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ORIGINAL RESEARCH ARTICLE

Effect of Rivoceranib 200 mg Once Daily on the Pharmacokinetics of a Cocktail Probe Substrate of Cytochrome P450 Enzymes: A Phase I Trial in Healthy Volunteers

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Abstract

Background and Objective Rivoceranib, a vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor with antitumor activity, is metabolized in the liver mostly by cytochrome P450 (CYP)3A4/5. In vitro studies suggest that rivoceranib at clinically relevant concentrations may inhibit metabolism of various CYP substrates. This study evaluated the effects of rivoceranib 200 mg once daily (QD) on the pharmacokinetics of various CYP substrates using the Cooperstown 5+1 cocktail. The dosing regimen of rivoceranib used in this study is similar to the proposed rivoceranib regimen (250 mg QD) in combination with camrelizumab for the treatment of patients with hepatocellular carcinoma.

Methods This open-label, fixed-sequence, crossover, drug–drug interaction phase I study evaluated the impact of multiple oral doses of rivoceranib 200 mg QD on the single oral dose pharmacokinetics of CYP enzyme substrates administered in the modified Cooperstown 5+1 cocktail (caffeine 200 mg [CYP1A2], warfarin 10 mg [*S*-warfarin as CYP2C9 substrate] + vitamin K 10 mg, omeprazole 40 mg [CYP2C19], dextromethorphan 30 mg [CYP2D6], and midazolam 2 mg [CYP3A4]) in 18 healthy volunteers. After fasting, volunteers received a single dose of the Cooperstown 5+1 cocktail on day 1 and rivoceranib plus Cooperstown 5+1 cocktail on day 11. After completing a meal, volunteers received a single dose of rivoceranib on days 6–10 and 12–15. Blood samples for pharmcokinetic analyses of substrates were collected pre-dose and up to 120 h post-Cooperstown 5+1 cocktail dosing on days 1 and 11. Volunteers returned once between days 21 and 25 for safety follow-up.

Results Rivoceranib 200 mg QD decreased the cumulative area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0–inf}$) for caffeine by 20% and maximum observed plasma concentration (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 1.9-fold, and increased midazolam $AUC_{0–inf}$ by 1.44-fold and C_{max} by 1.15-fold.

Conclusions Rivoceranib 200 mg QD may substantially inhibit the metabolism of CYP2D6 substrates. Therefore, concomitant use of CYP2D6 substrate drugs with rivoceranib should be approached with caution, and dose adjustment of substrates of CYP2D6 may be necessary when co-administration cannot be avoided. Rivoceranib 200 mg QD may also exert weak inhibitory effects on the metabolism of CYP3A, CYP2C9, and CYP2C19 substrates. In such cases, close monitoring for substrate-related adverse reactions is recommended, particularly when toxicity is sensitive to increased exposures of these substrate drugs.

Clinical Trial Registration ClinicalTrials.gov identifier: NCT03561298.

Key Points

Results of this phase I pharmacokinetic study in healthy volunteers suggest that rivoceranib 200 mg once daily may act as a moderate inhibitor of cytochrome P450 2D6 substrates.

Patients receiving rivoceranib concomitantly with cytochrome P450 2D6 substrate drugs may require dose adjustments and/or careful monitoring for potential adverse events.

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1 Introduction

Rivoceranib is an oral kinase inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2) and other kinases, including VEGFR-1, VEGFR-3, RET, KIT, and PDGFR-beta [1]. Rivoceranib (apatinib) has been approved for patients with advanced metastatic gastric cancer in China [2–4] and has demonstrated benefit across a variety of other advanced or metastatic cancers, including breast cancer [5, 6], hepatocellular carcinoma (HCC) [7], non-small cell lung cancer [8, 9], ovarian cancer [10], and thyroid cancer [11]. Clinical trials of combination approaches using rivoceranib, including with camrelizumab in patients with advanced HCC [12] or advanced triple-negative breast cancer [13] and with pegylated liposomal doxorubicin in patients with recurrent ovarian cancer [14], have used a rivoceranib dose of 250 mg once daily (QD).

In the CARES-310 (NCT03764293) randomized, open-label, international phase III study in patients with unresectable HCC not previously treated with systemic therapy, participants received rivoceranib 250 mg orally QD in combination with camrelizumab 200 mg intravenously once every 2 weeks versus sorafenib 400 mg orally twice daily. Rivoceranib plus camrelizumab significantly improved median progression-free survival (5.6 months [95% confidence interval (CI) 5.5–6.3] vs 3.7 months [95% CI 2.8–3.7]) and significantly extended median overall survival (23.8 months [95% CI 20.6–27.2] vs 15.2 months [95% CI 13.0–18.5] with sorafenib [hazard ratio: 0.64, 95% CI 0.52–0.79; one-sided $p < 0.0001$], demonstrating a clinically meaningful improvement in survival [15]. The most common treatment-related adverse events with camrelizumab plus rivoceranib were hypertension (38.2%), increased aspartate aminotransferase (17.3%), and palmar-plantar erythrodysesthesia syndrome (12.1%), compared with palmar-plantar erythrodysesthesia syndrome (15.6%), increased aspartate aminotransferase (5.2%), and diarrhea (5.2%) with sorafenib [15]. In patients with unresectable HCC, rivoceranib plus camrelizumab had a manageable safety profile.

