Apalutamide Population PK Model Development

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Objective: To determine the population pharmacokinetics of apalutamide following single and repeated oral administration in subjects with castration-resistant prostate cancer.

Background: Apalutamide is a second generation orally bioavailable, potent and selective antagonist of the androgen receptor, which is being developed for the treatment of prostate cancer.

Methods: Subjects received once-daily apalutamide doses ranging from 30 to 480-mg, resulting in 2,583 concentrations for analysis. In Phase 1, thirty subjects had full profile data after a single dose and at steady-state, with sparse sampling continued into Phase 2. In Phase 2, ninety-six additional subjects had sparse samples throughout the study. Samples were collected for more than 2-years in some subjects. Parameter estimation was performed with NONMEM v7.3.

Results: The data were best fit by a two-compartment model with first-order absorption and elimination with an absorption lag-time and time-dependent induction of baseline clearance to steady-state (approximately 2-fold increase) with an induction half-life of 117 hours, leading to an elimination half-life of 135 hours at steady-state. Exponential random effects described inter-individual variability, and a log-additive error model was used for intra-individual variability. Goodness of fit plots showed that the data were fit well. Final model population estimates were similar to the median of the bootstrap replicates, and were all contained within the 95 % confidence intervals. Visual predictive check plots showed good concordance between model predicted intervals and the data, with only a slight over prediction of observed concentrations in some plots.

Conclusions: Apalutamide pharmacokinetics were well described by a two compartment model with linear distribution, first-order absorption with a lag-time and induction of clearance. Clearance is increased by 2-fold at steady-state after 4 weeks of dosing in a dose independent manner. The model predicted AUC values for apalutamide indicated the kinetics are dose proportional in the tested dose range of 30 to 480 mg.