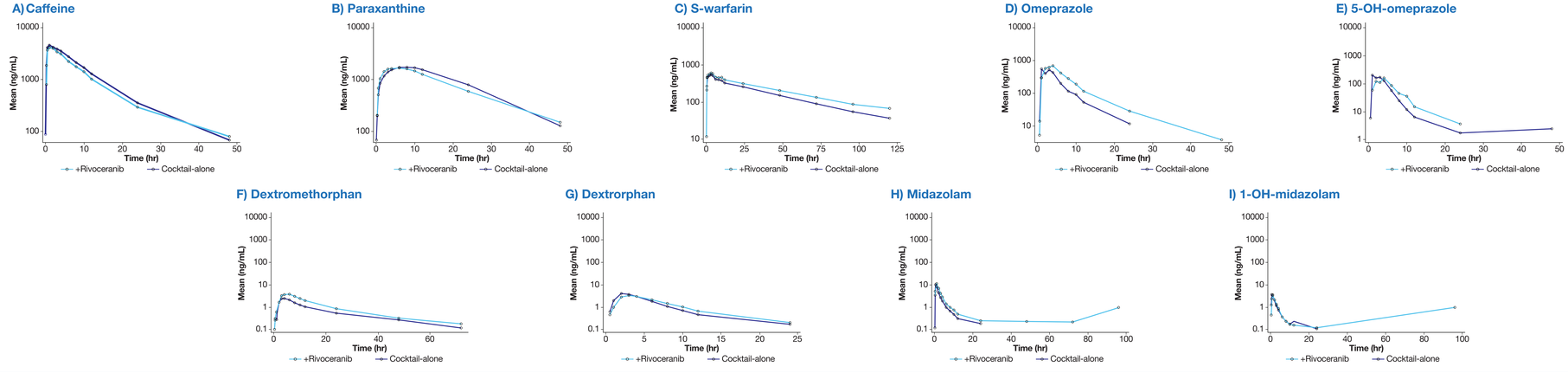
Table 2: Summary of plasma pharmacokinetics of probe drugs alone and with rivoceranib 200 mg QD

Probe drug or metabolite	PK parameter	Probe drug only		Probe drug + rivoceranib 200 mg QD		
		n	Geometric mean (%CV)	n	Geometric mean (%CV)	Ratio (90% CI)
CYP1A2						
Caffeine	C_{max} (ng/mL)	18	4907 (23.8)	16	4551 (23.3)	0.93 (0.85, 1.02)
	AUC_{0-t} (h*ng/mL)	18	41251 (41.5)	16	32957 (48.9)	0.81 (0.71, 0.91)
	AUC_{0-inf} (h*ng/mL)	18	42037 (41.7)	16	33965 (48.5)	0.82 (0.72, 0.92)
	$t_{1/2}$ (h)	18	5.29 (29.3)	16	4.54 (39.8)	
	T_{max} (h)[a]	18	0.95 (0.2, 1.95)	16	0.95 (0.45, 1.95)	
Paraxanthine	C_{max} (ng/mL)	18	1231 (20.0)	16	1198 (25.5)	0.99 (0.92, 1.07)
	AUC_{0-t} (h*ng/mL)	18	23814 (22.6)	16	19169 (28.9)	0.81 (0.73, 0.91)
	AUC_{0-inf} (h*ng/mL)	18	24010 (21.7)	14	20414 (22.9)	0.87 (0.79, 0.94)
CYP2C9						
S-warfarin	C_{max} (ng/mL)	18	641 (20.8)	16	675 (22.9)	1.05 (0.96, 1.16)
	AUC_{0-t} (h*ng/mL)	18	1831 (21.7)	16	22135 (41.1)	1.20 (1.03, 1.40)
	AUC_{0-inf} (h*ng/mL)	17	20267 (24.2)	13	26117 (28.1)	1.35 (1.28, 1.43)
	$t_{1/2}$ (h)	18	33.6 (18.3)	15	42.1 (23.4)	
	T_{max} (h)[a]	18	1.98 (0.48, 3.98)	16	1.98 (0.48, 12.0)	
CYP2C19						
Omeprazole	C_{max} (ng/mL)	18	585 (95)	16	950 (50.9)	1.64 (1.28, 2.10)
	AUC_{0-t} (h*ng/mL)	18	1589 (142)	16	3484 (82.3)	2.31 (1.87, 2.86)
	AUC_{0-inf} (h*ng/mL)	15	2101 (113)	16	3721 (79.8)	2.06 (1.64, 2.59)
	$t_{1/2}$ (h)	15	2.28 (60.6)	15	1.69 (51.8)	
	T_{max} (h)[a]	18	2.93 (0.93, 5.93)	16	2.93 (1.93, 9.93)	
5-OH-omeprazole	C_{max} (ng/mL)	18	218 (55.6)	16	174 (62.8)	0.80 (0.69, 0.94)
	AUC_{0-t} (h*ng/mL)	18	771 (31.8)	16	810 (29.5)	1.09 (1.03, 1.16)
	AUC_{0-inf} (h*ng/mL)	17	776 (30.7)	15	827 (30.3)	1.08 (1.01, 1.06)
CYP2D6						
Dextromethorphan	C_{max} (ng/mL)	18	1.60 (156)	16	2.73 (136)	1.90 (1.40, 2.59)
	AUC_{0-t} (h*ng/mL)	18	12.0 (277)	16	26.0 (208)	2.54 (1.86, 3.48)
	AUC_{0-inf} (h*ng/mL)	15	20.2 (157)	12	49.2 (110)	2.67 (2.00, 3.55)
	$t_{1/2}$ (h)	16	6.50 (45.1)	14	3.63 (42.6)	
	T_{max} (h)[a]	18	2.92 (0.92, 5.92)	16	3.42 (1.92, 8.05)	
Dextrorphan	C_{max} (ng/mL)	18	3.87 (61.6)	16	3.35 (46.3)	0.90 (0.75, 1.08)
	AUC_{0-t} (h*ng/mL)	18	20.4 (59.0)	16	22.1 (49.0)	1.15 (0.99, 1.34)
	AUC_{0-inf} (h*ng/mL)	17	23.4 (46.1)	16	24.0 (45.3)	1.11 (0.97, 1.27)
CYP3A4						
Midazolam	C_{max} (ng/mL)	18	9.88 (38.3)	16	11.5 (28.7)	1.15 (1.00, 1.31)
	AUC_{0-t} (h*ng/mL)	18	23.8 (42.0)	16	37.2 (44.8)	1.56 (1.32, 1.84)
	AUC_{0-inf} (h*ng/mL)	18	25.2 (41.8)	15	36.9 (41.8)	1.44 (1.27, 1.64)
	$t_{1/2}$ (h)	18	3.53 (36.7)	15	3.89 (58.2)	
	T_{max} (h)[a]	18	0.5 (0.25, 1.00)	16	1.00 (0.50, 1.00)	
1-OH-midazolam	C_{max} (ng/mL)	18	3.62 (51.8)	16	3.18 (34.0)	0.89 (0.73, 1.09)
	AUC_{0-t} (h*ng/mL)	18	8.61 (50.0)	16	10.7 (54.2)	1.26 (1.01, 1.58)
	AUC_{0-inf} (h*ng/mL)	18	9.15 (48.9)	14	10.3 (32.4)	1.14 (1.03, 1.26)

