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Title: The safety, tolerability and pharmacokinetics of AZD5069, a novel CXCR2 antagonist, in healthy Japanese volunteers

Ulrike 15934 Lorch u.lorch@richmondpharmacology.com MD [1], Hedigo 15935 Negi H.Negi@astrazeneca.com [2], Hirobumi 15936 Tabata Hirobumi.Tabata@astrazeneca.com [2], Heather 15937 Wray Heather.Wray@astrazeneca.com MD [3], Marie 15938 Cullberg Marie.Cullberg@astrazeneca.com [3] and Bengt 15944 Larsson Bengt.Larsson@astrazeneca.com [3]. [1] Richmond Pharmacology, St. George's University, London, United Kingdom ; [2] Research & Development, AstraZeneca K.K., Osaka, Japan and [3] Research & Development, AstraZeneca, Mölndal, Sweden .

Body: BACKGROUND:AZD5069 is a reversible antagonist at the human CXC chemokine receptor-2, with potential as an oral treatment of inflammatory diseases such as COPD. It has previously only been administered to Caucasian healthy volunteers and patients. METHODS:This was a Phase I, randomised, double-blind, placebo-controlled, single-centre, 6 cohort study in healthy Japanese males (n=63; 22–39 yrs). Subjects received a single dose of AZD5069 (10–120 mg) on Day 1 (n=42), then twice-daily doses of AZD5069 (10–80 mg) for 7 days and a single dose on the last dosing day (n=36), or placebo (n=21). The safety and tolerability of AZD5069 was assessed primarily, with pharmacokinetics assessed by non-compartmental analysis. RESULTS:AZD5069 ≤80 mg twice-daily was well-tolerated with an acceptable safety profile. Expected clinically significant changes in laboratory safety parameters led to study withdrawals due to low blood neutrophil levels and elevated high sensitivity-C-reactive protein (hs-CRP) levels, meeting stopping criteria. Circulating neutrophil levels decreased with increasing plasma AZD5069 concentrations, but were recovering by 12 hrs post-dose and had returned to near normal at follow-up, 7–10 days post-last dose. AZD5069 was rapidly absorbed and AUC and C_{max} increased dose-proportionally with single and multiple doses. Steady-state was reached within 2–3 days following twice-daily dosing, with no, or minor, drug accumulation. CONCLUSIONS:AZD5069 was well-tolerated. Decreases in neutrophil counts and increases in hs-CRP levels were observed as expected. No safety concerns were identified to preclude future evaluation. Systemic exposure to AZD5069 was dose proportional.