European Respiratory Society
Annual Congress 2012

Title: Lack of relevant pharmacokinetic and pharmacodynamic interactions between the new dual endothelin receptor antagonist macitentan and warfarin in healthy subjects

Ms. Patricia 1557 Sidharta patricia.sidharta@actelion.com [1], Dr. Hartmut 1558 Dietrich hartmut.dietrich@clinpharmcologne.de [2] and Dr. Jasper 1559 Dingemanse Jasper.Dingemanse@actelion.com [1]. [1] Clinical Pharmacology, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland and [2] ClinPharmCologne, MEDA Manufacturing GmbH, Cologne, Germany .

Body: Macitentan, a new, potent, dual endothelin receptor antagonist (ERA), is a potential treatment for pulmonary arterial hypertension (PAH). In this study (AC-055-105), the effect of macitentan on the pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of warfarin was investigated in 14 healthy male subjects. Subjects received treatment sequence A/B or B/A separated by a 2-week washout. Treatment A: macitentan for 8 days (loading dose of 30 mg, thereafter 10 mg o.d.). On Day 4, a single dose of 25 mg warfarin was given with macitentan. Treatment B: A single dose of 25 mg warfarin on Day 1. Blood samples were assessed for warfarin PK (R- and S-warfarin) and PD (INR and Factor VII). Plasma trough levels of macitentan and its active metabolite, ACT-132577, were determined. Twelve subjects were included in the PK/PD analysis. The plasma concentration-time profiles of R- and S-Warfarin (Figure 1) and PD parameters of INR and Factor VII were comparable between treatments. Warfarin did not impact the trough levels of macitentan and ACT-132577. Both treatments were well tolerated. Based on these results, no dose correction of macitentan or warfarin is needed when using these drugs together. Figure: Plasma concentration-time profile of R- and S-warfarin with and without macitentan (mean ± SD, n=12).