Twelve Weeks Interferon-Free PSI-7977 Regimen Cures 100 Percent Hep C Genotype 2/3

November 6, 2011

A twelve-week course of Pharmasset's once-daily experimental nucleotide analog PSI-7977, combined with ribavirin, cured 10 of 10 people living with genotype 2/3 hepatitis C virus (HCV) who used the regimen—without pegylated interferon—in a Phase II clinical trial. The highly encouraging results were reported Sunday, November 6, at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in San Francisco.

Compared with the three other groups included in the study, which involved taking PSI-7977 plus ribavirin with either four, eight or 12 weeks of pegylated interferon, significant improvements in safety and tolerability were also documented among those using PSI-7977 plus ribavirin alone, according to Edward Gane, MD, of the Auckland City Hospital in Auckland, New Zealand, and his ELECTRON study colleagues.

Results from early studies of PSI-7977 have been promising. In the PROTON study, PSI-7977 combined with pegylated interferon plus ribavirin resulted in sustained virologic responses (SVRs)—viral cures—in 96 percent of study volunteers with HCV genotype 2/3 and 91 percent of those with HCV genotype 1 (the most common yet hardest-to-treat form of the virus in the United States).

ELECTRON, initiated in December 2010, was conducted to determine the shortest duration of pegylated interferon—if any—required to achieve SVRs when PSI-7977 plus ribavirin are given for 12 weeks. HCV genotype 2/3 patients were initially selected for this unorthodox study—pegylated interferon has long been a mainstay agent in hepatitis C drug regimens—given pegylated interferon and ribavirin tend to be much more effective for individuals with genotype 2/3 virus and could be called upon in the event of poor responses to PSI-7977/ribavirin in the study.

No "rescue" therapy proved necessary. At virtually all study time points—weeks 4, 8 and 12 during therapy and weeks 4, 8, 12 and 24 following the completion of treatment—100 percent of the patients in each group maintained undetectable HCV viral loads. Eleven patients received PSI-7977/ribavirin plus 12 weeks of pegylated interferon, 10 received PSI-7977/ribavirin plus eight weeks of pegylated interferon, nine received PSI-7977/ribavirin plus pegylated interferon and ten received PSI-7977/ribavirin without pegylated interferon.

Gane noted that HCV viral load suppression was rapid in all four treatment groups—virtually everyone had HCV below the level of detection within three weeks of beginning treatment.

At least one side effect—including headache, fatigue, depression, insomnia, anxiety, irritability, muscle soreness and upper respiratory tract infections—was more likely to be documented in those in the 12-week pegylated interferon group (72 percent), compared with those who didn't receive any pegylated interferon (40 percent).

Similarly, whereas moderate-to-severe drops in neutrophils—a type of white blood cell—was documented in roughly 70 percent of those in the 12-week pegylated interferon group, no volunteers in the interferon-free PSI-7977/ribavirin group experienced this toxicity. Interferon-free PSI-7977 plus ribavirin also had much less of an impact on hemoglobin levels, a marker of anemia.

Also encouraging, all patients in the study experienced a rapid normalization of ALT, a key liver enzyme. Among those in the interferon-free treatment group, normal ALT levels were documented in all patients by the end of the third week of treatment.

In summary, Gane noted, "PSI-7977 [400 milligrams once daily] remains very well tolerated with no attributable safety signal, no treatment discontinuations and no treatment emergency laboratory abnormalities." As for potency, he concluded that PSI-7977/ribavirin "elicited rapid suppression" of HCV viral load in study volunteers with HCV genotype 2 or 3 and that all 40 patients in the study achieved an SVR, regardless of whether or not interferon was used. Additionally, not a single case of drug-resistant virus emerged during the study.

Further results from ELECTRON are expected. The study has been amended, adding several new treatment groups. One group is exploring PSI-7977 used as monotherapy—without pegylated interferon or ribavirin—to treat genotype 2/3 infection. Preliminary data reported by Gane's team suggest that four patients in this group have maintained undetectable HCV levels four weeks after discontinuing treatment.

Another group is studying PSI-7977 in combination with pegylated interferon plus ribavirin, again in genotype 2/3 patients, but for only eight weeks.

Three additional groups are now enrolling patients. One is studying 12 weeks of PSI-7977 plus ribavirin, without interferon, in HCV genotype 2/3 patients who weren't able to clear the virus with 24 weeks of previous pegylated interferon/ribavirin therapy. A second is evaluating PSI-7977 plus ribavirin in HCV genotype 1 patients beginning therapy for the first time. The third group consists of individuals with HCV genotype 1 null responders (patients who responded very poorly to prior pegylated interferon/ribavirin treatment); they will receive PSI-7977/ribavirin for a total of 12 weeks.

Pharmasset recently announced its Phase III clinical trial program. Two studies—FISSION and POSITRON—will further explore the safety and efficacy of PSI-7977 plus ribavirin, but without pegylated interferon, in approximately 725 people with genotype 2/3 HCV infection. A third study

will explore PSI-7977 in HCV genotype 1 patients, with the design of the study determined by the ongoing ELECTRON clinical trial and another study still under way.
