(PF564) PHARMACOKINETIC ASSESSMENT OF REVUMENIB IN PATIENTS WITH RELAPSED/REFRACTORY ACUTE LEUKEMIAS HARBORING A KMT2A REARRANGEMENT OR NPM1 MUTATION: IMPACT OF FOOD AND CONCOMITANT MEDICATIONS

Topic: 04. Acute myeloid leukemia - Clinical

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Background

Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction, which disrupts multiple key drivers of leukemogenesis (*KMT2A* rearrangement [*KMT2A*r], *NPM1* mutation [*NPM1*m], and *NUP98* rearrangement). Revumenib is used for the treatment of relapsed/refractory (R/R) acute leukemias harboring a *KMT2A* translocation or R/R acute myeloid leukemia with *NPM1* mutation in adult and pediatric patients 1 year and older. Given the severity of disease, frequent polypharmacy, and variable clinical status in this population, dosing flexibility is essential to support consistent treatment delivery and optimize outcomes.

Aims

To characterize the pharmacokinetics (PK) of revumenib and its major metabolite (M1), with emphasis on factors that may influence dosing flexibility, including food and concomitant medications such as CYP3A4 inhibitors (CYP3A4i) and gastric acid–reducing agents such as antacids, H2 blockers (H2Bs), and proton pump inhibitors (PPIs).

Methods

PK data were obtained from 286 adult (≥18 years) and 49 pediatric (<18 years) patients with *KMT2A*r or *NPM1*m acute leukemia enrolled in the phase 1/2 AUGMENT-101 trial (NCT04065399) following single and multiple doses of revumenib. Non-compartmental analyses were performed in selected subgroups, while population PK modeling was conducted using data from all patients to systematically quantify PK variability and evaluate covariate effects.

Results

As compared to fasted state, a low-fat meal (400–500 calories with <25% fat content) reduced revumenib C_{max} and AUC by 27% and 12%, respectively, and M1 C_{max} and AUC by 14% and 18%, respectively, although exposure ranges overlapped under fasted and fed (low-fat meal) conditions. Median T_{max} was unchanged for revumenib and delayed by 1.8 hours for M1.
Co-administration with strong CYP3A4i (eg, voriconazole, posaconazole, itraconazole) resulted in ~2-fold increase in revumenib C_{max} and AUC, whereas moderate CYP3A4i (eg, fluconazole, isavuconazole) had no meaningful effect. M1 exposure was unaffected by strong or moderate CYP3A4i. Approximately 52% of patients received antacids, H2Bs, or PPIs; revumenib and M1 C_{max} and AUC were not altered, consistent with the high solubility of revumenib across physiological pH range (1.2–6.8).

Summary/Conclusion

Revumenib exposure increases ~2-fold with strong CYP3A4i, supporting dose reduction in this setting, while M1 exposure remains unaffected. Low-fat meals do not cause clinically meaningful changes in revumenib or M1 PK. Similarly, antacids, H2Bs, and PPIs, which are frequently used in this patient population, had no impact on revumenib or M1 PK. These findings reinforce the flexible administration of revumenib that may support treatment adherence and patient convenience.

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