Pharmacokinetic (PK) analyses in patients with advanced solid tumors have indicated that single-dose rivoceranib reaches maximum observed plasma concentration (C_{max}) in 2–4 h and has a mean half-life of approximately 9 h [16]. Maximum observed plasma concentration and cumulative area under the plasma concentration–time curve from time 0 to infinity (AUC_{0-inf}) of rivoceranib generally increase in a dose-proportional manner at doses that range from 81 mg to 685 mg following either single- or multiple-dose administration. Rivoceranib is metabolized in human liver microsomes primarily by cytochrome P450 (CYP)3A4/5, with minor contributions from CYP2D6, CYP2C9, and CYP2E1 [17]. In a clinical drug interaction study, rivoceranib mean C_{max} increased 3.1-fold and AUC_{0-inf} increased 3.2-fold following coadministration of itraconazole 200 mg (a strong CYP3A4 and P-glycoprotein inhibitor) and a single dose of rivoceranib 200 mg, indicating that CYP3A4 primarily contributed to the metabolism of rivoceranib [18]. Results from a human absorption, distribution, metabolism, and excretion study showed that rivoceranib is primarily excreted in feces with almost no unmetabolized rivoceranib recovered from urine.

In vitro studies using human liver microsomes have demonstrated that rivoceranib has the potential to inhibit multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The mean half-maximal inhibitory concentration values, based on three independent experiments, were 3.74, 1.14, 0.49, 0.32, 0.31, 2.56, 0.81, and 0.4 μM for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 (midazolam as substrate), and CYP3A4 (testosterone as substrates), respectively. Except for CYP1A2 and CYP2D6, the R value for basic models of reversible inhibition (R_1) for CYP2C9, CYP2C19, and CYP3A were all greater than or equal to the threshold of 1.02. The *R* value for basic models of reversible intestinal inhibition ($R_{1,gut}$) for CYP3A was greater than the threshold of 11. Therefore, the inhibition of the above CYP enzymes by rivoceranib could not be ruled out. In vitro, rivoceranib also induced a ≥ 2-fold increase in messenger RNA of CYP1A2 and CYP3A in human hepatocytes. Clinically, the potential for drug–drug interactions (DDIs) exists when rivoceranib is administered concomitantly with drugs that are primarily metabolized by these CYP enzyme substrates. Therefore, it is important to evaluate the effect of rivoceranib on the pharmacokinetics of these CYP enzyme substrates.

The use of CYP phenotyping cocktails is a validated approach for assessing the DDI potential of a drug on multiple CYP enzymes simultaneously in a single study. The Cooperstown 5 probe drugs plus one vitamin K (5+1) cocktail include substrates of CYP1A2 (caffeine, 3 mg/kg orally), CYP2C9 (warfarin, 10 mg and vitamin K 10 mg orally), CYP2C19 (omeprazole, 40 mg orally), CYP3A (midazolam, 0.025 mg/kg intravenously), and CYP2D6 (dextromethorphan, 30 mg orally). The addition of vitamin K counteracts the blood-thinning effects of the warfarin [19]. A modified version of the Cooperstown 5+1 cocktail uses oral instead of intravenous midazolam, enabling the assessment of the effect of the tested drug on intestinal as well as hepatic CYP3A activity [20–26]. The cocktail approach to assess potential DDIs is supported by M12 Drug Interaction Studies guidance for industry [27].

Hence, this clinical drug interaction study was designed to evaluate the effect of multiple oral doses of rivoceranib 200 mg on the pharmacokinetics of a single dose of multiple CYP enzyme substrates in healthy volunteers, using the modified Cooperstown 5+1 cocktail approach. The safety and tolerability of oral rivoceranib in healthy volunteers

were also assessed. This study did not evaluate the effect of CYP substrates on the pharmacokinetics of rivoceranib.