[a]Median (min, max) data are provided for T_{max}.

Figure 2: Plasma Concentration versus Time Profiles of CYP Probe Substrates and Metabolites Alone and in Combination with Rivoceranib

- Mean plasma drug concentrations versus time profiles of caffeine **(A)** and its metabolite, paraxanthine **(B)**, S-warfarin **(C)**, omeprazole **(D)** and its metabolite, 5-OH-omeprazole **(E)**, dextromethorphan **(F)** and its metabolite, dextrorphan **(G)**, midazolam **(H)** and its metabolite, 1-OH-midazolam **(I)**, following administration of Cooperstown cocktail alone and following rivoceranib 200 mg QD plus Cooperstown cocktail.



DISCUSSION

- The Cooperstown 5+1 cocktail approach, involving simultaneous administration of substrates for multiple CYP isozymes to subjects, has been shown to be effective for evaluation of whether rivoceranib has the potential for clinically significant drug-drug interactions with multiple enzymes.
- According to the classification criteria of CYP inducers or inhibitors per the FDA and EMA guidances[3,4],the results of this study indicate that rivoceranib 200 mg QD has marginal effect on CYP1A2 (AUC decrease <20%) but is a weak inhibitor of CYP2C9 and CYP3A4/5 (AUC increase ≥ 1.25-fold but < 2-fold), and a moderate inhibitor of CYP2C19 and CYP2D6 (AUC increase ≥ 2-fold but < 5-fold).
- Large PK variability was observed for omeprazole (CYP2C19 substrate) and dextromethorphan (CYP2D6 substrate). This is probably due to the polymorphism of these enzymes, which might result in the inclusion of poor, intermediate, efficient, or ultrarapid metabolizers in the study.

CONCLUSIONS

- Rivoceranib at 200 mg QD does not substantially affect the exposure of the substrates of CYP1A2, CYP2C9, CYP2C19, and CYP3A4/5. Therefore, recommendation of contraindication or dose adjustment of these CYP substrates is not needed when administered with rivoceranib at 200 mg QD. However, for CYP3A and CYP2C9 substrate drugs which toxicity is sensitive to increase in exposure, we recommend referring to Prescribing Information of these substrates and monitoring more frequently for substrate-related adverse reactions.
- Rivoceranib may increase the exposure of the substrate of CYP2D6 by 2.67-fold. We recommend avoiding concomitant use of CYP2D6 substrate drugs with rivoceranib or referring to substrate Prescribing Information when concomitant use cannot be avoided.
- Cooperstown cocktail, alone or in combination with rivoceranib, was generally well tolerated.

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