

A phase 1 exploratory study of RX-3117 to determine oral bioavailability in cancer subjects with solid tumors.

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**Background:** RX-3117 (fluorocyclopentenylcytosine) is a novel antimetabolite, that requires activation by uridine-cytidine kinase (UCK), a cancer cell specific kinase, that interferes with cancer cell division and nucleic acid synthesis, causes cellular arrest in the G1 phase and induces apoptosis. **Methods:** This study was a first-in-human, open-label, exploratory pharmacokinetic study of RX-3117. The study duration was 14-15 days (7-day screening period; 3-day treatment period; 4 (+1)-day safety follow-up period). Nine adult male and female subjects with histologically confirmed, solid tumors were enrolled and completed the study. Subjects received RX-3117 (n = 3 subjects per dose) as a single oral dose (50 mg or 100 mg) or a single intravenous dose (20 mg). **Results:** Pharmacokinetics (PK): The absolute bioavailability (F) for oral RX-3117 was 55.67% and 33.42% for the 50 and 100 mg doses, respectively. The mean  $T_{max}$  was 2.16 hours and 2.49 hours for the 50 and 100 mg doses, respectively. The mean  $C_{max}$  was 303.3 ng/mL and 311.43 ng/mL for the 50 and 100 mg doses, respectively. The greater absolute bioavailability and  $C_{max}$  results of the 50 mg dose compared to the 100 mg dose suggests that oral bioavailability of RX-3117 in plasma may not be dose-proportional or due to the low subject number tested. The  $t_{1/2}$  for the 50 mg and 100 mg doses was 13.95 hours and 20.92 hours, respectively, indicating that RX-3117 may show dose proportionality on some parameters but not on others at the doses tested. The plasma PK profile of intravenous RX-3117 differed from the plasma PK profile of oral RX-3117.

The 20 mg dose of intravenous RX-3117 recovered rapidly after bolus infusion ( $T_{\max} = 0.25$  hours). The 20 mg dose of intravenous RX-3117 had a mean  $C_{\max}$  of 1143.63 ng/mL, which was approximately a 4-fold increase over the peak concentrations of the oral doses. RX-3117 was safe and well-tolerated at the doses tested in all subjects. No AEs, TEAEs or SAEs occurred. **Conclusions:** This exploratory first-in-human study shows that RX-3117 was orally bioavailable and well-tolerated at the doses tested. The results support the study of higher and multiple doses in a standard Phase 1 study

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