Theravance Biopharma Announces Positive Top-Line Results from Phase 2b Study of Velusetrag (TD-5108) in Patients with Gastroparesis

August 2, 2017

Improvements in Symptoms and Normalized Gastric Emptying Demonstrated in both Diabetic and Idiopathic Gastroparesis Patients

DUBLIN, Ireland, Aug. 2, 2017 /PRNewswire/ -- Theravance Biopharma, Inc. (NASDAQ: TBPH) ("Theravance Biopharma" or the "Company") today announced positive results from a 12-week, Phase 2b study of velusetrag (TD-5108), an oral investigational drug in development for the treatment of patients with diabetic and idiopathic gastroparesis. Top-line results from the study demonstrated statistically significant improvements in gastroparesis symptoms and gastric emptying in patients receiving 5 mg of velusetrag as compared to placebo. Additionally, velusetrag was shown to be generally well-tolerated, with 5 mg and placebo having comparable rates of adverse events (AEs) and serious adverse events (SAEs).

Theravance Biopharma Logo

The study was conducted in 232 patients with either diabetic or idiopathic gastroparesis who received either velusetrag (5, 15 or 30 mg) or placebo, administered orally as a once daily dose. After four weeks of dosing, when the primary assessments were made, patients in the 5 mg velusetrag treatment arm demonstrated statistically significant improvements in symptom scores compared to placebo in two separate patient reported outcome (PRO) tools: the Gastroparesis Cardinal Symptom Index (GCSI) (nominal $p = 0.0327$) and the Gastroparesis Rating Scale (GRS) (nominal $p = 0.0159$). Improvements in GRS total score were maintained at 12 weeks of treatment (nominal $p = 0.0427$). Compared to placebo, patients in the 5 mg treatment arm also demonstrated statistically significant improvements in gastric emptying time (nominal $p < 0.001$) and in individual disease-specific symptom scores including post-prandial fullness/early satiety, bloating and upper abdominal pain (all nominal $p < 0.05$). Importantly, the symptom improvements seen with 5 mg of velusetrag were observed in both diabetic and idiopathic gastroparesis patients.

The primary endpoint analysis included a pre-specified analysis of each dose against placebo to report nominal p-values. The analysis also included multiplicity adjustments of p-values to account for three dose comparisons to placebo. Patients in the 15 and 30 mg velusetrag study arms did not demonstrate nominally statistically significant improvements in gastroparesis symptoms versus placebo, possibly due to an increased frequency in gastrointestinal side effects at these doses that may have been caused by rapid emptying of the stomach. The lack of dose response resulted in a lack of statistical significance across the three doses when adjusted for multiplicity. As a result, the statistical comparisons for the 5 mg dose are not adjusted for multiple comparisons, and all are quoted as nominal. Of note, the 15 mg and 30 mg doses remained highly statistically significant compared to placebo in gastric emptying time (nominal $p < 0.001$), as measured by scintigraphy.

"We are very encouraged by the results of this study as they demonstrate not only consistent evidence of improved gastric emptying but also meaningful improvement in gastroparesis symptoms following treatment with 5 mg of velusetrag. The findings from this study demonstrate that a 5 mg dose was sufficient to ameliorate the symptoms of gastroparesis. We believe that these findings provide clear evidence of the potential benefit of velusetrag in patients with gastroparesis, a debilitating disease in significant need of therapeutic innovation," said Brett Haumann, MD, Chief Medical Officer of Theravance Biopharma. "We are now preparing to meet with regulators to discuss the next phase in our development plan."

Velusetrag was shown to be generally well-tolerated, with rates of AEs and SAEs comparable between the 5 mg dose and placebo. The most commonly reported AEs across all groups (active treatment and placebo) were diarrhea, nausea and headache. Consistent with velusetrag's mechanism of action, patients receiving treatment demonstrated higher rates of diarrhea and nausea/vomiting than those receiving placebo, and these rates were numerically highest in the 15 and 30 mg arms of the study. Diabetic subjects treated with velusetrag generally maintained adequate glucose control throughout the study, and there were no episodes of hyperglycemia reported. There was no difference in the number of cardiac adverse events, with four events reported in placebo subjects and four events reported in all velusetrag treated subjects. There were no deaths reported in the study.

Theravance Biopharma intends to present additional results from the study at upcoming medical conferences, as well as in appropriate scientific journals.

