Merck Announces Presentation of Phase III Investigational Studies Evaluating DULERA® (mometasone furoate and formoterol fumarate dihydrate) Inhalation Aerosol in Chronic Obstructive Pulmonary Disease (COPD)

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Results Presented at CHEST 2011

HONOLULU--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced results from two 26-week investigational Phase III clinical studies evaluating the efficacy and safety of two dose strengths of DULERA® (mometasone furoate and formoterol fumarate dihydrate) in adults 40 years and older with moderate to very severe chronic obstructive pulmonary disease (COPD). The two dose strengths evaluated in the studies were DULERA 100 mcg/5 mcg and DULERA 200 mcg/5 mcg, both administered as two inhalations twice daily (i.e. 200 mcg/10 mcg and 400 mcg/10 mcg, twice daily). In both studies, DULERA 200 mcg/10 mcg and DULERA 400 mcg/10 mcg significantly improved lung function as measured by forced expiratory volume in one second (FEV1) area under the curve over 0-12 hours (AUC0−12hr) at Week 13 (one of the co-primary endpoints) compared to treatment with mometasone furoate 400 mcg (administered as two inhalations of mometasone furoate 200 mcg twice daily), the primary treatment comparison for this endpoint, or placebo alone.

In Study 1, DULERA 200 mcg/10 mcg and DULERA 400 mcg/10 mcg significantly improved AM predose FEV1 at Week 13 (the other co-primary endpoint) compared to treatment with formoterol 10 mcg (administered as two inhalations of formoterol 5 mcg twice daily), the primary treatment comparison for this endpoint, or placebo alone. In Study 2, DULERA 200 mcg/10 mcg and DULERA 400 mcg/10 mcg significantly improved AM predose FEV1 at Week 13 compared to treatment with placebo, but neither dose of DULERA reached statistical significance compared to treatment with formoterol 10 mcg.

The safety profile of DULERA in the maintenance treatment of COPD was also evaluated over the 26 week trials. Results of an additional 26-week extension of these studies, evaluating the drug’s safety profile over 52 weeks, were also presented. Data from these studies will be presented for the first time on Wednesday at CHEST 2011, the 77th annual meeting of the American College of Chest Physicians (ACCP), in Honolulu, Hawaii.

"This is the first presentation of data from these Phase III investigational studies evaluating the efficacy and safety of DULERA in patients 40 years and older with moderate to very severe COPD," said Dr. Dennis E. Doherty, M.D., professor of medicine in the Division of Pulmonary, Critical Care and Sleep Medicine at the University of Kentucky in Lexington, KY, and a study investigator. "It’s important that the scientific community continue evaluating potential treatment options for our patients with COPD."

DULERA is indicated in the United States for the treatment of asthma in patients 12 years and older.1 It is not indicated for the relief of acute bronchospasm or for the treatment of COPD. A supplemental new drug application (sNDA) for DULERA for the treatment of COPD has been accepted for standard review by the U.S. Food and Drug Administration (FDA).

"These investigational studies confirm Merck's commitment to research in respiratory diseases," said James E. Fish, M.D., executive director, Global Scientific Affairs, Merck Research Laboratories. "We're excited to see these data for this investigational use of DULERA presented and discussed at CHEST."

Study Design for Investigational Phase III COPD Clinical Trials

In two 26-week, multicenter, double-blind, placebo controlled trials assessing the efficacy and safety of DULERA, 2,251 adults 40 years and older with moderate to very severe COPD were randomized to receive inhaled DULERA 400 mcg/10 mcg, DULERA 200 mcg/10 mcg, mometasone furoate 400 mcg, formoterol 10 mcg or placebo, each administered twice daily. A two-week open label run-in on as-needed short-acting beta-agonist (SABA)/short-acting anticholinergic fixed-dose combination was followed by randomization to 26 weeks of treatment. Scheduled assessments included screening (Day 14); baseline (Day 1); and Weeks 1, 4, 13, and 26. At Week 26, all patients randomized to placebo were discontinued, and 75 percent of patients (n=1,803) randomized to an active treatment were randomly selected to participate in the 26-week
treatment safety extension and were evaluated twice more, at Week 39 and at Week 52.

