



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

MSD's Integrase Inhibitor, 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

MONTREAL, 9 February 2009 – In new subgroup analyses of a Phase III study (STARTMRK) that compared Merck Sharp & Dohme's (MSD) 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 today at the 16th Conference on Retroviruses and Opportunistic Infections (CROI) in Montreal, Canada.

"As physicians continue to use raltegravir in treatment-experienced patients, newly presented longer-term data from BENCHMRK-1 and -2 continue to inspire confidence among clinicians when treating patients that are more advanced in their treatment course. Furthermore, the STARTMRK studies in treatment-naïve patients showed that raltegravir may become an important new option for a broader spectrum of patients beginning treatment for HIV infection, if the drug is approved for this use," said Daniel S. Berger, M.D., clinical associate professor, College of Medicine, University of Illinois at Chicago and medical director of NorthStar Medical Centre.

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.

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.

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/mm³ for women receiving the raltegravir-based treatment compared with 168 cells/mm³ 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/mm³; n=26 versus 125 cells/mm³; n=21), Asians (185 cells/mm³; n=32 versus 152 cells/mm³; n=28), Hispanics (196 cells/mm³; n=58 versus 150 cells/mm³; n=62) and multiracials (182 cells/mm³; n=34 versus 168 cells/mm³; 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/mm³ for patients receiving the regimen with raltegravir compared with 192 cells/mm³ 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 today. 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/mm³) compared to patients receiving placebo plus OBT (49 cells/mm³) 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).

More 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.

Additional posters on raltegravir presented at CROI

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, two other posters were also presented today further evaluating the safety and efficacy of raltegravir. These posters include:

- A review of cancer incidence in raltegravir clinical trials in treatment-naïve and treatment-experienced patients, which found to date no difference in the risk of cancer in HIV-infected patients receiving raltegravir versus other antiretroviral therapy (Poster 859) and
- A review of preliminary data from an ongoing prospective, open-label, non-randomised, dose finding study of raltegravir plus OBT in treatment-

experienced children aged six to 18 (IMPAACT P1066). These results will be presented by the National Institutes of Health

Review of cancer incidence in raltegravir clinical trials

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.

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.

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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