Exposure-Response Analysis of Efficacy and Safety Endpoints for Crizotinib in the Treatment of Patients with ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

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Objectives: Evaluate the exposure-response relationship of crizotinib for efficacy and safety endpoints in patients with ALK-positive advanced NSCLC using data from the randomized phase 3 trial PROFILE-1007 and the single-arm phase 2 trial PROFILE-1005.

Methods: PROFILE-1007 had 174 patients and PROFILE-1005 included 934 patients. All patients from both studies received crizotinib 250mg BID orally on a continuous basis. Efficacy endpoints, Objective-Response Rate (ORR) and Progression-free Survival (PFS), were analyzed separately for each trial. Safety endpoints, analyzed with pooled data from both studies, included on-treatment adverse events or lab abnormalities of interest: Pneumonitis (Grade≥1), ALT Elevation (baseline Grade≤2 to ≥3 post-baseline), Neutropenia (baseline Grade≤2 to ≥3 post-baseline), Fatigue (Grade≥2), Vision Disorder (Grade ≥1), Renal Cyst (Grade≥1), Diarrhea (Grade≥2) and Vomiting (Grade≥2). A modeling approach to control for potential baseline confounders was used; confounders were included as main effects and potential effect-modifiers (interactions between covariates and exposure). Logistic regression was used for binary endpoints (ORR, safety endpoints); proportional-hazards regression was used for PFS. Exposure was the predicted average steady-state concentration for crizotinib based on the steady-state clearance for each patient estimated from the population PK model and average total daily dose (log-transformed).

Results: Efficacy – There were statistically significant exposure-response relationships for ORR and PFS, with higher exposure being associated with higher ORR and longer PFS in PROFILE-1005. The exposure-response relationship in PROFILE-1007 showed similar trends seen with PROFILE-1005; however, this relationship was not statistically significant. ECOG performance status was the only statistically significant effect modifier of the exposure-response relationship for PFS. Combined Safety – exposure-response analyses revealed a statistically significant relationship for neutropenia and renal cyst with increasing crizotinib exposure resulting in higher incidence rates. Safety event rates were generally low (<20%) even at higher drug exposures.

Conclusions: Results from exposure-response analyses of PROFILE-1005 and -1007 support a favorable benefit/risk assessment at the approved 250mg BID dosing regimen for ALK-positive advanced NSCLC patients.