Effect of Rivoceranib on the Pharmacokinetics of Cytochrome P450 Enzyme Substrates: A Phase 1 Trial in Healthy Volunteers

Janelle Weyer,[1] Xianzhang Meng,[2] Joseph Reitano,[2] Vinoo Urity,[2] Cheol Hee Park,[2] Bill Strickland,[2] Seong Jang[2]

[1]Celerion, Tempe, AZ; [2]Elevar Therapeutics, Fort Lee, NJ

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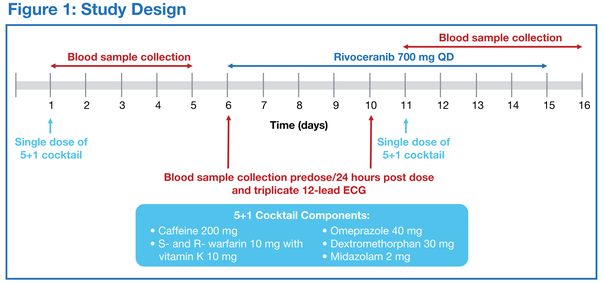
BACKGROUND

- Rivoceranib (known as apatinib in China) is an oral, small molecule, selective vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor with potent in vitro and in vivo antitumor activity.[1]
- Rivoceranib is metabolized in the liver mostly by cytochrome P450 (CYP)3A4/5, with minor contributions from CYP2D6, CYP2C9, and CYP2E1.[2]
- In vitro and in vivo studies suggest rivoceranib may interact with various CYP substrates, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.[3]
- Herein, we evaluated the effect of rivoceranib 700 mg once daily (QD) on the pharmacokinetics (PK) of various CYP substrates to determine drug-drug interactions of rivoceranib.

METHODS

- This open-label, 2-treatment, fixed-sequence drug-drug interaction phase 1 study evaluated the impact of multiple oral doses of rivoceranib 700 mg QD on the single-dose PK of CYP enzyme substrates administered in a 5+1 probe cocktail (caffeine [CYP1A2], S- and R-warfarin [CYP2C9] + vitamin K, omeprazole [CYP2C19], dextromethorphan [CYP2D6], and midazolam [CYP3A]) in healthy volunteers (N=32) (**Figure 1**).

Figure 1: Study Design



RESULTS

DEMOGAPHICS OF HEALTHY VOLUNTEERS

Table 1: Baseline Demographics

Characteristic	Safety Population (N=32)
Age (years), mean (SD)	43.5 (8.2)
Sex, n (%)	
Female	16 (50)
Male	16 (50)
Race, n (%)	
Black or African American	3 (9)
White	29 (91)
Ethnicity, n (%)	
Hispanic or Latino	25 (78)
Not Hispanic or Latino	7 (22)
Body mass index (kg/m^2), mean (SD)	27.4 (3.3)
Height (cm), mean (SD)	167.5 (9.3)
Weight (kg), mean (SD)	77.1 (11.4)

REFERENCES: **1.** Tian S, et al.*Cancer Sci*. 2011;102(7):1374-80; **2.** Ding J, et al. *Drug Metab Dispos.* 2013;41(6):1195-210; **3.** Elevar Therapeutics. *Data on file*.
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CONTACT FOR POSTER INFORMATION/QUESTIONS: medicalinformation@elevartherapeutics.com

RIVOCERANIB AND CYP1A2

- Rivoceranib 700 mg QD reduced caffeine $AUC_{0\text{-}inf}$ by 15%, and did not change caffeine C_{max}, indicating a minimal effect of rivoceranib 700 mg QD on the PK of CYP1A2 substrates (**Table 2**; **Figure 2**).

