Population Pharmacokinetics and Exposure-Efficacy and Safety Analyses of Alectinib in Crizotinib-Progressed or Intolerant Population

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Objectives: To characterize the pharmacokinetics (PK) and exposure-efficacy/safety relationships of alectinib (a potent and selective CNS-active ALK inhibitor which has received FDA accelerated approval) and its main active metabolite M4 in patients with ALK+ NSCLC who have progressed on, or are intolerant to, crizotinib.

Methods: A population PK analysis was conducted to characterize the PK of alectinib and M4 in the target patient population using data from two Phase 2 studies (NONMEM 7.2). The potential influence of covariates (weight, race, disease status, etc.) that contribute significantly to the between-patient variability in PK parameters were explored and quantified.

Graphical analyses were conducted to investigate the exposure-efficacy/safety relationship for alectinib and M4 and to determine whether variability in efficacy and occurrence of safety events could be attributed to variability in exposure. In addition, relationship between alectinib and M4 exposure and progression free survival (PFS) was characterized using a Cox proportional-hazards regression model.

Results: The concentration-time course for alectinib and M4 were best described by a one-compartment open model with first-order elimination and with a sequential zero and first-order absorption/formation. Weight was the only covariate found to statistically influence the clearance and volume for both alectinib and M4. No other covariate had a statistically significant effect.

There was a clear exposure-efficacy relationship across 300-900 mg BID, with lower exposure associated with less decrease in tumor size. This relationship appeared to plateau at exposures achieved with the 600 mg BID regimen. Based on results from the Cox proportional-hazards analysis, there was no statistically significant relationship between exposure and PFS following 600 mg BID. There was also no significant relationship between exposure and any AEs analyzed.

Conclusions: Results of these analyses demonstrated that the 600 mg BID dose is appropriate in a crizotinib-progressed or intolerant population.