Ampreloxetine Data in Neurogenic Orthostatic Hypotension to be Presented at the 33rd International Symposium on the Autonomic Nervous System

November 2, 2022

- *Totality of Evidence from the Phase 3 Clinical Program Demonstrates Ampreloxetine was Effective in Treating Symptoms and Improving Activities of Daily Living in MSA Patients with Neurogenic Orthostatic Hypotension*
- *Safety Profile of Ampreloxetine was Similar to that of Placebo*

DUBLIN, Nov. 2, 2022 /PRNewswire/ -- Theravance Biopharma, Inc. ("Theravance Biopharma" or the "Company") (NASDAQ: TBPH) today will present new ampreloxetine data in neurogenic orthostatic hypotension (nOH) from the Company's Phase 3 program at the 33rd International Symposium on the Autonomic Nervous System, a meeting of the American Autonomic Society (AAS). Ampreloxetine is an investigational, once-daily norepinephrine reuptake inhibitor in development for the treatment of symptomatic nOH in patients with multiple system atrophy (MSA).

"*These ampreloxetine data are encouraging for patients with MSA suffering with neurogenic orthostatic hypotension. There is an urgency to treat MSA patients with nOH due to the impact on quality of life and the extreme caregiver burden. Ampreloxetine appears to broadly impact a critical group of symptoms related to blood pressure control and may represent a potential therapy for MSA patients*," said Roy Freeman, MBChB, Professor of Neurology, Director, Center for Autonomic and Peripheral Nerve Disorders, Beth Israel Deaconess Medical Center, who assisted in the design and interpretation of the ampreloxetine Phase 3 program and is an author on all three abstracts presented at the AAS meeting.

Disclosure: Dr. Freeman is a consultant serving as an advisor for drug development and clinical trial design for Theravance Biopharma.

Study results presented at the 2022 AAS meeting, session 1 include:

Clinical Effectiveness of Ampreloxetine

- Clinically meaningful and nominal statistically significant ($p < 0.05$) differences relative to placebo in MSA patients on the following endpoints in Study 0170:
    - Orthostatic Hypotension Symptom Assessment Scale (OHSA) composite score (LS mean difference: -1.6 [95% CI: -2.7, -0.5])
    - Orthostatic Hypotension Questionnaire (OHQ) composite score (LS mean difference: -1.2 [95% CI: -2.3, -0.2])
    - Orthostatic Daily Activities Scale (OHDAS) Item 1 – Standing a short time (LS mean difference: -2.0 [95% CI: -3.6, -0.4])
- Symptomatic improvement in patients with MSA was broadly demonstrated on the individual components of the OHSA composite in Study 0170 including:
    - dizziness (LS mean difference: -1.5 [95% CI: -3.2, 0.2])
    - vision (LS mean difference: -1.7 [95% CI: -3.2, -0.3])
    - weakness (LS mean difference: -0.7 [95% CI: -2,3, 0.9])
    - fatigue (LS mean difference: -1.5 [95% CI: -3.1, 0.1])
    - trouble concentrating (LS mean difference -1.8 [95% CI: -3.3, -0.4])
    - head/neck discomfort (LS mean difference: -2.2 [95% CI: -3.7, -0.7])
- Durability of clinical effect was demonstrated by ampreloxetine in MSA patients as reflected in the reduction of the OHSA composite score and OHDAS item 1 over the course of 20 weeks (5 months) across the Phase 3 program (studies 0169 and 0170 open-label period).

Blood Pressure and Pharmacodynamics

- Standing systolic blood pressure across all studied patients (including MSA, Parkinson's disease and Pure Autonomic

Failure) with nOH was maintained by ampreloxetine and worsened after withdrawal to placebo [treatment difference: 8.6 mm Hg; p<0.05] during the randomized withdrawal phase of study 0170. The benefit was most pronounced in patients with MSA [treatment difference: 15.7 mm Hg; p < 0.05].

- Ampreloxetine increased levels of plasma norepinephrine (NE) [47%; p< 0.05] and decreased levels of dihydroxyphenyl glycol (DHPG) [-22%; p < 0.05] over the course of 4 weeks in patients with nOH, consistent with its mechanism of action. The increase in NE [57%; p< 0.05] was especially notable in the sub-group of patients with MSA.

Safety and Tolerability

- Ampreloxetine was generally well-tolerated in patients with nOH, including in the sub-group of MSA patients. Treatment-emergent adverse events were similar between the placebo and ampreloxetine groups with no clinically significant differences in laboratory parameters, ECG changes, ambulatory BP monitoring, and vital signs.

- No adverse events of supine hypertension were observed in the Phase 3 randomized withdrawal period (Study 0170).

