Population Pharmacokinetic (PK) and Exposure Simulation Analyses for Cediranib (AZD2171) in Pooled Phase I/II Studies in Patients with Cancer

Jianguo Li¹, Nidal Al-Huniti¹, Anja Henningsson², Weifeng Tang¹, Eric Masson¹

¹Quantitative Clinical Pharmacology, AstraZeneca, Waltham, MA; ²qPharmetra, LLC, Stockholm, SE

Objectives: To develop a population PK model for cediranib, and simulate cediranib exposure for different doses in cancer patients.

Methods: Cediranib plasma concentration and covariate data from 625 cancer patients after single or multiple oral dose administration (ranging from 0.5 to 90 mg) with the majority of patients treated in the dose range of 20 to 45 mg in 19 Phase I and II studies were used for analyses. A stepwise covariate modelling procedure with forward selection and backwards elimination was used for covariate screening. The final population PK model was used to simulate cediranib exposure for 20 or 15 mg dose alone or for 30 mg dose co-administered with 400 mg rifampicin to evaluate cediranib target coverage, potential need for dose adjustment due to covariate effects or co-administration with rifampicin. NONMEM (Version 7.3) and R3.03 were primarily used for analyses.

Results: A two-compartment disposition model with a sequential zero and first order absorption and first order linear elimination from the central compartment adequately describes cediranib concentration time courses. Body weight and age were identified with statistically significant impact on apparent clearance or apparent volume of central compartment. However, the effects of body weight and age on the area under plasma concentration-time curve and maximum cediranib concentration were <21%. The simulated lower bound of 90% prediction interval or median of unbound cediranib concentrations after 20 or 15 mg doses at steady-state overall exceed the IC₅₀ for vascular endothelial growth factor receptors (VEGFR-1, -2 and -3). Simulations supported an increase of dose to 30 mg when cediranib is co-administered with rifampicin.

Conclusions: No covariate was identified to require a priori dose adjustment for cediranib. Cediranib exposure following 20 or 15 mg multiple dose administration is overall adequate for the inhibition of VEGFR-1, -2 and -3 activities. Increase in cediranib dose may be needed for cediranib co-administered with strong UGT/Pgp inducers like rifampicin.