Theravance Biopharma Reports New Data from Phase 2 Study of Ampreloxetine (TD-9855) in Oral Presentation at 32nd European Neurology Congress

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Durable reductions in OHSA and OHDAS Composite scores reflect improvements in overall symptoms and daily activity throughout 20 weeks of treatment

Findings consistent with previously reported reductions in the cardinal symptom of dizziness as measured by OHSA #1 and supportive of ongoing registrational Phase 3 program in symptomatic nOH

DUBLIN, July 22, 2019 /PRNewswire/ -- Theravance Biopharma, Inc. (NASDAQ: TBPH) ("Theravance Biopharma" or the "Company") today reported new data from the Company's Phase 2 clinical trial of ampreloxetine (TD-9855) in patients with neurogenic orthostatic hypotension (nOH) in an oral presentation at the 32nd European Neurology Congress. New data demonstrated that patients experienced improvements in their overall nOH symptoms and in their ability to perform daily activities following four weeks of treatment, and that these improvements were sustained until the completion of 20 weeks of ampreloxetine therapy. Following withdrawal of treatment at the end of 20 weeks, patients experienced a worsening in their symptoms and their daily activity scores deteriorated, returning to baseline pre-treatment levels. These results are consistent with previously reported data from the trial demonstrating similarly durable improvements in OHSA #1 (a cardinal measure of nOH severity that assesses the sensation of dizziness, light-headedness or the feeling of being about to black out). The 32nd European Neurology Congress (ENC) is being held July 22-24, 2019 in London.

Ampreloxetine is an investigational, once-daily oral norepinephrine reuptake inhibitor (NRI) in development for the treatment of patients with symptomatic nOH. Theravance Biopharma is conducting an ongoing Phase 3 registrational program which includes a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ampreloxetine in symptomatic nOH patients with a four-week endpoint. The registrational program's second study, which is designed to evaluate the durability of response to ampreloxetine, includes a four-month open label phase followed by a six-week randomized, placebo-controlled withdrawal phase.

The ENC presentation reported data from the Company's completed Phase 2 clinical study, which evaluated the efficacy, durability and safety of once-daily oral ampreloxetine in patients with nOH. Following the completion of the single ascending dose portion of the study, patients entered the open-label extension phase, which was designed to evaluate improvement in patients' symptoms and impact on blood pressure.

A total of 21 patients entered the open-label extension phase of the study. 16 subjects completed the first four weeks of treatment and demonstrated evidence of improved symptom severity and daily activity by the end of four weeks of treatment. For these 16 subjects, the mean improvement in daily activity was 1.1 points at four weeks, as measured by Orthostatic Hypotension Daily Activity Scale (OHDAS) and the mean improvement in symptom severity was 1.0 point at four weeks, as measured by Orthostatic Hypotension Symptom Assessment (OHSA). Importantly, the mean daily activity improvement (1.5 points) and mean symptom severity improvement (1.8 points) was greatest in the 13 subjects who were categorized as symptomatic due to their reporting of dizziness symptoms (OHSA Question #1 > 4). The pre-defined regulatory and clinical threshold of OHSA #1 $\geq$ 4 is being applied as an inclusion criterion in the ongoing Phase 3 ampreloxetine program.

The durability of these improvements in daily activity and symptom severity were highlighted through the presentation of results for the full 20-week open-label extension phase of the study. A total of 12 symptomatic patients and four asymptomatic patients continued ampreloxetine therapy beyond the first four weeks of treatment, with seven symptomatic and four asymptomatic patients completing the full 20-week extension phase.

Results showed durable improvements in daily activity throughout the entire 20 weeks of treatment in the symptomatic patients. The mean reduction in OHDAS scores for these symptomatic patients at timepoints during the extension phase was 1.8 points at Week 8 (n=12), 2.2 points at Week 12 (n=9), 1.6 at Week 16 (n=9) and 1.8 points at the end of Week 20 (n=7). Similar durable improvements in symptom severity were seen throughout the entire 20 weeks of treatment in these patients. The mean reduction in OHSA was 1.5 points at Week 8 (n=12), 1.0 point at Week 12 (n=9), 2.2 at Week 16 (n=9) and 2.4 points at the end of Week 20 (n=7).

All patients were then followed for an additional four weeks after withdrawal of therapy and demonstrated a worsening of their symptoms and daily activity performance. At the end of the four-week follow-up, OHDAS approached pre-treatment levels, with a mean change from baseline of -0.6 points at Week 24 in the symptomatic patients. The OHSA showed similar changes, with a mean change from baseline of -0.1 points at Week 24 in symptomatic patients.

These durable improvements in OHDAS and OHSA scores are consistent with the study's previously reported improvements in patients' key symptom of dizziness severity as measured by OHSA #1. The mean reduction in OHSA #1 scores for the study's symptomatic patients was 3.8 points at Week 4 (n=13), 3.2 points at Week 8 (n=12), 1.7 points at Week 12 (n=9), 2.7 at Week 16 (n=9) and 3.1 points at the end of Week 20 (n=7). At the end of the four-week follow-up, OHSA #1 scores approached pre-treatment levels in symptomatic patients, with a mean change from baseline of 0.3 points at Week 24.

As also previously reported, results from this study demonstrated that ampreloxetine treatment increased symptomatic patients' standing systolic blood pressure (SBP) to normal levels at the three-minute assessment at all time points on all weekly clinic visits compared to the low pre-treatment baseline for these patients. The mean increase in standing SBP compared to baseline was > 7mmHg at the end of Week 4 and > 20mmHg at all subsequent assessment time points throughout the study. There were no drug-related serious adverse events reported during the active treatment phase of the study and ampreloxetine was generally well tolerated. Based on these results, the Company initiated registrational Phase 3 clinical trials of ampreloxetine in symptomatic nOH patients in January 2019.

"The totality of data from this open-label trial are encouraging as the results demonstrate consistent and durable improvements across both symptom severity and daily activity performance for nOH patients following ampreloxetine treatment. While larger, placebo-controlled studies are required to further evaluate the compound's therapeutic impact, the findings from this study offer optimism for the potential of ampreloxetine therapy to address the debilitating affect that nOH has on patients," stated Horacio Kaufmann, M.D., Felicia B. Axelrod Professor of Dysautonomia Research, Department of Neurology at New York University School of Medicine.

"We are pleased to see that the observed improvements in composite OHSA and OHDAS scores align with our previously reported improvements in dizziness severity as measured by OHSA #1. Despite the small size of this exploratory open-label study, we believe that these latest data offer further support for the durable therapeutic potential of ampreloxetine in patients struggling with nOH," said Brett Haumann, M.D., chief medical officer of Theravance Biopharma. "Considering the significant unmet medical needs of nOH patients, we are working diligently to continue evaluation of the therapeutic potential of ampreloxetine through our ongoing placebo-controlled registrational Phase 3 program for the compound."

About the Phase 2 Study in nOH

The Phase 2 study of ampreloxetine consisted of three parts. Part A was a single ascending dose (from 1 mg up to 20 mg based on patient response) designed to evaluate impact on blood pressure and standing time for ampreloxetine as compared to placebo. Part B was a double-blind, single dose study designed to evaluate impact on blood pressure and standing time for ampreloxetine as compared to placebo. Part B was discontinued when the trial was amended to include Part C, following the enrollment of ten patients in Part B (five on ampreloxetine; five on placebo). Part C was an open label extension to Part A designed to evaluate improvement in patients' symptoms and impact on blood pressure. Responders in Part A were eligible to enroll in Part C at up to their highest tolerated Part A dose, which included 5 mg, 10 mg and 20 mg. The primary endpoint of the study was measured after four weeks, although patients were able to continue to receive medication for up to five months.

