

## New Data for Gilead Sciences' Ambrisentan Show Clinical Improvements in a Diverse Pulmonary Hypertension (PH) Population

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SAN DIEGO--(BUSINESS WIRE)--May. 18, 2009-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced results from ARIES-3, an open-label, single-arm, Phase III study evaluating the efficacy and safety of ambrisentan in patients with pulmonary hypertension (PH), which showed a mean 21-meter improvement from baseline in six-minute walk distance (6MWD) at 24 weeks. Ambrisentan is approved under the tradename Letairis<sup>®</sup> (ambrisentan 5 mg and 10 mg tablets) as a once-daily treatment for pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO functional class II or III symptoms to improve exercise capacity and delay clinical worsening. The ARIES-3 study included patients with PAH (WHO Group 1) as well as patients with pulmonary hypertension due to other etiologies (WHO Groups 3, 4 and 5). Data from this study were presented today at the 2009 American Thoracic Society (ATS) International Conference, taking place May 15-20 in San Diego.

“In previous clinical trials, ambrisentan has been shown to improve exercise capacity and delay clinical worsening in WHO Group 1 PAH patients with WHO functional class II and III symptoms,” said David Badesch, MD, Professor of Medicine and Clinical Director of the Pulmonary Hypertension Center at the University of Colorado Health Sciences Center and lead study author. “However, many patients seen in clinical practice have pulmonary hypertension associated with other diseases. ARIES-3 is important because it represents the first safety and efficacy data for ambrisentan in a more diverse PH patient population, including patients already on background therapy.”

### About ARIES-3

ARIES-3 was an open-label, single-arm, multicenter, Phase III study designed to evaluate the efficacy and safety of ambrisentan in a broader PH population than was studied in the ARIES-1 and ARIES-2 studies. The study enrolled 224 patients with WHO Group 1 PAH (n=140) or PH due to other etiologies (n=84), including 23 patients with PH secondary to chronic obstructive pulmonary disease (PH-COPD) (WHO Group 3), 21 patients with PH secondary to interstitial lung disease (PH-ILD) (WHO Group 3) and 29 patients with PH due to chronic thromboembolic disease (CTEPH) (WHO Group 4). Patients received ambrisentan at a dose of 5 mg once daily until the primary analysis of efficacy at 24 weeks. The primary endpoint was the change from baseline in 6MWD at Week 24. Secondary objectives were to evaluate the effects of ambrisentan on other clinical measures of PH, including the number of patients still alive at specified time points and time to clinical worsening, which was defined as the time from initiation of ambrisentan to the first occurrence of death, lung transplantation, hospitalization for PH, atrial septostomy, a change to chronic prostanoid therapy or sildenafil due to protocol-defined worsening criteria or study withdrawal due to addition of other PH medications. In addition, the safety and tolerability of ambrisentan was evaluated in the overall study population and in various subgroups.

At baseline, 29 percent of patients were classified as having WHO functional class II symptoms and 65 percent of patients had WHO functional class III symptoms. The mean baseline 6MWD for patients was 317±84 meters. At baseline, 52 percent of all patients were receiving sildenafil and/or prostanoid therapy. Twenty-seven patients in the study had previously discontinued use of bosentan and/or sitaxsentan due to liver enzyme (aminotransferase) elevations greater than three times the upper limit of normal (ULN).

In the overall study population, patients experienced a mean 6MWD improvement of 21 meters (95 percent CI: 11.8 to 29.3; p<0.001) from baseline at 24 weeks. At 24 weeks, 97 percent of patients were still alive (95 percent CI: 94 to 99). The probability of no clinical worsening at 24 weeks across all patients was 90 percent (95 percent CI: 85 to 93), as assessed by kaplan-meier estimates.

Six (2.7 percent) of the 224 patients experienced aminotransferase elevations greater than three times ULN during the 24-week study period. Two (0.8 percent) of these patients discontinued treatment due to aminotransferase elevations

greater than eight times ULN. Of the 27 patients who had previously discontinued bosentan and/or sitaxsentan due to aminotransferase abnormalities prior to ARIES-3 study entry, one patient experienced a recurrence of aminotransferase elevation greater than three times ULN.

The most frequent adverse events occurring in greater than or equal to 10 percent of patients during the 24-week study period were peripheral edema, headache, dyspnea, upper respiratory tract infection, nasal congestion, fatigue and nausea. Most reports of peripheral edema were reported to be mild or moderate in severity. The most frequent adverse events leading to discontinuation were peripheral edema (n=7), right ventricular failure (n=4) and pulmonary hypertension (n=3). Patients could have had more than one adverse event leading to study withdrawal.

As study ARIES-3 is not placebo-controlled, these findings do not allow for comparison with a group not given ambrisentan and cannot be used to definitively determine the efficacy and safety of ambrisentan. Similarly, due to the small sample sizes and open-label design of the study, no definitive conclusions regarding efficacy and safety can be drawn from the subgroup analyses observed in this study.

