



Data from Raltegravir, MSD's HIV Integrase Inhibitor, 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, 9 February 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 Sharp & Dohme's (MSD) 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, MSD discontinued these two studies.

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

Raltegravir is the first integrase inhibitor approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients with evidence of viral replication with HIV-1 strains resistant to multiple antiretroviral agents. This indication is based on analyses of plasma HIV-1 RNA levels up through 48 weeks in two controlled studies of raltegravir. These studies

were conducted in clinically advanced, three-class antiretroviral [nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs)] treatment-experienced adults. In these studies the use of other active agents with raltegravir is associated with a greater likelihood of treatment response. The safety and efficacy of raltegravir have not been established in treatment-naïve adult or paediatric patients. There are no study results demonstrating the effect of raltegravir on clinical progression of HIV-1 infection.

As with all HIV treatment regimens, raltegravir should be used with other active antiviral agents.

Important safety information about raltegravir

Raltegravir does not cure HIV or AIDS and does not prevent passing HIV to others. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *pneumocystis jiroveci* pneumonia, *Mycobacterium tuberculosis* or reactivation of varicella zoster virus), which may necessitate further evaluation and treatment.

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, MSD 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 MSD is conducting thorough analyses of both studies to better understand the results.

“MSD 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.

Mean Percent Change from Baseline in Fasting Lipid Parameters at Week 12; p<0.001

	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.

Additional important safety information about raltegravir

Due to rifampin's potent induction of uridine diphosphate glucuronosyltransferase (UGT) 1A1, the recommended dosage of raltegravir is 800 mg twice daily during coadministration with rifampin. Caution should be used when coadministering raltegravir with other strong inducers of UGT1A1 due to reduced plasma concentrations of raltegravir.

The most common adverse reactions of moderate to severe intensity (less than or equal to two percent) which occurred at a higher exposure adjusted rate compared to placebo are headache, nausea, asthenia and fatigue.

Creatine kinase elevations were observed in subjects who received raltegravir. Myopathy and rhabdomyolysis have been reported; however, the relationship of raltegravir to

these events is not known. Raltegravir should be used with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medication known to cause these conditions.

Reference:

1. UNAIDS. 2008 Report on the global AIDS epidemic. Available at: http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp. Accessed on January 30, 2009.

Für weitere Informationen wenden Sie sich bitte an:

Fulvia Kipper, MSD SHARP & DOHME GMBH, Lindenplatz 1, 85540 Haar
Tel: 089/4561-1917, Fax: 089/4561-1329, E-Mail: fulvia_kipper@msd.de

Allgemeine Informationen sind im Internet unter www.msd.de unter "Presse" abrufbar. Mit dem Benutzernamen "msd" und dem Passwort "aktuell" haben Sie Zugang zu unseren Presseseiten.

Über MSD SHARP & DOHME GMBH

MSD SHARP & DOHME GMBH gehört zu Merck & Co., Inc., Whitehouse Station, N.J. (USA), einem weltweit tätigen forschenden Arzneimittelhersteller, der Arzneimittel und Impfstoffe in verschiedenen Therapiebereichen erforscht, entwickelt, produziert und vertreibt. Für das Unternehmen steht das Wohl des Patienten an erster Stelle. Es ist ihm ein Anliegen, die Versorgung mit dringend benötigten Medikamenten weltweit zu gewährleisten und zu verbessern. Hierzu unterstützt MSD zahlreiche bedürftige Länder mit Medikamentenspenden vor Ort. MSD hat sich auch die Verbreitung der aktuellen medizinischen Erkenntnisse zum Ziel gesetzt. Als Beitrag dazu publiziert der Arzneimittelhersteller seit über 100 Jahren das renommierte "MSD-Manual", ein Standardwerk für Ärzte und Apotheker (www.msd.de/msdmanual/). Medizinisches Wissen und ärztlicher Rat für die ganze Familie werden seit 1994 im "MSD-Manual Handbuch Gesundheit" publiziert.

In Deutschland arbeiten über 1.200 Mitarbeiter für das Unternehmen, das seinen Sitz in Haar bei München hat. MSD ist erreichbar unter Tel: 0800 673 673 673; Fax: 0800 673 673 329; E-Mail: infocenter@msd.de; Internet: www.msd.de, www.univadis.de