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Phase 1, randomized, open-label, single-dose, crossover study to evaluate the bioequivalence of four formulations of oral rivoceranib tablets in healthy subjects.

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Background: Rivoceranib is a novel oral tyrosine kinase inhibitor that potently and selectively inhibits VEGFR2. Rivoceranib is being investigated for indications targeted towards solid malignancies as either monotherapy or in combination with other anticancer therapies. Herein, we assessed the bioequivalence of a single dose of rivoceranib administered as 4 different formulations in healthy subjects. **Methods:** This single-center, open-label, randomized, single-dose, 4-way crossover study evaluated the bioequivalence of 4 different formulations of rivoceranib oral tablets in healthy adults. Each subject participated in 4 treatment periods, where they were randomized to 1 of 4 sequences: ABCD, BDAC, CADB, and DBAC (Formulation A = rivoceranib 250 mg tablet/clinical formulation used in the pivotal phase 3 study, Formulation B = rivoceranib 200 mg tablet/clinical formulation used in early clinical studies, Formulation C = rivoceranib 250 mg tablet/formulation to be developed for future use, Formulation D = rivoceranib 250 mg tablet/to-be-marketed formulation). **Results:** Of the 60 subjects enrolled, 66.7% were male, 88.3% were white, and median age was 43 years. The median plasma rivoceranib T_{max} was similar following all treatments (2 hours post-dose). The 90% CIs around the geometric mean ratios (GMRs) of plasma rivoceranib $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} for Formulation B vs. Formulation A and Formulation D vs. Formulation A were within the 80-125% reference interval, demonstrating bioequivalence between Formulation B and Formulation A as well as Formulation D and Formulation A. The 90% CIs around the GMRs of plasma rivoceranib $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} for Formulation C vs. Formulation A were slightly outside of the 80%-125% reference interval. **Conclusions:** Formulations B (clinical formulation used in early clinical studies) and D (to-be-marketed formulation) were bioequivalent to Formulation A (clinical formulation used in the pivotal phase 3 study). Formulation C (formulation to be developed for future use) and Formulation A were similar, but the difference was slightly outside of the bioequivalence criteria. It remains to be evaluated whether the difference in bioavailability between Formulation C and Formulation A is clinically meaningful. Clinical trial information: NCT05287360. Research Sponsor: Elevar Therapeutics; Celerion.

Summary of statistical comparisons of pharmacokinetic parameters of rivoceranib formulations.

	Formulation B vs A	Formulation C vs A	Formulation D vs A
GMR $AUC_{0\text{-}t}$, 90% CI	96.22 - 114.92*	106.21 - 126.72	92.86 - 110.79
GMR $AUC_{0\text{-}inf}$, 90% CI	98.07 - 116.12*	106.41 - 126.11	93.24 - 110.39
GMR C_{max}, 90% CI	87.99 - 113.68*	97.04 - 125.20	87.44 - 112.82

*GMR of dose-normalized values.