

**Raltegravir, in Combination with Other HIV Medicines Shown as Effective as Efavirenz in Suppressing Viral Load and Increasing CD4 Cell Counts in Treatment-Naïve HIV-infected Patients with High Levels of Virus, Across Various Populations, in Investigational Study**

**Phase III Studies Showed Raltegravir in Combination Therapy Provided Significant Viral Load Reductions through 96 Weeks in Treatment-Experienced Patients with Triple-Class Resistant HIV**

MONTREAL, Quebec, FEBRUARY 11, 2009 – In new subgroup analyses of a Phase III study (STARTMRK) that compared Merck integrase inhibitor raltegravir to efavirenz [one of the leading antiretrovirals prescribed for previously untreated (treatment-naïve) HIV-infected patients], raltegravir was found to be as effective as efavirenz at suppressing viral load and provided improvements in immune system function across a broad spectrum of patient subpopulations through 48 weeks. The use of raltegravir in previously untreated HIV-infected patients is an investigational use of the drug. Both medicines were taken in combination with tenofovir/emtricitabine. (Poster 573).

In other Phase III studies, BENCHMRK-1 and -2, raltegravir in combination with optimised background therapy (OBT) demonstrated greater reductions in viral load compared to placebo plus OBT through 96 weeks of therapy in treatment-experienced patients with triple-class resistant HIV who were failing antiretroviral therapy. (Poster 571b).

These results as well as data from three additional studies were presented this week at the 16<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) in Montreal, Canada.

"As physicians continue to include raltegravir in treatment-experienced patients as part of combination therapy, newly presented longer-term follow-up data from BENCHMRK-1 and -2 continue to add confidence to the role of this agent when treating patients that are more advanced in their treatment course," said Sharon L. Walmsley, FRCPC, MD, MSc, Professor of Medicine, University of Toronto.

**Raltegravir demonstrated consistent efficacy in reduction of viral load across various patient groups in STARTMRK study**

Results from the STARTMRK subgroup analyses showed that at Week 48 raltegravir in combination therapy reduced viral load to undetectable levels (less than 50 copies/mL) in 96 percent of women (47 out of 49) compared with 93 percent of women (42 out of 45) receiving efavirenz in combination therapy.

Raltegravir was also as effective as efavirenz at reducing viral load in patients whose racial background was either black [89 percent for the regimen with raltegravir (24 out of 27) compared with 91 percent for the regimen with efavirenz (20 out of 22)], Asian [91 percent (31 out of 34) versus 87 percent (26 out of 30)], Hispanic [93 percent (54 out of 58) versus 86 percent (53 out of 62)] or multiracial [91 percent (31 out of 34) versus 83 percent (30 out of 36)].

The mean increase in CD4 cell counts at 48 weeks was 170 cells/mm<sup>3</sup> for women receiving the raltegravir-based treatment compared with 168 cells/mm<sup>3</sup> for women receiving the regimen with efavirenz. The mean increase from baseline in CD4 cell counts were consistent in patients with diverse racial background and are as follows for patients receiving the regimen

with raltegravir compared to patients receiving efavirenz-based therapy, respectively: blacks (163 cells/mm<sup>3</sup>; n=26 versus 125 cells/mm<sup>3</sup>; n=21), Asians (185 cells/mm<sup>3</sup>; n=32 versus 152 cells/mm<sup>3</sup>; n=28), Hispanics (196 cells/mm<sup>3</sup>; n=58 versus 150 cells/mm<sup>3</sup>; n=62) and multiracials (182 cells/mm<sup>3</sup>; n=34 versus 168 cells/mm<sup>3</sup>; n=36).

Of those patients with high baseline viral loads (greater than 100,000 copies/mL), 91 percent of patients receiving the regimen with raltegravir reduced viral load to undetectable levels versus 89 percent of patients receiving efavirenz-based therapy. The mean increase in CD4 cell counts for patients with high baseline viral loads (greater than 100,000 copies/mL) was 196 cells/mm<sup>3</sup> for patients receiving the regimen with raltegravir compared with 192 cells/mm<sup>3</sup> for patients receiving the regimen with efavirenz.

