Antiviral Activity of the Non-Nucleoside Polymerase Inhibitor, HCV-796, in Patients With Chronic Hepatitis C Virus: Preliminary Results From a Randomized, Double-Blind, Placebo-Controlled, Ascending Multiple Dose Study

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Purpose: HCV-796 is an inhibitor of hepatitis C virus (HCV) RNA-dependent RNA polymerase that has demonstrated potent antiviral activity in vitro. We performed an ascending multiple-dose study to determine the antiviral activity, pharmacokinetics (PK), and safety of HCV-796 in patients with chronic HCV infection.
Methods: This phase 1b trial was a randomized, double-blind, placebo-controlled study of HCV-796 administered orally for 14 days to patients with chronic HCV infection (> 6 months) who were naïve to treatment. Patients aged 18 to 64 years with $\geq 10^4$ IU/mL HCV RNA levels were enrolled in sequential, ascending dose cohorts of up to 16 patients (12 active, 4 placebo) per cohort. Patients received 50, 100, 250, 500, 1000, or 1500 mg oral doses of HCV-796 or placebo given as monotherapy twice daily (q12h).
Results: The mean baseline HCV RNA level was 6.6 $\log_{10}$, and 72% of patients were infected with HCV genotype 1. HCV-796 was generally well tolerated with no dose-limiting toxicities or serious treatment-emergent adverse events. Mild to moderate headache was the most frequently reported adverse event. The mean (± SD) PK parameters for the 1000 mg cohort on day 14 were as follows: C_{max} = 2186 ± 764 ng/mL; T_{max} = 1.8 ± 0.9 hr; $t_{1/2}$ = 53.7 ± 28.7 hr; AUC_{τ} = 20046 ± 7633 ng•hr/mL; CL/F = 58.0 ± 25.5 L/hr; V/F = 4163 ± 1960 L; and the accumulation ratio was 4.2 ± 1.7. HCV-796 treatment resulted in reduced plasma HCV RNA levels. Maximal antiviral effects were achieved at study day 4, with peak mean reductions in HCV RNA across all doses ranging from 0.3 to 1.4 $\log_{10}$ (50% to 97%). In the 1000 mg cohort, the mean reduction in HCV RNA was 1.4 $\log_{10}$ (96%) on day 4, 1.3 $\log_{10}$ (95%) on day 7, and 0.7 $\log_{10}$ (80%) on day 14. In this group, 83% of patients had reductions from baseline > 1.0 $\log_{10}$ on day 4; 33% of these patients had reductions > 1.5 $\log_{10}$ and 25% had reductions > 2.0 $\log_{10}$. On day 14, 17% of patients in the 1000 mg cohort had reductions from baseline > 2.0 $\log_{10}$. Antiviral activity appeared similar among patients infected with HCV genotype 1 compared with those infected with other genotypes of HCV.
Conclusions: HCV-796 demonstrated antiviral activity and was generally safe and well tolerated when given for 14 days. PK exposure was less than dose-proportional with increasing dose, and appeared to reach a plateau at the 1000 mg q12h dose.