Investigation of potential pharmacodynamic and pharmacokinetic interactions between selexipag and warfarin in healthy male subjects

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BACKGROUND: Patients with pulmonary arterial hypertension (PAH) have a deficiency in prostacyclin and prostacyclin synthase. Therefore, targeting the prostacyclin pathway is an effective treatment option for PAH. Selexipag is a novel, orally available, selective prostacyclin receptor (IP) agonist that is under development for the treatment of PAH. ACT-333679, the active metabolite of selexipag, is also a selective and potent agonist at the IP receptor.

METHODS: In this two-period, cross-over Phase I study, the potential pharmacodynamic and pharmacokinetic interactions between selexipag and warfarin were investigated in 18 healthy male subjects aged 21–42 years. In Period 1, subjects received a single dose of selexipag or placebo on Day 1 followed by twice daily dosing on Days 2 to 12. In Period 2 subjects received the alternative treatment (placebo or selexipag) to that received in Period 1. Subjects received a single oral dose of 20 mg warfarin on the morning of Day 8 of both Periods 1 and 2.

RESULTS: Repeated administration of 400 μg selexipag had no influence on the rate and extent of absorption (AUC and C_max) of R- and S-warfarin. Selexipag AUC₀–τ, ACT-333679 AUC₀–τ, and ACT-333679 C_max at steady state were not affected by warfarin. Selexipag C_max was decreased by approximately 6% (not clinically significant). Steady-state levels of selexipag and ACT-333679 at a dose regimen of 400 μg selexipag b.i.d. had no influence on the pharmacodynamic variables as demonstrated by international normalized ratios (INR) calculated for INR AUC₀–(144h), INR_max, or INR_tmax. Multiple doses of selexipag 400 μg were well tolerated by subjects. There were no consistent differences in the number of treatment-emergent adverse events between subjects treated with selexipag and warfarin, and those treated with placebo and warfarin. There was no evidence of a drug effect on laboratory safety parameters, echocardiography, telemetry, or orthostatic hypotension.

CONCLUSIONS: There was no significant interaction between selexipag (400 μg multiple doses), ACT-333679, and warfarin (20 mg single dose).

TYPE: Clinical Science

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