

# 15th International HIV Drug Resistance Workshop



13-17 June 2006, Sitges, Spain

## ROBUST SUPPRESSION OF VIRAL REPLICATION IN HCV INFECTED CHIMPANZEES BY A NUCLEOSIDE INHIBITOR OF THE NS5B POLYMERASE

*Antivir Ther.* 2006, 11:S7 (abstract no. 5)

DB Olsen<sup>1</sup>, SS Carroll<sup>1</sup>, M-El Davies<sup>2</sup>, L Handt<sup>3</sup>, K Koeplinger<sup>4</sup>, R Zhang<sup>4</sup>, S Ludmerer<sup>1</sup>, M MacCoss, DJ Hazuda<sup>1</sup>

<sup>1</sup>Antiviral Research Department, <sup>2</sup>Vaccines and Biologics Research, <sup>3</sup>Laboratory Animal Resources, <sup>4</sup>Department of Drug Metabolism, Merck Research Laboratories, West Point, PA, USA

---

Currently approved therapies to treat infection by hepatitis C virus (HCV) consist of combinations of pegylated interferon  $\alpha$  and ribavirin which have limited utility in patients infected with genotype 1 viruses. The development of agents that can enhance both the efficacy and tolerability of HCV therapy is therefore highly desired and much effort has recently focused on direct antiviral agents targeting the virally encoded RNA-dependent RNA polymerase (RdRp), NS5B, and protease, NS3. To date, robust antiviral activity in HCV infected patients has been demonstrated for protease inhibitors where decreases in viral RNA levels exceeding 99.9% were observed within less than 2 weeks of dosing with several inhibitors. While clinical efficacy has also been established for both nucleoside and non-nucleoside inhibitors of the HCV polymerase, the overall antiviral activity of these compounds in similar monotherapy studies has not been as dramatic. Previously, we have shown that the non-obligate chain terminating nucleoside inhibitors of the NS5B polymerase can potently inhibit HCV RNA replication in the bicistronic replicon assay. We now demonstrate profound suppression of viral replication in chimpanzees chronically infected with HCV by a prototypical inhibitor in this class. Once daily administration of a potent nucleoside inhibitor for 7 days resulted in a rapid, dose-dependent decrease in plasma viral RNA. At the highest dose evaluated, viral RNA levels decreased to below the limit of quantitation of the assay (20 IU/ml) within a few days, representing a  $\geq 5$  log decrease in plasma viremia in animals with the highest pre-dose viral load. Upon termination of therapy, viral RNA levels returned to baseline without evidence of genotypic resistance. The antiviral activity of this nucleoside inhibitor in HCV infected chimpanzees is comparable to the efficacy observed with NS3 protease inhibitors in HCV infected patients suggesting potent suppression of viral replication can be achieved with inhibitors of the HCV polymerase *in vivo*.

---

Copyright © 2006 - [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.