Modeling of Relationships of Cediranib Exposure to Hypertension and Diarrhoea for Cediranib Phase I and II Studies in Patients with Cancer

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Objectives: to establish relationships of cediranib exposure to safety endpoints of diastolic and systolic blood pressures (DBP&SBP) and diarrhoea events in cancers patients with cediranib monotherapy, and apply models to predict DBP&SBP and diarrhoea outcomes for the proposed cediranib dose regimen in cancer patients.

Methods: Paired DBP&SBP data, and diarrhoea events with grades of mild, moderate and severe from 631 subjects in 10 Phase I and II cediranib monotherapy studies were pooled for this analysis. DBP&SBP were simultaneously modelled with an indirect response model for predicted cediranib concentrations from the cediranib population PK model. Diarrhoea was modelled through an ordered categorical proportional odds model incorporating a Markov element and with probabilities of observing none, mild, moderate or severe diarrhoea on a given day being predicted by average cediranib concentrations on the day of the observation. NONMEM (Version 7.3) was primarily used for the analysis.

Results: Increase of DBP&SBP can be described by Emax models with typical increase in DBP&SBP for 20 mg cediranib being predicted to be 7 and 8 mmHg respectively. Probabilities of observing none or any grade diarrhoea was described by an Emax model, and predicted to be highly dependent on the grade on the previous day. At the 20 mg dose, the probability of mild diarrhoea was predicted to increase overtime but not the severity, and the probability of severe diarrhoea was predicted to resolve to grade none approximately 5 days upon discontinuing the cediranib treatment. No demographic covariates were identified to impact the relationships of DBP&SBP or diarrhoea to cediranib exposure.

Conclusions: Cediranib increases DBP&SBP with Emax relationships to cediranib concentrations with a predicted small mean increase in DBP&SBP for 20 mg cediranib. The frequency but not the severity of diarrhoea increases with mean cediranib concentration but is far more dependent on the status of diarrhoea on the previous day.