Table 2: CYP1A2 Substrates: Caffeine and Paraxanthine[a] PK Parameters after 5+1 Cocktail Alone or Rivoceranib Plus 5+1 Cocktail

PK Parameter	5+1 Cocktail Alone		Rivoceranib Plus 5+1 Cocktail		Geometric Mean Ratio[b], % (90% CI)	Intra-participant CV%
	Mean (CV%)	Geometric LSM	Mean (CV%)	Geometric LSM		
Caffeine						
$AUC_{0\text{-}t}$ (ng*hr/mL)	52,630 (49.9) [n=32]	52,630	44,480 (74.7) [n=24]	43,190	82.08 (74.72–90.17)	19.31
$AUC_{0\text{-}inf}$ (ng*hr/mL)	53,440 (50.9) [n=32]	53,440	47,620 (72.6) [n=28]	45,360	84.87 (77.91–92.46)	19.03
C_{max} (ng/mL)	5,193 (23.9) [n=32]	5,193	5,329 (36.5) [n=28]	5,214	100.41 (93.55–107.77)	15.75
Paraxanthine[a]						
$AUC_{0\text{-}t}$ (ng*hr/mL)	30,950 (28.9) [n=32]	30,950	26,400 (38.2) [n=24]	26,750	86.42 (81.26–91.91)	12.62
$AUC_{0\text{-}inf}$ (ng*hr/mL)	28,730 (21.7) [n=16]	31,720	25,040 (44.0) [n=15]	24,990	78.80 (72.22–85.98)	10.25
C_{max} (ng/mL)	1,436 (23.9) [n=32]	1,436	1,430 (21.4) [n=28]	1,429	99.49 (93.48–105.90)	13.93

LSM, least square mean. [a]Paraxanthine is a metabolite of caffeine; [b]Geometric Mean Ratio: 100* LSM of Rivoceranib Plus 5+1 Cocktail/LSM of 5+1 Cocktail Alone

Figure 2: Rivoceranib and CYP1A2

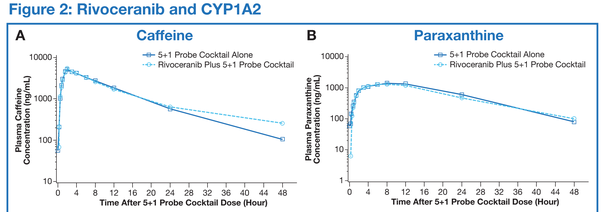

Figure 2: Mean plasma concentrations versus time profiles of caffeine (**A**) and its metabolite, paraxanthine (**B**) following administration of 5+1 cocktail alone and following rivoceranib 700 mg QD plus 5+1 cocktail.

RIVOCERANIB AND CYP2C9

- When co-administered with rivoceranib 700 mg QD, S-warfarin and R-warfarin $AUC_{0\text{-}inf}$ increased by 68% and 32% and C_{max} by 19% and 15%, respectively, indicating rivoceranib moderately inhibits CYP2C9 (**Table 3**; **Figure 3**).

Table 3: CYP2C9 Substrates: R- and S-Warfarin PK Parameters after 5+1 Cocktail Alone or Rivoceranib Plus 5+1 Cocktail

PK Parameter	5+1 Cocktail Alone		Rivoceranib Plus 5+1 Cocktail		Geometric Mean Ratio*, % (90% CI)	Intra-participant CV%
	Mean (CV%)	Geometric LSM	Mean (CV%)	Geometric LSM		
R-Warfarin						
$AUC_{0\text{-}t}$ (ng*hr/mL)	29,860 (21.9) [n=32]	29,860	36,660 (30.7) [n=24]	36,090	120.86 (113.69–128.48)	12.60
$AUC_{0\text{-}inf}$ (ng*hr/mL)	36,750 (24.4) [n=32]	36,750	49,220 (38.5) [n=25]	48,560	132.12 (122.90–142.02)	15.24
C_{max} (ng/mL)	701.2 (24.7) [n=32]	701.2	816.0 (22.5) [n=28]	804.9	114.79 (107.75–122.29)	14.13
S-Warfarin						
$AUC_{0\text{-}t}$ (ng*hr/mL)	18,880 (19.2) [n=32]	18,880	28,920 (28.6) [n=24]	28,490	150.88 (141.30–161.10)	13.62
$AUC_{0\text{-}inf}$ (ng*hr/mL)	20,640 (20.7) [n=32]	20,640	34,780 (33.4) [n=27]	34,670	167.95 (155.99–180.83)	16.25
C_{max} (ng/mL)	701.1 (24.9) [n=32]	701.1	840.2 (23.4) [n=28]	832.5	118.74 (110.54–127.54)	16.03

