Theravance Biopharma Completes Enrollment in Pivotal Phase 3 CYPRESS Study of Ampreloxetine in Patients with Symptomatic Neurogenic Orthostatic Hypotension due to Multiple System Atrophy

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- *Topline results anticipated in Q1 2026 and, if successful, planning for expedited NDA submission*
- *If approved, ampreloxetine could address a critical unmet need as the first therapy with the potential to provide durable benefit for the 40,000 patients in the U.S. with symptomatic neurogenic orthostatic hypotension (nOH) in patients with multiple system atrophy (MSA)*
- *Ampreloxetine has Orphan Drug Designation in the U.S., underscoring the unmet need in symptomatic nOH due to MSA*

DUBLIN, Aug. 25, 2025 /PRNewswire/ -- Theravance Biopharma, Inc. ("Theravance Biopharma" or the "Company") (NASDAQ: TBPH), today announced completion of enrollment in the open-label portion of its pivotal Phase 3 CYPRESS study in patients with symptomatic neurogenic orthostatic hypotension (nOH) due to multiple system atrophy (MSA), a rare and progressive neurodegenerative disorder. nOH is a devastating condition affecting approximately 80% of MSA patients and is characterized by sudden drops in blood pressure upon standing, leading to symptoms such as dizziness, fainting, and blurry vision. These symptoms can lead to serious consequences, including falls, disability, and loss of independence. Despite its severity and impact, there is a lack of effective and durable treatment options that are specifically designed to treat nOH in patients with MSA.

"nOH is one of the most debilitating manifestations of MSA, which affects about 40,000 patients in the U.S. alone. Yet current therapies often fail to provide lasting symptoms relief, require frequent dosing and carry a boxed warning for supine hypertension," said Dr. Horacio Kaufmann, F. B. Axelrod Professor of Neurology and Professor of Medicine at NYU Grossman School of Medicine. "Ampreloxetine is designed to address the underlying cause of nOH. In Study 0170, it showed compelling improvement in OHSA composite score without worsening supine hypertension.[1] If these benefits are confirmed, I would expect to use ampreloxetine in the majority of my patients living with nOH due to MSA. I am encouraged that enrollment in CYPRESS, the first randomized-withdrawal trial designed specifically for the MSA population, has been completed, and I look forward to seeing the data early next year."

The registration-enabling Phase 3 CYPRESS (NCT05696717) study is a global, randomized-withdrawal study evaluating ampreloxetine in patients with symptomatic nOH due to clinically diagnosed MSA. Patients were enrolled in the 12-week open-label portion of the study at sites across four continents. At the end of the open-label portion, responders are randomized 1:1 to continue ampreloxetine or switch to placebo for eight weeks in the randomized-withdrawal portion of the study. The primary endpoint is change in orthostatic hypotension symptom assessment (OHSA) composite score from randomized-withdrawal baseline to Week 8.

"Completing enrollment in CYPRESS marks a major step toward bringing this potentially transformative therapy to patients with symptomatic nOH due to MSA – an underserved patient population in dire need for a new, effective and durable treatment with a favorable safety profile," said Áine Miller, Ph.D., Head of Development at Theravance Biopharma. "Ampreloxetine is intended to target the root cause driving MSA-associated nOH by selectively inhibiting norepinephrine reuptake, and demonstrated benefit in this patient population in Study 0170. The CYPRESS randomized withdrawal trial was designed with insights from Study 0170, and we are confident that, along with our careful study execution, this derisked program strongly positions us to evaluate ampreloxetine's full potential in this patient population."

The Company expects to report topline data from the Phase 3 CYPRESS trial in Q1 2026. In parallel, Theravance is preparing for an expedited NDA submission following the results and is planning to request priority FDA review, if data are supportive. This milestone reinforces our strategic focus and delivers on Theravance's commitment to advancing high-impact catalysts, as previously highlighted in our recent Q2 earnings call.

About Ampreloxetine

Ampreloxetine, an investigational, once-daily, selective 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 the Phase 3 CYPRESS (Study 0197) Study

The CYPRESS Study (NCT05696717) 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 Phase 3 SEQUOIA (Study 0169) and REDWOOD (Study 0170) Studies

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.[1]

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).[2] There are approximately 50,000 MSA patients in the US[3] and 70-90% of MSA patients experience nOH symptoms.[4] 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 disorder, 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.

Dr. Kaufmann is a member of an advisory committee supporting the CYPRESS clinical trial and a paid consultant to Theravance Biopharma.

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, Inc. (the "Company") 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 expectations regarding its future profitability, expenses and uses of cash, the Company's goals, designs, strategies, plans and objectives, future growth of YUPELRI sales, future royalty payments, the ability to provide value to shareholders, the Company's regulatory strategies and timing of clinical studies, possible safety, efficacy or differentiation of our investigational therapy, the status of patent infringement litigation initiated by the Company and its partner against certain generic companies in federal district courts; contingent payments due to the Company from the sale of the Company's TRELEGY ELLIPTA royalty interests to Royalty Pharma, 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 the conference call 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: factors that could increase the Company's cash requirements or expenses beyond its expectations and any factors that could adversely affect its profitability, whether the milestone thresholds can be achieved, 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, and risks associated with establishing and maintaining sales, marketing and distribution capabilities with appropriate technical expertise and supporting infrastructure, 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 August 13, 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] https://www.medrxiv.org/content/10.1101/2025.08.12.25332833v1 Precision therapy with ampreloxetine for neurogenic orthostatic hypotension in multiple system atrophy
Roy Freeman, Horacio Kaufmann, Italo Biaggioni, Valeria Iodice, Jens Jordan, Ross Vickery, Tadhg Geurin, Matthew J. Kmiecik, Lucy Norcliffe-Kaufmann

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

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

[4] 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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