Conference Call Today at 8:00 am ET

Theravance Biopharma will hold a conference call and webcast presentation today at 8:00 am ET to discuss the results of the Phase 2b study of velusetrag. To participate in the live call by telephone, please dial (855) 296-9648 from the U.S., or (920) 663-6266 for international callers, using the confirmation code 61886684. To listen to the conference call live via the internet please visit Theravance Biopharma's website at www.theravance.com, under the Investor Relations section, Presentations and Events. To listen to the live call please go to Theravance Biopharma's website 15 minutes prior to its start to register, download, and install any necessary audio software.

A replay of the conference call will be available on Theravance Biopharma's website through September 2, 2017. An audio replay will also be available through 8:00 am ET on August 9, 2017 by dialing (855) 859-2056 from the U.S., or (404) 537-3406 for international callers, using the confirmation code 61886684.

About the Phase 2b Study

The study was a multicenter, double-blind, placebo-controlled, parallel group Phase 2b characterizing the impact on symptoms and gastric emptying of multiple doses of velusetrag administered once daily over 12 weeks of therapy. The study enrolled 232 subjects with diabetic or idiopathic gastroparesis with documented gastric delay, by either gastric emptying scintigraphy (GES) or gastric emptying breath test (GEBT), and documented symptoms prior to and throughout the baseline period. Two daily patient reported outcomes (PRO) tools were used to characterize symptom change: the Gastroparesis Cardinal Symptom Index (GCSI), which assessed the severity of three cardinal symptom domains; and the Gastroparesis Rating Scale (GRS), which assessed severity, frequency and timing of seven symptom domains, including the three symptom domains in the GCSI. GRS is a proprietary PRO tool being developed by the Company with academic collaboration. The primary endpoint in the study was mean GCSI score at the end of week 4 of the treatment period.

About Gastroparesis

Gastroparesis is a disorder characterized by delayed gastric emptying and symptoms of gastric retention in the absence of mechanical obstruction. In the United States

, it is estimated to affect approximately six million individuals, or 1.8% of the population, and includes two major sub-classes: those with diabetic gastroparesis (29% of the overall gastroparesis population) and those with idiopathic gastroparesis (36%).[1] Symptoms of gastroparesis are variable but typically include nausea, vomiting, early satiety, postprandial bloating/fullness or upper abdominal discomfort. Severe cases may also suffer from dehydration, electrolyte disturbances, weight loss and malnutrition. There is also a correlation between severity of symptoms and impairment of quality of life.[2]

About Velusetrag

Velusetrag is an oral, once-daily investigational medicine discovered internally and developed for gastrointestinal motility disorders. The compound has been granted Fast Track designation by the U.S Food and Drug Administration (FDA) for the treatment of symptoms associated with idiopathic and diabetic gastroparesis.

Velusetrag is a highly selective agonist with high intrinsic activity at the human 5-HT4 receptor. 5-hydroxytryptamine receptor 4 (5-HT_4) agonists are established as gastrointestinal (GI) prokinetic agents for the treatment of GI tract dysfunction, such as chronic constipation. Velusetrag (or TD-5108) is a 5-HT_4 receptor agonist that demonstrates high *in vitro* intrinsic activity and selectivity for the 5-HT_4 receptor and has no significant affinity for all other receptor types, ion channels, or enzymes tested.

A previous Phase 2 trial of velusetrag showed that all three doses of velusetrag (5, 15 and 30 mg) reduced gastric emptying time (GE $t_{1/2}$) compared to placebo in patients with either diabetic or idiopathic gastroparesis. The completed Phase 2 trial was the first study to evaluate gastric emptying, a diagnostic criterion for gastroparesis, in a patient population including both diabetic and idiopathic gastroparesis patients, as opposed to diabetic gastroparesis patients only. In addition, velusetrag has completed a 400-patient Phase 2 proof-of-concept study in chronic idiopathic constipation, demonstrating statistically significant prokinetic activity at all three doses tested in that study.

Velusetrag is being developed by Theravance Biopharma in collaboration with Alfasigma (S.p.A.) ("Alfasigma"). Under the terms of the agreement, Alfasigma has an exclusive option to develop and commercialize velusetrag in the European Union, Russia, China, Mexico and certain other countries, while Theravance Biopharma retains full rights to velusetrag in the United States, Canada, Japan and certain other countries.

About Theravance Biopharma

Theravance Biopharma is a diversified biopharmaceutical company with the core purpose of creating medicines that make a difference in the lives of patients suffering from serious illness.

