Population Pharmacokinetic and Exposure-Efficacy/Safety Analyses for Bridging J-ALEX to Global Population with Alectinib 600mg BID Dose Regimen

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Objectives: To confirm the appropriateness of alectinib 600mg BID dose regimen for the ALK-positive non-small cell lung cancer (NSCLC) global patient population using a pharmacometrics approach.

Methods: The pharmacokinetics of alectinib, a tyrosine kinase inhibitor, was evaluated in ALK-inhibitor naïve ALK-positive NSCLC patients in J-ALEX (randomized, open-label study with 96 patients treated with 300mg BID alectinib and 104 patients treated with crizotinib) and ALEX (ongoing, randomized, open-label study with pharmacokinetic data from 132 patients treated with 600mg BID alectinib). 1964 plasma concentrations of alectinib and major metabolite M4 were analyzed using the Bayesian feedback approach. Effects of exposure on main efficacy measures and key safety events were evaluated graphically for J-ALEX. Relationship between exposure and progression-free survival (PFS) was investigated by a Cox proportional hazards (CPH) analysis using J-ALEX. Influence of prognostic factors (baseline tumor size, CNS metastasis… etc.) was also investigated.

Results: Population pharmacokinetic models developed for NSCLC patients [1] previously treated with crizotinib were able to adequately describe alectinib and M4 concentration-time course for J-ALEX and ALEX. Consistent with previous analyses, body weight was the only significant covariate for the pharmacokinetics of alectinib and M4. Administration of alectinib 600mg BID ensures exposure across the body weight range in global population are not inferior to that achieved following 300mg BID in J-ALEX. Results of CPH analysis demonstrated a significant relationship between exposure and PFS in J-ALEX. Alectinib 600mg BID ensures the distribution of achieved exposure maximize the expected PFS benefit while lower doses could result in reduced efficacy. No significant exposure-safety relationships were identified in J-ALEX.

Conclusions: Results of these analyses demonstrated that alectinib 600mg BID is the appropriate dose for the ALK-inhibitor naïve ALK-positive NSCLC global patient population.