2 Methods

2.1 Study Design

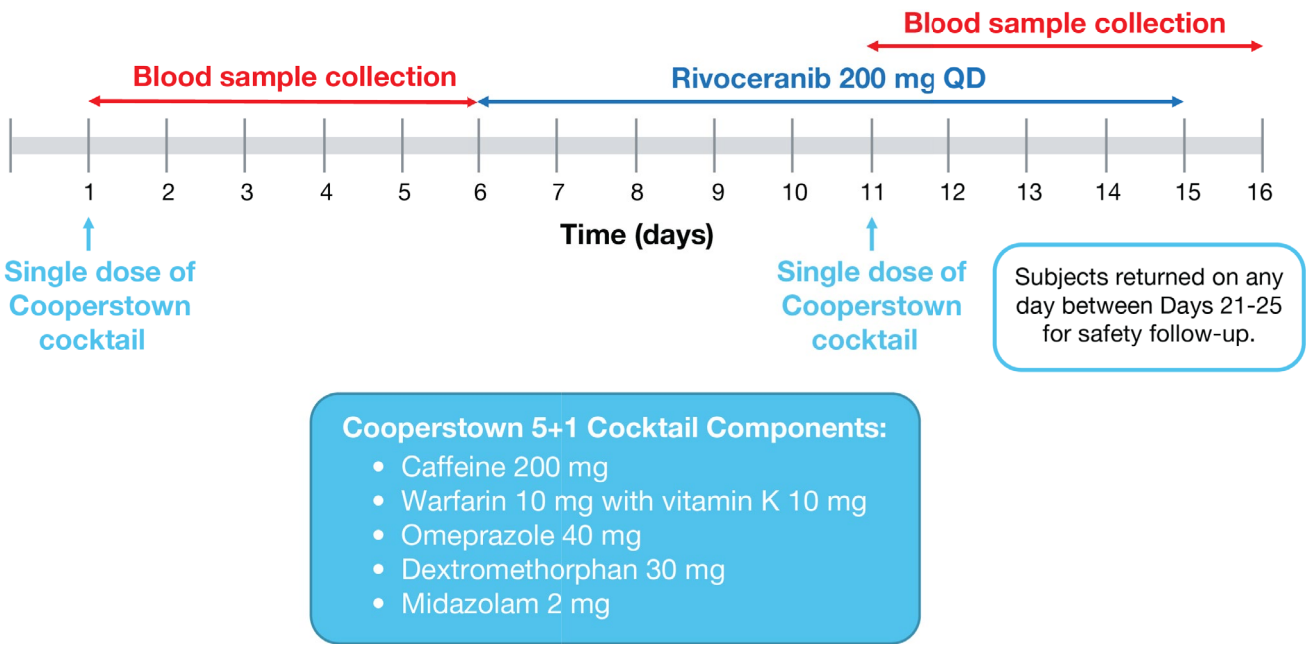
This cocktail DDI study was registered on ClinicalTrials.gov (NCT03561298). The study protocol was approved by the Alpha Institutional Review Board and conducted in compliance with the study protocol, the International Standard of Good Clinical Practice, the ethical principles of the Declaration of Helsinki, and applicable regulatory requirements. All of the healthy volunteers provided written informed consent prior to enrollment.

This was an open-label fixed-sequence crossover study designed to investigate the effect of coadministration of multiple doses of rivoceranib on the pharmacokinetics of probe substrates for different CYP enzymes in healthy volunteers. After overnight fasting on day 1, volunteers received a single dose of the Cooperstown 5+1 cocktail comprising caffeine 200 mg, warfarin 10 mg with vitamin K 10 mg, omeprazole 40 mg, dextromethorphan, and midazolam 2 mg (Fig. 1). On days 6 through 10 and days 12 through 15, volunteers received rivoceranib 200 mg 60 min after the start of a standard meal, which had to be eaten within 30 min. On day 11, after fasting overnight, a single oral dose of rivoceranib 200 mg was co-administered with the Cooperstown 5+1 cocktail.

Volunteers were housed in a clinical research unit starting 2 days before dosing for coronavirus disease 2019 screening. The stay in the clinical research unit lasted until completion of end-of-treatment assessments on day 16. Between days 21 and 25, volunteers returned once to the clinical research unit for safety follow-up procedures. Healthy volunteers were called 30 ± 2 days after the last dose to collect follow-up information on any unresolved adverse events, new adverse events, and any concomitant medications used within 30 days after the last dose.

2.2 Study Volunteers

Eighteen volunteers were enrolled to ensure that at least 12 evaluable volunteers completed the study. Eligible volunteers were healthy men and women aged between 18 and 45 years, with a body mass index of 19–29 kg/m^2, and weight >50 kg for male individuals and ≥ 45 kg for female individuals. All volunteers were in good health determined by medical history, physical examination, vital signs, clinical laboratory tests (hematology, urinalysis, blood chemistry), and 12-lead electrocardiogram. Inclusion also required coronavirus disease 2019 negative status. Eligibility also required that female participants were not pregnant or breastfeeding and were either not of childbearing potential or taking a highly effective non-hormonal contraceptive. To avoid



QD, once daily.

Fig. 1 Study design. *QD* once daily

any interference with the Cooperstown 5+1 cocktail, study volunteers abstained from taking any caffeine- and xanthine-containing products, tobacco/nicotine-containing products, and alcohol from 5 days prior to baseline until collection of final PK blood samples (at day 16). In addition, study volunteers discontinued intake of drinks and foods containing poppy seed or grapefruit-related fruits and juices (e.g., pomelos, Seville oranges) from 14 days prior to the first dose until collection of the final PK blood sample. Study volunteers also abstained from strenuous exercise from 7 days prior to dosing until collection of the final PK blood sample.

Exclusion criteria included evidence or history of clinically significant disease or any condition such as hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, neuropsychiatric, or allergic disease. Volunteers were excluded if they consumed or intended to use any medications/products known to alter the absorption, distribution, metabolism, and excretion processes of the study drugs within 30 days prior to the first dose administration.

