

HCV-796 Displays Potent Antiviral Activity in Replicon and in Chimeric Mice Infected with Hepatitis C Virus (HCV)

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Background: HCV-796, a non-nucleoside HCV polymerase inhibitor, demonstrates potent antiviral activity *in vitro* and in a small animal model of HCV replication.

Methods: *In vitro* antiviral activity was evaluated in HCV replicon cells. Pharmacokinetics and *in vivo* efficacy studies were conducted in SCID-Alb/uPA mice carrying chimeric human livers infected with HCV genotype 1a. Mice with HCV titers 10^4 - 10^7 IU/ml were treated with HCV-796, interferon alpha 2b (IFN α -2b), or both, for 5-10 days.

Results: In the 1a replicon assay, HCV-796 reduced HCV RNA levels 3-4 log₁₀ HCV copies/ μ g total RNA (EC₅₀=4.5nM). In the SCID mouse model, mean plasma concentrations at 8 hr after a single dose and dosing for 5 days with 50 mg/kg were 5- and 12-fold, respectively, above replicon EC₅₀ (t_{1/2}=2hr). HCV-796 (50 mg/kg, 3x daily [tid]) reduced mean HCV titers 2.0 log₁₀ (P=0.01 vs. control) and 1.8 log₁₀ (P=0.009 vs control) after 5 or 10 days of dosing, respectively. The specific antiviral activity of HCV-796 is further confirmed by the viral rebound to baseline within 1 week of stopping treatment. Control mice demonstrated a 0.3 log₁₀ drop in HCV titers while IFN α -2b (1350 IU/g IM daily, 10 days) reduced HCV titers by 1.1 log₁₀ (P=0.04 vs control). In a 10-day experiment that explored the combination of HCV-796 with IFN α -2b, a lower dose of HCV-796 (30 mg/kg, tid) reduced 0.7 log₁₀ HCV titers, IFN α -2b (1,350 IU/ml daily) reduced 1.4 log₁₀ HCV titers while controls increased 0.1 log₁₀. The combination of HCV-796 (30 mg/kg, tid) and IFN α -2b (1350 IU/ml) showed a mean HCV titer reduction of 2.4 log₁₀ (P<0.5 vs HCV-796 or IFN α -2b alone). In all experiments serum

levels of hAAT were stable throughout dosing periods indicating the presence of intact human liver grafts.

Conclusion: HCV-796 represents a potential antiviral for the treatment of HCV infection in humans.