Absorption, Metabolism, and Excretion of ACT-1004-1239, a First-In-Class CXCR7 Antagonist:; In Vitro; , Preclinical, and Clinical Data.

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4656042
Author(s) Huynh, Christine; Seeland, Swen; Segrestaa, Jerome; Gnerre, Carmela; Hogeback, Jens; Meyer Zu Schwabedissen, Henriette E; Dingemanse, Jasper; Sidharta, Patricia N
Author(s) at UniBasel Meyer zu Schwabedissen, Henriette ; Huynh, Christine ;
Year 2022
Title Absorption, Metabolism, and Excretion of ACT-1004-1239, a First-In-Class CXCR7 Antagonist:; In Vitro; , Preclinical, and Clinical Data.
Journal Frontiers in pharmacology
Volume 13
Pages / **Article-Number** 812065
Keywords 14C-ACT-1004-1239; ADME; CXCR7; CYP3A4; accelerator mass spectrometry; first-in-human; microtracer
ACT-1004-1239 is a potent, selective, first-in-class CXCR7 antagonist, which shows a favorable preclinical and clinical profile. Here we report the metabolites and the metabolic pathways of ACT-1004-1239 identified using results from; in vitro; and; in vivo; studies. Two complementary; in vitro; studies (incubation with human liver microsomes in the absence/presence of cytochrome P450- [CYP] specific chemical inhibitors and incubation with recombinant CYPs) were conducted to identify CYPs involved in ACT-1004-1239 metabolism. For the; in vivo; investigations, a microtracer approach was integrated in the first-in-human study to assess mass balance and absorption, distribution, metabolism, and excretion (ADME) characteristics of ACT-1004-1239. Six healthy male subjects received orally 100ămg non-radioactive ACT-1004-1239 together with 1ăμCi; 14; C-ACT-1004-1239. Plasma, urine, and feces samples were collected up to 240ăh post-dose and; 14; C-drug-related material was measured with accelerator mass spectrometry. This technique was also used to construct radiochromatograms of pooled human samples. Metabolite structure elucidation of human-relevant metabolites was performed using high performance liquid chromatography coupled with high resolution mass spectrometry and facilitated by the use of rat samples. CYP3A4 was identified as the major CYP catalyzing the formation of M1; in vitro; . In humans, the cumulative recovery from urine and feces was 84.1% of the dose with the majority being eliminated via the feces (69.6%) and the rest via the urine (14.5%). In human plasma, two major circulating metabolites were identified, i.e., M1 and M23. Elimination; via; M1 was the only elimination pathway that contributed to $\geq$25% of ACT-1004-1239 elimination. M1 was identified as a secondary amine metabolite following oxidative N-dealkylation of the parent. M23 was identified as a difluorophenyl isoxazole carboxylic acid metabolite following central amide bond hydrolysis of the parent. Other metabolites observed in humans were A1, A2, and A3. Metabolite A1 was identified as an analog of M1 after oxidative defluorination, whereas both, A2 and A3, were identified as a reduced analog of M1 and parent, respectively, after addition of two hydrogen atoms at the isoxazole ring. In conclusion, CYP3A4 contributes to a relevant extent to ACT-1004-1239 disposition and two major circulating metabolites were observed in humans.; Clinical Trial Registration:; (https://clinicaltrials.gov/ct2/show/NCT03869320) ClinicalTrials.gov Identifier NCT03869320.

ISSN/ISBN 1663-9812
Full Text on edoc ;
Digital Object Identifier DOI 10.3389/fphar.2022.812065

PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/35431953