

Special Report: Drug Pipeline Updates from AASLD

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November 8, 2008

At the recent American Association for the Study of Liver Diseases (AASLD) conference there were many posters and presentations on new drugs that are in development to treat hepatitis C. This overview will present top line results on many new drugs. A more detailed overview will appear in the December issue of the *HCV Advocate* newsletter. It is important to remember that the drugs that are furthest along in clinical development are in phase III studies, but the data presented below is from phase I and II clinical trials. Vertex's telaprevir and Schering's boceprevir are currently in Phase III studies and the information from the phase III studies will give us a much better picture of the effectiveness and safety of these drugs. The other medications listed below are in very early clinical development but also offer hope that they will eventually prove to be effective in treating hepatitis C.

Telaprevir

Vertex's telaprevir is the HCV protease inhibitor that is furthest along in clinical development. Various posters and presentations were presented at AASLD:

- Interim SVR 12 and 24 results from **PROVE3** found that an overall over SVR rate of 52% in prior HCV genotype 1 patients who did not achieve an SVR with a previous course of pegylated interferon plus ribavirin. The results below are given as type of non-response, but the SVR12 and SVR 24 results have been combined:
 - Non-responders (66 patients) – 41%
 - Relapsers (40 patients)—73%
 - Breakthroughs (9 patients)—44%
- The final results for Vertex's **PROVE2** study were released at AASLD. The bottom line is that the SVR24 rate in the telaprevir arm was 69%. This included 323 HCV genotype 1 treatment-native patients who were assigned into one of four treatment arms.
- A phase II study (**C208**) that evaluated different doses of telaprevir: the dose that Vertex is using for their phase III study (750 mg every 8 hours) vs. 1125 mg every 12 hours. All four groups received a combination of telaprevir plus ribavirin and either Pegasys or PegIntron. The total study population included 161 HCV genotype 1 treatment naïve-patients. The preliminary 12-week results found that all treatment arms achieved somewhat similar viral load reductions and the safety profile was consistent with previous studies of triple combination regimes that included telaprevir. There is hope that if these results carry through to the end of treatment that telaprevir will be able to be dosed twice daily instead of the current clinical regime of three times a day.
- In another study of telaprevir, the interim results from a phase II study (**C107**) that retreated HCV genotype 1 patients who were prior pegylated relapsers, non-responders, and/or partial responders was released. The study included 104 patients. At week 24 of treatment 58% of patients were HCV RNA negative (< 10 IU/mL). The authors reported that the side effects were consistent with the side effects reported in previous telaprevir studies – four patients discontinued because of rash and one for anemia.

Boceprevir

Data from Schering's phase II study of boceprevir (**HCV SPRINT-1**) was presented at this year's conference:

- In the five arm study of boceprevir, the arm that included 103 patients achieved an SVR12 (twelve weeks post treatment) of 74% – this regime included a 4 week lead-in phase of PegIntron plus ribavirin followed by triple combination therapy of boceprevir, PegIntron and ribavirin for 44 weeks. Total duration of treatment was 48 weeks. The side effects in the boceprevir arms were similar to side effects that are usually seen in pegylated interferon and ribavirin except there was a higher incidence of anemia and taste changes in the boceprevir arms.

Nitazoxanide

A study with a different lead-in time using nitazoxanide in combination with pegylated interferon plus ribavirin was released at AASLD:

- 4 week lead-in: 500 mg twice a day (taken with food) of nitazoxanide followed by nitazoxanide plus Pegasys for 36 weeks. SVR rates are listed by genotype:
 - 3 of 3 patients with HCV genotype 1 – 100% SVR;
 - 1 of 1 patient with HCV genotype 2 – 100% SVR;
 - 31 of 40 patients with HCV genotype 4 – 78% SVR.

These results compare favorably with another clinical trial of nitazoxanide used in combination with pegylated interferon plus ribavirin that used a 12 week lead-in phase. It appears that the 4-week lead-in phase would be as effective as the 12-week lead-in phase.

