Safety, Pharmacodynamics and Pharmacokinetics of the Oral Selective Hypoxia-inducible Factor Prolyl Hydroxylase Inhibitor Molidustat in Japanese Healthy Subjects

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Background: Molidustat is a selective hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor under development for the treatment of renal anemia. This study evaluated the safety, pharmacodynamics and pharmacokinetics of Molidustat in Japanese healthy volunteers.

Methods: This study was conducted in a single-center, randomized, double-blinded, placebo-controlled, dose escalation, group comparison design. Twelve Japanese healthy male subjects in each dose step received molidustat (n=9) or placebo (n=3) as single oral administration on Day 1 followed by a washout day and a 5-day multiple dose phase. For multiple dosing, molidustat was given 5, 25, 50, 75, 100, 125 and 150 mg once daily and 50 mg twice daily. Assessments included safety, tolerability, pharmacodynamics (erythropoietin (EPO), reticulocytes/erythrocytes, hemoglobin, and hematocrit) and pharmacokinetics (molidustat and its metabolite M-1 in plasma and urine). Exploratory biomarkers included vascular endothelial growth factor (VEGF).

Results: All 96 subjects completed the study without major deviations. Demographic and baseline characteristics were similar between treatment groups. No serious AEs or other significant AEs were reported. Overall, 1 subject (1.0%) experienced 2 treatment-emergent AEs in the 150 mg molidustat group. There were no clinically relevant changes in vital signs or ECG. EPO increased dose-dependently after single and multiple dosing. The difference in mean AUC(0-24) for EPO between single and multiple dosing increased with the molidustat dose. A clear dose-dependent increase in reticulocytes/erythrocytes compared to placebo was observed after multiple-dosing for all treatments ≥ 50 mg od molidustat. Hemoglobin was not increased based on short treatment duration. No effect on VEGF was observed. Mean AUC and Cmax of molidustat increased dose-proportionally from 5 to 150 mg reaching steady state after 5-day multiple administration. PK was linear over time.

Conclusions: In Japanese healthy male subjects, molidustat was well tolerated in the investigated dose range. EPO increased dose-dependently after single and multiple dose administration resulting in stimulation of erythropoiesis. Therefore, it will be a new treatment option for patients with renal anemia.