UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 8-K

Current Report Pursuant
to Section 13 or 15(d) of the
Securities Exchange Act of 1934

Date of Report (Date of earliest event Reported): **November 2, 2022**

THERAVANCE BIOPHARMA, INC.
(Exact Name of Registrant as Specified in its Charter)

Cayman Islands	**001-36033**	**Not Applicable**
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

PO Box 309
Ugland House, South Church Street
George Town, Grand Cayman, Cayman Islands KY1-1104
(650) 808-6000
(Addresses, including zip code, and telephone numbers, including area code, of principal executive offices)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Ordinary Share $0.00001 Par Value	TBPH	NASDAQ Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01. Regulation FD Disclosure.

On November 2, 2022, Theravance Biopharma issued a press release and presented additional data from its Phase 3 clinical trial of ampreloxetine in patients with neurogenic orthostatic hypotension (nOH) at the 33rd International Symposium on the Autonomic Nervous System, a meeting of the American Autonomic Society. The press release is furnished as Exhibit 99.1 and data are furnished in Exhibit 99.2 to this Current Report on Form 8-K and are incorporated by reference herein.

The information in this Item 7.01 and in Item 9.01 of this Current Report on Form 8-K, including Exhibits 99.1 and 99.2, is being furnished and shall not be deemed "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Securities Exchange Act of 1934"), or otherwise subject to the liabilities of that Section, nor shall it be incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, except as expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

99.1	Press Release dated November 2, 2022
99.2	Presentation entitled Ampreloxetine Data in Neurogenic Orthostatic Hypotension Presented at the 33rd International Symposium on the Autonomic Nervous System
104	Cover Page Interactive Data File (cover page XBRL tags embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

THERAVANCE BIOPHARMA, INC.

Date: November 2, 2022

By: /s/ Brett Grimaud
Brett Grimaud
Senior Vice President, General Counsel and Secretary

Exhibit 99.1

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

- *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, November 2, 2022 -- 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.

[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

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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Theravance Biopharma®

Medicines That Make a Difference®

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

November 2, 2022

AMERICAN AUTONOMIC SOCIETY

Blood pressure and pharmacodynamic response of ampreloxetine, a norepinephrine reuptake inhibitor, in patients with symptomatic neurogenic orthostatic hypotension

Horacio Kaufmann[1], Roy Freeman[2], David L. Bourdet[3], Ross Vickery[4], Lucy Norcliffe-Kaufmann[1], Tadhg Guerin[3], Pietro Guaraldi[5], Alexandru Barboi[6], Valeria Iodice[7], Italo Biaggioni[8]

[1]NYU Langone Health, New York University School of Medicine, New York, NY, USA; [2]Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]Theravance Biopharma US, Inc., South San Francisco, CA, USA; [4]Theravance Biopharma Ireland Limited, Dublin, Ireland; [5]University of Bologna, Bologna, Italy; [6]NorthShore University Health System, Pritzker School of Medicine, University of Chicago, Chicago, IL, USA; [7]National Hospital for Neurology and Neurosurgery, Queen Square, Institute of Neurology, University College London, London, UK; [8]Vanderbilt University Medical Center, Nashville, TN, USA

Presenting Author Disclosure

Dr. Horacio Kaufmann reports the following conflicts of interest:

Related to this presentation:

- Theravance Biopharma: Consultant

Unrelated to this presentation:

- Editor-In-Chief, *Clinical Autonomic Research*
- Research Support: Biogen
- Royalties: UpToDate
- Scientific Advisory Board: Lilly USA, Ono Pharma UK Ltd, Vaxxinity, Takeda Pharmaceuticals,

Ampreloxetine

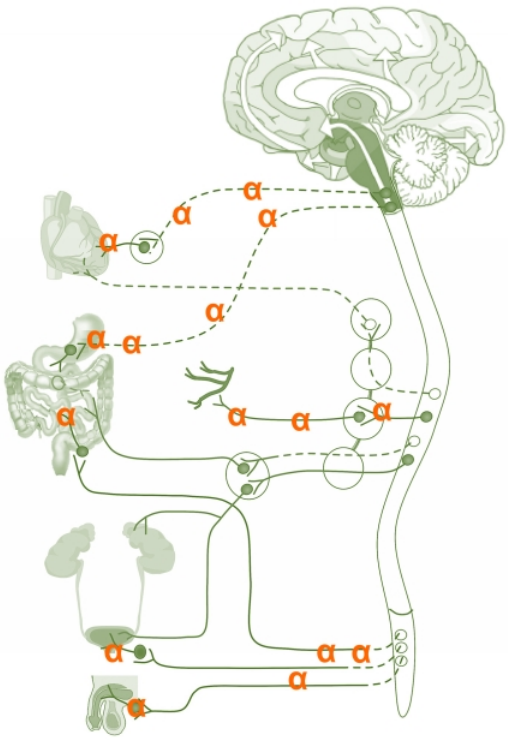
- Why ampreloxetine
- Clinical trials with ampreloxetine
- Phenotype with best ampreloxetine response

Neurogenic Orthostatic Hypotension (nOH)

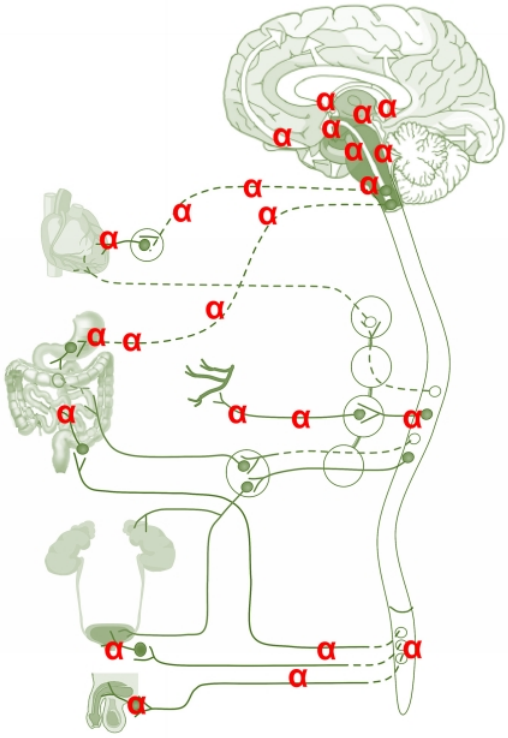
- nOH is a sustained fall in BP upon standing due to lack of ac of the sympathetic postganglionic neurons innervating the vasculature and controlled by the baroreflex

BP, blood pressure.

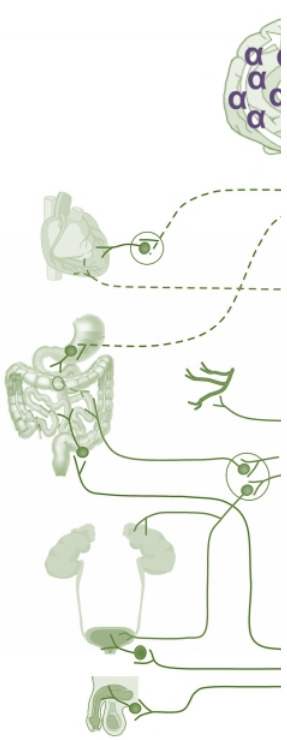
Pure autonomic failure



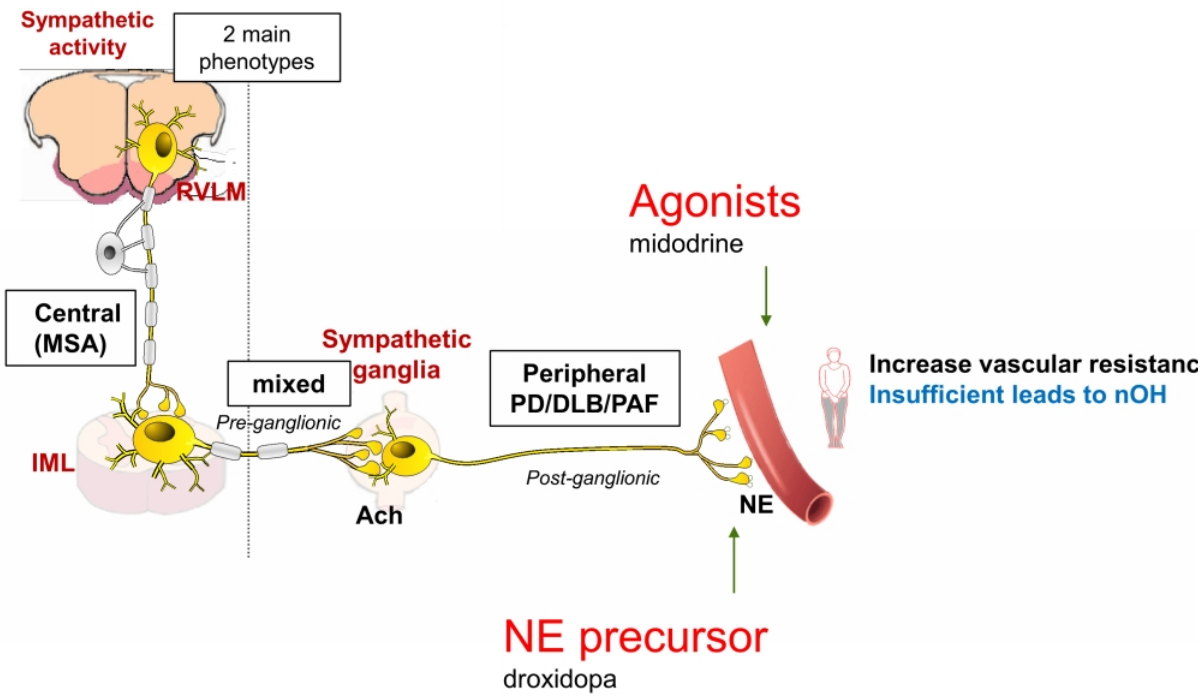
Parkinson's disease



Multiple syster



Control of Sympathetic Activity to the Peripheral Vasc

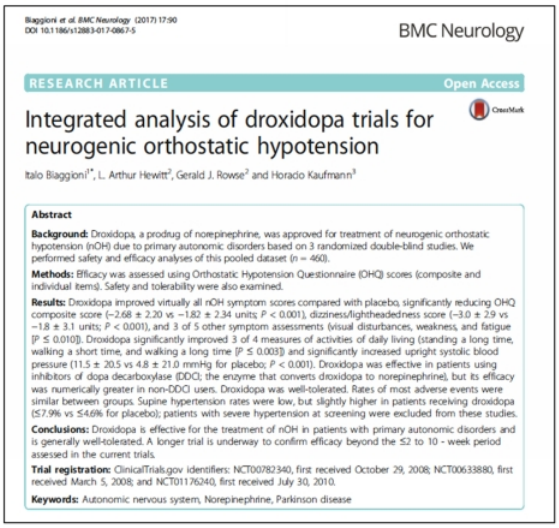


Ach, acetylcholine; DLB, dementia with Lewy bodies; IML, intermediolateral cell column; MSA, multiple system atrophy; NE, norepinephrine; nOH, neurogenic orthostatic hypotension; PAF, pure autonomic failure; PD, RVLM, rostral ventrolateral medulla.

Still an Unmet Need

40% of patients with nOH taking pressor agents are still symptomatic

Clinical trials showed that ~30% of patients taking droxidopa had no increase in blood pressure.



