A mechanistic population pharmacokinetic model of abemaciclib and its metabolites and the impact of diarrhea

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Objectives: Abemaciclib is an orally administered anticancer drug that inhibits CDK4 and CDK6 and is metabolized by CYP3A in the intestines and liver to active metabolites LSN2839567 (M2) and LSN3106726 (M20), both of which are also partly eliminated by CYP3A4. Using results and insights from an empiric model which simultaneously described the pharmacokinetics (PK) of the parent drug only and occurrence of diarrhea, we sought to develop a mechanistic population model to describe the slow and highly variable absorption kinetics as well as disposition of abemaciclib, M2, and M20.

Methods: Plasma concentration-time data from seven Phase 1 studies and two Phase 2 studies including 421 patients with cancer and 65 healthy subjects were pooled for population-based modeling analysis using NONMEM 7.3.0. The complex absorption process was described using a parallel dual absorption model that included intestinal metabolism. A well-stirred hepatic elimination model was used to describe the elimination of abemaciclib, M2 and M20 in relation to hepatic blood flow, protein binding and enzyme activity.

Results: 86.8% of the administered dose was absorbed either as abemaciclib, M2 or M20, of which 54.2% was absorbed via a zero order pathway with a typical duration of 3.18 h, and 45.8% was absorbed via a series of 4 transit compartments with a mean transit time of 1.44 h. The apparent intrinsic clearances of abemaciclib, M2 and M20 were 985 L/h, 254 L/h and 431 L/h, respectively. For a 200 mg dose, the absolute decrease in bioavailability due to diarrhea was estimated to be 3.11%.

Conclusions: A well-stirred liver model with intestinal metabolism successfully characterized first pass metabolism, elimination of abemaciclib and the formation and elimination of its active metabolites. The PK was similar between patients and healthy subjects and the effect of diarrhea on the PK of abemaciclib was negligible.