

Data from Raltegravir in Patients Whose HIV is Controlled on a Lopinavir/Ritonavir-Based Therapy Presented at the 16th Conference on Retroviruses and Opportunistic Infections

- **Switching from Lopinavir/Ritonavir-Based to Raltegravir-Based Combination Antiretroviral Therapy Significantly Improved Total Cholesterol, Triglycerides, Non-HDL-Cholesterol at Week 12,**
- **Switching from Lopinavir/Ritonavir-Based to Raltegravir-Based Combination Antiretroviral Therapy Did Not Demonstrate Non-Inferior Virologic Efficacy**

MONTREAL, Quebec, FEBRUARY 11, 2009 – Two Phase III studies (SWITCHMRK-1 and -2) evaluating the effect of switching patients whose HIV is controlled on a lopinavir/ritonavir-based regimen to a regimen containing Merck HIV integrase inhibitor raltegravir tablets showed that raltegravir significantly improved total cholesterol, triglycerides and non-HDL-cholesterol. Also, the study showed that raltegravir did not demonstrate non-inferior virologic efficacy at maintaining viral load suppression. As a result of the viral load findings in these trials, Merck discontinued these two studies.

Findings from the 24-week interim analyses of SWITCHMRK-1 and -2 were presented this week at the 16th Conference on Retroviruses and Opportunistic Infections (CROI) in Montreal, Canada.

Study results

In one study, Protocol 032 (also called SWITCHMRK-1), 81 percent of patients receiving a regimen with raltegravir maintained undetectable viral levels (less than 50 copies/mL) compared with 87 percent of patients receiving a regimen with lopinavir/ritonavir. In the second study, Protocol 033 (also called SWITCHMRK-2), the regimen with raltegravir maintained undetectable viral load levels in 88 percent of patients compared with 94 percent of patients receiving a regimen with lopinavir/ritonavir. In both studies, switching treatment to a regimen with raltegravir resulted in significantly greater decreases in total cholesterol, triglycerides and non-HDL-cholesterol ($p < 0.001$) compared to continuing the lopinavir/ritonavir-based regimen.

Primary endpoints from the study include mean percent change in fasting lipids (total cholesterol, triglycerides, non-HDL and LDL) at Week 12, proportion of patients with viral load suppressed to undetectable levels (less than 50 copies/mL) at Week 24 and safety and tolerability at Week 24.

Raltegravir did not demonstrate non-inferiority in maintaining viral load suppression

In regard to suppression of viral load, results at Week 24 showed that raltegravir did not demonstrate non-inferiority (one of the primary endpoints for both trials) as compared to lopinavir/ritonavir as measured by proportion of patients with undetectable viral levels. These results were based on an intent-to-treat analysis which assumes all study dropouts are virologic failures.

The viral load results are represented in the chart below:

HIV Viral Load (vRNA) Summary at Week 24

Number (%) of Patients

	Protocol 032		Protocol 033	
	Lopinavir/Ritonavir	Raltegravir	Lopinavir/Ritonavir	Raltegravir
vRNA <50 copies/mL	152/174 (87.4)	139/172 (80.8)	167/178 (93.8)	154/175 (88.0)
vRNA <400 copies/mL	156/174 (89.7)	148/172 (86.0)	173/178 (97.2)	164/175 (93.7)

Based on post-hoc data collection, 84 percent (27 out of 32) of patients with confirmed virologic failure (viral levels greater than 50 copies/mL) in the group receiving raltegravir reported that their regimen at study entry was not their first antiretroviral regimen; and 66 percent (18 out of 27) of these patients reported a history of virologic failure on prior regimens.

“The observation that treatment with raltegravir did not achieve non-inferiority as measured by the proportion of patients with a viral load of less than 50 copies/mL as compared with lopinavir/ritonavir-based regimens underscores the complicated considerations involved in selecting the optimal treatment regimen for patients. Physicians should carefully evaluate all patient background information and previous treatment outcomes, including any change in viral load or tolerability concerns, when introducing a new therapy or considering a switch in treatment regimen,” said Joseph Eron, M.D., professor of medicine, Division of Infectious Diseases, University of North Carolina Chapel Hill School of Medicine.

