Results From the AMBITION Study of First-Line Treatment With Letairis and Tadalafil in Pulmonary Arterial Hypertension Published in The New England Journal of Medicine

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FOSTER CITY, Calif.--(BUSINESS WIRE)--Aug. 26, 2015-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced detailed results from the AMBITION study (a randomized, double-blind, multicenter study of first-line combination therapy with **AMBr**I**s**entan and **T**adalafil in patients with pulmonary arterial hypertens**ION**). In AMBITION, conducted in collaboration with GlaxoSmithKline (GSK), combination therapy with Letairis® (ambrisentan) and tadalafil reduced the risk of clinical failure by 50 percent compared to the pooled Letairis and tadalafil monotherapy arm (hazard ratio = 0.50; 95 percent CI: 0.35, 0.72; p<0.001). These data were published in *The New England Journal of Medicine*.

Letairis, a selective endothelin type-A receptor antagonist, and tadalafil, a PDE5 inhibitor, are each approved in the United States (U.S.), the European Union (EU) and other countries as once-daily treatments for patients with pulmonary arterial hypertension (PAH) (WHO Group 1) with WHO/NYHA functional class II and III symptoms. Letairis is indicated in the U.S. to improve exercise ability and delay clinical worsening and in the EU under the tradename Volibris® to improve exercise capacity. Tadalafil 40 mg is indicated in the U.S. and the EU to improve exercise ability and capacity, respectively. Preclinical data have suggested these therapies may have synergistic effects. However, combination use with Letairis and tadalafil is currently not approved.

“The only other published, large-scale, event-driven study to date in PAH compared an endothelin receptor antagonist to placebo in patients who were either treatment-naïve or on background therapy, however, all patients in AMBITION received an approved therapy for PAH,” said Lewis J. Rubin, MD, Emeritus Professor, University of California, San Diego and Co-Chair of the AMBITION Steering Committee. “Thus, the magnitude of the effect with this combination in comparison to active monotherapy is impressive, particularly in WHO functional class II patients where we observed nearly an 80 percent reduction in risk of clinical failure versus monotherapy.”

AMBITION was a multicenter, randomized, double-blind phase 3/4 study designed to compare the safety and efficacy of investigational first-line combination therapy (Letairis and tadalafil) to first-line monotherapy (Letairis or tadalafil) in patients with WHO/NYHA functional class II and III PAH. In the primary study analysis, 500 patients were randomized (2:1:1) to receive Letairis and tadalafil (n=253) or monotherapy with Letairis (n=126) or tadalafil (n=121) (titrated from 5 mg to 10 mg once-daily and from 20 mg to 40 mg once-daily for Letairis and tadalafil, respectively).

The primary endpoint was time to first clinical failure event, a composite endpoint that incorporates both the traditional components of clinical worsening (death, hospitalization and disease worsening) with a component of unsatisfactory long-term clinical response (all events adjudicated by an independent, blinded committee).

The treatment effect for the composite primary endpoint of time to clinical failure was driven mainly by a reduced number of hospitalizations due to PAH, with a reduced risk of hospitalization due to PAH of 63 percent (hazard ratio = 0.37; 95 percent CI: 0.22, 0.64; p<0.001).

Consistently favorable reductions in clinical failure events were observed based on etiology, WHO functional class, age, geographical area and gender. The predefined subgroup analysis of the primary endpoint suggested that patients with WHO functional class II (n=155; hazard ratio = 0.21; 95 percent CI: 0.07, 0.63); p=0.005) responded even more positively than patients with WHO functional class III (n=345; hazard ratio = 0.58; 95 percent CI: 0.39, 0.86; p=0.006).

Statistically significant improvements were also observed with the following secondary endpoints versus the pooled monotherapy arm: change from baseline at week 24 in N-terminal pro-B-type natriuretic peptide (NT-proBNP) (-67 percent vs. -50 percent; p<0.001), percentage of patients with satisfactory clinical response at week 24 (39 percent vs. 29 percent; odds ratio 1.56; p=0.03) and median change from baseline to week 24 in six-minute walk distance (6MWD) (49 meters vs. 24 meters; p<0.001). There was no difference between treatment groups in the change from baseline to week 24

for WHO functional class.

No new safety signals were detected with the combination of Letairis and tadalafil. Adverse events occurring more frequently in the combination arm than in either monotherapy arm were peripheral edema (Combination: 45 percent; Letairis: 33 percent; tadalafil: 28 percent), headache (Combination: 42 percent; Letairis: 33 percent; tadalafil: 35 percent), nasal congestion (Combination: 21 percent; Letairis: 15 percent; tadalafil: 12 percent) and anemia (Combination: 15 percent; Letairis: 6 percent; tadalafil: 12 percent).

Additional results from the study are available at www.nejm.org.

