Gilead's Ranexa® Reduces Angina Frequency in Study of Chronic Angina Patients With Type 2 Diabetes

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- Data Presented at Late-Breaking Clinical Trial Session at the American College of Cardiology's Annual Scientific Session -

SAN FRANCISCO--(BUSINESS WIRE)--Mar. 10, 2013-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced data from the Phase 4 TERISA (**T**ype 2 Diabetes **E**valuation of **R**anolazine **I**n **S**ubjects With Chronic Stable **A**ngina) study, which demonstrated that the addition of ranolazine to background antianginal therapy in chronic angina patients with type 2 diabetes significantly reduced the frequency of weekly angina episodes compared to placebo and background antianginal therapy. Results were presented today during a Late-Breaking Clinical Trial session at the American College of Cardiology's 62nd Annual Scientific Session (ACC.13) in San Francisco and were published online ahead of print in the *Journal of the American College of Cardiology*.

Ranexa® (ranolazine) is indicated for the treatment of chronic angina. Ranexa is not indicated for the treatment of diabetes and should not be considered a treatment for diabetes.

Chronic angina, the most common symptom of coronary artery disease, can be a debilitating heart condition. Angina typically manifests as recurrent pain or tightness in the chest upon exertion or emotional stress. Patients with diabetes have more extensive coronary artery disease and a propensity for greater angina burden compared to patients without diabetes.

"Given the high prevalence of angina in patients with diabetes, there is a need for effective therapeutic strategies in this difficult-to-treat population," said Mikhail Kosiborod, MD, Associate Professor of Medicine at the University of Missouri, Kansas City, cardiologist at St. Luke's Mid America Heart Institute and lead author of the TERISA study. "Although the safety and efficacy profile of ranolazine is well established, this is the first study to prospectively evaluate the antianginal effectiveness of ranolazine in patients with chronic angina and concurrent type 2 diabetes."

Following a single-blind, four-week placebo run-in phase, 927 randomized patients received ranolazine (twice-daily 500 mg up-titrated to twice-daily 1,000 mg on Day 8) (n=462) or matching placebo (n=465) in addition to background antianginal therapy for eight weeks. Patients were asked to document the number of angina episodes and sublingual (under the tongue) nitroglycerin doses taken on a daily basis using an electronic diary.

During weeks 2-8, average weekly angina frequency was significantly lower with ranolazine versus placebo (3.8 [3.6-4.1] versus 4.3 [4.0-4.5] episodes, P=0.008), as was weekly sublingual nitroglycerin use (1.7 [1.6-1.9] versus 2.1 [1.9-2.3] doses, P=0.003).

The rate of serious adverse events and the rate of discontinuations due to adverse events were similar between the ranolazine and placebo groups. Notable non-serious adverse events included nausea, reported in 17 ranolazine and two placebo patients; dizziness, reported in 17 ranolazine and six placebo patients; and constipation, reported in eight ranolazine and two placebo patients; see below for important safety information.

About the TERISA Study

TERISA was a randomized, double-blind, placebo-controlled, parallel study designed to evaluate the efficacy of ranolazine in chronic stable angina patients with concurrent type 2 diabetes who remain symptomatic for angina despite receiving a stable dose of one or two concomitant antianginal agents, including beta-blockers, calcium channel blockers or long-acting nitrates.

A total of 949 patients were randomized (1:1, 473 and 476 in the ranolazine and placebo arms, respectively), 22 of whom either never initiated or discontinued treatment during the first two weeks (11 in each treatment arm), leaving 927 evaluable patients (462 and 465 in the ranolazine and placebo arms, respectively). Their mean age was 64 and 61 percent were male. The patients had a mean diabetes duration of 7.5 years and a mean baseline hemoglobin A1c (HbA1c, a laboratory measure of blood glucose) level of 7.3 percent. At randomization, 56 percent of patients were receiving one antianginal agent and 44 percent were receiving two antianginal agents.

The primary efficacy endpoint was average angina frequency during weeks 2-8, with the effect of ranolazine treatment estimated as a ratio of ranolazine to placebo frequency. During the four-week, single-blind, placebo run-in phase, average weekly angina frequency was similar between the ranolazine and placebo groups (6.6 [6.3-7.0] versus 6.8 [6.4-7.2]; ratio 0.98 [0.91-1.05]). During weeks 2-8, weekly angina frequency was significantly lower in the ranolazine group than in the placebo group (3.8 [3.6-4.1] versus 4.3 [4.0-4.5] episodes; ratio 0.89 [0.82-0.97] P=0.008).

Similarly, at baseline, average weekly sublingual nitroglycerin use was similar between treatment arms (4.1 [3.7-4.6] versus 4.5 [4.1-5.0]; ratio 0.92 [0.80-1.06]). During weeks 2-8, the average weekly number of sublingual nitroglycerin doses was significantly lower in patients receiving ranolazine compared to placebo (1.7 [1.6-1.9] versus 2.1 [1.9-2.3] doses; ratio 0.83 [0.73-0.94] P=0.003).

In prespecified subgroup analyses, the efficacy of ranolazine was consistent irrespective of baseline average weekly angina episodes (<3 versus ≥3), number of concomitant antianginal medications (one versus two), age (<65 versus ≥65) and sex. There was, however, a significant difference in the effect of ranolazine versus placebo on the primary endpoint by the geographic region of enrollment (Russia, Ukraine and Belarus versus other countries; $P_{interaction}$=0.016): The average number of weekly angina episodes between the ranolazine and placebo arms among patients enrolled in Russia, Ukraine and Belarus was not statistically significantly different (4.1 [3.9-4.4] versus 4.3 [4.1-4.6]; ratio 0.95 [0.87-1.05] P=0.31). Among patients enrolled in other countries, there was a significant reduction in average weekly angina episodes in the ranolazine group versus placebo (3.1 [2.8-3.5] versus 4.1 [3.7-4.6]; ratio 0.77 [0.65-0.90] P=0.002).

