# Target engagement of the first-in-class CXCR7 antagonist ACT-1004-1239 following multiple-dose administration in mice and humans.

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Antagonism of the chemokine receptor CXCR7 has shown promising effects in diverse disease areas through modulation of its ligands, CXCL11 and CXCL12. Preclinical data of the first-in-class CXCR7 antagonist, ACT-1004-1239, showed efficacy in animal models of multiple sclerosis and acute lung injury. In healthy humans, single-dose administration of ACT-1004-1239 revealed a favorable clinical profile. Here, we report the target engagement of ACT-1004-1239 in healthy mice and humans after multiple doses using CXCL11 and CXCL12 as biomarkers. In addition, safety/tolerability, concentration-QTc relationship, and pharmacokinetics (PK) were assessed in a randomized, double-blind, placebo-controlled Phase 1 clinical study. Multiple-dose ACT-1004-1239 dose-dependently increased CXCL12 plasma concentration across the investigated dose range in mice and humans (mice: 1-100ămg/kg b.i.d.; humans: 30-200ămg o.d.) when compared to vehicle/placebo demonstrating target engagement. Mouse and human PK/PD models predicted that CXCL12 concentration approached a plateau within these dose ranges. In humans, ACT-1004-1239 was rapidly absorbed (t; max; : 1.75-3.01ăh) and the terminal t; 1/2; was approximately 19ăh. Steady-state conditions were reached by Day 3 with an accumulation index of 1.2. Female subjects had overall higher exposure compared to males. Multiple-dose ACT-1004-1239 was well tolerated up to 200ămg once daily in humans. There was no evidence of ACT-1004-1239-mediated QTc interval prolongation. Overall, multiple oral doses of ACT-1004-1239 showed target engagement with CXCR7 in healthy mice and humans, therefore, assessment of CXCL12 as translational tool for further investigations in patients is warranted. Favorable safety/tolerability and PK profiles allow for further clinical development.

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