# Conclusions

Growth factor receptor alpha (PDGFRα) and PDGFRβ (Figures 1 and 2) (1-3). Previous dose finding studies have shown that 300 mg per day is safe for patients with glioma, and TID dosing relapsed / refractory AML. About 27 - 37% of little drug accumulation. Clearance that does not depend on hepatic function. FLT3 mutation(s) in FLT3 (7). Objectives

To determine the pharmacokinetics of crenolanib in AML patients with FLT3-ITD and/or FLT3-D835 mutations. This abstract summarizes the population pharmacokinetics (PK) study of crenolanib in patients with relapsed / refractory AML with FLT3-ITD and/or FLT3-D835 mutations. The purpose of pharmacokinetic study, with the exception of four patients who received three doses.

**Pharmacokinetic Modeling**

The pharmacokinetic model is parameterized in terms of ka (1/hr), the first-order absorption; Tlag (hr), lag time; CL/F, apparent clearance; V/F, apparent volume; and α, apparent alpha phase. The non-compartmental pharmacokinetic model was used to analyze the data for the pharmacokinetic analysis.

**Assessment of Crenolanib Concentrations**

All crenolanib serum concentrations were measured by validated high performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) method. The pharmacokinetic modeling showed that TID dosing optimized Cmax, AUC, t1/2 and Ctrough of patients treated with 66.7 mg/m² and 100 mg.

**Similar Exposure Observed with BSA-based Versus Flat Dosing**

No significant difference was observed between flat (100 mg TID) and BSA-based (66.7 mg/m²) dosing, and twenty-nine (29) patients had 100 mg TID dosing.

**Similar Interpatient Variability Observed with BSA-based Versus Flat Dosing**

Four key pharmacokinetic parameters were compared. Flat dosing of 100 mg TID gave similar interpatient variability as BSA-based dosing.

**Conclusions**

Good exposure of crenolanib was achieved in relapsed patients. Pharmacokinetic modeling showed that TID dosing optimized Cmax and Ctrough to minimize peak concentrations while maintaining effective exposures of crenolanib over the 24-hour dosing period. High drug exposure was observed between flat (100 mg TID) and BSA-based (66.7 mg/m²) dosing. 100 mg TID of crenolanib was selected as the dosing scheme for phase 1 randomized trials.

**References**


2. St Jude Children’s Research Hospital, Memphis, TN, 1MD Anderson Cancer Center, Houston, TX, University of Texas Southwest Medical Center, Dallas, TX, AROG Pharmaceuticals, Dallas, TX.

**ABSTRACT**

Population Pharmacokinetics of Crenolanib, a Type I FLT3 Inhibitor, in Patients with Relapsed/Refractory Acute Myeloid Leukemia

**Introduction**

Features of an ideal FLT3 kinase inhibitor

- Good oral bioavailability
- Uniform interpatient variability
- Low protein binding
- Predictable metabolism and is not active metabolite
- Dose-response that does not depend on hepatic function
- Short half-life for elimination with optimal chemotherapy
- No induction of metabolic enzymes that will reduce drug level

**Crenolanib - A Potent FLT3 Inhibitor**

Crenolanib is a highly potent and selective type I inhibitor of FLT3 tyrosine kinase (FLT3). Plotted dose-response curve (Figure 1) and the corresponding exposure as a function of dose in individual patients (Figure 2). The pharmacokinetic model is parameterized in terms of ka (1/hr), the first-order absorption; Tlag (hr), lag time; CL/F, apparent clearance; V/F, apparent volume; and α, apparent alpha phase. The non-compartmental pharmacokinetic model was used to analyze the data for the pharmacokinetic analysis.

**Objective**

- To determine the pharmacokinetics of crenolanib in AML patients
- To compare the pharmacokinetics of crenolanib with flat dose (100 mg TID) and BSA-based dosing (66.7 mg/m²) in patients with relapsed / refractory AML.

**PK Model for TID Dosing**

TID Dosing Lowered Cmax and Increased Ctrough

- Simulations were performed to predict the anticipated peak and trough concentrations (Figure 5 and 6). Based on experimental observations, the pharmacokinetic model was parameterized (Figure 4) to simulate the concentration-time profile assuming a patient’s individual pharmacokinetic parameters.

**Similar Profile Across Dose Levels**

Similar exposure and PK parameters were observed for Crenolanib across dose levels of 200 mg/m² and 100 mg TID.

**PK Modeling**

Consistent PK on Day 1 and 15

The pharmacokinetic parameters estimated at day 1 and day 15, and consistency with the pharmacokinetic parameters. The pharmacokinetic parameters estimated at day 1 and day 15, and consistency with the day 1 values across dose levels (Figure 9).

**Similar Exposure Observed with BSA-based Versus Flat Dosing**

Similar exposure and PK parameters were observed for Crenolanib across dose levels of 200 mg/m² and 100 mg TID.

**Objectives**

- To determine the pharmacokinetics of crenolanib in AML patients
- To compare the pharmacokinetics of crenolanib with flat dose (100 mg TID) and BSA-based dosing (66.7 mg/m²) in patients with relapsed / refractory AML.

**Methods**

Serum blood samples were collected on Day 1, at pre-dose and at 5, 30, 60, 120, 240, and 24, 24, 24 and 24 hours after doses were administered on Day 1. All crenolanib serum concentrations were measured by validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. The pharmacokinetic modeling showed that TID dosing optimized Cmax, AUC, t1/2 and Ctrough of patients treated with 66.7 mg/m² and 100 mg.

**Consistent PK on Day 1 and 15**

The pharmacokinetic parameters estimated at day 1 and day 15, and consistency with the day 1 values across dose levels (Figure 9).

**PK Model for TID Dosing**

TID Dosing Lowered Cmax and Increased Ctrough

- Simulations were performed to predict the anticipated peak and trough concentrations (Figure 5 and 6). Based on experimental observations, the pharmacokinetic model was parameterized (Figure 4) to simulate the concentration-time profile assuming a patient’s individual pharmacokinetic parameters.

**Similar Exposure Observed with BSA-based Versus Flat Dosing**

Similar exposure and PK parameters were observed for Crenolanib across dose levels of 200 mg/m² and 100 mg TID.

**Similar Exposure Observed with BSA-based Versus Flat Dosing**

Similar exposure and PK parameters were observed for Crenolanib across dose levels of 200 mg/m² and 100 mg TID.

**Conclusions**

Good exposure of crenolanib was achieved in relapsed patients. Pharmacokinetic modeling showed that TID dosing optimized Cmax and Ctrough to minimize peak concentrations while maintaining effective exposures of crenolanib over the 24-hour dosing period. High drug exposure was observed between flat (100 mg TID) and BSA-based (66.7 mg/m²) dosing. 100 mg TID of crenolanib was selected as the dosing scheme for phase 1 randomized trials.

**References**


2. St Jude Children’s Research Hospital, Memphis, TN, 1MD Anderson Cancer Center, Houston, TX, University of Texas Southwest Medical Center, Dallas, TX, AROG Pharmaceuticals, Dallas, TX.