Vicriviroc Falls Short in Treatment-Experienced HIV Studies

February 18, 2010 By Tim Horn

Merck's CCR5 receptor antagonist vicriviroc, combined with an optimized regimen of approved drugs, failed to prove itself superior to an optimized regimen alone in two Phase III clinical trials involving treatment experienced patients reported on Wednesday, February 17, at the 17th Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco.

Though the data are generally sobering and shed light on Merck's recent decision to terminate plans to seek approval for the drug for treatment-experienced patients, some of the reported data are encouraging, specifically regarding the patients who used vicriviroc and who have HIV sensitive to some approved HIV drugs.

Vicriviroc, a once-daily drug that works similarly to ViiV Healthcare's Selzentry (maraviroc), was initially scheduled to be approved this year, based on the successful completion of two Phase III clinical trials—dubbed VICTOR-E3 and E4—involving treatment-experienced HIV-positive patients.

The two international studies, reported at CROI by Joseph Gathe, MD, of Therapeutic Concepts PA in Houston and his colleagues, compared vicriviroc (30 mg once daily) to placebo in combination with an optimized regimen in which at least two fully active antiretroviral drugs were required and which included a Norvir (ritonavir)-boosted protease inhibitor. More than 60 percent of patients in these studies had three or more active drugs in their optimized regimen, which is a substantially greater proportion than in recent studies for other HIV therapies.

A total of 857 patients were enrolled in the trials, 721 of whom were found to have HIV that was exclusively using the CCR5 coreceptor to infect cells. Patients were, on average, 43 years old when they entered the study; 29 percent were female; and 40 percent were people of color. The average viral load upon entering the studies was 4.6 log copies.

Of the 721 CCR5-positive patients included in the analysis, 64 percent of those receiving vicriviroc in both studies and 62 percent of those who received an optimized regimen without vicriviroc had viral loads below 50 copies after 48 weeks of treatment. Considering that the primary objective of the study wasn't met—a statistically significant difference, in favor of the vicriviroc groups in both studies—the trial was considered unsuccessful.

This is not to say that vicriviroc therapy is without potential advantages. When Gathe's group

looked at patients who were only able to include two or fewer drugs in their optimized regimens due to significant drug resistance, 70 percent in the vicriviroc groups and 55 percent in the optimized regimen-only groups had viral loads below 50 copies after 48 weeks—a statistically significant difference. But because the majority of patients enrolled in the study were able to include three or more active drugs in their optimized regimens, the overall study results failed to show vicriviroc's superiority.

The most commonly seen adverse events for vicriviroc were similar to those for placebo: diarrhea (23 versus 21 percent), nausea (15 versus 7 percent) and headache (12 versus 15 percent). There were no significant differences between the two groups in terms of AIDS-defining illnesses, cancers or other adverse conditions that have been watched closely in CCR5 receptor antagonist research studies.

Interestingly, Gathe didn't discuss deaths seen in the study during his presentation. When asked about this during the question-and-answer period, one of Gathe's colleagues answered that there were seven deaths among those receiving vicriviroc, compared with zero deaths among those receiving optimized therapy alone. No clear explanations for these deaths—notably their causes—were provided. These will likely be discussed upon official publication of the results in a peer-reviewed medical journal.

"With several new potent antiretrovirals now available," the study investigators conclude, "the goal of treatment at all stages of HIV infection is full viral suppression, using at least two, and preferably three, active drugs. Additional active drugs rarely provide incremental benefit. This compendium of antiretrovirals is a remarkable achievement that benefits HIV patients for whom the drugs are available. However, for patients with limited treatment options, these data suggest that vicriviroc may provide useful benefit. Future trials designed for advanced patients must account for changes in the therapeutic landscape."

Merck said it plans to further evaluate these findings and to define a potential path forward for vicriviroc. Merck is also committed to completing its study involving patients starting antiretroviral therapy for the first time and will likely seek approval for the drug upon the successful completion of these clinical trials.

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