In this study, 563 treatment-naïve, HIV-infected patients received either 400 mg raltegravir administered orally twice daily in combination with tenofovir/emtricitabine or 600 mg efavirenz dosed orally once daily in combination with the same agents. The primary endpoints were reductions in HIV viral load to less than 50 copies/mL at Week 48 and an evaluation of safety and tolerability. Secondary endpoints included antiretroviral activity as measured by reductions in HIV viral load to less than 400 copies/mL and the change from baseline in CD4 cell counts at Week 48.

### **Durability and persistent tolerability of raltegravir demonstrated through 96 weeks in treatment-experienced patients (BENCHMRK-1 and -2)**

Ninety-six week results from two Phase III studies, BENCHMRK-1 and -2 were also presented this week. Results from these studies showed that at Week 96, 57 percent of patients (262 out of 460) receiving raltegravir plus OBT achieved undetectable viral load (less than 50 copies/mL) versus 26 percent of patients (62 out of 237) receiving placebo plus OBT; p<0.001. Additionally, patients receiving the regimen with raltegravir experienced significantly greater increases in CD4 cell counts (123 cells/mm<sup>3</sup>) compared to patients receiving placebo plus OBT (49 cells/mm<sup>3</sup>) at Week 96; p<0.001.

In the BENCHMRK studies, patients received either 400 mg raltegravir administered orally twice daily in combination with OBT (n=462) or 400 mg placebo dosed orally twice daily in combination with OBT (n=237). Data demonstrated that raltegravir plus OBT provided potent and greater antiretroviral and immunological efficacy compared to placebo plus OBT. Reductions in viral load and immunological efficacy were sustained through Week 96: 57 percent of patients receiving raltegravir plus OBT maintained viral suppression to less than 50 copies/mL; up to 79 percent of patients receiving enfuvirtide and darunavir in OBT with raltegravir maintained viral suppression to less than 50 copies/mL. There were few discontinuations due to adverse experiences, four percent for raltegravir plus OBT versus five percent for placebo plus OBT, respectively. The risk of developing malignancy was comparable between raltegravir and the control group.

Exposure-adjusted rates (per 100 patient-years) of the most commonly drug-related clinical adverse events (greater than or equal to 2.0 percent, and of any intensity) in patients receiving raltegravir plus OBT compared to those receiving placebo plus OBT were headache (2.7 per 100 patient-years versus 4.5 per 100 patient-years), nausea (2.3 per 100 patient-years versus 4.1 per 100 patient-years), diarrhoea (1.8 per 100 patient-years versus 4.5 per 100 patient-years), fatigue (1.8 per 100 patient-years versus 0.7 per 100 patient-years), abdominal distension (1.2 per 100 patient-years versus 1.5 per 100 patient-years), vomiting (0.8 per 100 patient-years versus 1.9 per 100 patient-years) and pyrexia (0.5 per 100 patient-years versus 2.2 per 100 patient-years), respectively.

The rate of cancer in patients receiving raltegravir plus OBT in both BENCHMRK-1 and -2 was 3.0 per 100 patient-years, compared with 2.6 per 100 patient-years in those patients receiving placebo plus OBT, resulting in a relative risk of 1.1 (0.5, 3.1). The rate of new or recurrent AIDS-defining conditions was 2.2 per 100 patient-years for the group receiving

raltegravir versus 4.1 per 100 patient-years for the placebo group, respectively, resulting in a relative risk of 0.5 (0.2, 1.3).

### **Review of cancer incidence in raltegravir clinical trials**

In addition to the STARTMRK study comparing raltegravir with efavirenz and the BENCHMRK-1 and -2 studies in treatment-experienced patients with triple-class resistant HIV, a review of cancer incidence in raltegravir clinical trials in treatment-naïve and treatment-experienced was presented. The occurrence of cancer, a known complication of HIV infection, was reviewed in five randomised, double-blind clinical trials of raltegravir in treatment-naïve and treatment-experienced patients, as well as an open-label expanded access program. A pooled data analysis of two Phase II (Protocols 004 and 005) and three Phase III trials (BENCHMRK-1, BENCHMRK-2 and STARTMRK) with follow-up of at least 48 to 120 weeks (over 1,700 patient-years exposure to raltegravir), found that during the double-blind phase cancer rates were slightly lower for those patients receiving the regimen with raltegravir (rate of 1.7 per 100 patient-year, broad cancer case definition, including recurrences, non-melanoma skin cancers and carcinoma in situ) but not significantly different from patients receiving comparator antiretroviral treatments (rate of 2.2 per 100 patient-year, broad cancer definition). This resulted in a relative risk of 0.75 with a confidence interval of 0.40 to 1.46.

