Gilead Announces Results from Phase 2 Study Showing Reduction in Atrial Fibrillation Burden with the Investigational Combination of Ranolazine and Low-Dose Dronedarone

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-- Data Presented at Heart Rhythm Society Annual Meeting Support Plans for Phase 3 Development of a Fixed-Dose Combination of Ranolazine and Low-Dose Dronedarone in Atrial Fibrillation Patients --

SAN FRANCISCO--(BUSINESS WIRE)--May 10, 2014-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced results from HARMONY, a randomized, double-blind, placebo-controlled Phase 2 study evaluating the effect of ranolazine and low-dose dronedarone, each given alone and in combination, on atrial fibrillation burden (AFB) in patients with paroxysmal atrial fibrillation (AF). In HARMONY, the combination of ranolazine and low-dose dronedarone provided greater reductions in AFB from baseline than either therapy used alone. Detailed results from the study (Abstract #LB03-05) will be presented today during a late-breaking clinical trials session at the annual meeting of the Heart Rhythm Society in San Francisco.

Ranolazine is approved in the United States under the tradename Ranexa® for the treatment of chronic angina at marketed doses of 500 mg and 1,000 mg twice daily. Ranexa with or without dronedarone is not approved for the treatment of AF.

In the study, patients in the ranolazine 750 mg / dronedarone 150 mg (RD150) and ranolazine 750 mg / dronedarone 225 mg (RD225) arms experienced respective reductions of 45 percent and 59 percent in AFB from baseline over 12 weeks (p=0.072 and p=0.008, respectively, versus placebo). Among patients receiving RD225, 45 percent achieved AFB reductions from baseline of ≥70 percent over 12 weeks. Neither ranolazine 750 mg (p=0.49) nor dronedarone 225 mg (p=0.78) alone caused statistically significant reductions in AFB from baseline compared to placebo. These results are consistent with pre-clinical findings of a synergistic effect when these therapies are used in combination.

“There currently are a limited number of safe and effective anti-arrhythmic therapies for AF patients, underscoring the need to evaluate new treatment strategies,” said Peter R. Kowey, MD, William Wikoff Smith Chair in Cardiovascular Research, Lankenau Medical Center and Professor of Medicine and Clinical Pharmacology, Jefferson Medical College, Thomas Jefferson University. “HARMONY suggests that a new therapeutic approach of combining ranolazine and low-dose dronedarone is more effective than either therapy alone in lowering AF burden. Pending larger Phase 3 evaluation, a combination of ranolazine and low-dose dronedarone has the potential to help address a significant and growing unmet need for additional treatment options for people living with this serious disease.”

In HARMONY, 134 patients were randomized to one of five treatment arms: placebo (n=26); ranolazine 750 mg tablet twice daily (n=26); dronedarone 225 mg capsule twice daily (n=26); RD150 twice daily (n=26); or RD225 twice daily (n=27).

There was no clinically significant difference between active treatment groups in the overall incidence of adverse events or adverse events leading to discontinuations. Among the most frequent adverse events leading to discontinuation within each treatment group were: atrial fibrillation (placebo, two patients), vertigo and dizziness (ranolazine 750 mg, two patients each), dyspnea and pruritus (dronedarone 225 mg, two patients each), hypotension (RD225, two patients) and no adverse events leading to discontinuation were reported for more than one patient in the RD150 group (e.g., dizziness and constipation).

The primary endpoint was change in AFB over 12 weeks. AFB was defined as the total time a patient was in atrial tachycardia/atrial fibrillation expressed as percentage of total recording time continuously from 0 to 12 weeks.

About Atrial Fibrillation (AF)

AF is the most common type of abnormal heartbeat, or arrhythmia. It is caused by abnormal electrical discharges in the atria (upper two chambers of the heart), which prevent the heart from pumping blood normally, and usually causing the heart to beat too rapidly. Symptoms include palpitations, dizziness, fatigue and shortness of breath, with complications that can include heart failure and stroke. Current treatment options are aimed at controlling underlying causes, maintaining sinus rhythm (anti-arrhythmic therapies), slowing the heart rate and stroke prevention using blood-thinning medications.

About Gilead’s Ranolazine/Dronedarone FDC Program

Ranolazine is approved under the tradename Ranexa® as a treatment for chronic angina at doses of 500 mg and 1000 mg. Dronedarone is approved for treatment in patients with a history of paroxysmal or persistent AF at 400 mg twice daily.

Preclinical data published in the *Journal of the American College of Cardiology* in 2010 suggested the combination of ranolazine and dronedarone has synergistic effects, with greater suppression of atrial fibrillation (AF) than either of the two therapies alone. Based on this research and on results from the Phase 2 HARMONY study, Gilead is currently planning Phase 3 clinical trials for a fixed-dose combination (FDC) of ranolazine and low-dose dronedarone for paroxysmal/persistent (non-permanent) AF.

The Ranolazine/Dronedarone FDC is an investigational product and its safety and efficacy have not been established. Ranexa is not approved for treatment of paroxysmal or persistent AF.

Important Safety Information about Ranexa (Ranolazine) in Chronic Angina

Indication

- Ranexa is indicated for the treatment of chronic angina.
- Ranexa may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

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, rifapentine, phenobarbital, phenytoin, carbamazepine, and St John's wort)
  - With liver cirrhosis

Warnings and Precautions

- Ranexa blocks I_{Kr} and prolongs the QTc interval in a dose-related manner.
- Clinical experience in an acute coronary syndrome population did not show an increased risk of proarrhythmia or sudden death. However, 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.
- Acute renal failure has been observed in patients with severe renal impairment while on Ranexa. Monitor renal function after initiation and periodically in patients with moderate to severe renal impairment. Discontinue Ranexa if acute renal failure develops.

Adverse Reactions

- The most common adverse reactions (> 4 percent 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. Ranexa should be swallowed 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). *See* Drug Interactions for additional dosing considerations.

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 once daily 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.
- **Drugs transported by OCT2**: Limit metformin to 1700 mg per day when used with Ranexa 1000 mg twice daily. Monitor blood glucose and risks associated with high metformin exposure.

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 and South 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 the possibility of unfavorable results from additional clinical trials involving an FDC of ranolazine and low-dose dronedarone. In addition, Gilead may be unable to initiate the Phase 3 trials for an FDC of ranolazine and low-dose dronedarone for paroxysmal/persistent (non-permanent) AF in the currently anticipated timelines and may be unable to enroll patients in the studies and may need to modify or delay these studies. Further, Gilead may make a strategic decision to discontinue development of an FDC of ranolazine and low-dose dronedarone if, for example, Gilead believes commercialization will be difficult relative to other opportunities in its pipeline. As a result, an FDC of ranolazine and low-dose dronedarone may never be commercialized. 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 Quarterly Report on Form 10-Q for the quarter ended March 31, 2014, 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.

Ranexa is a registered trademark of Gilead Sciences, Inc.

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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