About nOH

Neurogenic orthostatic hypotension (nOH) is a rare disorder defined as a sustained orthostatic fall in systolic blood pressure (SBP) of ≥ 20 mm Hg or diastolic blood pressure (DBP) of ≥ 10 mm Hg within three minutes of standing. Severely affected patients are unable to stand for more than a few seconds because of their decrease in blood pressure, leading to cerebral hypoperfusion and syncope. A debilitating condition, nOH results in a range of symptoms including dizziness, lightheadedness, fainting, fatigue, blurry vision, weakness, trouble concentration and head and neck pain. nOH is caused by autonomic nervous system (ANS) malfunction and is associated with several underlying medical conditions including multiple system atrophy (MSA), pure autonomic failure (PAF) and Parkinson's disease (PD).

The Orthostatic Hypotension Questionnaire is a validated patient-reported rating scale to assess two separate elements of nOH: the symptoms of nOH (using the Orthostatic Hypotension Symptom Assessment - OHSA) and the impact of nOH of patients' activity levels (using the Orthostatic Hypotension Daily Activity Score - OHDAS).

The OHSA assesses six symptoms (dizziness, weakness, problems with vision, fatigue, trouble concentrating and head/neck discomfort) on a scale from 0 (no symptoms) to 10 (worst possible severity of a symptom), with reductions in OHSA points indicating symptom improvement and increases in OHSA score indicating symptom worsening. OHSA #1 specifically measures patients' dizziness, lightheadedness, feeling faint, or feeling like they might black out. OHSA #1 has been accepted as a suitable endpoint in the investigation of neurogenic orthostatic hypotension by FDA.

The OHDAS assesses how nOH affects activities of daily life, and assesses four elements (activities that require standing for a short time, activities that require standing for a long time, activities that require walking for a short time, activities that require walking for a long time) on a scale from 0 (no interference) to 10 (total interference).

About Ampreloxetine (TD-9855)

Ampreloxetine is an investigational, once-daily norepinephrine reuptake inhibitor (NRI) being developed for the treatment of patients with symptomatic neurogenic orthostatic hypotension (nOH). The compound has high affinity for binding to norepinephrine transporters. By blocking the action of these transporters, ampreloxetine causes an increase in extracellular concentrations of norepinephrine.

About Theravance Biopharma

Theravance Biopharma, Inc. ("Theravance Biopharma") is a diversified biopharmaceutical company primarily focused on the discovery, development and commercialization of organ-selective medicines. Our purpose is to create transformational medicines to improve the lives of patients suffering from serious illnesses. Our research is focused in the areas of inflammation and immunology.

In pursuit of our purpose, we apply insights and innovation at each stage of our business and utilize our internal capabilities and those of partners around the world. We apply organ-selective expertise to biologically compelling targets to discover and develop medicines designed to treat underserved localized diseases and to limit systemic exposure, in order to maximize patient benefit and minimize risk. These efforts leverage years of experience in developing lung-selective medicines to treat respiratory disease, including FDA-approved YUPELRI™ (revefenacin) inhalation solution indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Our pipeline of internally discovered programs is targeted to address significant patient needs.

We have an economic interest in potential future payments from Glaxo Group or one of its affiliates (GSK) pursuant to its agreements with Innoviva, Inc. relating to certain programs, including TRELEGY ELLIPTA.

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

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This press release 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 (including the data therefrom), the potential characteristics, benefits and mechanisms of action of the Company's product and product candidates, and the Company's expectations for product candidates through development and potential regulatory approval and commercialization (including their potential as components of combination therapies and their differentiation from other products or potential products). 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, enrolling 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), risks that product candidates do not obtain approval from regulatory authorities, the feasibility of undertaking future clinical trials for our product candidates based on policies and feedback from regulatory authorities, 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, manufacture and commercialize products, 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'sForm 10-Q filed with the Securities and Exchange Commission (SEC) on May 10, 2019and 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.

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