Currently Nitazoxanide is being tested in HCV genotype 1 treatment non-responders and treatment-naïve patients.

R7128

HCV genotype 2 and 3 prior non-responders were treated with R7128 (1500 mg twice a day) in combination with Pegasys plus ribavirin for 28 days. There was a mean viral log reduction of 5.0 log₁₀. R7128 was generally well-tolerated and further development in genotype 2 and 3 patients is being planned.

BI 201335

One study of BI 201335, a new HCV protease inhibitor that is being developed by Boehringer Ingelheim Pharma, was released at AASLD.

- In a small study of 19 prior HCV genotype 1 treatment-experienced patients, the patients were divided into three groups and were given once-a-day dosing of either 48, 120 or 240 mg of BI 201335 a day in combination with pegylated interferon and ribavirin for 28 days. The drug was found to produce a virologic response in all treatment doses through day 28. The higher dose of 240 mg/day produced the best virologic response. There were no serious side effects reported and the side effects experienced were consistent with the side effects seen in pegylated interferon plus ribavirin therapy. One patient discontinued treatment due to anxiety. Boehringer announced that further development is being planned.

TMC435350 (TMC435)

Tibotec is testing a new protease inhibitor, TMC435, and released two posters at AASLD:

- The first poster was on a pre-clinical study that looked at the antiviral activity of TMC435 in HCV genotypes 1 through 6. This test was conducted on cloned HCV genotype 1 through 6 proteases and it was found to be a potent inhibitor of the NS3/4A serine protease in all the genotypes tested.
- The second poster reported on the interim results from a phase II study conducted in healthy volunteers as well as in HCV genotype 1 patients who were treatment-naïve and treatment-experienced. In the arm containing the healthy volunteers – the once-a-day 200 mg dose – the pharmacokinetics (absorption, distribution, metabolism and excretion) of TMC435 reached a steady state in 7 days as a capsule. In the 48 HCV-infected patients who received either the 25 mg or 75 mg dose (once a day) given as a monotherapy or in combination with pegylated interferon plus ribavirin, the results were:
 - **Monotherapy** given for 7 days results in a mean reduction of 2.63 log₁₀ IU/mL in the 25 mg arm and 3.43 log₁₀ IU/mL in the 75 mg/day arm.
 - **Triple** (TMC435, pegylated interferon, ribavirin) given for 28 days produced mean viral load reductions of 3.47 log₁₀ IU/mL in the 25 mg arm and 4.55 log₁₀ IU/ml in the 75 mg/day arm.

There were no serious side effects reported with TMC435 – the most common side effect reported were nausea, diarrhea, and headache.

PF-00868554

Results from a new non-nucleoside inhibitor, PF-00868554, were presented in a poster that studied the safety, tolerability and pharmacokinetics of this new compound. The study drug was administered to 33 healthy male subjects between 18-55 years old in one of 4 treatment arms. Thirty-one patients finished the study with no serious adverse events, drug discontinuation or dose reductions when the drug was given twice a day for 14 days. The plasma concentrations were as expected, and another study with patients infected with HCV treatment naïve-patients is currently underway.

ANA598

Data from a new study on ANA598, an HCV polymerase inhibitor, was also presented at AASLD. The study was conducted in healthy volunteers at doses of 400 mg, up to 3,000 mg. It was reported that there were no serious adverse events or treatment discontinuations. In two other posters the drug was found to have a potent antiviral effect against HCV when tested in a chimpanzee; in a test tube analysis it was found to have a synergistic effect when combined with interferon, telaprevir and R7128, and the potential to overcome viral resistance when used with the aforementioned drugs.

GI-5005

A study from GlobeImmune on their HCV therapeutic Vaccine, GI-5005, given to HCV patients with a high HCV viral load (>600,00 IU/mL) found that it doubled the clearance of HCV RNA. There were 140 HCV genotype 1 patients – 74% treatment naïve; 26% prior treatment non-responders in the 4 week trial.