Serious adverse events with onset during the treatment phase were reported in 16 of the 470 ranolazine patients and 20 of the 474 placebo patients who took at least one dose. Five patients died during the treatment phase, including three patients in the ranolazine group (two myocardial infarctions and one sudden cardiac death) and two patients in the placebo group (one patient with acute cardiac failure and one with pulmonary embolism). The discontinuation rate due to adverse events was also comparable between both treatment groups (nine and 11 in the ranolazine and placebo groups, respectively). Notable non-serious adverse events included nausea, reported in 17 ranolazine and two placebo patients; dizziness, reported in 17 ranolazine and six placebo patients; and constipation, reported in eight ranolazine and two placebo patients.

About Gilead’s Ranolazine Diabetes Program

TERISA is one of several Gilead studies evaluating the role of ranolazine in patients with chronic angina and/or type 2 diabetes. Results of a Phase 2 study and post-hoc analyses of previous clinical trials with ranolazine suggest that ranolazine may reduce HbA1c when added to antidiabetic therapy. Gilead is now conducting three Phase 3 clinical trials in patients with type 2 diabetes, which will determine the effects of ranolazine on glycemic control as monotherapy and in combination with other antidiabetic therapies. Top-line results from these three trials are expected in late 2013.

Ranolazine is an investigational medication for type 2 diabetes and has not been proven safe and efficacious for this indication.

About Ranexa

Ranexa is an extended-release tablet approved as a treatment for chronic angina. Ranexa may be used in combination with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors and angiotensin receptor blockers. Ranexa was approved in the United States in January 2006. In 2008, the U.S. Ranexa indication was updated to include first-line treatment for chronic angina.

Ranexa at therapeutic levels can inhibit the cardiac late sodium current. However, the mechanism of Ranexa’s antianginal effects has not been determined. The relationship between the inhibition of the late sodium current and angina symptoms is uncertain.

Important Safety Information

Contraindications

- Ranexa is contraindicated in patients:
- Taking strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir)

- Taking inducers of CYP3A (e.g., rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St John's wort)
- With liver cirrhosis

Warnings and precautions

- Ranexa blocks lKr and prolongs the QTc interval in a dose-related manner.
- Clinical experience did not show an increased risk of proarrhythmia or sudden death.
- There is little experience with high doses (> 1000 mg twice daily) or exposure, with other QT-prolonging drugs, with potassium channel variants resulting in a long QT interval, in patients with a family history of (or congenital) long QT syndrome, or in patients with known acquired QT interval prolongation.

Adverse reactions

- The most common adverse reactions (> 4% and more common than with placebo) during treatment with Ranexa were dizziness, headache, constipation, and nausea.

Dosage and administration

- Begin treatment with 500 mg twice daily and increase to the maximum recommended dose of 1000 mg twice daily, based on clinical symptoms. Swallow tablets whole; do not crush, break, or chew.
- Limit the dose of Ranexa to 500 mg twice daily in patients on moderate CYP3A inhibitors (e.g., diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products).

Drug interactions

- **Inducers and strong inhibitors of CYP3A:** Do not use Ranexa (see Contraindications).
- **Moderate CYP3A inhibitors:** Limit Ranexa to 500 mg twice daily (see Dosage and Administration).
- **P-gp inhibitors (e.g., cyclosporine):** Ranexa exposure increased; titrate Ranexa based on clinical response.
- **CYP3A substrates:** Limit simvastatin to 20 mg when used with Ranexa. Doses of other sensitive CYP3A substrates (e.g., lovastatin) and CYP3A substrates with narrow therapeutic range (e.g., cyclosporine, tacrolimus, sirolimus) may need to be reduced with Ranexa.
- **Drugs transported by P-gp (e.g., digoxin) or metabolized by CYP2D6 (e.g., tricyclic antidepressants and antipsychotics):** Doses of these drugs may need to be reduced.

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 Asia Pacific.

Forward-Looking Statement

This press release includes forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995, that are subject to risks, uncertainties and other factors, including risks related to the possibility of unfavorable results from other clinical trials involving ranolazine for the treatment of type 2 diabetes. In addition, Gilead may also be unable to obtain Phase 3 clinical trial results from the studies in the timelines currently anticipated and may need to modify or delay the clinical trials or to perform additional trials. In addition, Gilead may make a strategic decision to discontinue development of ranolazine for type 2 diabetes if, for example, Gilead believes commercialization will be difficult relative to other opportunities in its pipeline. These risks, uncertainties and other factors could cause actual results to differ materially from those referred to in the forward-looking statements. The reader is cautioned not to rely on these forward-looking statements. These and other risks are described in detail in Gilead's Annual Report on Form 10-K for the year ended December 31, 2012, as filed with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Gilead, and Gilead assumes no obligation to update any such forward-looking statements.

U.S. full prescribing information for Ranexa® is available at www.gilead.com.

For more information on Gilead Sciences, please visit the company's website at www.gilead.com, follow Gilead on Twitter (@GileadSciences) or call Gilead Public Affairs at 1-800-GILEAD-5 or 1-650-574-3000.

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