LSM, least square mean. *Geometric Mean Ratio: 100* LSM of Rivoceranib Plus 5+1 Cocktail/LSM of 5+1 Cocktail Alone

Figure 3: Rivoceranib and CYP2C9

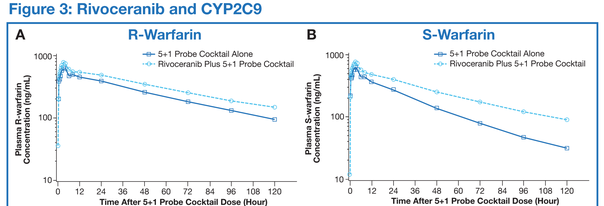

Figure 3: Mean plasma drug concentrations versus time profiles of R-warfarin (**A**) and S-warfarin (**B**) following administration of 5+1 cocktail alone and following rivoceranib 700 mg QD plus 5+1 cocktail.

RIVOCERANIB AND CYP2C19

- Rivoceranib 700 mg QD appeared to act as a moderate inhibitor of CYP2C19, increasing omeprazole $AUC_{0\text{-}inf}$ 3.3-fold and increasing C_{max} 2-fold (**Table 4**; **Figure 4**).

Table 4: CYP2C19 Substrates: Omeprazole and 5-OH-Omeprazole[a] PK Parameters after 5+1 Cocktail Alone or Rivoceranib Plus 5+1 Cocktail

PK Parameter	5+1 Cocktail Alone		Rivoceranib Plus 5+1 Cocktail		Geometric Mean Ratio[b], % (90% CI)	Intra-participant CV%
	Mean (CV%)	Geometric LSM	Mean (CV%)	Geometric LSM		
Omeprazole						
$AUC_{0\text{-}t}$ (ng*hr/mL)	2,048 (96.0) [n=32]	2,048	7,072 (75.5) [n=28]	6,985	341.08 (287.98–403.96)	38.81
$AUC_{0\text{-}inf}$ (ng*hr/mL)	2,449 (87.2) [n=27]	2,336	7,740 (70.5) [n=26]	7,660	327.97 (279.77–384.48)	32.03
C_{max} (ng/mL)	928.3 (62.7) [n=32]	928.3	1,900 (59.1) [n=28]	1,895	204.18 (172.41–241.80)	39.08
5-OH-Omeprazole[a]						
$AUC_{0\text{-}t}$ (ng*hr/mL)	1,080 (27.3) [n=32]	1,080	1,243 (33.3) [n=28]	1,234	114.18 (105.67–123.38)	17.34
$AUC_{0\text{-}inf}$ (ng*hr/mL)	1,096 (27.4) [n=31]	1,096	1,336 (27.7) [n=25]	1,345	122.65 (116.59–129.04)	10.38
C_{max} (ng/mL)	374.2 (41.0) [n=32]	374.2	243.3 (51.1) [n=28]	242.6	64.84 (57.92–72.58)	25.45

LSM, least square mean. [a]5-OH-omeprazole is a metabolite of omeprazole; [b]Geometric Mean Ratio: 100* LSM of Rivoceranib Plus 5+1 Cocktail/LSM of 5+1 Cocktail Alone

Figure 4: Rivoceranib and CYP2C19

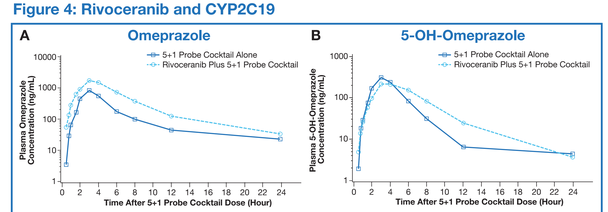

Figure 4: Mean plasma drug concentrations versus time profiles of omeprazole (**A**) and its metabolite, 5-OH-omeprazole (**B**) following administration of 5+1 cocktail alone and following rivoceranib 700 mg QD plus 5+1 cocktail.

