

POSTER 52**LONGITUDINAL CLONAL RESISTANCE ANALYSIS OF TREATMENT-NAÏVE PATIENTS WITH CHRONIC HEPATITIS C (CHC) GENOTYPE 1 INFECTION TREATED WITH MK-7009, A NOVEL NS3/4A PROTEASE INHIBITOR, IN COMBINATION WITH PEGYLATED INTERFERON ALPHA-2A AND RIBAVIRIN FOR 28 DAYS**

Richard J.O. Barnard¹, Adetoun Adeniji-Adele¹, Gabriela Ramos¹, Richard Wiedmann², Peggy M. Hwang³, Erin Quirk², Nicholas Kartsonis², Andrew W. Lee², Robert Tipping³, Mike Miller¹, and Daria Hazuda¹

¹Antiviral Research, ²ID/Vaccines Clinical Research, ³Biostatistics, Merck Research Laboratories, West Point, PA, USA

MK-7009 is a noncovalent competitive inhibitor of HCV NS3/4A protease which significantly improved rapid viral response (RVR) rates in CHC patients when administered in combination with pegylated interferon (peg-IFN) and ribavirin (RBV) for 28 days (i.e., "triple therapy"). We now report updated efficacy and resistance studies for patients treated with continued peg-IFN/RBV for 12 weeks total.

This is a randomized, placebo-controlled, double-blind study of MK-7009 in treatment-naïve CHC patients. MK-7009 was administered for 28 days with peg-IFN/RBV in 1 of 5 regimens: placebo, 300 mg BID, 600 mg BID, 600 mg QD, or 800 mg QD; all patients subsequently continue peg-IFN/RBV for an additional 44 weeks. HCV RNA was determined by Roche Cobas Taqman PCR with a lower limit of detection (LLOD) ~ 10 IU/mL. RVR and EVR are defined as the percentage of treated patients below LLOD at 4 and 12 weeks, respectively. For resistance studies, the NS3 region of the HCV genome was amplified by RT-PCR from RNA purified from patient plasma. Both population and clonal sequencing was performed on the resultant NS3 amplicons.

94 subjects (mean age 46.1 years, 59% male, mean baseline HCV RNA 6.70 log₁₀ IU/mL) were randomized and treated. The proportion of subjects who achieved RVR in the MK-7009-containing arms ranged from 69% to 82%, vs. 6% of the control ($p < 0.0001$ for each MK-7009 dose group, per-protocol analysis). Preliminary data for 81 patients through Week 12 indicate continued viral suppression on peg-IFN/RBV only treatment, as 77 to 89% of subjects originally treated with triple therapy achieved EVR vs. 60% of control (per-protocol analysis). 5 patients had viral breakthrough at levels sufficient to perform resistance testing by week 12. Resistant HCV variants in the NS3/4a region of the HCV genome were detected in the three viral breakthrough patients randomized to receive MK-7009 by day 42 of the study. Three patients had viruses that exhibited the R155K variant by day 42 of the study. The virus from one of these patients also exhibited low levels of the D168V variant. One patient exhibited a mixture of D168T by day 56 of the study. Clonal and population sequencing analysis was performed at multiple time points through week 12 from these patients where samples were available.