Once-Daily HCV Protease Inhibitor Meets Efficacy and Safety Goals in Phase II Studies

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In people living with genotype 1 HCV attempting treatment for the first time, BI 201335 combined with standard pegylated interferon/ribavirin (IFN/RBV) was associated with sustained virologic response (SVR) rates in 71 to 83 percent of patients treated with all three agents, compared with only 56 percent of patients treated with IFN/RBV alone. And in patients who didn't respond favorably to at least 12 weeks of earlier treatment, adding BI 201355 to IFN/RBV during retreatment resulted in SVRs in 28 to 41 percent of patients.

BI 201335 is one of several protease inhibitors being developed to treat HCV. While Vertex's telaprevir and Merck's Victrelis (boceprevir) are currently furthest along in development and are expected to be approved by the U.S. Food and Drug Administration in the coming months, both of these drugs need to be taken three times a day. Boehringer Ingelheim's lead HCV protease inhibitor may only require once-daily dosing. What's more, it is being studied with BI 207127—a non-nucleoside polymerase inhibitor—to treat HCV without the need for pegylated interferon.

The two Phase II studies reported in Berlin were SILEN-C1, involving first-time treatment takers, and SILEN-C2, which enrolled HCV treatment-experienced individuals. Data from SILEN-C1 were reported by Tarik Asselah, MD, PhD, of Hôpital Beaujon, Clichy Cedex, France, and results from SILEN-C2 were highlighted by Mark Sulkowski, MD, of Johns Hopkins University School of Medicine in Baltimore.

SILEN-C1: BI 201335 in Treatment-Naive Patients

This clinical trial assigned 429 people living with HCV, all with genotype 1 virus, to one of four groups. One group received a three-day lead-in dose of IFN/RBV and then added BI 201335, 120 milligrams (mg) once a day. The second group received a three-day lead-in dose of IFN/RBV and then added BI 201335, 240 mg once a day. The third group received BI 201335, 240 mg once a day plus IFN/RBV without lead-in dosing. The fourth group received IFN/RBV without BI 201355 throughout the study.

BI 201335 was given for 24 weeks together with IFN/RBV. Patients in the two groups involving the 240 mg daily dose of BI 201335 who achieved an extended rapid virologic response

(eRVR)—defined as an undetectable HCV viral load at week four and at weeks 8 through 20—were re-allotted to either stop all treatment at week 24 or continue IFN/RBV for a total of 48 weeks of treatment.

Overall SVR rates, Asselah reported, reached 83 percent in the 240 mg group that didn't do IFN/RBV lead-in dosing. A three-day lead-in with IFN/RBV before starting BI 201335 reduced responses by 12 percent and 10 percent in the 120 mg group and the second 240 mg group, respectively.

Lead-in dosing was also associated with higher rates of viral breakthrough. Of the patients in the 240 mg group who achieved eRVRs and were instructed to stop all treatment after 24 weeks, 93 percent achieved an SVR.

The most frequent side effects in the study were gut problems (e.g., diarrhea), rash or sun hypersensitivity, and yellowing of the skin (jaundice) resulting from elevated levels of bilirubin. Average levels of the liver enzyme ALT improved in all BI 201335 groups compared with those who only received IFN/RBV. What's more, there was no excess anemia reported in the study.

SILEN-C2: BI 201335 in Treatment-Experienced Patients

SILEN-C2 evaluated the activity and safety of BI 201335 in treatment-experienced patients who did not respond to at least 12 weeks of earlier treatment with IFN/RBV. This patient population is particularly difficult to treat, as patients who have not responded to IFN/RBV alone tend to have low response rates during retreatment.

SILEN-C2 only included patients who did not see their viral load decrease by at least 2 log or become undetectable during earlier treatment. The study did not enrolled individuals who initially saw their HCV viral loads become undetectable, followed by a viral load rebound, during prior treatment.

The study enrolled 288 volunteers. One group of patients received 240 mg BI 201335 once-daily with a three-day lead-in of IFN/RBV. A second group also received 240 mg 201335 once-daily with IFN/RBV, but without lead-in dosing. A third group received 240 mg BI 201335 twice-daily plus a three-day lead-in of IFN/RBV.

As with patients in SILEN-C1, patients in the two BI 201335 240mg once-daily dosing groups who achieved an eRVR were reassigned to either stop all treatment at week 24 or continue IFN/RBV until week 48.

SVRs ranged from 28 percent in the group receiving 240 mg once-daily BI 201335 plus lead-in IFN/RBV dosing to 41 percent among those receiving 240 mg once-daily BI 201335 without lead-in IFN/RBV dosing. As is seen in SILEN-C1, three-day lead-in dosing of IFN/RBV was associated with decreased efficacy.

Also similar to SILEN-C1, the most common side effects were gut problems and jaundice due to

elevated bilirubin levels. Serious or severe adverse side effects, along with discontinuation of therapy due to side effects, were more common in the twice-daily BI 201335 group.

Boehringer Ingelheim is planning Phase III studies of BI 201335 in both populations—treatment naive and treatment experienced—of people living with HCV.
