Merck’s ISENTRESS® (raltegravir) in Combination Therapy Demonstrated Efficacy and Tolerability in an Observational Trial in a Diverse Population of Adults with HIV-1 Regardless of Gender or Race

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REALMRK Study Team Worked with HIV Community on Recruitment, Retention and Support Efforts for Patients in Real-World Clinical Trial

CHICAGO--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced results from the REALMRK clinical study showing that after 48 weeks of treatment in an open-label, single-arm, observational study, the integrase inhibitor ISENTRESS® (raltegravir) tablets in combination therapy demonstrated efficacy and tolerability, regardless of gender or race, in a diverse population of adult patients with HIV-1 infection similar to results from other Phase III studies. Data from this Phase III study, which enrolled treatment-naive adult HIV-1-infected patients as well as treatment-experienced adult HIV-1-infected patients who were failing or intolerant to current antiretroviral (ARV) treatment, were presented for the first time at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2011) in Chicago.

“Results from the REALMRK study demonstrate the benefits of ISENTRESS in combination therapy in a diverse patient population that reflects the faces of many people living with HIV-1 today,” said Kathleen Squires, M.D., director of the division of infectious disease and environmental medicine, Jefferson Medical College of Thomas Jefferson University, and lead investigator of the study. “Blacks and women are disproportionately affected by the HIV epidemic.”

The REALMRK study enrolled 74.6 percent Black patients (156 out of 209) and 46.9 percent female patients (98 out of 209).

ISENTRESS is indicated in combination with other ARV agents for the treatment of HIV-1 infection in adult patients. The label for ISENTRESS is based on analyses of plasma HIV-1 RNA levels through 96 weeks in three double-blind controlled Phase III clinical studies of ISENTRESS. Two of these studies were conducted in clinically advanced, three-class ARV [non-nucleoside reverse transcriptase inhibitor (NNRTI), nucleoside reverse transcriptase inhibitor (NRTI), protease inhibitor (PI)] treatment-experienced adults and one was conducted in treatment-naive adults. The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response. The safety and efficacy of ISENTRESS have not been established in pediatric patients.

“Women with HIV are less likely to use healthcare resources, including enrolling in clinical studies, because of a complex set of issues ranging from competing priorities and lack of information as well as barriers such as not being able to afford the childcare or transportation they need in order to access care,” said Dawn Averitt Bridge, founder and president of the board of The Well Project, a not-for-profit organization with a comprehensive focus on the needs of HIV-positive women.

“Fortunately, the REALMRK study investigators and sites recognized many of these concerns and specifically recruited, engaged and supported a diverse patient population throughout the clinical trial.”

REALMRK study design

The Phase III, multicenter, open-label, single-arm observational study enrolled a diverse cohort of 209 HIV-1-infected adult patients, including treatment-naive HIV-1-infected adult patients (n=22), as well as treatment-experienced HIV-1-infected adult patients who were failing previous treatment (n=98) or were intolerant to current therapy (n=89). The treatment group included 97 female and 153 Black HIV-1-infected adult patients, all of whom received ISENTRESS 400 mg twice daily in combination therapy for up to 48 weeks. The antiretroviral treatments used as part of combination therapy were selected at baseline and limited to approved and licensed agents. Of the 209 patients who entered the study, three were randomized but not treated. Patients were enrolled at trial sites in North America, South America, the Caribbean and Southern Africa.

The primary endpoint of the study was the proportion of patients with viral load levels less than 50 copies/mL at week 48. Secondary endpoints, at week 48, included the proportion of patients with viral load levels less than 400 copies/mL, mean change from baseline in CD4 cell count, change from baseline for viral load and time to loss of virologic response.
ISENTRESS in combination therapy maintained viral load suppression at 48 weeks regardless of gender or race

Based on the Treatment-Related Discontinuation equals failure approach, 11 randomized and treated patients were excluded from the primary analysis due to discontinuation prior to week 48 for non-treatment related reasons.

After 48 weeks, treatment with ISENTRESS in combination therapy suppressed HIV-1 viral load levels to below 50 copies/mL in 70.3 percent of the patients (137 out of 195) overall in this diverse cohort of HIV-1-infected adults.

Results showed that 67.8 percent (61 out of 90) of HIV-1-infected female patients and 72.4 percent (76 out of 105) of male patients achieved viral load levels of less than 50 copies/mL. Additionally, 67.6 percent (98 out of 145) of Black HIV-1-infected patients and 78.0 percent (39 out of 50) of non-Black patients achieved viral load levels of less than 50 copies/mL.

### Percent of Patients with HIV RNA <50 Copies/mL at Week 48*

<table>
<thead>
<tr>
<th></th>
<th>Previously Treated</th>
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<th>Treatment-Naïve</th>
<th></th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Failure</td>
<td>Intolerant**</td>
<td></td>
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<tr>
<td></td>
<td>n/N</td>
<td>% (95% CI)</td>
<td>n/N</td>
<td>% (95% CI)</td>
<td>n/N</td>
</tr>
<tr>
<td>Male</td>
<td>66.0</td>
<td>(51.2, 78.8)</td>
<td>80.5</td>
<td>(41.9, 91.6)</td>
<td>71.4</td>
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<tr>
<td></td>
<td>33/50</td>
<td></td>
<td>33/41</td>
<td></td>
<td>76/105</td>
</tr>
<tr>
<td>Female</td>
<td>61.4</td>
<td>(45.5, 75.6)</td>
<td>71.8</td>
<td>(42.1, 99.6)</td>
<td>85.7</td>
</tr>
<tr>
<td></td>
<td>27/44</td>
<td></td>
<td>28/39</td>
<td></td>
<td>67.8</td>
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<tr>
<td>Black</td>
<td>63.8</td>
<td>(51.3, 75.0)</td>
<td>69.4</td>
<td>(49.2, 95.3)</td>
<td>78.6</td>
</tr>
<tr>
<td></td>
<td>44/69</td>
<td></td>
<td>43/62</td>
<td></td>
<td>98/145</td>
</tr>
<tr>
<td>Non-Black</td>
<td>64.0</td>
<td>(42.5, 82.0)</td>
<td>100</td>
<td>(29.0, 96.3)</td>
<td>71.4</td>
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<tr>
<td></td>
<td>16/25</td>
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<td>18/18</td>
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<tr>
<td>Total</td>
<td>63.8</td>
<td>(53.3, 73.5)</td>
<td>76.3</td>
<td>(52.8, 91.8)</td>
<td>70.3</td>
</tr>
<tr>
<td></td>
<td>60/94</td>
<td></td>
<td>61/80</td>
<td></td>
<td>137/195</td>
</tr>
</tbody>
</table>

** Baseline HIV RNA ≤50 copies/ML: 44/50 (88.0) (75.7, 95.5)**

** Baseline HIV RNA >50 copies/ML: 17/30 (56.7) (37.4, 74.5)**

* Treatment-related discontinuation = failure (TRD=F) approach

In the REALMRK study, the overall increase from baseline in mean CD4 cell count was 111 cells/mm³ after 48 weeks of treatment with ISENTRESS in combination therapy (95 percent CI). Patients who discontinued due to lack of efficacy prior to week 48 had their baseline values carried forward according to the observed failure approach of handling missing data; otherwise, patients were excluded who discontinued prior to week 48 or had missing data at week 48.

### CD4 Cell Count (cells/mm³): Change from Baseline to Week 48*

<table>
<thead>
<tr>
<th></th>
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<tr>
<td></td>
<td>N</td>
<td>Mean Change (95% CI)</td>
<td>N</td>
<td>Mean Change (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>(77, 145)</td>
<td>38 (15, 94)</td>
<td>13 (59, 232)</td>
<td>99 (69, 119)</td>
</tr>
<tr>
<td>Female</td>
<td>41</td>
<td>(120, 202)</td>
<td>38 (27, 119)</td>
<td>6 (140, 448)</td>
<td>85 (99, 163)</td>
</tr>
<tr>
<td>Black</td>
<td>66</td>
<td>(110, 173)</td>
<td>61 (27, 98)</td>
<td>12 (109, 309)</td>
<td>139 (88, 136)</td>
</tr>
<tr>
<td>Non-Black</td>
<td>23</td>
<td>(62, 164)</td>
<td>15 (17, 122)</td>
<td>7 (13, 316)</td>
<td>45 (70,143)</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>(107, 160)</td>
<td>76 (34, 93)</td>
<td>19 (117, 268)</td>
<td>184 (91, 131)</td>
</tr>
</tbody>
</table>

* Observed failure (OF) approach; baseline values carried forward

** Tolerability profile

After 48 weeks, patients treated with ISENTRESS in combination therapy had an overall discontinuation rate of 14.8 percent. The overall discontinuation rate was 17.3 percent in women and 12.6 percent in men.

The study found that 69.1 percent of female patients and 75.2 percent of male patients experienced clinical adverse events (AEs). Drug-related clinical AEs were noted in 26.8 percent of female patients and 14.7 percent of male patients, with 3.1 percent of female and 0.9 percent of male patients discontinuing treatment due to clinical AEs.
Results showed that 69.9 percent of Black patients and 79.2 percent of non-Black patients experienced clinical AEs. Drug-related clinical AEs occurred in 21.6 percent of Black and 17.0 percent of non-Black patients, with 2.6 percent of Black and zero percent of non-Black patients discontinuing treatment due to clinical AEs.

The most commonly reported drug-related clinical AEs (present in greater than or equal to 2 percent of any group) from the study included abdominal discomfort, diarrhea, nausea, vomiting, myalgia and headache.

**REALMRK study emphasized patient recruitment, retention and support**

To enable patient recruitment and retention, the REALMRK study team engaged and supported patients throughout the study. For example, patients received follow-up phone calls between visits, reimbursement for travel and childcare expenses, carry-all bags for study medications, and the Johns Hopkins University AIDS Clinic’s “Guide to Living with HIV Infection.”

Additionally, the study team implemented recruitment strategies in order to enroll a diverse patient population. Strategies included identifying study sites with access to diverse patient populations, limiting enrollment of male and non-Black patients, and providing sufficient time for patient enrollment. Although a two-year enrollment period was planned, enrollment for the study was completed seven months ahead of schedule.

**ISENTRESS data at ICAAC 2011**

**Poster presentations**

-- H2-789 - Safety, Tolerability and Efficacy of Raltegravir (RAL) in a Diverse Cohort of HIV-Infected Patients: 48-week Results from the REALMRK Study (Exhibit Hall F1 – Sunday, Sept. 18, 11:15 a.m. – 1:15 p.m. CDT)

-- H2-790 - Durable and Consistent Efficacy of Raltegravir (RAL) with Tenofovir (TDF) and Emtricitabine (FTC) Across Demographic and Baseline Prognostic Factors in Treatment-naive Patients from STARTMRK at Wk 156 (Exhibit Hall F1 – Sunday, Sept. 18, 11:15 a.m. – 1:15 p.m. CDT)

**About ISENTRESS**

ISENTRESS is Merck's integrase inhibitor for the treatment of HIV-1 infection in treatment-naive and treatment-experienced adult patients as part of combination therapy. ISENTRESS is currently the only approved integrase inhibitor for the treatment of HIV-1. ISENTRESS works by inhibiting the insertion of HIV-1 DNA into human DNA by the integrase enzyme and has demonstrated rapid antiviral activity. Inhibiting integrase from performing this essential function limits the ability of the virus to replicate and infect new cells. Other HIV-1 drugs in use inhibit two other enzymes critical to the HIV-1 replication process – protease and reverse transcriptase – but ISENTRESS is the only approved drug that inhibits the integrase enzyme.

ISENTRESS is now approved in combination therapy in more than 45 countries for use in treatment-naive adult patients with HIV-1 and in more than 90 countries for use in treatment-experienced adult patients with HIV-1. Merck is continuing to move forward with filings in additional countries around the world.

**Important safety information about ISENTRESS**

ISENTRESS does not cure HIV or AIDS and does not prevent passing HIV to others. Healthcare providers should know that during the initial phase of treatment immune reconstitution syndrome can occur, which may necessitate further evaluation and treatment. Monitor for immune reconstitution syndrome.

The most common adverse reactions of moderate to severe intensity greater than or equal to two percent that occurred at a higher rate than the comparator were insomnia in treatment-naive patients and headache in treatment-experienced patients. 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 2-4 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.

Rash occurred more commonly in treatment-experienced patients receiving regimens containing ISENTRESS and darunavir/ritonavir compared to patients 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.

**Dosing and administration**

For the treatment of adult patients with HIV-1 infection, the dosage of ISENTRESS is 400 mg administered orally, twice daily with or without food, in combination therapy. During coadministration with rifampin, the recommended dosage of ISENTRESS is 800 mg twice daily with or without food.

**Drug interactions**

Coadministration of ISENTRESS with drugs that are strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 may result in reduced plasma concentrations of raltegravir. Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of ISENTRESS. Therefore, the dose of ISENTRESS should be increased during coadministration with rifampin. The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown.
In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, methadone, lamivudine, tenofovir, etravirine and darunavir/ritonavir. Coadministration of ISENTRESS with drugs that inhibit UGT1A1 may increase plasma levels of raltegravir.

About Merck

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies, and consumer care and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.com.

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. Such statements may include, but are not limited to, statements about the benefits of the merger between Merck and Schering-Plough, including future financial and operating results, the combined company’s plans, objectives, expectations and intentions and other statements that are not historical facts. Such statements are based upon the current beliefs and expectations of Merck’s management and are subject to significant risks and uncertainties. Actual results may differ from those set forth in the forward-looking statements.

The following factors, among others, could cause actual results to differ from those set forth in the forward-looking statements: the possibility that the expected synergies from the merger of Merck and Schering-Plough will not be realized, or will not be realized within the expected time period; the impact of pharmaceutical industry regulation and health care legislation; the risk that the businesses will not be integrated successfully; disruption from the merger making it more difficult to maintain business and operational relationships; Merck’s ability to accurately predict future market conditions; dependence on the effectiveness of Merck’s patents and other protections for innovative products; the risk of new and changing regulation and health policies in the United States and internationally and the exposure to 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 2010 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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Exchange: NYSE