Co-primary endpoints for efficacy included mean changes from baseline FEV1 AUC0−12hr and AM predose FEV1 after 13 weeks of treatment. FEV1 AUC0−12hr was used to assess the contribution of formoterol to the combination, and AM predose FEV1 assessed the contribution of mometasone furoate to the combination.

Efficacy Results in Investigational Phase III COPD Clinical Trials

Results from the studies (Study 1 and Study 2) showed that both doses of DULERA significantly improved lung function from baseline compared to mometasone furoate 400 mcg (the primary treatment comparison), as measured by FEV1 AUC over 12 hours. DULERA 400 mcg/10 mcg achieved improvements over baseline of 166 mL (Study 1) and 179 mL (Study 2) in FEV1 over 12 hours, which are statistically significant improvements of 109 mL (Study 1; P<0.001) and 126 mL (Study 2; P<0.001) when compared to mometasone furoate 400 mcg. DULERA 200 mcg/10 mcg demonstrated improvements over baseline of 126 mL (Study 1) and 139 mL (Study 2) in FEV1 AUC over 12 hours, which are statistically significant improvements of 69 mL (Study 1; P=0.007) and 86 mL (Study 2; P<0.001) when compared to mometasone furoate 400 mcg.

In Study 1, both doses of DULERA significantly improved lung function from baseline compared to formoterol 10 mcg (the primary treatment comparison), as measured by AM predose FEV1 at week 13. DULERA 400 mcg/10 mcg demonstrated a statistically significant improvement of 111 mL (P<0.001) in AM predose FEV1 versus formoterol 10 mcg. DULERA 200 mcg/10 mcg demonstrated a statistically significant improvement of 58 mL (P=0.029) versus formoterol 10 mcg. In Study 2, statistical significance was not achieved for either dose of DULERA versus formoterol 10 mcg (the primary treatment comparison) in AM predose FEV1. DULERA 400 mcg/10 mcg demonstrated an improvement from baseline of 98 mL in AM predose FEV1, an improvement of 49 mL versus formoterol 10 mcg (P=0.062). DULERA 200 mcg/10 mcg demonstrated an improvement from baseline of 63 mL, an improvement of 14 mL versus formoterol 10 mcg.

In addition, both doses of DULERA, compared with placebo, demonstrated significant effects on lung function after 13 weeks of treatment in both Study 1 and Study 2, which ranged from 121 mL to 163 mL in the endpoint of FEV1 AUC over 12 hours (P<0.001); and from 66 mL to 128 mL in the endpoint of AM predose FEV1 (P=0.013).

Adverse Events in Investigational Phase III COPD Clinical Trials

At 26 weeks, the pooled incidence of treatment-related adverse events for the DULERA 400 mcg/10 mcg, DULERA 200 mcg/10 mcg, mometasone furoate 400 mcg, and placebo groups was 7.2 percent, 4.9 percent, 8.0 percent, 7.5 percent, and 5.4 percent, respectively.

26-Week Extension Study Evaluating Safety

At one year (52 weeks), no notable differences in the incidence or nature of adverse events were reported versus those reported during the first 26 weeks.

For the 52 weeks of active treatment, the pooled incidence of treatment-related adverse events in the DULERA 400 mcg/10 mcg, DULERA 200 mcg/10 mcg, mometasone furoate 400 mcg, and formoterol 10 mcg groups was 9.0 percent, 7.0 percent, 10.2 percent, and 8.2 percent, respectively.

The majority of treatment-related adverse events were mild to moderate in severity. The most common treatment-related adverse events across all active treatment groups over 52 weeks were oral fungal infection (1.2 percent) and cataracts and lenticular opacity (1.4 percent). During the treatment period, 28 (1.2 percent) patients experienced pneumonia among the pooled five treatment groups.

Exposure-adjusted rates of serious adverse events for the DULERA 400 mcg/10 mcg, DULERA 200 mcg/10 mcg, mometasone furoate 400 mcg, and formoterol 10 mcg groups were 16.8 percent, 12.1 percent, 16.6 percent and 16.2 percent events/100 subject-years, respectively. The exposure-adjusted pneumonia (including all types) rates over the 52-week period were 3.7 percent, 1.2 percent, 2.1 percent and 2.4 percent events/100 subject-years, respectively. All but one of these events was considered by the investigator to be unrelated to the study drug. A single case in the DULERA 400 mcg/10 mcg group was considered possibly related to the study drug. The exposure adjusted mortality rates over the 52-week period were 2.8 percent, 0.9 percent, 2.4 percent, and 4.2 percent events/100 subject-years, respectively.