With approximately 600 patient-years additional exposure to raltegravir during open-label phases, cancer rates remained similar (rate of 2.1 per 100 patient-years) to those observed during the double-blind phase. In an expanded access setting, with median follow-up of 24 weeks for over 5,400 patients (over 2,200 patient-years exposure to raltegravir), cancer rates were similar to those observed in clinical trials with raltegravir.

In Protocol 004, raltegravir was dosed at 100 to 600 mg twice daily up to 48 weeks and then at 400 mg thereafter. In Protocol 005, raltegravir was dosed at 200 to 600 mg twice daily until at least 24 weeks in the double-blind portion of the study, and then all were dosed at 400 mg in the open-label portion of the study. The analysis of the Phase II and Phase III trials combined included 1,039 patients who received raltegravir and 605 patients who were assigned to a comparator treatment, 173 of whom crossed over from the comparator treatment to raltegravir in the open-label phase(s). In all cases, raltegravir was used in combination regimens. Data were available through at least 48 weeks in the Phase III STARTMRK trial, 96 weeks in BENCHMRK-1 and BENCHMRK-2 trials and at least 120 weeks in the Phase II trials (Protocols 004 and 005). Double-blind and open-label data were included.

### **About ISENTRESS™**

ISENTRESS™ (raltegravir) was approved in Canada in November 2007 for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Raltegravir attacks the HIV virus in a way that's different to other available antiretroviral treatments. It is the only drug approved that blocks the action of integrase, an enzyme that is critical to the HIV replication process. By targeting the integrase enzyme, raltegravir limits the ability of the virus to replicate and infect new cells. Used in combination with other antiretroviral agents, raltegravir has been shown to be effective at both reducing viral load to undetectable levels and raising CD4 cell count in people living with HIV-AIDS who were previously treated with other antiretroviral agents. Raltegravir is administered as a single 400 mg tablet taken twice daily with or without food with other HIV medications.<sup>1</sup>

### **Merck Frosst's Commitment to HIV Research**

Merck Frosst is committed to developing innovative therapies that offer advances in the treatment of infectious diseases – including HIV. The Company's efforts to develop investigational treatments for HIV-AIDS have been under way for more than 20 years and

continue today. We began our HIV integrase inhibitor research in 1993 and were the first to demonstrate inhibition of HIV integrase *in vitro* and *in vivo*. Basic research on infectious diseases such as HIV is conducted by Merck at the Merck Frosst Centre for Therapeutic Research in Montreal.

### **Merck's commitment to providing access to treatment**

Merck is committed to ensuring access to our antiretroviral medicines (ARVs) through a differential pricing policy that provides our ARVs at dramatically lower prices-at which Merck does not profit-to people living in the world's least developed countries and those hardest hit by the pandemic, as defined by various United Nations indices. Also, Merck is committed to seeking additional ways to reduce the cost of its ARVs for people living in the world's poorest countries and those hardest hit by the pandemic, including through partnering with external manufacturers and suppliers to achieve incremental efficiencies and cost savings.

### **About Merck Frosst Canada Ltd.**

At Merck Frosst, patients come first. Merck Frosst Canada Ltd. is a research-driven pharmaceutical company discovering, developing and marketing a broad range of innovative medicines and vaccines to improve human health. Merck Frosst is one of the top 20 R&D investors in Canada, with an investment of close to \$110 million in 2007. More information about Merck Frosst and ISENTRESS™ is available at [www.merckfrosst.com](http://www.merckfrosst.com).

### **Forward-looking statement**

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements are based on management's current expectations and involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the cautionary statements in Item 1A of Merck's Form 10-K for the year ended Dec. 31, 2007, and in its periodic reports on Form 10-Q and Form 8-K, which the Company incorporates by reference.

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1. ISENTRESS™ product monograph