Biaggioni et al. BMC Neurology (2017) 17:90
DOI 10.1186/s12883-017-0867-5

BMC Neurology

RESEARCH ARTICLE Open Access

Integrated analysis of droxidopa trials for neurogenic orthostatic hypotension

Italo Biaggioni[1*], L. Arthur Hewitt[2], Gerald J. Rowse[2] and Horacio Kaufmann[3]

Abstract

Background: Droxidopa, a prodrug of norepinephrine, was approved for treatment of neurogenic orthostatic hypotension (nOH) due to primary autonomic disorders based on 3 randomized double-blind studies. We performed safety and efficacy analyses of this pooled dataset ($n = 460$).

Methods: Efficacy was assessed using Orthostatic Hypotension Questionnaire (OHQ) scores (composite and individual items). Safety and tolerability were also examined.

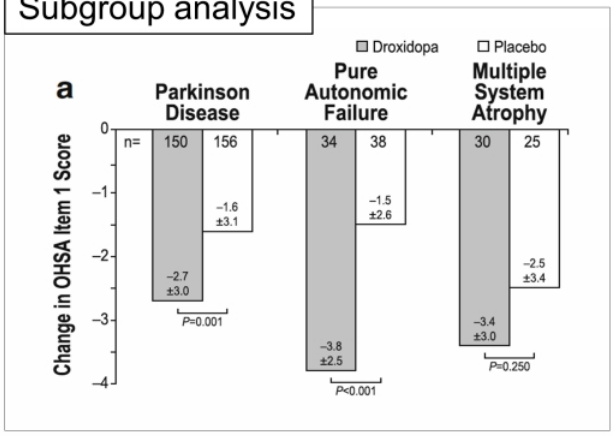
Results: Droxidopa improved virtually all nOH symptom scores compared with placebo, significantly reducing OHQ composite score (−2.68 ± 2.20 vs. −1.82 ± 2.34 units; $P < 0.001$), dizziness/lightheadedness score (−3.0 ± 2.9 vs. −1.8 ± 3.1 units; $P < 0.001$), and 3 of 5 other symptom assessments (visual disturbances, weakness, and fatigue [$P \leq 0.010$]). Droxidopa significantly improved 3 of 4 measures of activities of daily living (standing a long time, walking a short time, and walking a long time [$P \leq 0.003$]) and significantly increased upright systolic blood pressure (11.5 ± 20.5 vs 4.8 ± 21.0 mmHg for placebo; $P < 0.001$). Droxidopa was effective in patients using inhibitors of dopa decarboxylase (DDC); the enzyme that converts droxidopa to norepinephrine), but its efficacy was numerically greater in non-DDCI users. Droxidopa was well-tolerated. Rates of most adverse events were similar between groups. Supine hypertension rates were low, but slightly higher in patients receiving droxidopa (≤7.9% vs ≤4.6% for placebo); patients with severe hypertension at screening were excluded from these studies.

Conclusions: Droxidopa is effective for the treatment of nOH in patients with primary autonomic disorders and is generally well-tolerated. A longer trial is underway to confirm efficacy beyond the ≤2 to 10 - week period assessed in the current trials.

Trial registration: ClinicalTrials.gov identifiers: NCT00782340, first received October 29, 2008; NCT00633880, first received March 5, 2008; and NCT01176240, first received July 30, 2010.

Keywords: Autonomic nervous system, Norepinephrine, Parkinson disease

Subgroup analysis

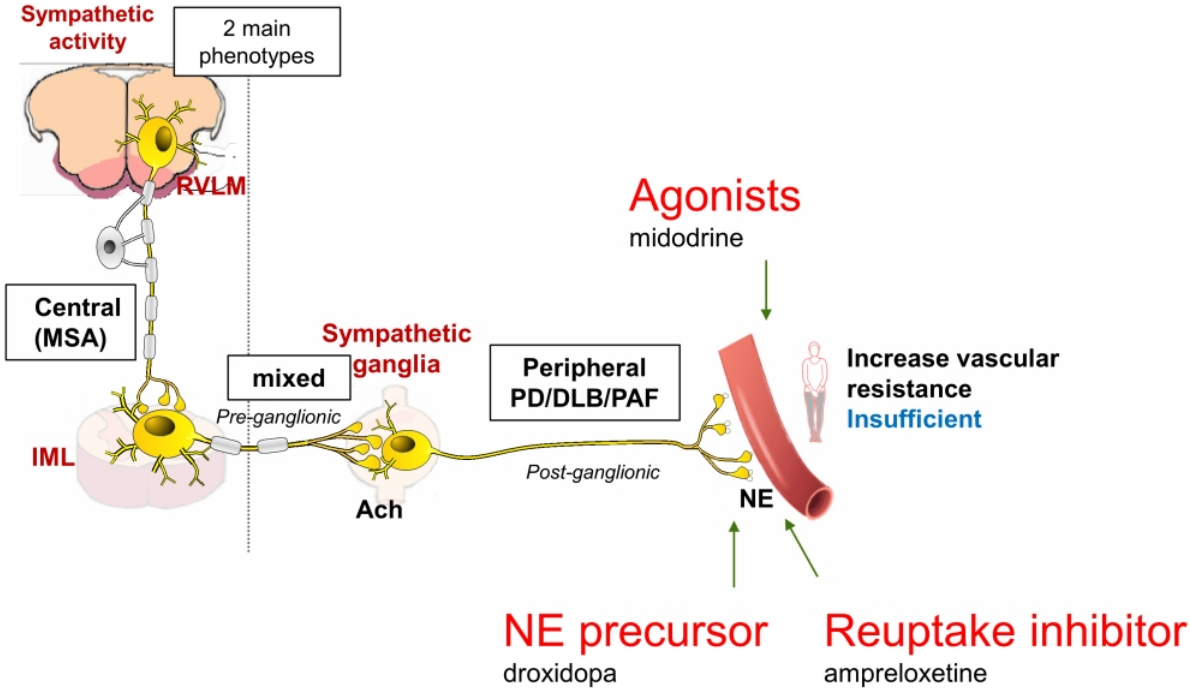


Wha the r treat

nOH symptoms did not significantly improve after taking droxidopa in patients with MSA

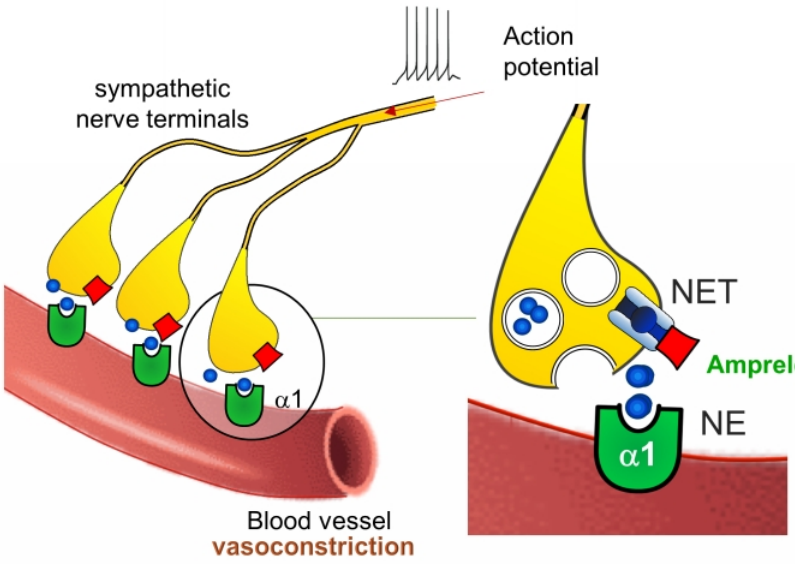
MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; OHSA, Orthostatic Hypotension Symptom Assessment.

Control of Sympathetic Activity to the Peripheral Vasc



Ach, acetylcholine; DLB, dementia with Lewy bodies; IML, intermediolateral cell column; MSA, multiple system atrophy; NE, norepinephrine; PAF, pure autonomic failure; PD, Parkinson's disease; RVLM, rostral ventro

Ampreloxetine: A Novel Pharmacological Strategy in r

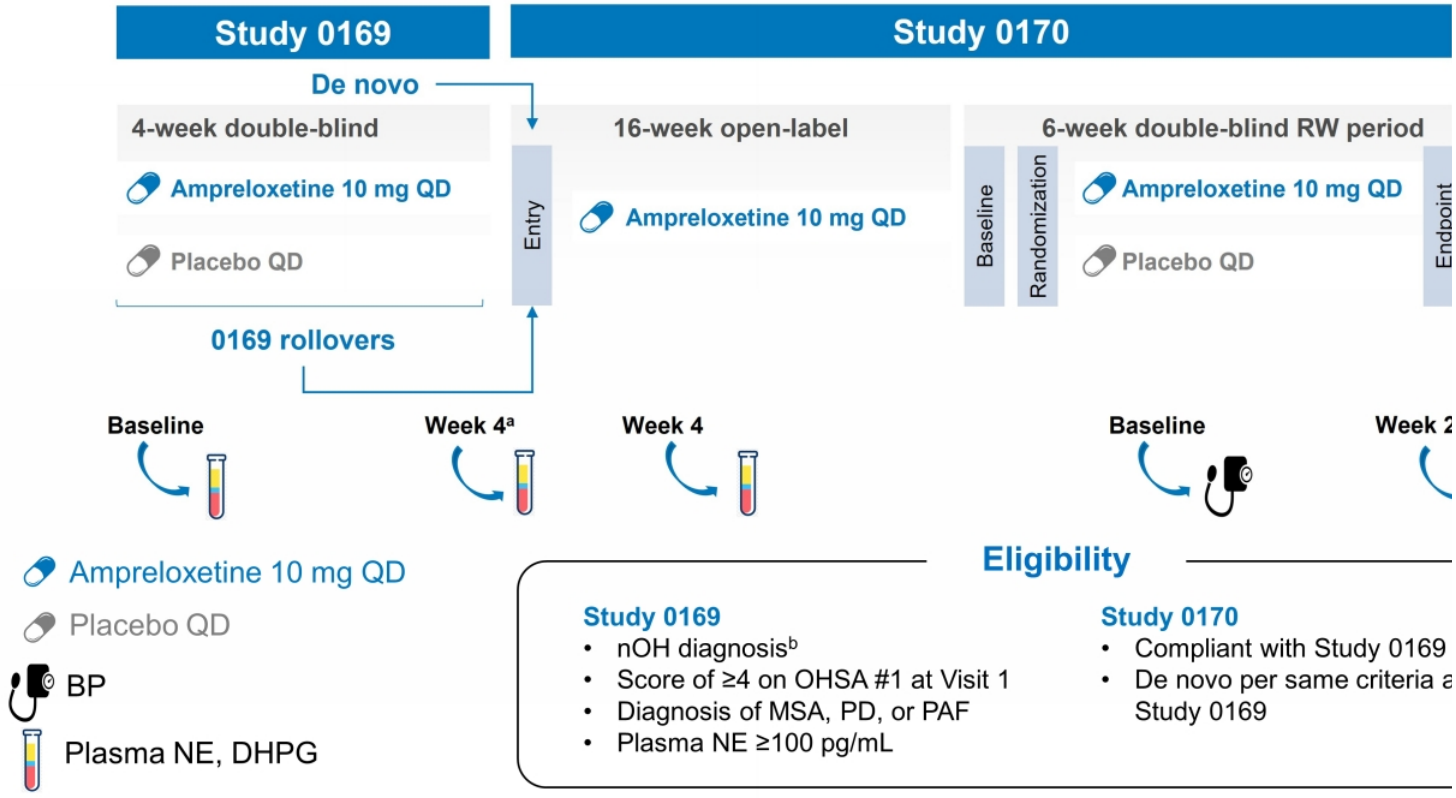


NE reuptake inhibition in nOH

- Harness the activity of the residual sympathetic nerves
- Potentiate the effect of NE when released at neurovascular junction
- Increase standing BP
- Lessen organ hypoperfusion
- Reduce symptoms of nOH

BP, blood pressure; NE, norepinephrine; NET, NE transporter; nOH, neurogenic orthostatic hypotension.

