New 96-Week ACTG Study Results Presented at CROI 2014; First Large Study Comparing ISENTRESS® (raltegravir) Regimen to Two Protease Inhibitor Regimens in Previously Untreated Adults with HIV-1

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BOSTON--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, said today that in a new 96-week, open-label AIDS Clinical Trials Group (ACTG) study designed to compare three different NNRTI-sparing HIV regimens in treatment-naïve patients – one containing Merck’s twice-daily ISENTRESS® (raltegravir) and two containing different once-daily ritonavir-boosted protease inhibitors, atazanavir and darunavir -- all three regimens achieved high and equivalent levels of efficacy, as measured by time to virologic failure (VF), the study’s co-primary endpoint. On the other co-primary endpoint of failure due to tolerability, the ISENTRESS and darunavir/r regimens were superior to the atazanavir/r regimen. In addition, on the key secondary endpoint of the combination of VF and tolerability failure (TF), the regimen with ISENTRESS was superior to both of the protease inhibitor regimens. The results of this ACTG study were presented in an oral session today at the 21st Conference on Retroviruses and Opportunistic Infections (CROI).

"These findings provide additional evidence of the efficacy and tolerability of ISENTRESS in a diverse population of treatment-naïve adults with HIV-1," said Dr. Randi Leavitt, executive director, Infectious Diseases, Merck Research Laboratories and co-author of the ACTG 5257 study. "We want to acknowledge the patients who participated in this study, the ACTG and the trial investigators for this important contribution to the therapeutic evaluation of medicines used to manage the consequences of HIV infection."

The 1,809-patient ACTG 5257 open-label study is the first large, well-powered study to compare ISENTRESS (raltegravir) to protease inhibitor-based treatment regimens in a treatment-naïve population. Patients were randomized to receive atazanavir/r (300 mg/100mg once daily), ISENTRESS (400 mg twice daily), or darunavir/r (800 mg once daily). All patients in the study also received emtricitabine/tenofovir disoproxil fumarate (200/300 mg once daily). The primary objective of this study was to demonstrate equivalence of the regimens with regard to virologic efficacy and tolerability over 96 weeks. The virologic endpoint was time to VF, defined from study entry to confirmed viral load above 1000 copies/mL (after week 16 and before week 24), or above 200 copies/mL (at or after week 24). Time to TF was defined from entry to discontinuation of the atazanavir/r, ISENTRESS or darunavir/r component of the regimen for toxicity. The key secondary composite endpoint was time to first of VF or TF.

In this Phase 3 prospective, randomized study, 34 percent of patients were non-Hispanic black and 22 percent were Hispanic. Twenty-four percent were women. Mean entry viral load was 4.6 log 10 copies/mL; 31 percent had viral load above 100,000 copies/mL. Mean baseline CD4 cell count was 308/mm³; CD4 was below 200/mm³ for 30 percent.

Equivalence was declared if the two-sided 97.5 percent confidence interval (CI) on the difference in 96-week cumulative probability of VF in pairwise comparisons between each study regimen was entirely within +/-10 percent. Comparisons of TF and a composite of VF/TF were similarly defined. In the event that equivalence was not shown, superiority was declared if the 97.5 percent CI excluded zero.

ACTG 5257 Trial Results

At CROI, the ACTG reported that 92 percent of patients completed 96 weeks of the study. Equivalent rates of virologic control were attained for all regimens. The percentage of patients maintaining ≤50 copies/mL at week 96 was 94 percent, 88 percent and 89 percent for ISENTRESS, atazanavir/r and darunavir/r, respectively, based on intent-to-treat analysis. One percent, 16 percent and five percent discontinued ISENTRESS, atazanavir/r and darunavir/r, respectively, for toxicity largely due to clinical jaundice and hyperbilirubinemia with atazanavir/r, and gastrointestinal symptoms with both atazanavir/r and darunavir/r. Other discontinuations were similarly distributed across all arms. The primary tolerability endpoint of discontinuation of the randomized treatment was equivalent between ISENTRESS and darunavir/r, while the incidence of discontinuation due to tolerability over 96 weeks in the atazanavir/r group was 13 percent (97.5% CI: 9.4%, 16%) higher than ISENTRESS and 9.2 percent (97.5% CI: 5.5%, 13%) higher than darunavir/r. In pairwise comparisons of the cumulative incidence to first of either VF or TF, ISENTRESS (raltegravir) was superior to both atazanavir/r (largely due to elevated bilirubin) and darunavir/r (driven by both virology and differences in gastrointestinal toxicity) when considering tolerability and virologic efficacy together. In this composite analysis, atazanavir/r was inferior to both ISENTRESS by 15 percent (97.5% CI:...
ISENTRESS does not cure HIV-1 infection or AIDS.

Severe, potentially life-threatening and fatal skin reactions have been reported. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction and toxic epidermal necrolysis. Immediately discontinue treatment with ISENTRESS and other suspect agents if severe hypersensitivity, severe rash, or rash with systemic symptoms or liver aminotransferase elevations develop and monitor clinical status, including liver aminotransferases closely.

Immune reconstitution syndrome can occur, including the occurrence of autoimmune disorders with variable time to onset, which may necessitate further evaluation and treatment.

Co-administration of ISENTRESS with drugs that are strong inducers of uridine diphosphate glucuronosyltransferase (UGT1A1) may result in reduced plasma concentrations of raltegravir. Co-administration of ISENTRESS and other drugs may alter the plasma concentration of raltegravir. The potential for drug-drug interactions (DDIs) must be considered prior to and during therapy. Co-administration or staggered administration (by 2 hours) of aluminum and/or magnesium hydroxide-containing antacids and ISENTRESS is not recommended. Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of ISENTRESS. Therefore, the dose of ISENTRESS (raltegravir) for adults should be increased to 800 mg twice daily during coadministration with rifampin. There are no data to guide co-administration of ISENTRESS with rifampin in patients below 18 years of age.

The most commonly reported (≥2%) drug-related clinical adverse reactions of moderate to severe intensity in treatment-naïve adult patients receiving ISENTRESS compared with efavirenz were insomnia (4% vs 4%), headache (4% vs 5%), nausea (3% vs 4%), fatigue (2% vs 3%) and dizziness (2% vs 6%), respectively. In treatment-experienced adult patients receiving ISENTRESS, the most commonly reported (≥2% in either treatment group) drug-related clinical adverse reactions of moderate to severe intensity and at a higher incidence compared with placebo was headache (2% vs 1%). Intensities were defined as follows: Moderate (discomfort enough to cause interference with usual activity); or Severe (incapacitating with inability to work or do usual activity).

Grade 2 to 4 creatine kinase laboratory abnormalities were observed in patients treated with ISENTRESS. Myopathy and rhabdomyolysis have been reported. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions and patients with a history of rhabdomyolysis, myopathy or increased serum creatine kinase.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing ISENTRESS (raltegravir) plus darunavir/ritonavir, compared to subjects receiving ISENTRESS without darunavir/ritonavir or darunavir/ritonavir without ISENTRESS. However, rash that was considered drug-related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To monitor maternal-fetal outcomes of pregnant patients exposed to ISENTRESS, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

About Merck

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Forward-Looking Statement

This news release includes “forward-looking statements” within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck’s management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rates and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; Merck’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Merck’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.
Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck's 2013 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).


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