# A Multipurpose First-in-Human Study With the Novel CXCR7 Antagonist ACT-1004-1239 Using CXCL12 Plasma Concentrations as Target Engagement Biomarker

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The C-X-C chemokine receptor 7 (CXCR7) has evolved as a promising, druggable target mainly in the immunology and oncology fields modulating plasma concentrations of its ligands CXCL11 and CXCL12 through receptor-mediated internalization. This ”scavenging” activity creates concentration gradients of these ligands between blood vessels and tissues that drive directional cell migration. This randomized, double-blind, placebo-controlled first-in-human study assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of ACT-1004-1239, a first-in-class drug candidate small-molecule CXCR7 antagonist. Food effect and absolute bioavailability assessments were also integrated in this multipurpose study. Healthy male subjects received single ascending oral doses of ACT-1004-1239 (n = 36) or placebo (n = 12). At each of six dose levels (1-200 mg), repeated blood sampling was done over 144 hours for pharmacokinetic/pharmacodynamic assessments using CXCL11 and CXCL12 as biomarkers of target engagement. ACT-1004-1239 was safe and well tolerated up to the highest tested dose of 200 mg. CXCL12 plasma concentrations dose-dependently increased and more than doubled compared with baseline, indicating target engagement, whereas CXCL11 concentrations remained unchanged. An indirect-response pharmacokinetic/pharmacodynamic model well described the relationship between ACT-1004-1239 and CXCL12 concentrations across the full dose range, supporting once-daily dosing for future clinical studies. At doses $\geq$ 10 mg, time to reach maximum plasma concentration ranged from 1.3 to 3.0 hours and terminal elimination half-life from 17.8 to 23.6 hours. The exposure increase across the dose range was essentially dose-proportional and no relevant food effect on pharmacokinetics was determined. The absolute bioavailability was 53.0% based on radioactivity data after oral vs. intravenous; 14; C-radiolabeled microtracer administration of ACT-1004-1239. Overall, these comprehensive data support further clinical development of ACT-1004-1239.
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