Theravance Biopharma Presents Two New Ampreloxetine Analyses in Oral Session at the American Academy of Neurology 2025 Annual Meeting

April 7, 2025

Analyses from Randomized Controlled Trials Further Support the Target Engagement and Safety Profile of Ampreloxetine in Neurodegenerative Disease

DUBLIN, April 7, 2025 /PRNewswire/ -- Theravance Biopharma, Inc. ("Theravance Biopharma" or the "Company") (NASDAQ: TBPH) today announced new analyses from its previous Phase 3 program evaluating ampreloxetine, an investigational medicine for the treatment of symptomatic neurogenic orthostatic hypotension (nOH). Both analyses were presented as platform presentations at the 77th Annual Meeting of the American Academy of Neurology (AAN) Meeting, taking place April 5-9, 2025, in San Diego, California. Findings support ampreloxetine's highly selective mechanism of action, with a safety profile that suggests no worsening of supine hypertension.

The previous Phase 3 program of ampreloxetine, a selective norepinephrine reuptake inhibitor included two back-to-back Phase 3 trials in patients with symptomatic nOH in multiple system atrophy (MSA), Parkinson's Disease and pure autonomic failure (Study 0169, NCT03750552 and Study 0170, NCT03829657). Results from these studies were supportive of a registrational study in patients with nOH and MSA that is currently ongoing (CYPRESS, NCT05696717). Analyses presented at AAN describe ampreloxetine's pharmacodynamic effects over time, demonstrating durable target engagement and a physiological effect on blood pressure.

"There is a persistent unmet need for effective long-term treatments for nOH in patients with MSA. Inadequately treated nOH is associated with rapid functional decline, and many patients fail to respond despite trials of two to three different antihypotensive agents. Currently, there are no approved therapies that improve symptoms long-term, and all carry potential risk of supine hypertension. These new analyses provide evidence of ampreloxetine's highly selective mechanism of action and precise targeting of peripheral nerve activity to relieve symptoms of nOH," said Dr. Valeria Iodice, Honorary Associate Professor in Neurology, National Hospital for Neurology and Neurosurgery, UCL, London UK.[1]

Targeted Mechanism of Action in Patients with nOH

Study 0169 enrolled patients with symptomatic nOH, as defined by a 4-point or greater score on a patient reported assessment (OHSA[2] scale). Pharmacokinetic and pharmacodynamic measures were taken at baseline and at the end of the 4-week randomized controlled trial period. This was followed by Study 0170 which involved a 16-week open-label period followed by a 6-week randomized withdrawal period.

Key findings include:

- In Study 0169, patients randomized to ampreloxetine experienced a mean increase of 58% in venous plasma norepinephrine levels after 4 weeks of treatment across all patients, which was most pronounced in patients with MSA (79% increase).
- The observed shift in the pharmacodynamic profiles demonstrated target inhibition and reduced pre-synaptic uptake of norepinephrine.
- At the end of Week 6 of the randomized withdrawal period in Study 0170, norepinephrine reuptake inhibition with ampreloxetine resulted in a sustained improvement in orthostatic blood pressure, most notably in patients with MSA, which is consistent with enhanced activity of the peripheral autonomic nerves; this was lost in patients that withdrew to placebo.

No worsening of comorbid supine hypertension

In addition to nOH, patients with autonomic failure often have supine hypertension, or high blood pressure when lying down. Currently, all pressor agents approved by the FDA to treat orthostatic hypotension have black-box warnings indicating that these drugs may exacerbate or increase the risk of supine hypertension. Patients enrolled in Study 0169 underwent remote ambulatory blood pressure monitoring at baseline, Day 14 and Day 21, as well as in-clinic blood pressure measurements at baseline and Days 7, 14, 21 and 28.

Key findings include:

- Patients randomized to ampreloxetine did not show worsening of supine hypertension as measured during in-clinic visits.
- Patients randomized to ampreloxetine who completed the ambulatory blood pressure monitoring test at home had no worsening of overnight supine hypertension compared to those on placebo.
- There was no difference in maximal blood pressure excursion detected during the 24-hour monitoring period in patients assigned to placebo or ampreloxetine.

"nOH is a difficult condition to treat, as available pressor agents also raise blood pressure while patients are lying down, which we know increases the risk of hypertensive organ damage to the heart, brain, and kidney," said Dr. Lucy Norcliffe-Kaufmann, Theravance Biopharma's Executive Director of Clinical Science. *"This new analysis of ambulatory blood pressure data, which is the 'gold-standard' method for detection, is very promising. Ampreloxetine's unique mechanism of action suggests that it may be an effective therapy for relieving symptomatic nOH without the side effect of high blood pressure in the supine position."*

Presentation information:

NET-Inhibition with Ampreloxetine, Blood Pressure, and Catecholamines in Patients with Neurogenic Orthostatic Hypotension

Presenter: Valeria Iodice, MD
Monday, April 7, 11:15 AM PDT (2:15 PM EDT)

The Impact of Ampreloxetine on Supine Hypertension: An Ambulatory Blood Pressure Monitoring Study

Presenter: Lucy Norcliffe-Kaufmann, PhD
Monday, April 7, 11:27 AM PDT (2:27 PM EDT)

Slides presented by Drs. Iodice and Norcliffe-Kaufmann may be found here in the Presentations section of Theravance Biopharma's website.

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 worsening of supine hypertension. In the US, the Company has been granted an Orphan Drug Designation for ampreloxetine for the treatment of symptomatic nOH in patients with MSA and, if results from the ongoing Phase 3 CYPRESS study are supportive, plans to file an NDA for full approval in this indication.

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 10 mg dose of placebo or 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 the ampreloxetine Phase 3 Program (Study 169 and Study 170)

Study 0169 (NCT03750552) was a Phase 3, 4-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ampreloxetine compared to placebo in patients with symptomatic nOH (n=195). Patients from Study 0169 were eligible to enter into Study 0170 (NCT03829657), a Phase 3, multi-center, 22-week study comprising a 16-week open-label period and a 6-week double-blind, placebo-controlled, randomized withdrawal period to evaluate the sustained benefit in efficacy and safety 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 once-daily norepinephrine reuptake inhibitor in development for symptomatic neurogenic orthostatic hypotension (nOH) in patients with Multiple System Atrophy (MSA), has the potential to be a first in class therapy effective in treating a constellation of cardinal symptoms in MSA patients. The Company is committed to creating/driving shareholder value.

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

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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 Company's goals, designs, strategies, plans, potential, and objectives, the Company's regulatory strategies and timing of clinical studies, potential or possible safety, efficacy or differentiation of our investigational therapy, and expectations around the use of OHSA scores as endpoints for clinical trials. 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 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-K filed with the SEC on March 7, 2025, 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. Iodice is a paid consultant of Theravance Biopharma US, LLC.

[2] Orthostatic Hypotension Symptom Assessment, a validated scale assessing the presence of a range of hypotension-related symptoms including dizziness, weakness, problems with vision, fatigue, trouble concentrating, and head/neck discomfort. It is based on a scale from 0 (no symptoms) to 10 (worst possible severity of a symptom).

[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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