Sequential Ampreloxetine Phase 3 Studies



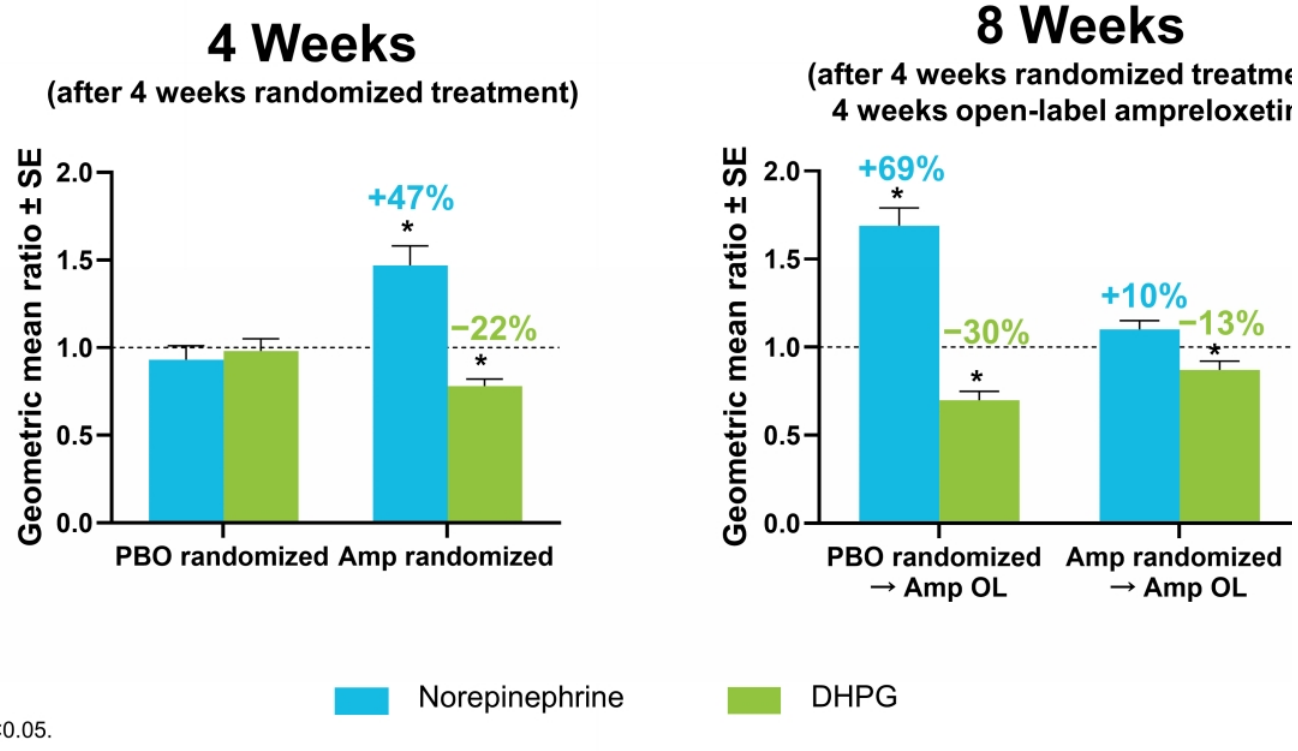
Eligibility

Study 0169
- nOH diagnosis[b]
- Score of ≥4 on OHSA #1 at Visit 1
- Diagnosis of MSA, PD, or PAF
- Plasma NE ≥100 pg/mL

Study 0170
- Compliant with Study 0169
- De novo per same criteria a Study 0169

[a]Week 4 of Study 0169 double-blind treatment used as baseline reading for Study 0170. [b]Defined as a sustained reduction ≥20 mmHg systolic BP or ≥10 mmHg diastolic BP within 3 min of being tilted up to ≥60° from determined by a tilt-table test.
BP, blood pressure; DHPG, 3,4-dihydroxyphenylglycol; MSA, multiple system atrophy; NE, norepinephrine; nOH, neurogenic orthostatic hypotension; OHSA #1, Orthostatic Hypotension Symptom Assessment item #1 failure; PD, Parkinson's disease; QD, once daily; RW, randomized withdrawal.

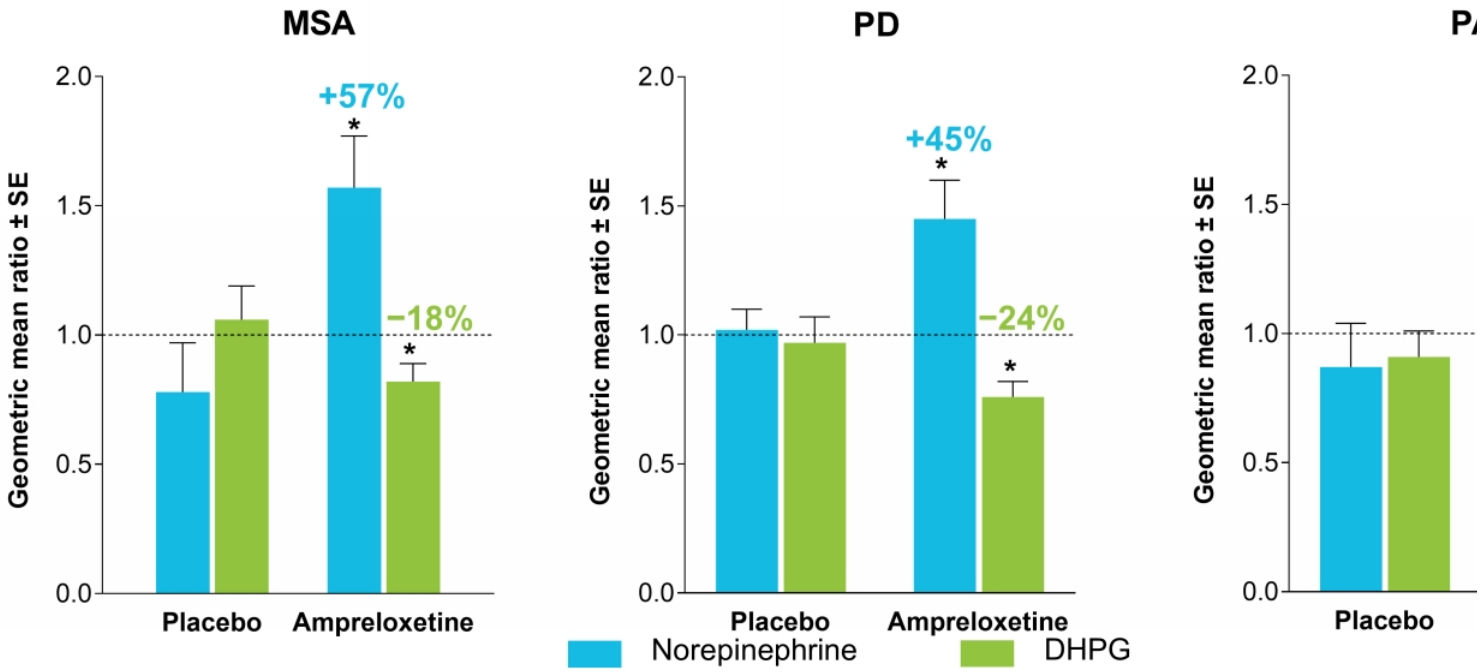
Ampreloxetine Elevates Plasma NE Levels in Patients With nOH



*P<0.05.

Amp, ampreloxetine; DHPG, 3,4-dihydroxyphenylglycol; OL, open label; NE, norepinephrine; nOH, neurogenic orthostatic hypotension; PBO, placebo; SE, standard error.

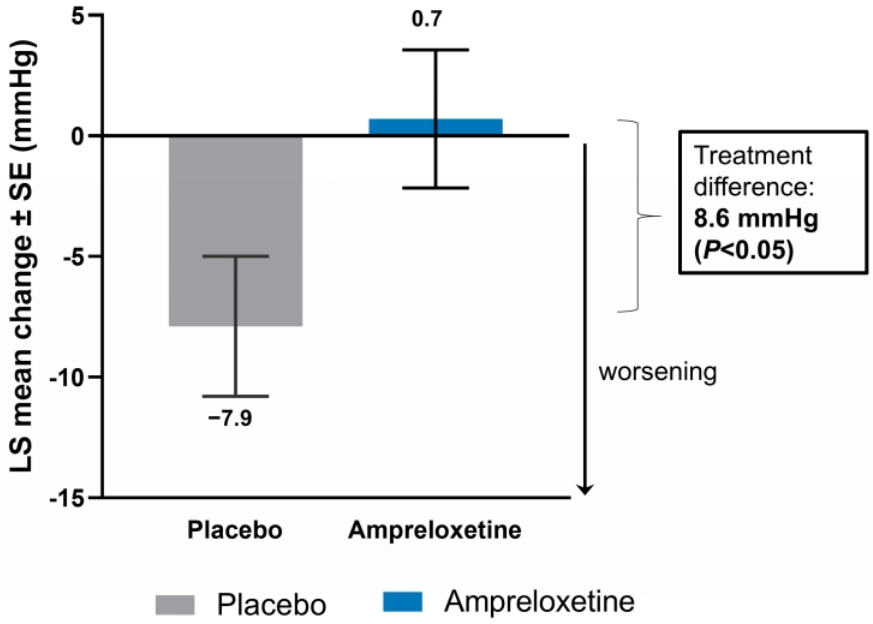
Greatest Improvements in Plasma NE Were Seen in Pa With MSA



*P<0.05.
Measurements assessed after 4 weeks of randomized treatment in Study 0169.

DHPG, 3,4-dihydroxyphenylglycol; MSA, multiple system atrophy; NE, norepinephrine; PAF, pure autonomic failure; PD, Parkinson's disease; SE, standard error.

