Durable Efficacy and Safety With Isentress Treatment

February 9, 2008 By Tim Horn

Year-long follow-up data from two Phase III clinical trials of Isentress (raltegravir) were reported this week at the 15th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. The studies, involving patients with multi-drug-resistant HIV and advanced infection, indicate that Merck's integrase inhibitor offers durable antiretroviral activity to those in desperate need of new treatment options.

Because integrase inhibitors work differently than other HIV drugs on the market, they potentially offer a lot of hope for HIV-positive people, especially those who have developed HIV resistance to older antiretrovirals (ARVs).

Isentress was approved by the U.S. Food and Drug Administration in October 2007. It was given the green light by the agency for use in ARV-experienced patients, based on 24-week data from two Phase III clinical trials, dubbed BENCHMRK-1 and BENCHMRK-2. At CROI, 48-week data from these two pivotal studies were reported.

The BENCHMRK clinical trials are randomized evaluations of Isentress (400mg twice daily) compared with placebo, both combined with an optimized background regimen (OBR), in patients with multiple-drug-resistant HIV and a history of treatment failure (including the regimens they were taking prior to enrollment).

BENCHMRK-1, conducted in Europe, Asia, the Pacific, and Peru, randomized 232 patients to Isentress plus OBR and 118 patients to placebo plus OBR. BENCHMRK-2, conducted in North and South America, assigned 230 patients to receive Isentress/OBR and 119 patients to receive placebo/OBR.

In BENCHMRK-1, the average viral load upon entering the study was approximately 40,000 copies in the Isentress group and 32,000 copies in the placebo group. CD4 counts, at baseline, averaged 140 cells in the Isentress group and 105 cells in the placebo group. In BENCHMRK-2, the average baseline viral load, in both groups, was 50,000 copies; pre-treatment CD4 counts averaged 102 cells in the Isentress group and 132 cells in the placebo group.

Efficacy Results

After 48 weeks of follow up in BENCHMRK-1, 65 percent of patients receiving Isentress/OBR maintained viral loads below 50 copies—undetectable by today's standards—compared with 31

percent of those receiving placebo/OBR. After 48 weeks of participation in BENCHMRK-2, 60 percent in the Isentress/OBR group, compared with 34 percent of those in the placebo/OBR group, had viral loads below 50 copies. The differences in the rates of undetectable viral loads between the two groups in both studies were statistically significant.

Differences between the two groups, with respect to CD4 gains, were also statistically significant. In BENCHMRK-1, Isentress/OBR recipients had an average 120 CD4-cell gain, compared with a CD4 gain of 49 cells in the placebo group. In BENCHMRK-2, CD4s increased by 98 cells in the Isentress/OBR group, compared with 40 cells in the placebo/ORB group.

Safety Results

There were few discontinuations of treatment of the study because of side effects. In BENCHMRK-1, 1.7 and 3.4 percent in the Isentress and placebo groups, respectively, discontinued due to adverse experiences. In BENCHMRK-2, 3 percent and 2.5 percent, respectively, stopped treatment because of side effects.

The most commonly reported side effects—occurring in at least 2 percent of patients—among patients receiving Isentress in either study were diarrhea, gas nausea, vomiting, fatigue, injection site pain or reaction (due to Fuzeon), joint pain, dizziness, headache and itching.

The authors of both studies concluded that Isentress, combined with OBR, has “potent and superior” virologic and immunologic efficacy compared to placebo, with sustained results through 48 weeks of treatment.
