Theravance Biopharma to Present New Ampreloxetine Data at the 34th International Symposium on The Autonomic Nervous System

November 16, 2023

DUBLIN, Nov. 16, 2023 /PRNewswire/ -- Theravance Biopharma, Inc. ("Theravance Biopharma" or the "Company") (NASDAQ: TBPH) today announced that a new, anchor-based analysis of ampreloxetine data in neurogenic orthostatic hypotension (nOH) will be presented at the 34th International Symposium on The Autonomic Nervous System, a meeting of the American Autonomic Society (AAS), taking place November 15-18, 2023, in Rio Grande, Puerto Rico. Anchor-based analyses help establish thresholds used to interpret the clinical meaningfulness of changes in patient-reported outcomes measures such as the Orthostatic Hypotension Questionnaire (OHQ).

"The results of this anchor-based analysis of prior ampreloxetine studies underscore the clinical relevance of the Orthostatic Hypotension Symptom Assessment domain of the Orthostatic Hypotension Questionnaire and further substantiate its use as a primary endpoint in clinical studies," said Horacio Kaufmann, M.D., Felicia B. Axelrod Professor of Dysautonomia Research, Department of Neurology at New York University School of Medicine. "Those suffering from symptoms of nOH could benefit greatly from the availability of new therapies and identifying clinically meaningful changes in outcome measures is critical to bringing new medicines forward for nOH."[1]

Data will be presented in a poster session on Thursday, November 16, 2023, starting at 7:00 PM Atlantic Standard Time (3:00 PM PST / 6:00 PM EST / 11:00 PM GMT):

- **Kaufmann H, et al.** **Poster #95**

Evaluating clinically meaningful changes in the Orthostatic Hypotension Symptom Assessment domain of the Orthostatic Hypotension Questionnaire

Data Presented at the 2023 AAS Annual Meeting:

Key observations from this anchor-based analysis of the ampreloxetine Phase 3 studies, Study 0169 [SEQUOIA] and Study 0170 [REDWOOD], include the following:

- Two measures of patient clinical status served as anchors to the Orthostatic Hypotension Symptom Assessment (OHSA) composite score for the analysis. Patient global assessment of change (PGI-C) at Week 4 served as an anchor in Study 0169 and patient global assessment of severity (PGI-S) at Week 6 of the randomized withdrawal period served as an anchor in Study 0170.
- The OHSA composite score was shown to correlate with both PGI-C and PGI-S, providing additional support for its use as an appropriate endpoint when evaluating nOH symptoms.
- Clinically meaningful thresholds of an improvement of 0.9 to 1.3 points and a worsening of 0.7 to 1.1 points in the OHSA composite score were identified.

Study Implications:

The 1.6 point benefit demonstrated by ampreloxetine relative to placebo in multiple system atrophy (MSA) patients during the randomized withdrawal period of Study 170 exceeds the OHSA composite score thresholds established in the presented analysis.[2]

The OHSA composite score was chosen as the primary efficacy endpoint in the Phase 3 CYPRESS study, which is currently enrolling patients. This anchor-based analysis model will aid in the interpretation of clinically meaningful changes to the OHSA composite score observed in CYPRESS. Further, establishment of an anchor-based, clinically meaningful change in the OHSA composite primary endpoint will be important for clinicians, regulators, and payors.

About Ampreloxetine

Ampreloxetine, an investigational, once-daily norepinephrine reuptake inhibitor in development for the treatment of symptomatic neurogenic orthostatic hypotension (nOH) in patients with multiple system atrophy (MSA). The unique benefits of ampreloxetine treatment reported in MSA patients from Study 0170 included an increase in norepinephrine levels, a favorable impact on blood pressure, clinically meaningful and durable symptom improvement, and no signal for supine hypertension. The company has been granted an orphan drug designation in the US and, if results support it, plans to file an NDA for full approval based on the Phase 3 CYPRESS study.

About CYPRESS (Study 0197), a Phase 3 Study

Study 0197 (NCT05696717) is currently enrolling. This is a registrational Phase 3, multi-center, randomized withdrawal study to evaluate the efficacy and durability of ampreloxetine in participants with MSA and symptomatic nOH after 20 weeks of treatment; the primary endpoint of the study is change in the Orthostatic Hypotension Symptom Assessment (OHSA) composite score. The Study includes four periods: screening, open label (12-week period, participants will receive a single daily 10 mg dose of ampreloxetine), randomized withdrawal (eight-week period, double-blind, placebo-controlled, participants will receive a single daily dose of placebo or 10 mg ampreloxetine), and a long-term treatment extension. Secondary outcome measures include change from baseline in Orthostatic Hypotension Daily Activity Scale (OHDAS) item 1 (activities that require standing for a

short time) and item 3 (activities that require walking for a short time).

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. This study followed study 0169, a Phase 3, four week randomized, double-blind, placebo-controlled, parallel-group study of ampreloxetine in patients with symptomatic nOH. The primary endpoint for Study 0170 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. The benefit to MSA patients was observed in multiple endpoints including OHSA composite, Orthostatic Hypotension Daily Activities Scale (OHDAS) composite, Orthostatic Hypotension Questionnaire (OHQ) composite and OHSA #1 (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).[3] There are approximately 50,000 MSA patients in the US[4] and 70-90% of MSA patients experience nOH symptoms.[5] 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 focus is to deliver *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). Ampreloxetine, its late-stage investigational norepinephrine reuptake inhibitor in development for symptomatic neurogenic orthostatic hypotension, has the potential to be a first in class therapy effective in treating a constellation of cardinal symptoms in multiple system atrophy patients. The Company is committed to creating/driving shareholder value.

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

Forward-Looking Statements

This press release will contain 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 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 Company's expectations for product candidates through development and potential regulatory approval and commercialization (including their differentiation from other products or potential products), the relevance of the anchor-based analysis model described above in the interpretation of clinically meaningful changes to the OHSA composite score observed in CYPRESS and the importance of the establishment of an anchor-based, clinically meaningful change in the OHSA composite primary endpoint to clinicians, regulators, and payors. 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: 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 or product are unsafe, ineffective or not differentiated, risks of decisions from regulatory authorities that are unexpected or unfavorable to the Company, 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, , ability to retain key personnel, the ability of the Company to protect and to enforce its intellectual property rights, volatility and fluctuations in the trading price and volume of the Company's shares, and general economic and market conditions. Other risks affecting the Company are in the Company's Form 10-Q filed with the SEC on November 9, 2023, 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] Disclosure: Dr. Kaufmann is a paid consultant of Theravance Biopharma US, Inc. and received consulting fees from Theravance Biopharma US, Inc. related to this presentation.

[2] Data from MSA patients at week 6 of the randomized withdrawal period of Study 0170.

[3] https://medlineplus.gov/genetics/condition/multiple-system-atrophy/

[4] UCSD Neurological Institute (25K-75K, with ~10K new cases per year); NIH National Institute of Neurological Disorders and Stroke (15K-50K).

[5] Delveinsight MSA Market Forecast (2023); Symptoms associated with orthostatic hypotension in pure autonomic failure and multiple systems atrophy, CJ Mathias (1999).

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