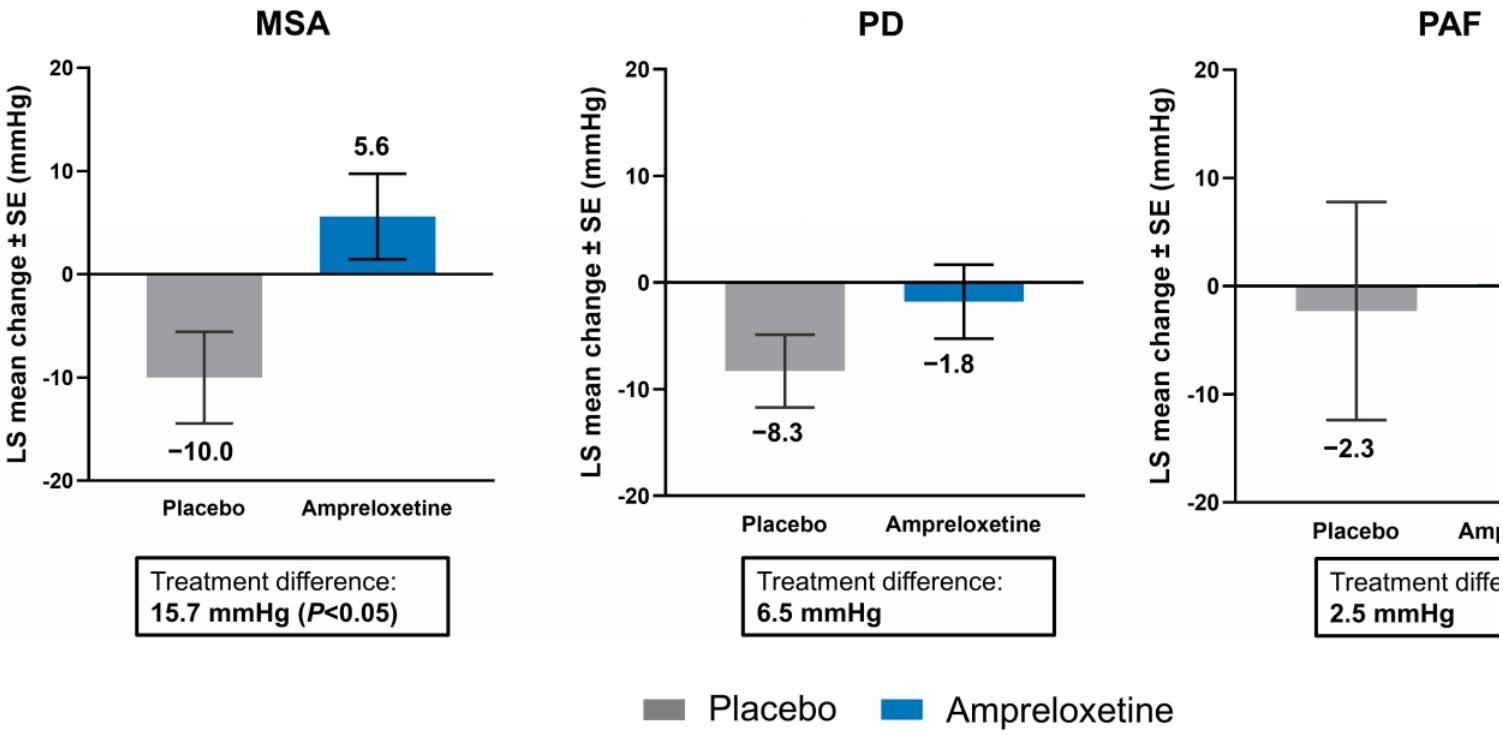
Patients Randomized to Placebo During the Withdraw Period Had Worsening 3-Minute Standing SBP



LS, least-squares; SBP, systolic blood pressure; SE, standard error.

The Effect of Ampreloxetine Treatment on 3-Minute St
SBP Was Most Pronounced in Patients with MSA

Randomized Withdrawal Period



LS, least-squares; MSA, multiple system atrophy; PAF, pure autonomic failure; PD, Parkinson's disease; SBP, systolic blood pressure; SE, standard error.

Conclusions

- Ampreloxetine showed biologically driven target engagement
- Ampreloxetine raised circulating NE levels and reduced biomarker of intraneuronal N metabolism (DHPG)
- Increases in standing BP after randomized withdrawal were most pronounced in pati with MSA
- Increasing bioavailability of NE with ampreloxetine may be particularly beneficial in p MSA

BP, blood pressure; DHPG, 3,4-dihydroxyphenylglycol; MSA, multiple system atrophy; NE, norepinephrine; nOH, neurogenic orthostatic hypotension.

AMERICAN AUTONOMIC SOCIETY

A phase 3, 22-week, multi-center, randomized withdrawal study of ampreloxetine in treating symptomatic neurogenic orthostatic hypotension

Italo Biaggioni[1], Horacio Kaufmann[2], Ross Vickery[3], Beiyao Zheng[4], Iryna Hovbakh[5], Valeria Iodice[6], Monika Rudzińska-Bar[7], Meredith Bryarly[8], Sergii Moskovko[9], Cyndya A Shibao[1], Roy Freeman[10]

[1]Vanderbilt University Medical Center, Nashville, TN, USA; [2]NYU Langone Health, New York University School of Medicine, New York, NY, USA; [3]Theravance Biopharma Ireland Limited, Dublin, Ireland; [4]Theravance Biopharma US, Inc., South San Francisco, CA, USA; [5]Clinical Hospital No. 9, Kharkiv, Ukraine; [6]National Hospital for Neurology and Neurosurgery, Queen Square, Institute of Neurology, University College London, London, UK; [7]Andrzej Frycz Modrzewski Krakow University, Krakow, Poland; [8]UT Southwestern Medical Center, Dallas, TX, USA; [9]Vinnytsia National Medical University, Vinnytsia Oblast, Ukraine; [10]Beth Israel Deaconess Medical Center, Boston, MA, USA

Presenting Author Disclosure

Dr. Italo Biaggioni reports the following conflicts of interest:

Related to this presentation:

- Theravance Biopharma: Consultant and institutional clinical trial support

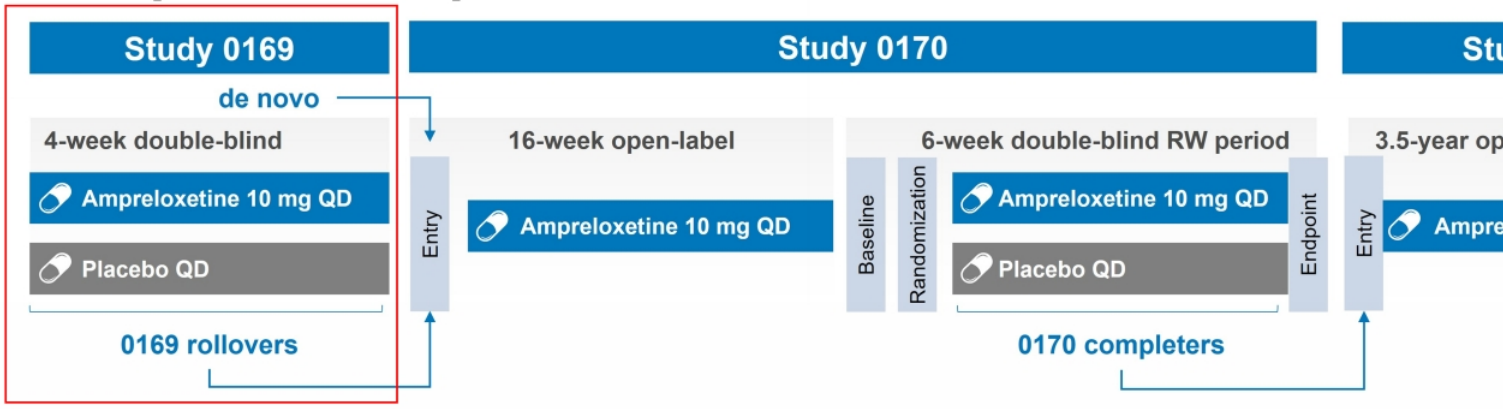
Unrelated to this presentation:

- Patent holder: Automated abdominal binder for the treatment of orthostatic hypotension
- Consultant: Amneal, Regeneron, Takeda

Funding for this study:

- The study was funded by Theravance Biopharma Ireland Limited

Sequential Ampreloxetine Phase 3 Trials



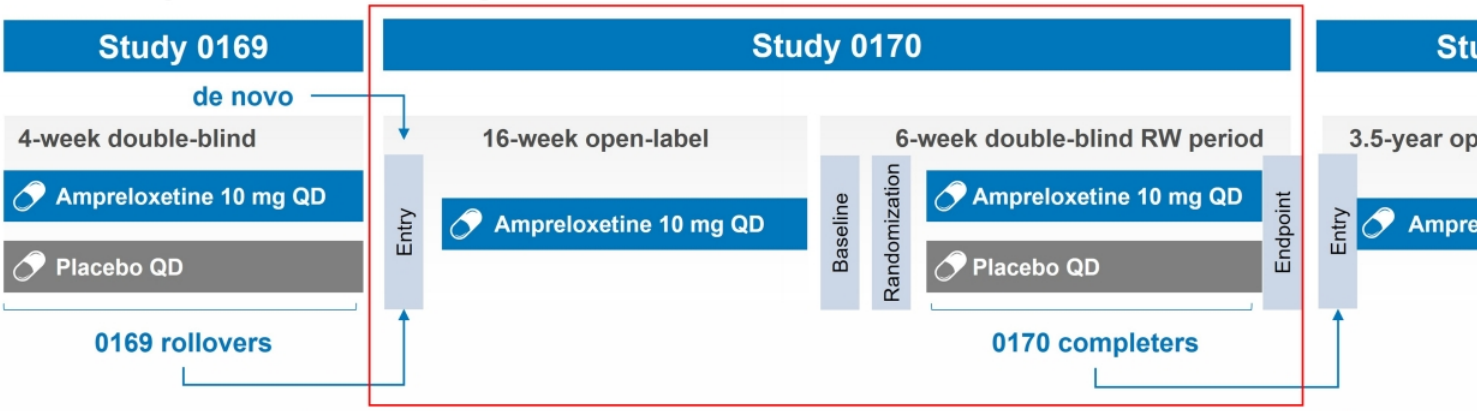
Study 0169 did not meet the primary endpoint based on reduction in OHSA#1

Eligibility

- Age ≥30 years
- nOH diagnosis
- Score of ≥4 on OHSA #1 at Visit 1
- Diagnosis of MSA, PD, or PAF
- Plasma NE ≥100 pg/mL
- Study 0170 – compliant in Study 0169 *or* de novo (same criteria as above)
- Study 0171 – completed Study 0170

Study 0170 was terminated early because of negative results from the prior Phase 3 study (Study 0169; NCT03750552).
MSA, multiple system atrophy; NE, norepinephrine; nOH, neurogenic orthostatic hypotension; OHDAS, Orthostatic Hypotension Daily Activity Scale; OHSA #1, Orthostatic Hypotension Symptom Assessment item 1; P
failure; PD, Parkinson's disease; PGI-S, Patient Global Impression of Severity; QD, once daily; RW, randomized withdrawal.