Clinical adverse experiences of all severities were similar among patients treated with raltegravir as compared to those treated with the lopinavir/ritonavir-based regimen respectively (69.9 percent vs. 62.9 percent in Protocol 033; 62.6 percent vs. 60.9 percent in Protocol 032) and drug-related adverse events (13.1 percent vs. 19.7 percent in Protocol 033; 13.8 percent vs. 10.9 percent in Protocol 032).

Protocols 032 and 033 stopped

As a result of the viral load findings in these trials, Merck has stopped Protocols 032 and 033 and has notified the appropriate regulatory agencies and trial investigators for raltegravir about these data. At this time, only preliminary data are available for Protocols 032 & 033 and Merck is conducting thorough analyses of both studies to better understand the results.

“Merck remains committed to understanding appropriate utilization of raltegravir in a broad spectrum of HIV patients, and has alerted the appropriate regulatory agencies and trial investigators for raltegravir of these findings,” said Robin Isaacs, M.D., vice president, Clinical Research, Merck Research Laboratories. “We will conduct continued analyses of these findings as soon as complete results are available.”

Raltegravir significantly improved total cholesterol, triglycerides, non-HDL cholesterol at Week 12

In regard to the co-primary endpoints of both studies, the data demonstrated that patients switched to raltegravir had significant decreases in total cholesterol, triglycerides and non-HDL cholesterol. There was no statistical difference in mean percent change from baseline in LDL. Results from the two studies are represented in the chart below.

	Protocol 032				Protocol 033			
	Lopinavir/ Ritonavir		Raltegravir		Lopinavir/ Ritonavir		Raltegravir	
	Base line mean	Mean % change	Base line mean	Mean % change	Base line mean	Mean % change	Base line mean	Mean % change
Total cholesterol (TC)	205	1	217	-13	211	1	214	-12
Triglycerides* (TG)	164	4	190	-41	219	8	210	-43
Non-HDL cholesterol (non-HDL-C)	158	2	166	-15	164	3	168	-15
LDL-C	105	2	116	-2	104	1	104	4
HDL-C	47	1	49	-1	48	-3	46	-1
*Median value presented for triglycerides								

Study Background

Protocol 032 and 033 studies are multi-centre, double-blind, randomised, active-controlled, non-inferiority studies to evaluate the safety, tolerability and efficacy of raltegravir in patients who are well controlled (viral load <50 copies/mL) on a stable lopinavir/ritonavir based regimen (400/100 mg twice daily) and were randomised to switch to raltegravir or continue on lopinavir/ritonavir. In these studies, 354 patients in Protocol 033 and 348 patients in Protocol 032 were randomised to remain on the lopinavir/ritonavir-based regimen or be switched to raltegravir 400 mg twice daily.

Patients enrolled in the study were required to be stable on the lopinavir/ritonavir-containing regimen, defined as having viral load suppressed to less than 50 copies/mL for at least three months, and were taking at least two nucleoside reverse transcriptase inhibitors (NRTIs) as part of their regimen. Because patients were enrolled in the study regardless of whether they had been on previous regimens prior to their lopinavir/ritonavir-based regimen, and regardless of the number of treatment failures previously experienced, the patient population in these studies had very diverse treatment experiences.

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.¹

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.

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.

™ Trademark of Merck & Co., Inc., used under license.

For more information or to arrange an interview, please contact:

Muriel Haraoui
HKDP Communications and Public Affairs
Tel: 514 395-0375, extension 235
mharaoui@hkdp.qc.ca

Martine Drolet
Merck Frosst Canada Ltd.
Tel: 514 428-3037
Cell: 514 833-6780
martine_drolet@merck.com

1. ISENTRESS™ product monograph