RIVOCERANIB AND CYP2D6

- Dextromethorphan metabolism (CYP2D6) was moderately inhibited by rivoceranib 700 mg once daily, with a 2- to 2.7-fold increase in dextromethorphan exposure (**Table 5**; **Figure 5**).

Table 5: CYP2D6 Substrates: Dextromethorphan and Dextrorphan[a] PK Parameters after 5+1 Cocktail Alone or Rivoceranib Plus 5+1 Cocktail

PK Parameter	5+1 Cocktail Alone		Rivoceranib Plus 5+1 Cocktail		Geometric Mean Ratio[b], % (90% CI)	Intra-participant CV%
	Mean (CV%)	Geometric LSM	Mean (CV%)	Geometric LSM		
Dextromethorphan						
$AUC_{0\text{-}t}$ (ng*hr/mL)	10.43 (241.2) [n=32]	10.43	23.66 (217.3) [n=28]	27.11	259.87 (208.26–324.27)	51.87
$AUC_{0\text{-}inf}$ (ng*hr/mL)	13.97 (196.0) [n=31]	13.30	33.24 (173.1) [n=27]	36.24	272.50 (225.72–328.96)	41.59
C_{max} (ng/mL)	1.397 (166.4) [n=32]	1.397	2.527 (165.4) [n=28]	2.778	198.80 (163.35–241.95)	45.45
Dextrorphan[a]						
$AUC_{0\text{-}t}$ (ng*hr/mL)	26.14 (61.6) [n=32]	26.14	34.50 (85.3) [n=28]	33.74	129.07 (115.14–144.68)	25.62
$AUC_{0\text{-}inf}$ (ng*hr/mL)	27.85 (57.9) [n=32]	27.85	37.84 (75.3) [n=28]	37.10	133.22 (120.85–146.85)	21.75
C_{max} (ng/mL)	4.657 (58.5) [n=32]	4.657	4.875 (72.4) [n=28]	4.736	101.70 (90.14–114.74)	27.16

LSM, least square mean. [a]Dextrorphan is a metabolite of detromethorphan; [b]Geometric Mean Ratio: 100* LSM of Rivoceranib Plus 5+1 Cocktail/LSM of 5+1 Cocktail Alone

Figure 5: Rivoceranib and CYP2D6

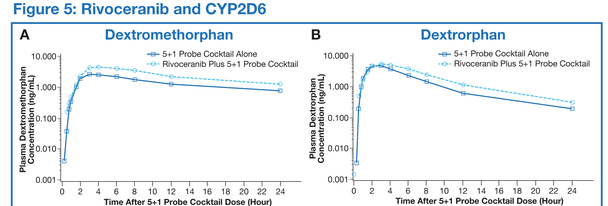

Figure 5: Mean plasma drug concentrations versus time profiles of dextromethorphan (**A**) and its metabolite, dextrorphan (**B**) following administration of 5+1 cocktail alone and following rivoceranib 700 mg QD plus 5+1 cocktail.

RIVOCERANIB AND CYP3A4

- Rivoceranib 700 mg QD appeared to moderately inhibit midazolam metabolism by CYP3A4, with 2.4- to 2.8-fold increases in midazolam exposures (**Table 6**, **Figure 6**).