Study 0170 Design



Study 0170 eligibility

0169 Rollovers
- Completion of Study 0169 with ≥80% study medication compliance

De novo
- nOH
- OHSA #1 ≥4 at Visit 1
- MSA, PD, or PAF
- Plasma NE levels ≥100 pg/mL

Enrichment Criteria
- Reduction of OHSA #1 ≥2 at Week 4
- OHSA #1 ≤7 at Week 16

Endpoints

Primary
Treatment failure:
Worsening from baseline of both OHSA #1 (≥1 point) and PGI-S (≥1 point)

Key Seconda
Change from ba
- OHSA #1
- OHSA compos
- OHDAS comp
- PGI-S

Study 0170 was terminated early because of negative results from the prior Phase 3 study (Study 0169; NCT03750552).
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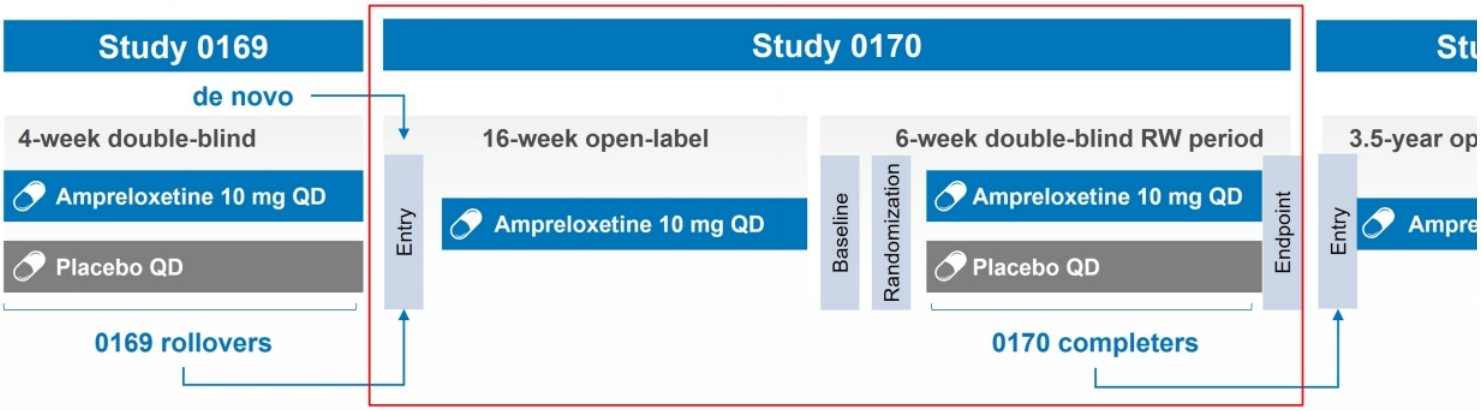
Study 0170 Design



N = 203 → 128 randomized

Enrichment failure: n = 20 (10%)
Adverse event: n = 18 (9%)
Physician decision: n = 1 (0.5%)
Early study termination: n = 13 (6%)
Withdrawal by subject: n = 18 (9%)
Other: n = 5 (2%)

Study 0170 was terminated early because of negative results from the prior Phase 3 study (Study 0169; NCT03750552).
QD, once daily; RW, randomized withdrawal.

Baseline Demographics and Clinical Characteristics

Randomized Withdrawal Period

	Placebo (n = 64)	Ampreloxetine (n = 64)	To (N =
Male, n (%)	49 (76.6)	42 (65.6)	91 (
Age, mean ± SD, years	68.2 ± 8.1	67.5 ± 8.6	67.9
White, n (%)	63 (98.4)	61 (95.3)	124
BMI, mean ± SD, kg/m^2	25.9 ± 4.7	25.4 ± 4.3	25.7
Primary neurological diagnosis, n (%)			
MSA	20 (31.3)	20 (31.3)	40 (
PD	34 (53.1)	34 (53.1)	68 (
PAF	10 (15.6)	10 (15.6)	20 (
OHSA #1, mean ± SD	2.5 ± 1.8	3.1 ± 2.0	2.8
OHSA #1 <4, n (%)	43 (67.2)	35 (54.7)	78 (
OHSA composite score, mean ± SD	2.2 ± 1.5	2.7 ± 1.7	2.4
OHDAS composite score, mean ± SD	3.4 ± 2.3	3.3 ± 2.4	3.3
PGI-S score, mean ± SD	2.4 ± 0.9	2.4 ± 0.8	2.4

Baseline for randomized withdrawal period is Week 16 of open-label period.
BMI, body mass index; MSA, multiple system atrophy; OHDAS, Orthostatic Hypotension Daily Activity Scale; OHSA, Orthostatic Hypotension Symptom Assessment; OHSA #1, OHSA item 1; PAF, pure autonomic failu
disease; PGI-S, Patient Global Impression of Severity; SD, standard deviation.

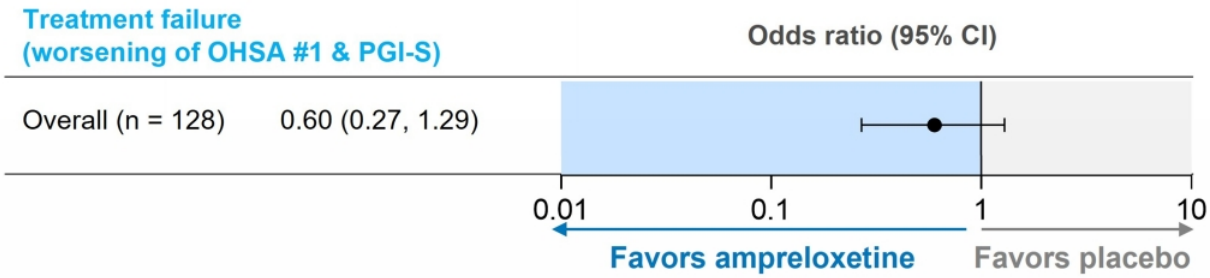
Study Disposition

Randomized Withdrawal Period

	Placebo (n = 64)	Ampreloxetine (n = 64)	Total (N = 128)
Completed treatment	61 (95.3)	58 (90.6)	119 (93.0)
Discontinued treatment	3 (4.7)	6 (9.4)	9 (7.0)
Adverse event	1 (1.6)	1 (1.6)	2 (1.6)
Study terminated by sponsor	2 (3.1)	3 (4.7)	5 (3.9)
Withdrawal by patient	0	1 (1.6)	1 (0.8)
Other	0	1 (1.6)	1 (0.8)

All data are presented as n (%).

Primary Endpoint: Treatment Failure (worsening of symptoms after *Randomized Withdrawal Period*

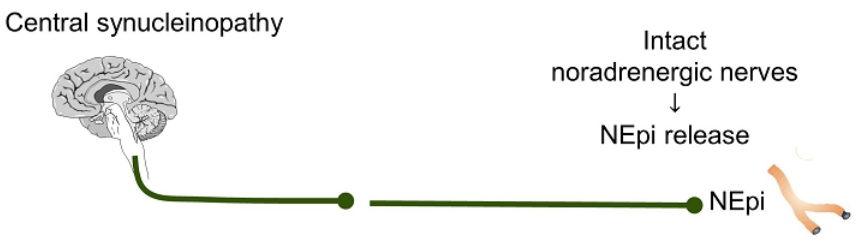


- Primary endpoint of reduction in treatment failure was not met
- …but, we had a **pre-specified** subgroup analysis planned based on diagnosis

The logistic regression model for treatment failure included terms for treatment, baseline OHSA #1, baseline PGI-S, and disease type (MSA, PAF, or PD). Profile-likelihood CI is shown.
CI, confidence interval; MSA, multiple system atrophy; OHSA #1, Orthostatic Hypotension Symptom Assessment item 1; PAF, pure autonomic failure; Parkinson's disease; PGI-S, Patient Global Impression of Severity

Rationale for a Pre-Specified Analysis Based on Diag

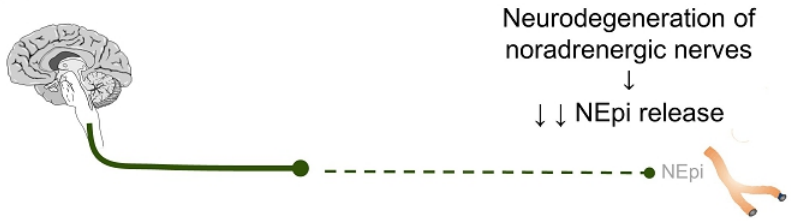
- NET inhibition with ampreloxetine potentiates **endogenously-released norepinephrine**
- **MSA**



Potentiation
Inhibiti

✓

- **PAF/PD**

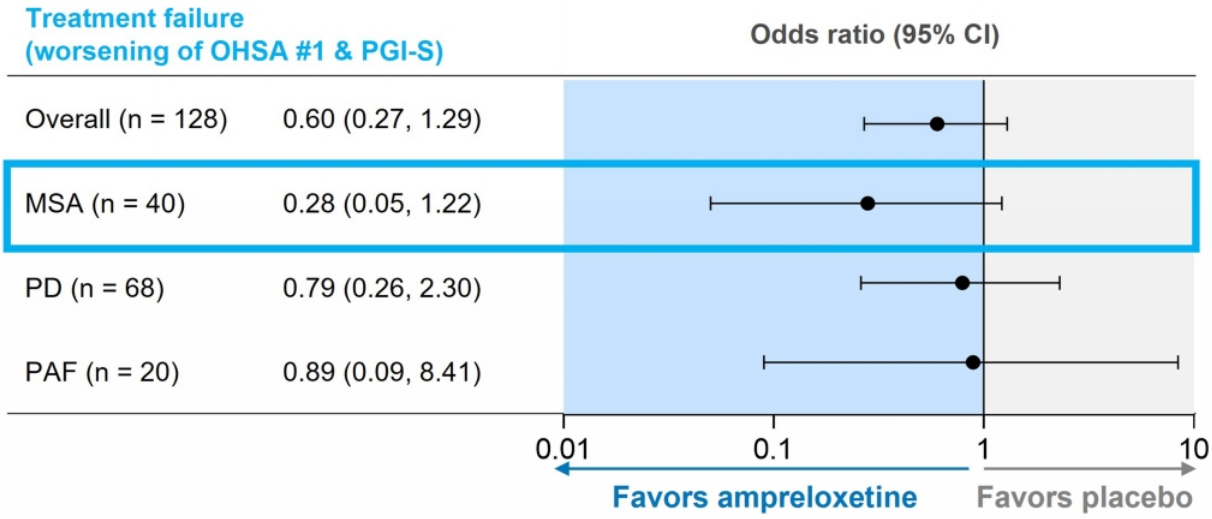


X

- ➔ Ampreloxetine will be more effective in central synucleinopathies (MSA)

NEpi, norepinephrine; NET, norepinephrine transporter; MSA, multiple systems atrophy; PAF, pure autonomic failure; PD, Parkinson's disease.

Primary Endpoint: Treatment Failure (worsening of symptoms after
Randomized Withdrawal Period

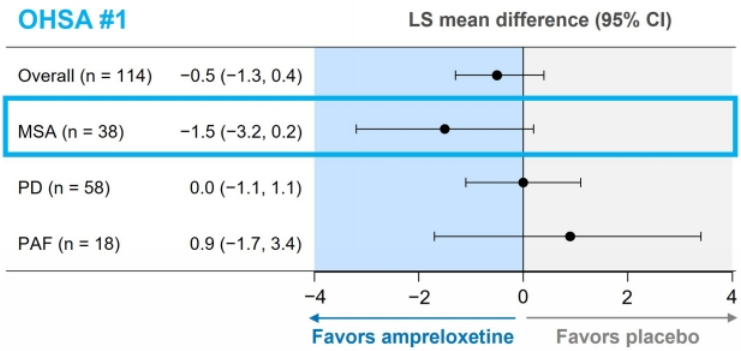


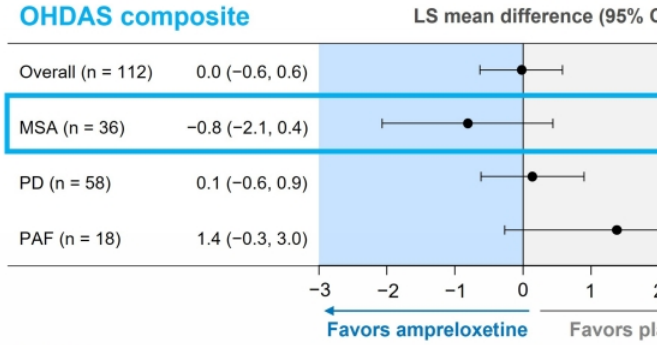
- Trend for benefit was observed in the MSA subpopulation based on prespecified subgroup ana

