

12th International HIV Drug Resistance Workshop



10–14 June 2003, Cabo del Sol, Los Cabos, Mexico

SENSITIVITY OF ENV-GENE RECOMBINANT VIRUSES DERIVED FROM ANTIRETROVIRAL DRUG-SENSITIVE AND -RESISTANT HIV-1 CLINICAL ISOLATES TO THE NOVEL CCR5 ANTAGONIST, UK-427,857

Antivir Ther. 2003; 8:S26 (abstract no. 23)

M Westby¹, C Napier¹, R Mansfield¹, D Collins¹, W Huang², N Hellmann², Y Lie² and M Perros¹

¹Pfizer Global Research and Development, Sandwich Laboratories, Kent, UK; and ²ViroLogic, Inc., South San Francisco, Calif., USA

UK-427,857 is a novel small molecule CCR5 antagonist that is currently being developed for the treatment of HIV infection. Its antiviral activity was evaluated against 200 clinically-derived R5 HIV-1 isolates using the ViroLogic PhenoSense HIV Entry inhibitor susceptibility assay. A panel of recombinant viruses was prepared using HIV-1 gp160 envelope genes derived from 100 clinical isolates lacking known ‘drug-selected’ mutations in either protease (PR) or reverse transcriptase (RT) (‘drug-sensitive’ isolates) and 100 clinical isolates with one or more drug selected PR or RT mutations (‘drug-resistant’ isolates). The virus panel comprised 160 clade B and 40 isolates from other clades.

UK-427,857 inhibited all 200 recombinant viruses tested with a geometric mean IC₅₀ of 1.6 nM (range 0.3–8.9 nM). The geometric mean IC₅₀s derived from drug-sensitive and drug-resistant isolates were 1.3 nM (range 0.3–3 nM) and 2.1 nM (range 0.7–8.9 nM), respectively. The difference between these two groups (1.6-fold) is statistically significant ($P < 0.05$) but less than the expected assay-to-assay variation. There was no difference in sensitivity between the clade B and nonclade B isolates, with geometric mean IC₅₀ of 1.6 nM (range 0.5–6.9 nM) and 1.6 nM (range 0.3–8.9 nM), respectively, consistent with a previous study demonstrating broad cross-clade activity of UK-427,857 against primary isolates grown in mitogen-activated peripheral blood lymphocytes.

These data provide further evidence that UK-427,857 is a potent antiviral compound with broad activity against recombinant viruses derived from a large number of clinically-relevant isolates and diverse clades. The compound inhibited CCR5-mediated infection of Env-recombinant viruses derived from antiretroviral drug-resistant R5 clinical isolates, suggesting that viruses selected *in vivo* during HIV drug treatment retain sensitivity to

UK-427,857. The study supports the continued development of this compound for the treatment of HIV-infected individuals.

PRESENTING AUTHOR: M Westby

2003-07-08

23

Copyright © 2003 - [International Medical Press Ltd.](#) Reproduction of this abstract (other than one copy for personal reference) must be cleared through the International Medical Press Ltd. 2-4 Idol Lane, London EC3R 5DD UK.