Table 6: CYP3A4 Substrates: Midazolam and 1-OH-Midazolam[a] PK Parameters after 5+1 Cocktail Alone or Rivoceranib Plus 5+1 Cocktail

PK Parameter	5+1 Cocktail Alone		Rivoceranib Plus 5+1 Cocktail		Geometric Mean Ratio[b], % (90% CI)	Intra-participant CV%
	Mean (CV%)	Geometric LSM	Mean (CV%)	Geometric LSM		
Midazolam						
$AUC_{0\text{-}t}$ (ng*hr/mL)	28.09 (47.5) [n=32]	28.09	75.46 (36.8) [n=28]	75.17	267.59 (234.28–305.64)	30.37
$AUC_{0\text{-}inf}$ (ng*hr/mL)	29.71 (48.7) [n=32]	29.71	82.47 (41.8) [n=28]	82.08	276.27 (242.21–315.12)	29.97
C_{max} (ng/mL)	10.79 (37.9) [n=32]	10.79	25.72 (32.9) [n=28]	25.67	237.88 (211.54–267.51)	26.76
1-OH-Midazolam[a]						
$AUC_{0\text{-}t}$ (ng*hr/mL)	9.643 (35.0) [n=32]	9.643	14.37 (33.8) [n=28]	13.89	144.05 (133.98–154.88)	16.13
$AUC_{0\text{-}inf}$ (ng*hr/mL)	10.18 (35.4) [n=31]	10.21	15.67 (34.2) [n=28]	15.16	148.48 (137.80–159.99)	16.34
C_{max} (ng/mL)	4.115 (38.0) [n=32]	4.115	4.797 (30.7) [n=28]	4.639	112.73 (105.21–120.79)	15.34

LSM, least square mean. [a]1-OH-midazolam is a metabolite of caffeine; [b]Geometric Mean Ratio: 100* LSM of Rivoceranib Plus 5+1 Cocktail/LSM of 5+1 Cocktail Alone

Figure 6: Rivoceranib and CYP3A4

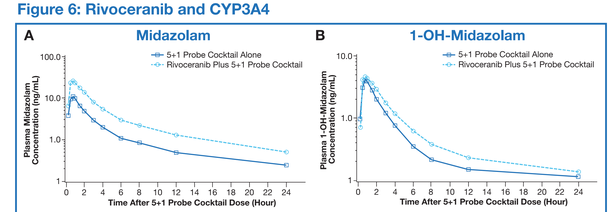

Figure 6: Mean plasma drug concentrations versus time profiles of midazolam (**A**) and its metabolite, 1-OH-midazolam (**B**) following administration of 5+1 cocktail alone and following rivoceranib 700 mg QD plus 5+1 cocktail.

SAFETY

- Among the 26 of 32 (81.3%) volunteers who experienced treatment emergent adverse events (TEAEs), 12 (37.5%) had a TEAE after 5+1 cocktail alone, 16 (53.3%) after rivoceranib alone, and 20 (71.4%) after rivoceranib plus 5+1 cocktail.
- There were no serious (grade ≥4) TEAEs.
- Eight participants discontinued the study due to TEAEs (including 7 due to grade 3 increased blood pressure) and 1 additional participant experienced TEAEs (chest discomfort, coughing, and fatigue) that led to dosing interruption and discontinuation from the study.
- The TEAEs reported by ≥4 participants were headache (62.5% of participants), constipation (34.4%), increased blood pressure (31.1%), back pain (18.8%), diarrhea (12.5%), and photophobia (12.5%).

CONCLUSIONS

- In the analysis, the effect of rivoceranib on the PK of CYP1A2 substrates did not appear to be clinically significant.
- Rivoceranib 700 mg QD may inhibit the metabolism of CYP2C9, CYP2C19, CYP2D6, and CYP3A4 substrates, suggesting that dose adjustment of substrates of these CYP isozymes and/or cautiously monitoring patients' adverse events may be needed when they are co-administered with rivoceranib.
- Possible ways to prevent these drug-drug interactions include preventing concomitant use with rivoceranib and using dose adjustments of CYP2C9, CYP2C19, CYP2D6, and CYP3A4 substrates for patients who must take these medications while undergoing treatment with rivoceranib 700 mg QD. Research is needed to establish how to adjust dose of the substrates for patients receiving rivoceranib 700 mg QD.
- The safety analysis found no new severe AEs related to rivoceranib and no AEs not reported in previous studies.