2.3 Pharmacokinetic (PK) Sampling and Analyses

For probe substrate drugs, serial venous blood samples with a volume of 8 mL were collected at the following timepoints on days 1 and 11: pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120 h post-dose. Blood samples were analyzed to determine plasma concentrations for caffeine and its metabolite paraxanthine, *R*-warfarin and *S*-warfarin, omeprazole and its metabolite 5-OH-omeprazole, dextromethorphan, and its metabolite dextrorphan, and midazolam and its metabolite 1-OH-midazolam. 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 methods developed separately for each component by Q^2 Solution (formally named AIT Bioscience, Indianapolis, IN, USA) [Q2 solutions, unpublished data]. Five bioanalytical methods (BAM) were developed to determine the plasma concentrations of rivoceranib (BAM.0118.06), midazolam and 1- hydroxymidazolam (BAM.0502.01), omeprazole, 5-hydroxyomeprazole, dextromethorphan, and dextrorphan (BAM.0582.02), caffeine and paraxanthine (BAM.0776.02), and *R*-warfarin and *S*-warfarin (BAM.0780.02). The protein precipitation extraction procedures were utilized to extract rivoceranib, *R*-warfarin and *S*-warfarin with their internal standards, and liquid-liquid extraction procedures were utilized to extract the other analytes with internal standards from human plasma containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) as an anticoagulant. Samples were then analyzed on a Waters ACQUITY liquid chromatograph interfaced with a Thermo Scientific TSQ Vantage triple quadrupole mass spectrometer with ESI ionization. Chiral separation of *R*-warfarin and *S*-warfarin was achieved using the Lux i-Amylose-3 chiral column. The calibration range of analytes in plasma was from 0.100 ng/mL to 100 ng/mL for both midazolam and 1-hydroxymidazolam, from 2.50 ng/mL to 2500 ng/mL for both *R*-warfarin and *S*-warfarin, from 0.100 ng/mL to 50.0 ng/mL for both dextromethorphan and dextrorphan, from 2.00 ng/mL to 1000 ng/mL for omeprazole, from 1.00 ng/mL to 500 ng/mL for 5-hydroxyomeprazole, from 10.0 ng/mL to 10,000 ng/mL for both caffeine and paraxanthine, and from 0.500 ng/mL to 500 ng/mL for rivoceranib.

2.4 PK and Statistical Analysis

Pharmacokinetic 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, USA). The PK parameter analysis population included all volunteers who had received one dose or more of the study drug (i.e., any component of the Cooperstown 5+1 cocktail or rivoceranib) and had completed one or more PK parameter.

Primary PK parameters analyzed for CYP probe substrates included C_{max}, cumulative area under the plasma concentration–time curve calculated from 0 to the last measurable plasma concentration (AUC_{0-t}) using the linear up and log down method, and AUC_{0-inf} if the portion extrapolated from time of last quantifiable measurement to infinity did not exceed 20%. Other PK parameters included terminal elimination half-life ($t_{1/2}$), and time of maximum observed plasma concentration (T_{max}). Descriptive statistics for plasma concentrations and PK parameters were provided for each probe drug with and without rivoceranib treatment, including number of volunteers, arithmetic mean, standard deviation, percent coefficient of variation, standard error of the mean, minimum, median, maximum, and geometric mean (GM) with 90% CI. The pre-dose plasma concentration of rivoceranib at steady state on day 11 was summarized as arithmetic mean, standard deviation, percent coefficient of variation, and standard error of the mean, minimum, median, maximum.

Statistical analyses were conducted using SAS Software Version 9.4 or later (SAS Institute, Inc., Cary, NC, USA). The effect of rivoceranib on the pharmacokinetics of each probe drug was evaluated by calculating a 90% CI of the geometric mean ratio (GMR) on the primary PK parameters of cocktail in combination with rivoceranib versus cocktail alone. The primary PK parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) were natural log-transformed before assessment using a linear mixed-effects model that included treatment as the fixed effect and volunteers as the random effect. Estimates

of the adjusted mean differences between treatment groups (with or without rivoceranib) and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted GMs for each treatment group (with or without rivoceranib) and 90% CIs for the ratios.

2.5 Safety Assessments

The safety population comprised all volunteers who received one or more doses of the study drug. Safety and tolerability were assessed based on monitoring of treatment-emergent adverse events (TEAEs), clinical laboratory tests (hematology, coagulation, blood chemistry, urinalysis), vital signs, physical examinations, and 12-lead electrocardiograms. Treatment-emergent adverse events were monitored by the investigators throughout the study up to 30 days (±2 days) after the last dose of the study drug and were graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

3 Results

3.1 Study Population

The study enrolled 18 healthy volunteers, 56% ($n = 10$) men and 44% ($n = 8$) women, with a median age of 34.5 years (range, 23–45 years) and mean body mass index of 24.4 kg/m^2 (range, 21.2–28.1 kg/m^2) [Table 1]. Thirteen volunteers were white (72%), two volunteers were African American (11%), one volunteer was Asian (6%), one volunteer was Native Hawaiian or other Pacific Islander (6%), and one volunteer was other race (6%). Fifteen (83%) volunteers completed the study and three (17%) left the study early. One volunteer did not receive the rivoceranib dose on days 12, 13, 14, or 15 because of an adverse event (a drug-induced panic attack). Two volunteers voluntarily withdrew from the study and did not receive any doses of rivoceranib or the dose of Cooperstown 5+1 cocktail on day 11.