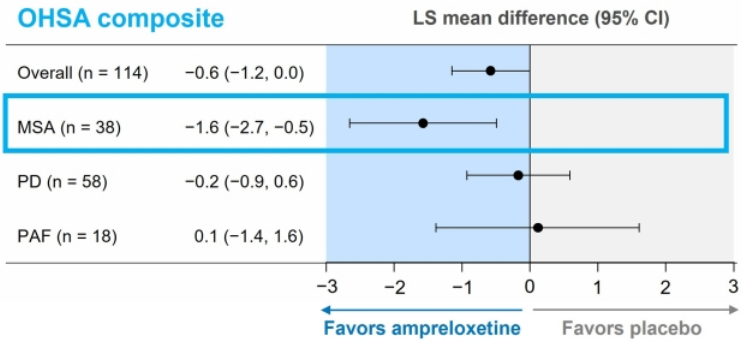
The logistic regression model for treatment failure included terms for treatment, baseline OHSA #1, baseline PGI-S, and disease type (MSA, PAF, or PD). Profile-likelihood CI is shown.
CI, confidence interval; MSA, multiple system atrophy; OHSA #1, Orthostatic Hypotension Symptom Assessment item 1; PAF, pure autonomic failure; PD, Parkinson's disease; PGI-S, Patient Global Impression of Se

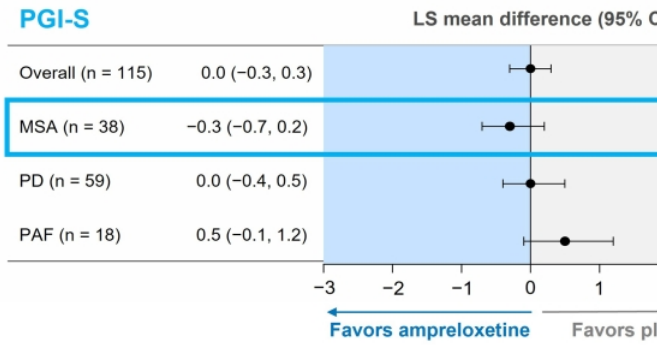
Key Secondary Endpoints: Trend for Benefit in MSA S

Randomized Withdrawal Period









- OHSA composite score demonstrated nominal statistical significance in prespecified subgroup analyses

CI, confidence interval; LS, least-squares; MSA, multiple system atrophy; OHDAS, Orthostatic Hypotension Daily Activity Scale; OHSA, Orthostatic Hypotension Symptom Assessment; OHSA #1, OHSA item 1; PAF, p
PD, Parkinson's disease; PGI-S, Patient Global Impression of Severity.

Safety Summary
Randomized Withdrawal Period

	Placebo (n = 64)	Ampreloxetine (n = 64)
Any TEAEs	16 (25.0)	17 (26.6)
TEAEs related to study drug	2 (3.1)	5 (7.8)
SAEs	2 (3.1)	4 (6.3)
SAEs related to study drug	1 (1.6)	2 (3.1)
TEAEs leading to permanent study drug discontinuation	1 (1.6)	1 (1.6)
Deaths during study	0	2 (3.1)

All data are presented as n (%). Ampreloxetine was administered at 10 mg once daily.

- TEAEs were similar between placebo and ampreloxetine groups
  - No adverse events of supine hypertension were observed
- No clinically significant differences for laboratory parameters, ECG changes, ambulatory BP m and vital signs
- Two deaths: 1 respiratory tract infection (unrelated) and 1 unknown cause[a]

[a]Death of unknown cause was imputed as related to treatment.
BP, blood pressure; ECG, electrocardiogram; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- Ampreloxetine demonstrated trend for benefit in the primary and key secondary endp prespecified MSA subgroup
- Ampreloxetine was generally well tolerated
- These results encouraged us to perform a longitudinal analysis in the subset of patie MSA

Longitudinal analysis of ampreloxetine for the treatment of symptomatic neurogenic orthostatic hypotension in subset o patients with multiple system atrophy

- **Roy Freeman**[1], Italo Biaggioni[2], Ross Vickery[3], Lucy Norcliffe-Kaufmann[4], Tadhg Gueri Saggar[5], Lydia Lopez Manzanares[6], Valeria Iodice[7], Monika Rudzińska-Bar[8], Maria Tere Pellecchia[9], Horacio Kaufmann[4]

MSA, multiple system atrophy.

AMERICAN AUTONOMIC SOCIETY

Longitudinal analysis of ampreloxetine for the treatment of symptomatic neurogenic orthostatic hypotension in subset of patients with multiple system atrophy

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Presenting Author Disclosure

- Dr. Roy Freeman has received personal compensation and/or stock options for serving on scie advisory boards of AlgoRx, Applied Therapeutics, Clexio, Cutaneous NeuroDiagnostics, Glenn Pharma, Glaxo-Smith Kline, Inhibikase, Eli Lilly, Maxona, Novartis, NeuroBo, Regenacy, Thera Biopharma, and Vertex; has received personal compensation for editorial activities (Editor) wit Neuroscience – Basic and Clinical; has received research support from the National Institutes (1R01NS10584401A1, R01HL111465-01A1); is a member of the Multiple System Atrophy Coa Advisory Board, and Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovatio Opportunities, and Networks; and is a Board member of the International Diabetic Neuropathy of the Peripheral Nerve Society and the Neuropathic Pain Consortium of the Peripheral Nerve
- The study was funded by Theravance Biopharma Ireland Limited

Ampreloxetine Phase 3 Program Results

- Ampreloxetine failed to meet its primary endpoint in two pivotal trials for the treatmen patients with MSA, PD, and PAF
- However, a prespecified subgroup analysis by primary disease type suggested a con benefit for ampreloxetine over placebo in patients with MSA across multiple endpoint randomized withdrawal period
- These results prompted an in-depth analysis across Phase 3 clinical studies of all pa MSA, and assessment for a potential future confirmatory trial
- We report the longitudinal results of a Phase 3 ampreloxetine program evaluating efficacy, durability of treatment effect, and safety for nOH treatment in the prespecifie subgroup of patients with MSA

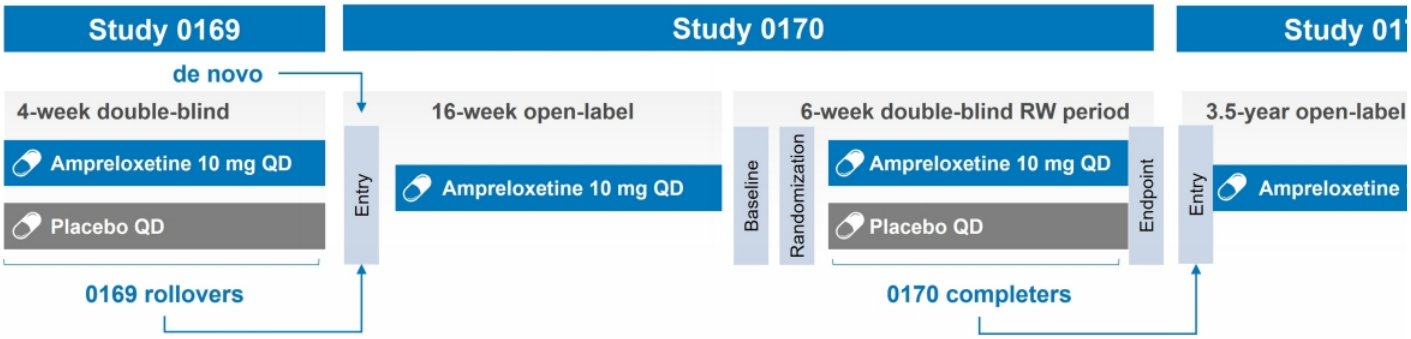
MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson's disease.

Neurogenic Orthostatic Hypotension in MSA and Ampr

- nOH is a chronic, debilitating condition caused by autonomic dysfunction[1,2]
- nOH is present in ~80% of patients with MSA[1]
- Central autonomic lesions are predominant in MSA, while peripheral postganglionic fibers may remain intact[2]
  - Due to integrity of peripheral postganglionic fibers, patients with MSA may therefore be particularly well suited for NE reuptake inhibition treatment compared to patients with PD or PAF
- Ampreloxetine is an oral, once-daily inhibitor of NE reuptake being developed for the treatment of nOH[2]

1. Kalra DK, et al. *Clin Med Insights: Cardiol.* 2020;14:1179546820953415. 2. Kaufmann H, et al. *Clin Auton Res.* 2021;31(6):699–711.
MSA, multiple system atrophy; NE, norepinephrine; NET, norepinephrine transporter; nOH, neurogenic orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson's disease.

Phase 3 Program[a]



Longitudinal analysis (prespecified MSA subgroup)

Eligibility

- Study 0169
  - Age ≥30 years
  - nOH diagnosis[b]
  - Score of ≥4 on OHSA #1 at Visit 1
  - Diagnosis of **MSA**, PD, or PAF
  - Plasma NE ≥100 pg/mL
- Study 0170
  - OL period: Compliant in Study 0169 *or* de novo (same criteria as Study 0169)
  - RW period: OHSA #1 reduction ≥2 points at Week 4 of OL period and OHSA #1 score ≤7 at Week 16 of OL period
- Study 0171: Completed Study 0170

Endpoints

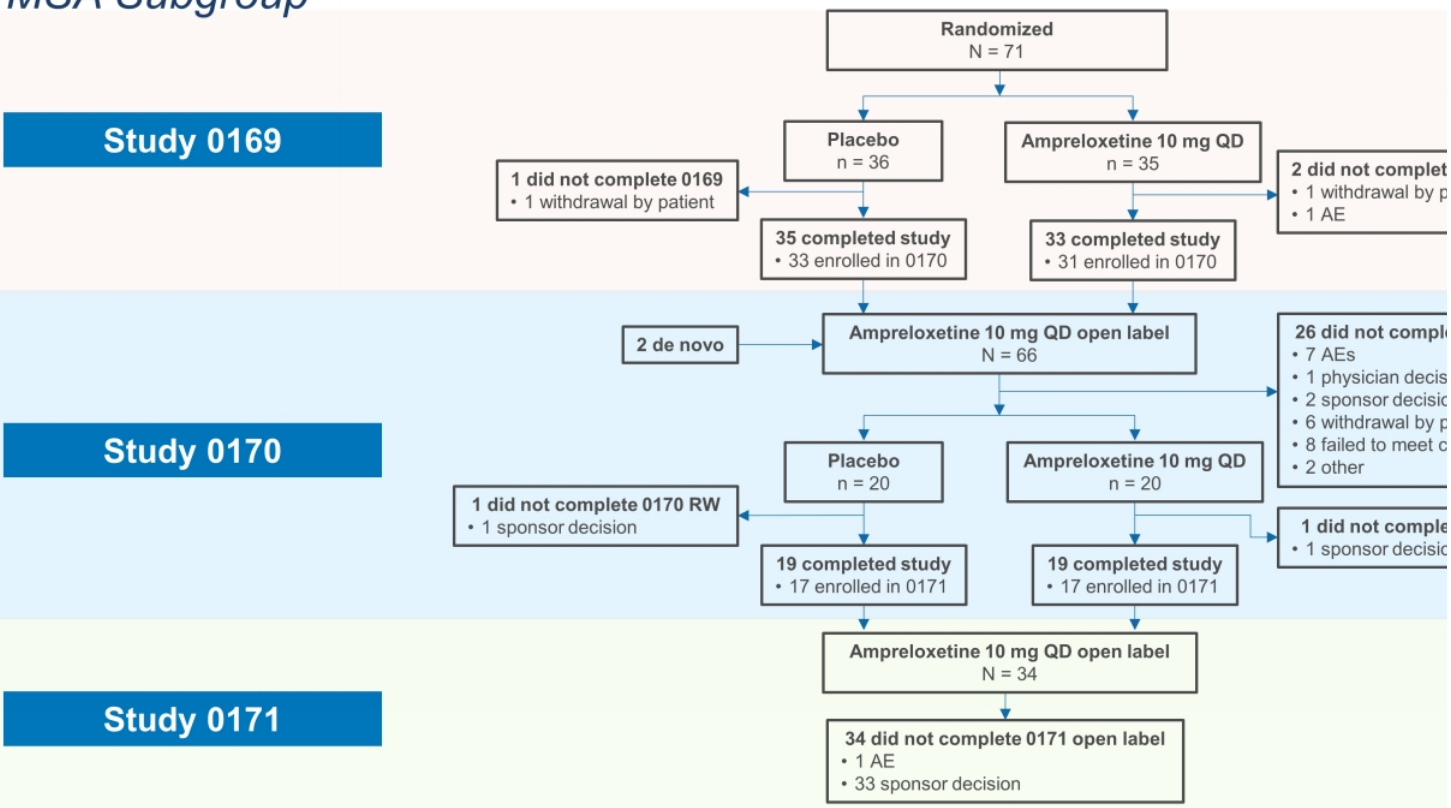
Efficacy
- OHQ
  - Composite scores
  - Individual items
- Orthostatic standing test
  - 3-minute standing SBP