Theravance Biopharma is focused on beginning the registrational Phase 3 Study in MSA patients with nOH: Study 0197, CYPRESS, a 12-week open-label, 8-week double-blind, placebo-controlled, randomized withdrawal study with a primary endpoint of change in OHSA composite score. Theravance Biopharma aims to start Study 0197 in the first quarter of 2023, moving the trial forward as expeditiously as possible building on the insights, experience and relationships gained from the ampreloxetine clinical trials already completed.

About Ampreloxetine

Ampreloxetine (TD-9855) is an investigational, once-daily norepinephrine reuptake inhibitor in development for the treatment of symptomatic nOH in patients with multiple system atrophy (MSA). Phase 3 results (Study 0170) showed a benefit to MSA patients in the study that was observed in multiple endpoints including Orthostatic Hypotension Symptom Assessment (OHSA) composite, Orthostatic Hypotension Daily Activities Scale (OHDAS) composite, Orthostatic Hypotension Questionnaire (OHQ) composite and OHSA #1. The Company held a Type C meeting with the FDA in June 2022 and agreed on a path to NDA filing with one new Phase 3 clinical study in MSA patients with symptomatic nOH. The Company plans to start the new Phase 3 study in early 2023, with a primary endpoint of Change in OHSA Composite Score.

Patients with MSA may benefit from ampreloxetine treatment due to the presence of central autonomic pathway degeneration and intact peripheral postganglionic fibers that is specific to MSA. As a NET re-uptake inhibitor, ampreloxetine may enhance the function of the residual sympathetic nerves resulting in increases in norepinephrine levels, standing BP, and reduction in symptoms of nOH in patients with MSA.

About Study 0170, a Phase 3 Study

Study 0170 (NCT03829657) was a 22-week Phase 3 study comprised of a 16-week open-label period and a 6-week double-blind, placebo-controlled, randomized withdrawal period. The primary endpoint of treatment failure at week 6 was defined as a worsening of both Orthostatic Hypotension Symptom Assessment Scale (OHSA) question #1 and Patient Global Impression of Severity (PGI-S) scores by 1.0 point. After Study 0169 did not meet its primary endpoint, the Company took actions to close out the ongoing clinical program including Study 0170. The study was more than 80% enrolled (n=128/154 planned) despite stopping early. The primary endpoint was not statistically significant for the overall population of patients, which included patients with Parkinson's disease, pure autonomic failure and MSA (odds ratio=0.6; p-value=0.196). The pre-specified subgroup analysis by disease type suggests the benefit seen in patients receiving ampreloxetine was largely driven by MSA patients (n=40). An odds ratio of 0.28 (95% CI: 0.05, 1.22) was observed in MSA patients indicating a 72% reduction in the odds of treatment failure with ampreloxetine compared to placebo (read more about the data here).

About Multiple System Atrophy (MSA) and Symptomatic Neurogenic Orthostatic Hypotension (nOH)

MSA is a progressive brain disorder that affects movement and balance and disrupts the function of the autonomic nervous system. The autonomic nervous system controls body functions that are mostly involuntary. One of the most frequent autonomic symptoms associated with MSA is a sudden drop in blood pressure upon standing (nOH).[1] There are approximately 50,000 MSA patients in the US[2] and 70-90% of MSA patients experience nOH symptoms.[3] Despite available therapies, many MSA patients remain symptomatic with nOH.

Neurogenic orthostatic hypotension (nOH) is a rare disorder defined as a fall in systolic blood pressure of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg, within 3 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 concentrating, and head and neck pain.

About Theravance Biopharma

Theravance Biopharma, Inc.'s overarching purpose and goal as a biopharmaceutical company is focused on delivering *Medicines that Make a Difference*® in people's lives. In pursuit of its purpose, Theravance Biopharma leverages decades of expertise, which has led to the development of FDA-approved YUPELRI® (revefenacin) inhalation solution indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Its pipeline of internally discovered programs is targeted to address significant unmet patient needs.

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

Forward-Looking Statements

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, as amended, and the Private Securities Litigation Reform Act of 1995. Examples of such statements include statements relating to: the Company's goals, designs, strategies, plans and objectives, the ability to provide value to shareholders, 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, the market for products being commercialized, potential regulatory actions and commercialization (including differentiation from other products or potential products and addressable market), and product sales or profit share revenue. These statements are based on the current estimates and assumptions of the management of Theravance Biopharma as of the date of this 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 the satisfaction of the conditions to the Offer, volatility and fluctuations in the trading price and volume of the Shares, and general economic and market conditions. Other risks affecting Theravance Biopharma are in the Company's Form 10-Q filed with the SEC on August 8, 2022, and other periodic reports filed 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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[1] https://medlineplus.gov/genetics/condition/multiple-system-atrophy/

[2] 2019 IQVIA Claims Analysis; NIH, UC San Diego Health Movement Disorder Center Multiple System Atrophy | UC San Diego Health (ucsd.edu)

[3] Mathias CJ, et al. J Neurol 1999 Oct;246(10):893-8

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