A Simultaneous PK-diarrhea model to assess the impact of diarrhea on bioavailability of abemaciclib

Siva Rama Prasad Kambhampati, Emmanuel Chigutsa, Amanda Karen Sykes, P. Kellie Turner
1 Global PK/PD & Pharmacometrics, Eli Lilly and Company, Indianapolis, IN

Objectives: To develop an empiric simultaneous PK-diarrhea model and investigate the impact of diarrhea (a frequent adverse event in patients taking abemaciclib) on abemaciclib pharmacokinetics (PK).

Methods: Plasma concentration-time data from seven Phase 1 studies (including JPBA[1]) and two Phase 2 (including MONARCH 1[2]) studies including 421 patients with cancer (198 breast cancer) and 65 healthy subjects were pooled for analysis. The range of doses was 50 to 275 mg Q12H. A simultaneous population PK-diarrhea model was developed using abemaciclib concentration-time data and time to the first diarrhea event. A 2-compartment structural model with simultaneous first and zero order absorption and a lag time in absorption described abemaciclib pharmacokinetics. The first diarrhea event was described using a time to event model. The impact of diarrhea on abemaciclib PK was evaluated as a factor on the bioavailability.

Results: The clearance (CL), volume of distribution of central (V1) and peripheral (V2) compartment of abemaciclib were 10.7 L/h (63.1% CV), 381 L (55.8% CV) and 12.5 L (15.1% CV), respectively. A Gompertz function that describes the change in hazard over time, best described the occurrence of diarrhea. The shape parameter was negative (-0.000692 for ≤150 mg and -0.00135 for > 150 mg), indicating that the risk of getting diarrhea was greatest early in the study and the risk decreased with time in the study. Median time to first diarrhea event was 9 days (>150 mg) and 42 days (≤150 mg).

Conclusions: A 2-compartment structural model with simultaneous first and zero order absorption adequately described the PK of abemaciclib. Abemaciclib dose was the most important determinant of the first diarrhea event, and the effect of diarrhea on abemaciclib PK was negligible.