Table 1 Demographics and baseline characteristics

Characteristics	Overall ($N = 18$)
Median age, years (min, max)	34.5 (23.0, 45.0)
Median height, m (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, *max* maximum, *min* minimum

3.2 Pharmacokinetics and Drug–Drug Interactions (DDIs)

Healthy volunteers received oral rivoceranib 200 mg QD from day 6 to day 12. The mean (minimum, maximum) predose plasma concentration of rivoceranib on day 11 was 78.4 (5.95, 141) ng/mL. The mean steady-state trough concentration of rivoceranib measured in this study is comparable to the exposures observed in patients with solid tumors who received rivoceranib 200 mg from other studies [mean (minimum, maximum) steady-state trough concentration of 59.6 (7.1, 78.2) ng/mL] and demonstrated the presence of rivoceranib in all volunteers prior to administration of the Cooperstown 5+1 cocktail plus rivoceranib.

Figure 2A–I presents the mean plasma concentration-versus-time profiles for caffeine, paraxanthine, *R*-warfarin, *S*-warfarin, omeprazole, 5-hydroxy-omeprazole, dextromethorphan, dextrorphan, midazolam, and 1-hydroxy-midazolam following administration of the Cooperstown 5+1 cocktail alone or rivoceranib plus Cooperstown 5+1 cocktail. Probe drug PK parameters (C_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$, and T_{max}) and the GMRs with 90% CIs for the change in C_{max}, AUC_{0-t}, and AUC_{0-inf} of the CYP probe substrates and selected metabolites in the presence of rivoceranib relative to without rivoceranib are summarized in Table 2.

Based on the linear mixed-effects model estimated GMRs (Table 2), coadministration of rivoceranib 200 mg QD decreased caffeine AUC_{0-inf} by 20% 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 1.9-fold, increased midazolam AUC_{0-inf} by 1.44-fold and C_{max} by 1.15-fold. When fold changes in AUC_{0-inf} and C_{max} for the cocktail substrates were calculated directly from the observed GM values with and without rivoceranib, the resulting GMRs were generally consistent with those estimated using the linear mixed-effects model. The only exception was omeprazole, for which lower fold increases were observed, with AUC_{0-inf} and C_{max} increasing by 1.77-fold and 1.62-fold, respectively, based on the observed GM values.

