

## **AASLD 2013: 100% of Hard-to-treat Patients Cured with Sofosbuvir/Ledipasvir + Ribavirin or GS-9669**

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Interferon-free regimens of sofosbuvir and ledipasvir plus either ribavirin or GS-9669 taken for 12 weeks produced sustained response in 100% of treatment-experienced genotype 1 chronic hepatitis C patients with advanced liver fibrosis or cirrhosis, according to the latest findings from the ELECTRON trial presented yesterday at the 64th AASLD Liver Meeting in Washington, DC. A related analysis of previously untreated people without cirrhosis found that reducing treatment duration to 6 weeks led to relapses.

Gilead Science's Phase 2 ELECTRON trial program has tested the nucleotide HCV polymerase inhibitor sofosbuvir (formerly GS-7977) in various all-oral regimens for increasingly difficult-to-treat patient populations.

A 12-week dual regimen of sofosbuvir plus ribavirin cures most people with easier-to-treat HCV genotypes 2 or 3, and an advisory committee of the U.S. Food and Drug Administration last month recommended approval for this indication.

The dual regimen was not adequate, however, for prior non-responders with HCV genotype 1. Researchers then tried adding the NS5A inhibitor ledipasvir (GS-5885), finding that the triple regimen taken for 12 weeks produced a sustained virological response rate at 12 weeks post-treatment (SVR12) of 100% for both treatment-naive patients and prior non-responders without cirrhosis.

The analysis presented at the Liver Meeting by Edward Gane of Auckland Clinical Studies evaluated a once-daily fixed-dose tablet containing 400 mg sofosbuvir and 900 mg ledipasvir, taken with either ribavirin or the non-nucleoside polymerase inhibitor GS-9669, for the most difficult-to-treat group: treatment-experienced genotype 1 patients with advanced fibrosis or cirrhosis.

Researchers first enrolled 20 treatment-experienced genotype 1 patients with cirrhosis (Metavir stage F4) who were randomly assigned to receive the sofosbuvir/ledipasvir fixed-dose combination either with or without ribavirin for 12 weeks.

Next, 50 treatment-experienced genotype 1 patients with advanced fibrosis or cirrhosis (stage F3-F4) were randomized to receive the sofosbuvir/ledipasvir fixed-dose tablet plus either ribavirin or GS-9669, again for 12 weeks.

About 70% of treatment-experienced participants were men, about 90% were white, and the mean age was approximately 56 years. About three-quarters had harder-to-treat HCV subtype 1a and about one-quarter had the favorable IL28B CC gene pattern.

Researchers also aimed to determine a minimum effective duration of sofosbuvir/ledipasvir/ribavirin for easier-to-treat patients. This analysis enrolled 25 genotype 1 treatment-naive participants with absent-to-moderate fibrosis (stage F0-F2). All were treated with the sofosbuvir/ledipasvir fixed-dose tablet plus ribavirin for 6 weeks and compared against previously studied patients.

Just over half of the treatment-naive group were men, most were white, and the average age was 51 years. Most (84%) had HCV subtype 1a and 20% had the favorable IL28B variant.

## Results

In the first comparison, 100% of cirrhotic patients treated with sofosbuvir/ledipasvir plus ribavirin achieved SVR12, compared to only 70% of those treated with sofosbuvir/ledipasvir alone.

In the second comparison, 100% of patients with advanced fibrosis or cirrhosis achieved SVR12 when treated with sofosbuvir/ledipasvir plus either ribavirin or GS-9669.

While response rates were the same in both arms, hemoglobin levels dropped significantly among people taking ribavirin but remained stable among GS-9669 recipients.

Among the easier-to-treat patients, several people treated for only 6 weeks relapsed after the end of therapy, resulting in an SVR12 rate of just 68%, compared with 100% of patients previously treated with the same regimen for 8 or 12 weeks.

No baseline factors predicted which individuals would relapse and all had good initial viral declines on treatment.

Across all treatment arms sofosbuvir/ledipasvir alone or with ribavirin or GS-9669 was generally safe and well tolerated.

Just 1 participant experienced a serious adverse event and no one discontinued treatment early due to side effects.

About 9% of treatment-experienced patients receiving any study regimen experienced grade 3-4 laboratory abnormalities, but this rose to 36% in the treatment-naive group.

15% of treatment-experienced and 40% of treatment-naive people taking ribavirin saw their hemoglobin levels fall below 10 g/dL, indicating anemia, compared with none in the ribavirin-sparing arms.

The most common side effects were headache (30% in the sofosbuvir/ledipasvir only arm, 35% in the sofosbuvir/ledipasvir/ribavirin treatment-experienced arm, 32% in the sofosbuvir/ledipasvir/ribavirin treatment-naive group, and 25% in the sofosbuvir/ledipasvir/GS-9669 arm), fatigue (10%, 18%, 24%, and 35%, respectively) and nausea (0%, 32%, 20%, and 42%).

"In treatment-experienced patients with advanced fibrosis/cirrhosis, either ribavirin or GS-9669 may enhance the efficacy of sofosbuvir/ledipasvir given for 12 weeks," the investigators concluded.

"The optimal duration of sofosbuvir/ledipasvir in treatment-naive genotype 1 patients (even with the addition of ribavirin) is more than six weeks," they added.

EJ Gane, CA Stedman, RH Hyland, et al. Once Daily Sofosbuvir/Ledipasvir Fixed Dose Combination with or without Ribavirin: the ELECTRON trial. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Washington, DC, November 1-5, 2013. Abstract 73.