Our pipeline of internally discovered product candidates includes potential best-in-class medicines to address the unmet needs of patients being treated for serious conditions primarily in the acute care setting. VIBATIV® (telavancin), our first commercial product, is a once-daily dual-mechanism antibiotic approved in the U.S., Europe and certain other countries for certain difficult-to-treat infections. Revefenacin (TD-4208) is a long-acting muscarinic antagonist (LAMA) being developed as a potential once-daily, nebulized treatment for chronic obstructive pulmonary disease (COPD). Our neprilysin (NEP) inhibitor program is designed to develop selective NEP inhibitors for the treatment of a range of major cardiovascular and renal diseases, including acute and chronic heart failure, hypertension and chronic kidney diseases, such as diabetic nephropathy. Our research efforts are focused in the areas of inflammation and immunology, with the goal of designing medicines that provide targeted drug delivery to tissues in the lung and intestinal tract in order to maximize patient benefit and minimize risk. The first program to emerge from this research is designed to develop intestinally restricted pan-Janus kinase (JAK) inhibitors for the treatment of a range of inflammatory intestinal diseases.

In addition, we have an economic interest in future payments that may be made by Glaxo Group Limited or one of its affiliates (GSK) pursuant to its agreements with Innoviva, Inc. relating to certain drug development programs, including the Closed Triple (the combination of fluticasone furoate, umeclidinium, and vilanterol), currently in development for the treatment of COPD and asthma.

For more information, please visit www.theravance.com.

This press release and the conference call will contain contains certain "forward-looking" statements as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding, among other things, statements relating to goals, plans, objectives, expectations and future events. Theravance Biopharma intends such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. Examples of such statements include statements relating to: the company's strategies, plans and objectives, the company's regulatory strategies and timing of clinical studies, the potential benefits and mechanisms of action of the company's product and product candidates, the company's expectations for product candidates through development, potential regulatory approval and commercialization (including their potential as components of combination therapies) and the company's expectations for product sales. These statements are based on the current estimates and assumptions of the management of Theravance Biopharma as of the date of the press release and are subject to risks, uncertainties, changes in circumstances, assumptions and other factors that may cause the actual results of Theravance Biopharma to be materially different from those reflected in the forward-looking statements. Important factors that could cause actual results to differ materially from those indicated by such forward-looking statements include, among others, risks related to: delays or difficulties in commencing or completing clinical studies, the potential that results from clinical or non-clinical studies indicate the company's product candidates are unsafe or ineffective (including when our product candidates are studied in combination with other compounds),the feasibility of undertaking future clinical trials for our product candidates based on FDA policies and feedback, dependence on third parties to conduct clinical studies, delays or failure to achieve and maintain regulatory approvals for product candidates, risks of collaborating with or relying on third parties to discover, develop and commercialize product and product candidates, and risks associated with establishing and maintaining sales, marketing and distribution capabilities with appropriate technical expertise and supporting infrastructure. Other risks affecting Theravance Biopharma are described under the heading "Risk Factors" contained in Theravance Biopharma's Form 10-Q filed with the Securities and Exchange Commission (SEC) on May 9, 2017 and Theravance Biopharma's other filings with the SEC. In addition to the risks described above and in Theravance Biopharma's filings with the SEC, other unknown or unpredictable factors also could affect Theravance Biopharma's results. No forward-looking statements can be guaranteed and actual results may differ materially from such statements. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Theravance Biopharma assumes no obligation to update its forward-looking statements on account of new information, future events or otherwise, except as required by law.

References:

[1]American Gastroenterological Association. "Technical Review on the Diagnosis and Treatment of Gastroparesis." http://www.gastrojournal.org/article/S0016-5085(04)01634-8/fulltext. Published online July 27, 2005.

[2]Journal of Neurogastroenterology and Motility. "Prevalence of Hidden Gastroparesis in the Community: The Gastroparesis 'Iceberg'." http://www.jnmjournal.org/journal/view.html?doi=10.5056/jnm.2012.18.1.34. Published online January 16, 2012.

Contact Information:

Theravance Biopharma
Alexander Dobbin
Head of Investor Relations
650-808-4045
investor.relations@theravance.com

Tim Brons
Vida Strategic Partners (media)
646-319-8981
tbrons@vidasp.com

View original content with multimedia:http://www.prnewswire.com/news-releases/theravance-biopharma-announces-positive-top-line-results-from-phase-2b-study-of-velusetrag-td-5108-in-patients-with-gastroparesis-300498086.html

SOURCE Theravance Biopharma, Inc.