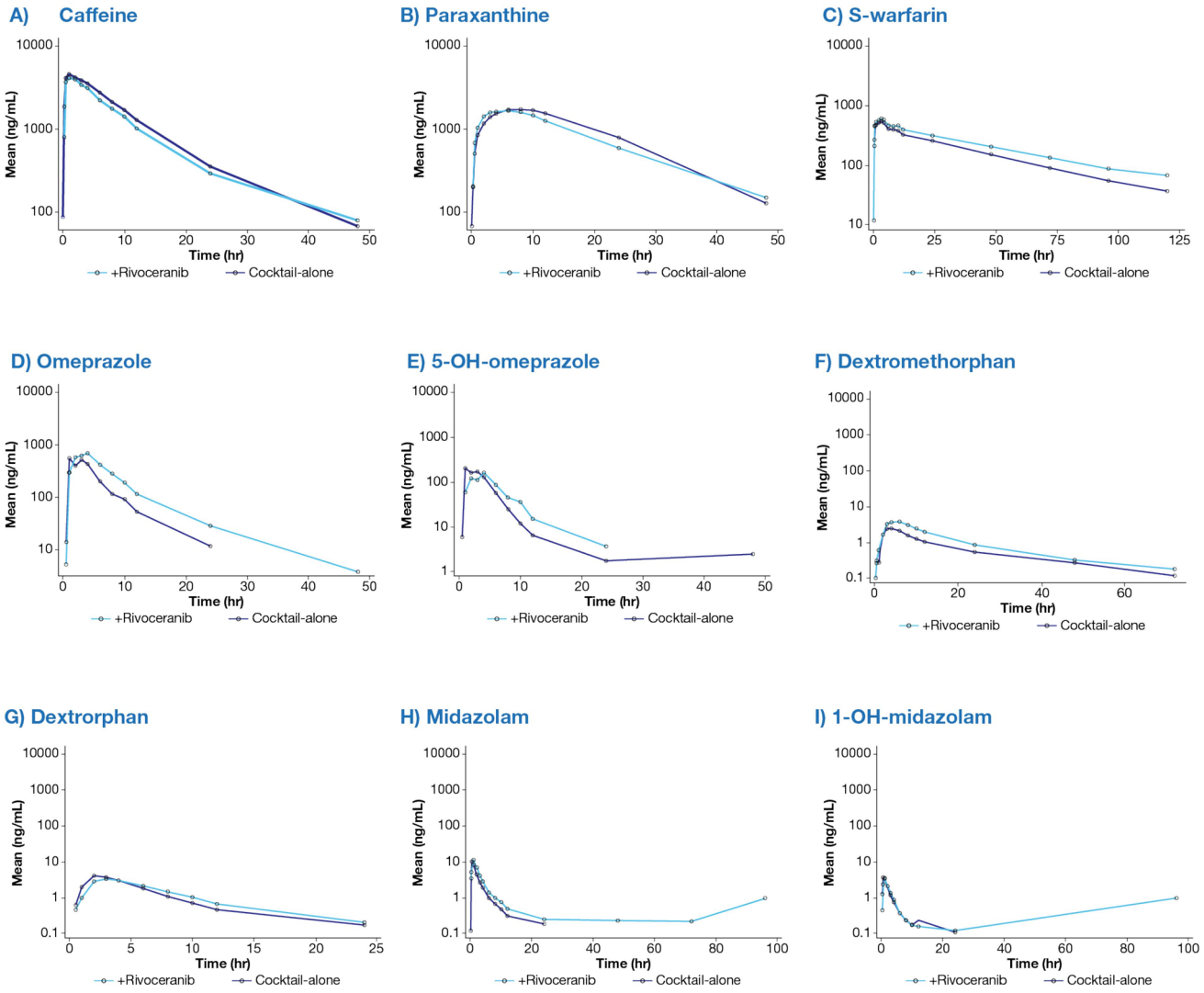


Fig. 2 Plasma concentration versus time profiles of cytochrome P450 probe substrates and metabolites following administration of the Cooperstown cocktail alone or following rivoceranib 200 mg once daily (QD) plus the Cooperstown cocktail. *hr* hours

In statistical comparisons of T_{max} for each probe drug analyte, no statistically significant differences were observed when the probe drugs were co-administered with rivoceranib compared to when administered alone. Coadministration with rivoceranib generally increased the $t_{1/2}$ of probe drugs, with the exception of caffeine, for which the $t_{1/2}$ was slightly shorter when administered concomitantly with rivoceranib.

In addition, coadministration of rivoceranib 200 mg QD had a minimal effect on the exposures (GMRs of C_{max}, AUC $_{0–inf}$ ranged from 0.81 to 1.26) of metabolites for all probe substrates. The metabolite-to-parent ratios for C_{max} and AUC $_{0–inf}$ were comparable for caffeine/paraxanthine in the presence (0.26 for C_{max}, 0.60 for $AUC_{0–inf}$) and absence (0.25 for C_{max}, 0.57 for $AUC_{0–inf}$) of rivoceranib 200 mg. In contrast, the metabolite-to-parent ratios decreased for all other CYP probe substrates when co-administered with rivoceranib 200 mg, likely reflecting the increased exposure to the parent substrates due to inhibition of their metabolism by rivoceranib.

3.3 Safety

In this study, eight volunteers (8/18, 44.4%) experienced TEAEs. Among them, one volunteer experienced at least one TEAE while receiving the Cooperstown 5+1 cocktail alone, and seven volunteers experienced at least one TEAE while receiving the Cooperstown 5+1 cocktail plus rivoceranib. The most common TEAEs were headache (3/18, 16.7%) and panic attack (5/18, 27.8%). The only TEAE considered to be related to administration of the Cooperstown 5+1 cocktail alone was headache (1/18, 5.6%). The TEAEs considered to

Table 2 Summary of plasma PK parameters of probe drugs and the associated metabolites when Cooperstown 5+1 cocktail probe substrates were administered alone or with rivoceranib 200 mg QD

Probe drug or metabolite	PK Parameter	Probe drugs only		Probe drugs + rivoceranib 200 mg QD		Ratio (90% CI)
		n	Geometric mean (%CV)	*n*	Geometric mean (%CV)	
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	41,251 (41.5)	16	32,957 (48.9)	0.81 (0.71, 0.91)
	AUC_{0-inf} (h*ng/mL)	18	42,037 (41.7)	16	33,965 (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	23,814 (22.6)	16	19,169 (28.9)	0.81 (0.73, 0.91)
	AUC_{0-inf} (h*ng/mL)	18	24,010 (21.7)	14	20,414 (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	18,381 (21.7)	16	22,135 (41.1)	1.20 (1.03, 1.40)
	AUC_{0-inf} (h*ng/mL)	17	20,267 (24.2)	13	26,117 (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)	15	3721 (79.8)	2.06 (1.64, 2.59)
	$t_{1/2}$ (h)	15	1.53 (52.6)	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, 1.16)
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)

AUC_{0-inf} cumulative area under the plasma concentration–time curve from time 0 to infinity, *AUC_{0-t}* cumulative area under the plasma concentration–time curve calculated from 0 to the last measurable plasma concentration, *CI* confidence interval, *C_{max}* maximum observed plasma concentration, *%CV* percent coefficient of variation, *CYP* cytochrome P450, *h* hours, *PK* pharmacokinetic, *QD* once daily, *$t_{1/2}$* terminal elimination half-life, *T_{max}* time to C_{max}

[a]Median (minimum, maximum) data are provided for T_{max}

be related to coadministration of rivoceranib and Cooperstown 5+1 cocktail were panic attacks (5/16, 31.3%), headache (2/16, 12.5%), upper abdominal pain (1/16, 6.3%), musculoskeletal chest pain (1/16, 6.3%), fatigue (1/16, 6.3%), and back pain (1/16, 6.3%). One volunteer withdrew from the study because of a moderate severity TEAE (panic attack) after coadministration of rivoceranib and the Cooperstown 5+1 cocktail. Five volunteers experienced a panic attack approximately 3–6 h following administration of the Cooperstown 5+1 cocktail plus rivoceranib. No panic attacks occurred on any other day of the study, including study days when rivoceranib was administered alone or on day 1 when the Cooperstown 5+1 cocktail was administered alone. Although the independent relationship to the Cooperstown 5+1 cocktail or rivoceranib cannot be determined, anxiety and nervousness are known side effects of two of the components of the Cooperstown 5+1 cocktail (i.e., caffeine and dextromethorphan) and, therefore, the panic attacks may be attributed to the Cooperstown 5+1 cocktail rather than to rivoceranib. All other TEAEs experienced during the study were mild in nature and were consistent with those observed in other studies of rivoceranib.

4 Discussion

Rivoceranib has demonstrated potent antitumor activity against multiple types of cancers either as a single agent or in combination with camrelizumab [2-14,]. In vitro data have suggested that rivoceranib can inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A in human liver microsomes at clinically relevant concentrations. In addition, rivoceranib upregulates the messenger RNA level of CYP1A2 and CYP3A in human cryopreserved hepatocytes. Together, the observed complicated in vitro DDIs warranted a further in vivo assessment following repeated rivoceranib administration. Cocktail DDI studies allow for a simultaneous assessment of the effect of a perpetrator drug on the pharmacokinetics of multiple DDI probe drugs. This study used the validated modified Cooperstown 5+1 cocktail approach, which consists of probes for substrates of CYP1A2 (caffeine), CYP2C9 (warfarin), CYP2C19 (omeprazole), CYP3A (midazolam), and CYP2D6 (dextromethorphan) [19]. The Cooperstown 5+1 cocktail does not include probe substrates of CYP2B6 and CYP2C8, which were also inhibited by rivoceranib in vitro. A separate clinical DDI study was conducted to evaluate the DDI potential of rivoceranib on substrates of CYP2B6 (bupropion) and CYP2C8 (repaglinide) in volunteers with solid tumors; results suggest that rivoceranib has negligible DDI with CYP2B6 but weakly inhibits CYP2C8.

Cocktail DDI studies are a valuable tool for efficiently assessing the DDI potential of a perpetrator drug on multiple probe substrates in a single study [19–31]. Cocktail DDI studies have been conducted in healthy volunteers for many tyrosine kinase inhibitor drugs with oncology indications, which aims to reduce interindividual variability [30]. Healthy volunteers were also used in this cocktail DDI study based on the overall safety profiles of rivoceranib, as well as the lower PK variability of rivoceranib observed in healthy volunteers compared with patients with cancer. A population PK model predicted that rivoceranib AUC_{0-inf} increases 28% in patients with HCC compared with healthy volunteers.

Rivoceranib 200 mg was selected in this DDI study based on the phase II trial of rivoceranib for recurrent or metastatic adenoid cystic carcinoma [32]. In this clinical study (RM-202), patients were initiated on rivoceranib 700 mg with dose modifications through a three-step downward dosage adjustment (500 mg to 300 mg to 200 mg) as needed to improve tolerability [32]. The 200-mg dosage of rivoceranib was selected as the minimum effective dose and used herein. Although the rivoceranib 200-mg dose is slightly lower than the rivoceranib 250-mg dose used in the phase III CARES-310 study with camrelizumab [15], the AUC_{0-inf} of rivoceranib 200 mg QD accounts for 83% of AUC_{0-inf} of 250 mg, which may reflect the DDI effect at 250 mg.

Food intake was shown to increase the exposure of rivoceranib (250 mg) by 63–98% and delayed the median t_{max} (Elevar Therapeutics, data on file). In this study, standard meals were allowed in those days when rivoceranib was administered alone to increase the bioavailability of rivoceranib. However, administration of the Cooperstown 5+1 cocktail and PK measurements were performed after overnight fasting to avoid the variability and confounding factors introduced by the food intake.