Gilead submitted the AMBITION data in a Letairis supplemental new drug application (sNDA) to the U.S. Food and Drug Administration (FDA) on December 5, 2014. FDA has granted a standard review and set a target review date under the Prescription Drug User Fee Act (PDUFA) of October 5, 2015.

In the U.S., Letairis has a labeled **BOXED WARNING** and an associated Risk Evaluation and Mitigation Strategy (REMS) program regarding the risk of embryo-fetal toxicity; see below for Important U.S. Safety Information for Letairis.

About AMBITION

AMBITION was cosponsored by Gilead and GSK. Eli Lilly and Company also provided funding and tadalafil drug supply for the trial. Gilead commercializes ambrisentan under the tradename Letairis in the U.S. and GSK commercializes ambrisentan under the tradename Volibris® in territories outside of the United States.

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.

Important U.S. Safety Information for Letairis

BOXED WARNING: EMBRYO-FETAL TOXICITY

Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals.

Exclude pregnancy before the initiation of treatment with Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment.

Because of the risk of embryo-fetal toxicity birth defects, females can only receive Letairis through a restricted program called the Letairis REMS program.

Contraindications

- Do not administer Letairis to a pregnant woman because it can cause fetal harm.
- Letairis is contraindicated in patients with Idiopathic Pulmonary Fibrosis (IPF) including IPF patients with pulmonary hypertension (WHO Group 3).

Warnings and precautions

- **Embryo-fetal Toxicity**: Letairis may cause fetal harm when administered during pregnancy.
- **Letairis REMS Program**: For all females, Letairis is only available through a restricted program called Letairis REMS. Some requirements of the Letairis REMS Program include:
    - Prescribers must be certified with the program by enrolling and completing training.
    - All females, regardless of reproductive potential, must enroll in the Letairis REMS Program prior to initiating Letairis. Male patients are not enrolled in the REMS.
      Pharmacies that dispense Letairis must be certified with the program and must dispense to female patients who are authorized to receive Letairis.

  Further information is available at www.letairisrems.com or 1-866-664-5327.

- **Mild to moderate peripheral edema**: Peripheral edema occurred more frequently in elderly patients (age ≥65 years) receiving Letairis (29 percent; 16/56) compared to placebo (4 percent; 1/28). Peripheral edema is a known class effect of endothelin receptor antagonists. In addition, there have been postmarketing reports of fluid retention occurring within weeks after starting Letairis that required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure.

- **Pulmonary Edema with PVOD**: If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as Letairis, pulmonary veno-occlusive disease should be considered, and if confirmed, Letairis should be discontinued.
- **Decreases in sperm count** have been observed in patients taking endothelin receptor antagonists and in animal fertility studies with ambrisentan. Counsel patients about potential effects on fertility.
- **Hematologic changes**: Decreases in hemoglobin have been observed within the first few weeks of treatment with Letairis, and may persist during treatment. There have been postmarketing reports of anemia requiring transfusion. Measure hemoglobin prior to initiation, at 1 month, and periodically thereafter. Initiation of Letairis therapy is not recommended for patients with clinically significant anemia.

Adverse reactions

Most Common Adverse Reactions (>3% compared to placebo)

	Placebo (N=132)	**LETAIRIS** (N=261)	
Adverse reaction	**n (%)**	**n (%)**	**Placebo-adjusted (%)**
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3

- During 12-week controlled clinical trials, the incidence of liver aminotransferase (AST, ALT) elevations >3x ULN was 0 percent for Letairis and 2.3 percent for placebo.
- In postmarketing experience, elevations of aminotransferases have been reported with Letairis use; in most cases alternative causes of liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). In practice, cases of hepatic injury should be carefully evaluated for cause.
- Other ERAs have been associated with aminotransferase elevations, hepatotoxicity, and cases of liver failure.
- Discontinue Letairis if aminotransferase elevations are >5x ULN or if elevations are accompanied by bilirubin >2x ULN or by signs or symptoms of liver dysfunction, and other causes are excluded.

Drug interactions

- Multiple-dose co-administration of Letairis and cyclosporine resulted in an approximately two-fold increase in Letairis exposure in healthy volunteers. Limit the dose of Letairis to 5 mg once daily when co-administered with

cyclosporine.

Dosage and administration

Adult Dosage: Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated. Tablets may be taken with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH).

Pregnancy Testing in Females of Reproductive Potential: Initiate treatment with, Letairis in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy tests during treatment.

Not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild hepatic impairment; however, exposure to Letairis may be increased in these patients.

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. Gilead has operations in more than 30 countries worldwide, with headquarters in Foster City, California.

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 that the FDA and other regulatory authorities may not approve the sNDA in the currently anticipated timelines or at all. In addition, any marketing approvals, if granted, may have significant limitations on use. Further, even if approved, physicians may not see the benefit of combination therapy with Letairis and tadalafil. 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 June 30, 2015, 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 including BOXED WARNING for Letairis is available at www.gilead.com.

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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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