Letairis is approved for the treatment of PAH (WHO Group 1) with WHO functional class II and III symptoms to improve exercise capacity and delay clinical worsening and is not indicated for other PH classifications, such as CTEPH or PH associated with COPD or ILD. **Full prescribing information for Letairis is available at [www.gilead.com](http://www.gilead.com) and at [http://www.letairis.com/downloads/LETAIRIS\\_prescribing\\_information.pdf](http://www.letairis.com/downloads/LETAIRIS_prescribing_information.pdf).**

#### **WARNING: POTENTIAL LIVER INJURY**

Letairis can cause elevation of liver aminotransferases (ALT and AST) to at least three times the upper limit of normal (ULN). Letairis treatment was associated with aminotransferase elevations greater than three times ULN in 0.8 percent of patients in 12-week trials and 2.8 percent of patients including long-term open-label trials out to one year. One case of aminotransferase elevations greater than three times ULN has been accompanied by bilirubin elevations greater than two times ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

Elevations in aminotransferases require close attention. Letairis should generally be avoided in patients with elevated aminotransferases greater than three times ULN at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin greater than two times ULN, treatment should be stopped. There is no experience with the re-introduction of Letairis in these circumstances.

#### **CONTRAINDICATION: PREGNANCY**

Letairis is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals. Pregnancy must therefore be excluded before the initiation of treatment with Letairis and prevented thereafter by the use of at least two reliable methods of contraception unless the patient is unable to become pregnant. Obtain monthly pregnancy tests.

#### **About the Letairis Education and Access Program (LEAP)**

Because of the risks of liver injury and birth defects, Letairis is available only through a special restricted distribution program called the Letairis Education and Access Program (LEAP) by calling 1-866-664-LEAP (1-866-664-5327). Only prescribers and pharmacies registered with LEAP are able to prescribe and distribute Letairis. In addition, Letairis may be dispensed only to patients who are enrolled in and meet all conditions of LEAP.

#### **Important Safety Information**

Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with Letairis. These decreases were observed within the first few weeks

of treatment with Letairis, and stabilized thereafter.

Peripheral edema is a known class effect of endothelin receptor antagonists and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg of Letairis compared to placebo. Most edema was mild to moderate in severity. Peripheral edema was similar in younger patients (age less than 65 years) receiving Letairis (14 percent; 29/205) or placebo (13 percent; 13/104), and was greater in elderly patients (age greater than or equal to 65 years) receiving Letairis (29 percent; 16/56) compared to placebo (4 percent, 1/28). The results of such subgroup analyses must be interpreted cautiously.

In addition, there have been post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting Letairis. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure. Because the post-marketing experience was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the relative frequency or establish a causal relationship to Letairis drug exposure.

Caution should be used when Letairis is co-administered with cyclosporine A, as it may cause increased exposure to Letairis.

Caution should be used when Letairis is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) or CYP2C19-inhibitors (e.g., omeprazole).

The most common adverse events that occurred at a higher frequency among Letairis-treated patients compared to placebo included (placebo-adjusted frequency): peripheral edema (6 percent), nasal congestion (4 percent), sinusitis (3 percent), flushing (3 percent), palpitations (3 percent), nasal pharyngitis (2 percent), abdominal pain (2 percent), constipation (2 percent), dyspnea (1 percent) and headache (1 percent).

No clinically relevant interactions of Letairis with warfarin or sildenafil have been observed.

Letairis is not recommended in patients with moderate to severe hepatic impairment.

### **About Letairis**

Letairis (ambrisentan) is an endothelin receptor antagonist that has a high affinity for the endothelin type-A (ET<sub>A</sub>) receptor. Activation of the ET<sub>A</sub> receptor by endothelin-1 (ET-1), a small peptide hormone, leads to vasoconstriction (narrowing of blood vessels) and cell proliferation. The clinical impact of high selectivity for ET<sub>A</sub> is not known. Endothelin concentrations are higher in the lung tissue of PAH patients, thus suggesting that ET-1 may play a critical role in the pathogenesis or progression of PAH.

### **About Pulmonary Arterial Hypertension (WHO Group 1)**

PAH is a debilitating disease characterized by constriction of the blood vessels in the lungs leading to high pulmonary arterial pressures. These high pressures make it difficult for the heart to pump blood through the lungs to be oxygenated. Patients with PAH suffer from shortness of breath as the heart struggles to pump against these high pressures, causing such patients to ultimately die of heart failure. PAH can occur with no known underlying cause, or it can occur secondary to diseases such as connective tissue disease, congenital heart defects, cirrhosis of the liver and HIV infection. PAH afflicts approximately 200,000 patients worldwide.

### **About Gilead Sciences**

Gilead Sciences is a biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need. The company's mission is to advance the care of patients suffering from life-threatening diseases worldwide. Headquartered in Foster City, California, Gilead has operations in North America, Europe and Australia.

*Letairis is a registered trademark of Gilead Sciences, Inc.*

*For more information on Gilead Sciences, please visit the company's website at [www.gilead.com](http://www.gilead.com) or call Gilead Public Affairs at 1-800-GILEAD-5 or 1-650-574-3000.*

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