According to the classification criteria of CYP inhibitors or inducers per the US Food and Drug Administration and European Medicines Agency guidance, the results of this study indicate that rivoceranib 200 mg QD had a minimal effect on CYP1A2 (AUC_{0-inf} decrease $<20\%$) but could be a weak inhibitor of CYP2C9 and CYP3A (AUC_{0-inf} increase ≥ 1.25-fold but <2-fold) and a moderate inhibitor of CYP2D6 (AUC_{0-inf} increase ≥ 2-fold but <5-fold). Rivoceranib 200 mg QD can be a weak-to-moderate inhibitor of CYP2C19 as coadministration of rivoceranib increased AUC_{0-inf} of omeprazole by 1.77-fold based on direct GMRs or by two-fold based on linear mixed-effect model estimates. Therefore, concomitant use of CYP2D6 substrate drugs with rivoceranib should be approached with caution. Dose adjustment should be considered with reference to the prescribing information of these substrate drugs when concomitant use cannot be avoided. For CYP3A, CYP2C9, and CYP2C19 substrate drugs for which rivoceranib may have a weak inhibitory effect, frequent monitoring of substrate-related adverse reactions is recommended, particularly when toxicity is sensitive to increased drug exposure. It is noteworthy

that the relatively higher in vitro IC_{50} value for CYP2D6 (2.56 μM) suggests a lower inhibitory potential of rivoceranib toward CYP2D6 compared with CYP2C9, CYP2C19, and CYP3A (half-maximal inhibitory concentration range: 0.31–0.81 μM). However, in this clinical cocktail study, rivoceranib exhibited the most pronounced inhibitory effect on CYP2D6 among the evaluated CYP isoforms. This discrepancy may indicate a potential time-dependent inhibition of CYP2D6 by rivoceranib in vivo, although no time-dependent inhibition was observed in vitro across these tested CYP isoforms.

There are some limitations to this study. First, no genotyping was conducted in this study. CYPs 2C9, 2C19, and 2D6 display polymorphisms that can characterize volunteers as poor, intermediate, extensive, or ultrarapid metabolizers. In this study, large PK variability was observed for omeprazole (CYP2C19 substrate) and dextromethorphan (CYP2D6 substrate), which was likely due to polymorphisms of these enzymes among participants in this study. Secondly, the concentration of rivoceranib was only determined at the predose on day 11 and the effect of Cooperstown 5+1 cocktail probe drugs on the pharmacokinetics of rivoceranib was not evaluated. However, steady-state pharmacokinetics of rivoceranib was achieved by day 11, and steady-state trough concentration measured on day 11 was comparable to exposures observed in patients with solid tumors receiving rivoceranib 200 mg. This indicates that rivoceranib was present in all volunteers prior to administration of the Cooperstown 5+1 cocktail in combination with rivoceranib. Although the cocktail effects were not measured for rivoceranib, the components of the cocktail are not anticipated to affect the pharmacokinetics of rivoceranib because none of the cocktail components is an inhibitor or inducer of CYP3A, which is the primary metabolism enzyme of rivoceranib.

The administration of the Cooperstown 5+1 cocktail in combination with rivoceranib was generally well tolerated. Five volunteers experienced a panic attack approximately 3–6 h following administration of the Cooperstown 5+1 cocktail plus rivoceranib, which may be attributed to the Cooperstown 5+1 cocktail rather than to rivoceranib. All other TEAEs experienced during the study were mild in severity and were consistent with those observed in other studies of rivoceranib.

5 Conclusions

The results from this study provide important information on the potential clinical impact of rivoceranib on Cooperstown 5+1 cocktail probe drugs. Rivoceranib 200 mg QD co-administered with a cocktail of CYP enzyme probe substrates demonstrated minimal clinically relevant DDIs for the CYP1A2 substrate. However, rivoceranib 200 mg QD was shown to be a moderate inhibitor of the CYP2D6 substrate and a weak inhibitor of CYP3A, CYP2C9, and CYP2C19 substrate drugs. Concomitant use of rivoceranib with these substrate drugs should be performed with caution. When concomitant use is required, dose adjustment or more frequent monitoring for substrate-related adverse reactions should be considered in accordance with the prescribing information for the substrate drugs.

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Declarations

Conflicts of Interest David Nguyen has no conflicts of interest that are directly relevant to the content of this article. Xiaohui (Tracey) Wei, Xianzhang Meng, and Kristin Ryan declare employment with Elevar Therapeutics. Laura Alexander and Seong Jang declare former employment with Elevar Therapeutics.

Ethics Approval The study protocol was approved by the Alpha Institutional Review Board and conducted in compliance with the study protocol, the International Standard of Good Clinical Practice, the ethical principles of the Declaration of Helsinki, and applicable regulatory requirements. All of the healthy volunteers provided written informed consent prior to enrollment.

Consent to Participate All study volunteers provided written informed consent prior to participating in this study.

Consent for Publication All study volunteers provided written informed consent for publication of the results of this study.

Availability of Data and Material The data that support the findings of this study are not publicly available but could be requested from the corresponding author.

Code Availability Not applicable.

Authors' Contributions DN, XW, XM, LA, KR, and SJ participated in the interpretation of the study results and in the drafting, critical revision, and approval of the final version of this manuscript.

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