Safety
- Adverse e

[a]After Study 0169 did not meet its primary endpoint, the ongoing clinical program was closed; Study 0170 was >80% enrolled at this point. [b]Sustained reduction of ≥20 mmHg in SBP or ≥10 mmHg in DBP within 3 min from a supine position as determined by a tilt-table test.
DBP, diastolic blood pressure; MSA, multiple system atrophy; NE, norepinephrine; nOH, neurogenic orthostatic hypotension; OHQ, Orthostatic Hypotension Questionnaire; OHSA #1, Orthostatic Hypotension Sympton OL, open-label; PAF, pure autonomic failure; PD, Parkinson's disease; QD, once daily; RW, randomized withdrawal; SBP, systolic blood pressure.

Study Disposition

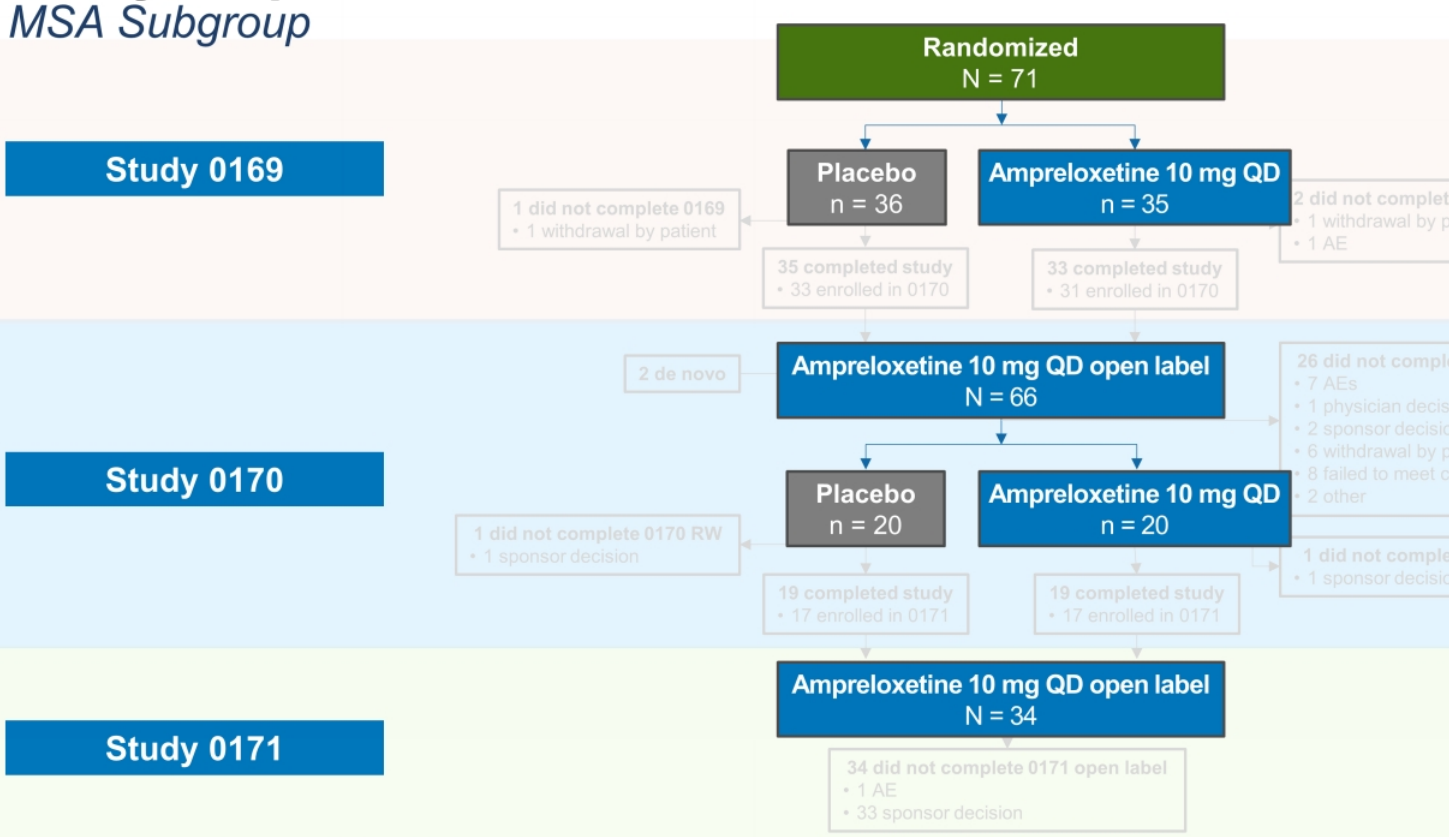
MSA Subgroup



AE, adverse event; MSA, multiple system atrophy; QD, once daily; RW, randomized withdrawal.

Study Disposition

MSA Subgroup



AE, adverse event; MSA, multiple system atrophy; QD, once daily; RW, randomized withdrawal.

Baseline Demographics and Clinical Characteristics
MSA Subgroup

	Study 0169			Study 0170 RW peri	
	Placebo (n = 33)	Ampreloxetine (n = 34)	Total (N = 67)	Placebo (n = 20)	Ampreloxetine (n = 20)
Male, n (%)	20 (60.6)	15 (44.1)	35 (52.2)	13 (65.0)	8 (40.0)
White, n (%)	31 (93.9)	32 (94.1)	63 (94.0)	19 (95.0)	17 (85.0)
Age, years	63.7 (9.6)	63.3 (8.5)	63.5 (9.0)	62.6 (6.7)	63.6 (9.0)
OHSA #1 score	6.6 (1.5)	6.7 (1.6)	6.6 (1.6)	3.2 (2.1)	2.8 (2.2)
OHSA composite score	5.3 (1.6)	5.4 (1.8)	5.3 (1.7)	2.8 (1.8)	2.6 (1.9)
OHDAS composite score	6.4 (2.0)	6.4 (2.5)	6.4 (2.2)	4.8 (2.3)	3.9 (2.4)
OHQ composite score	5.8 (1.6)	5.8 (2.0)	5.8 (1.8)	3.8 (1.7)	3.3 (2.0)
10-min supine SBP, mmHg	142.9 (22.8)	141.2 (20.1)	142.1 (21.3)	136.0 (19.5)	141.4 (23.4)
3-min standing SBP, mmHg	102.0 (27.0)	96.8 (23.0)	99.4 (25.0)	106.6 (18.1)	102.7 (21.6)

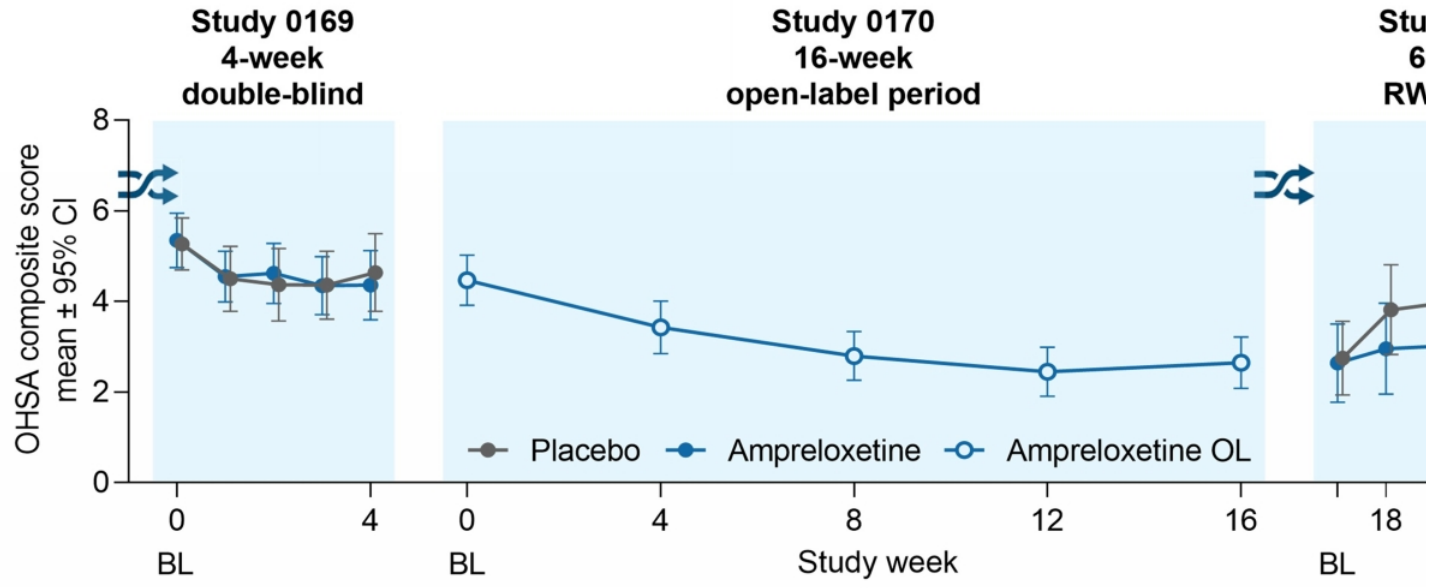
Data are presented as mean (SD) unless otherwise indicated.

- Demographic and clinical characteristics were generally well balanced across treatment group

[a]All 40 randomized patients in Study 0170 originated from Study 0169.
MSA, multiple system atrophy; OHDAS, Orthostatic Hypotension Daily Activity Scale; OHQ, Orthostatic Hypotension Questionnaire; OHSA, Orthostatic Hypotension Symptom Assessment; OHSA #1, OHSA item 1; RW, randomized withdrawal; SBP, systolic blood pressure; SD, standard deviation.