About DULERA

DULERA (mometasone furoate and formoterol fumarate dihydrate) Inhalation Aerosol is indicated for the treatment of asthma in patients 12 years and older. It is not indicated for the relief of acute bronchospasm. DULERA combines mometasone furoate, an inhaled corticosteroid, and formoterol fumarate, a long-acting beta2-agonist. It is a pressurized metered-dose inhaler with a built-in numeric counter that shows the number of remaining doses. DULERA is available for asthma patients 12 years and older in two strengths: DULERA 100 mcg/5 mcg, DULERA 200 mcg/5 mcg. Each inhalation contains 5 mcg of formoterol fumarate and either 100 mcg or 200 mcg of mometasone furoate. The recommended starting dose in the treatment of asthma is two inhalations of DULERA 200 mcg/5 mcg twice daily every day in the morning and evening.

Important Safety Information about DULERA®

Long-acting beta2-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

When treating patients with asthma, prescribe DULERA only for patients with asthma not adequately controlled on a long-
DULERA is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. DULERA is contraindicated in patients with known hypersensitivity to any of the ingredients in DULERA.

DULERA is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms. Increasing use of inhaled, short-acting beta2-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

Patients using DULERA should not use additional formoterol or other long-acting inhaled beta2-agonists for any reason.

Oropharyngeal candidiasis may occur. If candidiasis develops, it should be treated with appropriate antifungal therapy, but at times therapy with DULERA may need to be interrupted. Advise patients to rinse the mouth after inhalation.

DULERA should be used with caution in patients with tuberculosis, fungal, bacterial, viral (including chicken pox or measles), or parasitic infections; or ocular herpes simplex infections because of the potential for worsening of these infections. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients.

Particular care is needed for patients who are transferred from systemically active corticosteroids to DULERA. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids.

Hypercorticism and adrenal suppression may occur with very high dosages of DULERA or at the regular dosage in susceptible individuals. Patients treated with DULERA should be observed carefully for any evidence of systemic corticosteroid effects. If such changes occur, discontinue DULERA slowly.

Caution should be exercised when considering the co-administration of DULERA with long-term ketoconazole and other known strong CYP3A4 inhibitors, or in patients being treated with MAO inhibitors or tricyclic antidepressants.

Discontinue DULERA and institute alternative therapy if paradoxical bronchospasm occurs.

Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. DULERA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids, including mometasone furoate, a component of DULERA. Patients with major risk factors for decreased BMD should be monitored and treated with established standards of care.

Inhaled corticosteroids, including DULERA, may cause a reduction in growth velocity when administered in pediatric patients.

Glaucoma, increased intraocular pressure, and cataracts have been reported following the use of long-term inhaled corticosteroids, including mometasone furoate, a component of DULERA.

DULERA, like other medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta2-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Be alert to hypokalemia and hyperglycemia as beta2-agonist medications such as DULERA have the potential to produce adverse cardiovascular effects.

The most common treatment-emergent adverse events reported in ≥3 percent of patients and more common than placebo included nasopharyngitis, sinusitis, and headache.

Dysphonia was reported in a longer-term treatment trial at an incidence of 5 percent in patients receiving DULERA 100 mcg/5 mcg and 3.8 percent in patients receiving DULERA 200 mcg/5 mcg.

About COPD

COPD includes two main conditions – emphysema and chronic bronchitis – which are characterized by damage and inflammation that reduces airflow in and out of the lungs, making it difficult to breathe. Common symptoms include coughing that produces large amounts of mucus, wheezing, shortness of breath and chest tightness. COPD is a progressive disease, meaning it gets worse over time.

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 and connect with us on Twitter, Facebook and YouTube.

Forward-Looking Statement

This news release includes “forward-looking statements” within the meaning of the safe harbor provisions of the United States
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).

Please see full Prescribing Information, including Boxed Warning, for DULERA at www.spfiles.com/pidulera.pdf.