Ampreloxetine Improved OHSA Composite Score Ove and Maintained Effect During RW in Patients With MS

OHSA composite score

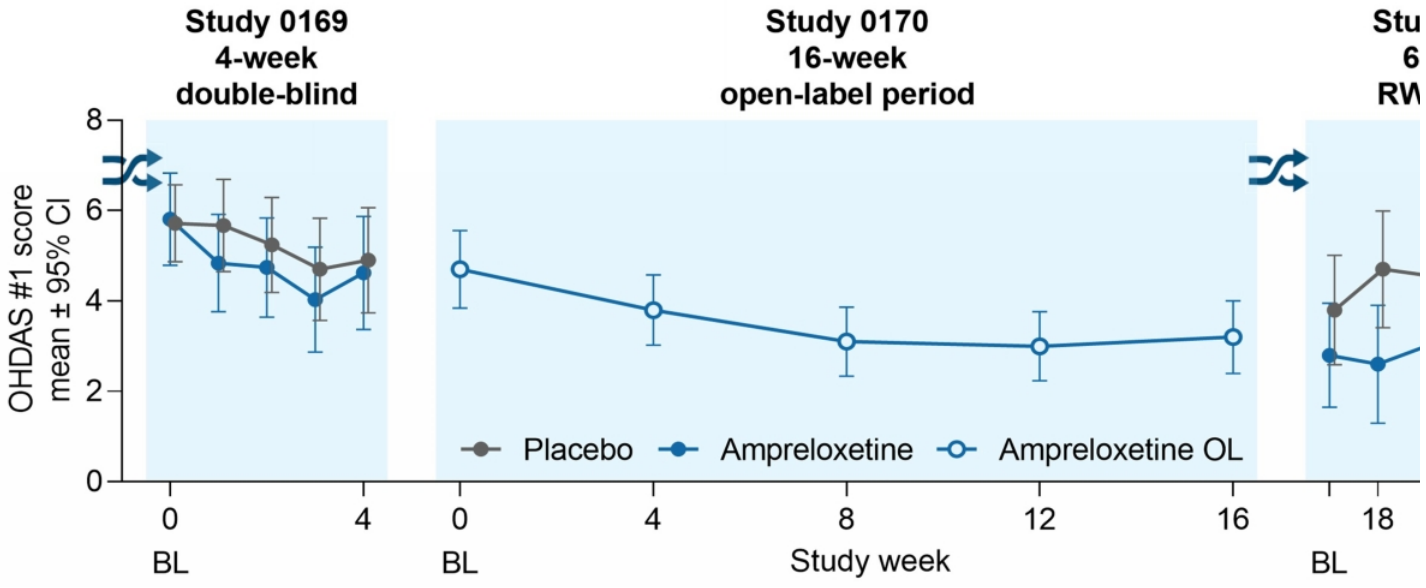


Placebo, n =	33	31			20	
Ampreloxetine, n =	34	32	64	42	20	

BL, baseline; CI, confidence interval; MSA, multiple system atrophy; OHSA, Orthostatic Hypotension Symptom Assessment; OL, open label; RW, randomized withdrawal.

Ampreloxetine Improved OHDAS #1 Score Over Time a Maintained Effect During RW in Patients With MSA

OHDAS #1: Standing short time



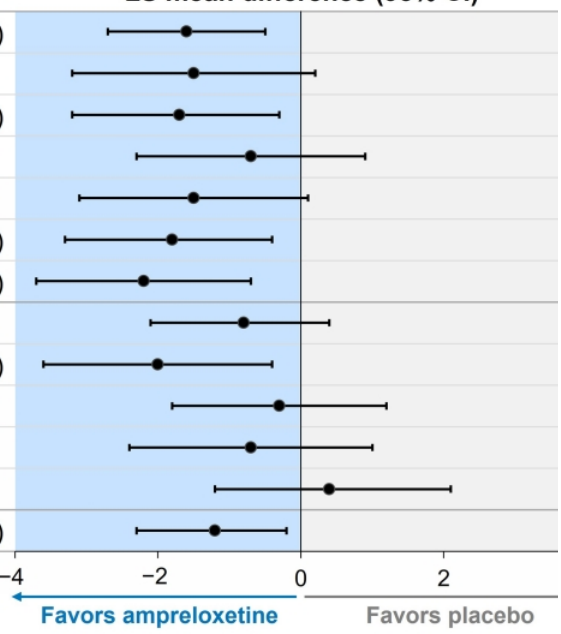
Placebo, n =	32	30			19	
Ampreloxetine, n =	32	29	60	41	20	

BL, baseline; CI, confidence interval; MSA, multiple system atrophy; OHDAS #1, Orthostatic Hypotension Daily Activity Scale item 1; OL, open label; RW, randomized withdrawal.

Individual Components of OHQ Demonstrate Benefits Ampreloxetine in MSA Subgroup

Randomized withdrawal period

		LS mean difference (95% CI)
OHSA	Symptom composite score	−1.6 (−2.7, −0.5)
	Dizziness	−1.5 (−3.2, 0.2)
	Vision	−1.7 (−3.2, −0.3)
	Weakness	−0.7 (−2.3, 0.9)
	Fatigue	−1.5 (−3.1, 0.1)
	Trouble concentrating	−1.8 (−3.3, −0.4)
	Head/neck discomfort	−2.2 (−3.7, −0.7)
OHDAS	Daily activities composite score	−0.8 (−2.1, 0.4)
	Standing short time	−2.0 (−3.6, −0.4)
	Standing long time	−0.3 (−1.8, 1.2)
	Walking short time	−0.7 (−2.4, 1.0)
	Walking long time	0.4 (−1.2, 2.1)
OHQ composite score		−1.2 (−2.3, −0.2)

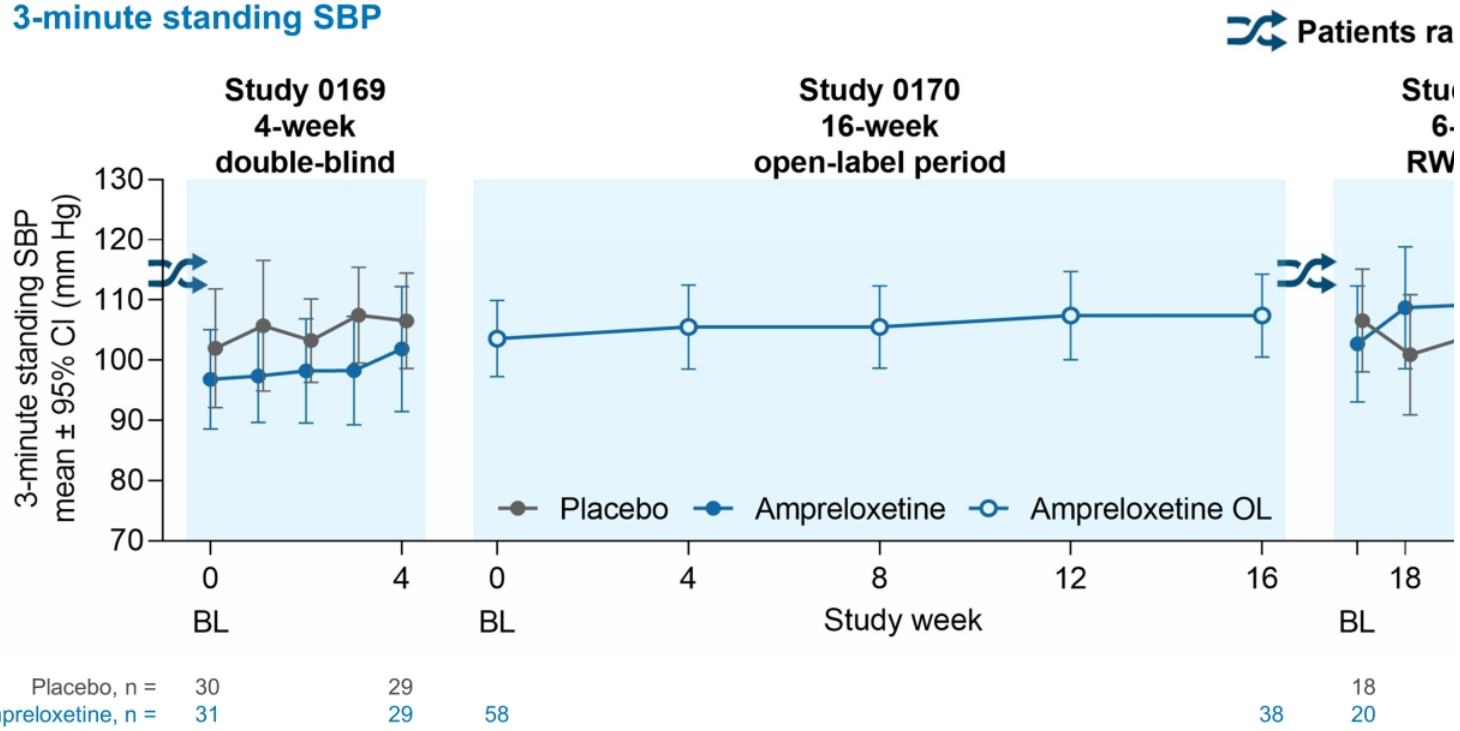


- Benefits observed in OHSA composite score and ability to stand for a short time

CI, confidence interval; LS, least-squares; MSA, multiple system atrophy; OHDAS, Orthostatic Hypotension Daily Activity Scale; OHQ, Orthostatic Hypotension Questionnaire; OHSA, Orthostatic Hypotension Symptom

Worsening in 3-Minute Standing SBP Was Observed Following Ampreloxetine Withdrawal in Patients With

3-minute standing SBP



Placebo, n =	30	29				18
Ampreloxetine, n =	31	29	58		38	20

BL, baseline; CI, confidence interval; BP, blood pressure; MSA, multiple system atrophy; OL, open label; RW, randomized withdrawal; SBP, systolic blood pressure.

Adverse Events During Randomized Controlled Phase

MSA Subgroup

	Study 0169		Study 0170 RW per	
	Placebo (n = 33)	Ampreloxetine (n = 35)	Placebo (n = 20)	Ampr (n
Any TEAEs	19 (57.6)	19 (54.3)	7 (35.0)	4
TEAEs related to study drug	5 (15.2)	5 (14.3)	1 (5.0)	1
SAEs	2 (6.1)	4 (11.4)	1 (5.0)	2
SAEs related to study drug	0	0	1 (5.0)	1
TEAEs leading to permanent study drug discontinuation	0	1 (2.9)	0	
Deaths during study	0	0	0	

All data are from the safety population and presented as n (%).
Ampreloxetine was administered at 10 mg once daily.
Patients are only counted once in each row.

- Overall, the AE profile was similar between placebo and ampreloxetine groups during the rand controlled phases

AE, adverse event; MSA, multiple system atrophy; RW, randomized withdrawal; SAE, serious AE; TEAE, treatment-emergent AE.

Conclusions

- Benefits of ampreloxetine were observed in patients with MSA, with consiste improvement in nOH symptoms over time
- Worsening of nOH symptoms and SBP was observed in patients with MSA u randomized withdrawal of ampreloxetine to placebo
  - Broad symptomatic impact across each OHSA component: dizziness, vision, weakness, fat concentrating, head/neck discomfort
- The safety profile of ampreloxetine was similar to that of placebo during rand controlled phases
- Patients with MSA may benefit from ampreloxetine treatment due to the pres central autonomic pathway degeneration and intact peripheral postganglionic

MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; OHSA, Orthostatic Hypotension Symptom Assessment; SBP, systolic blood pressure.

New Ampreloxetine Study in Patients With MSA

Phase 3 registrational study

Study 0197: 20 weeks

12-week, open-label; 8-week, randomized, double-blind, placebo-controlled, withdrawal

CYPRESS

An ampreloxetine study for MSA patients with nOH

Long-term extension

Study 0197: 2 years

Long-term, open-label

CYPRES

An ampreloxetine study for MSA patients with nO

- CYPRESS study initiation planned for first quarter of 2023

MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension.