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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

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Poster #117

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

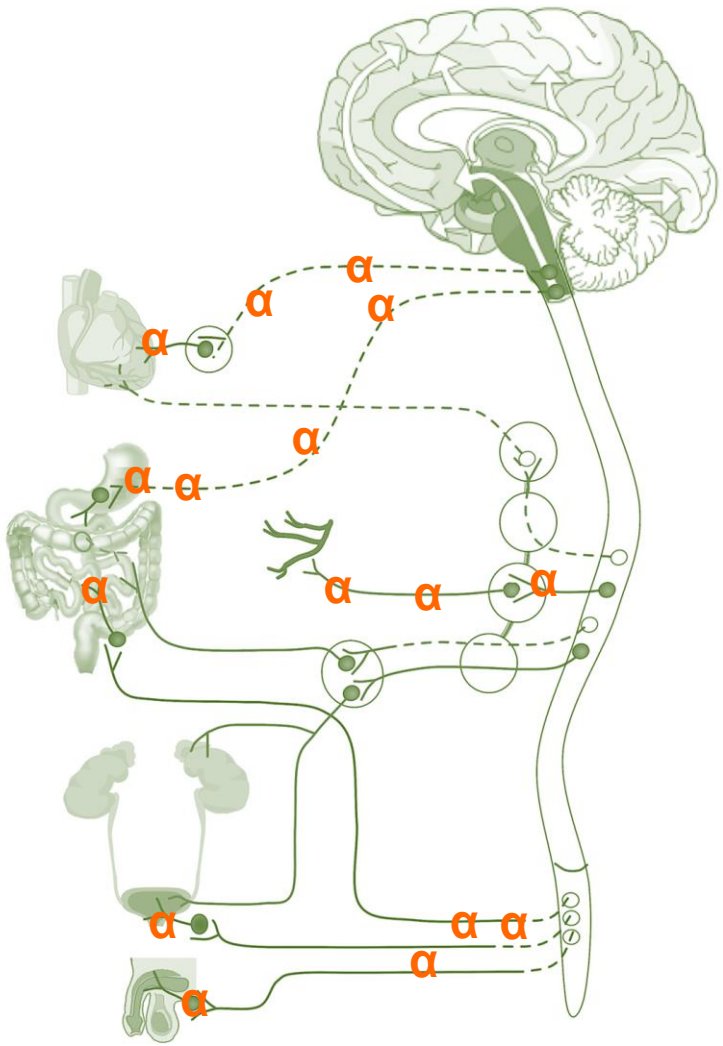
- Why ampreloxetine
- Clinical trials with ampreloxetine
- Phenotype with best ampreloxetine response

Neurogenic Orthostatic Hypotension (nOH)

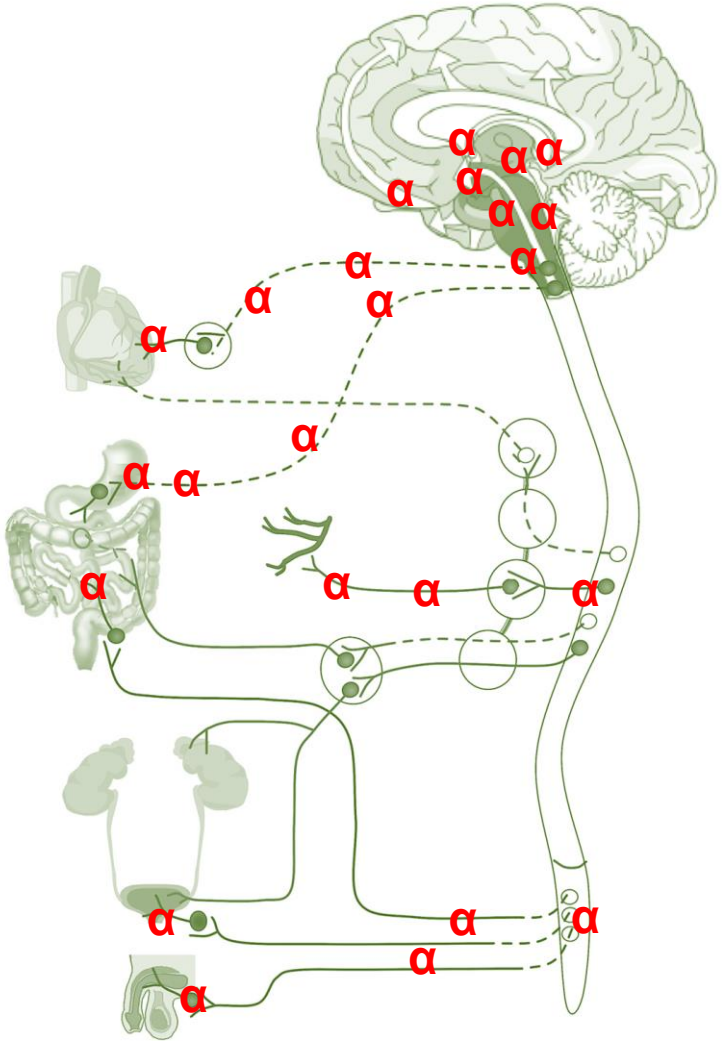
- nOH is a sustained fall in BP upon standing due to lack of activation of the sympathetic postganglionic neurons innervating the vasculature and controlled by the baroreflex

BP, blood pressure.

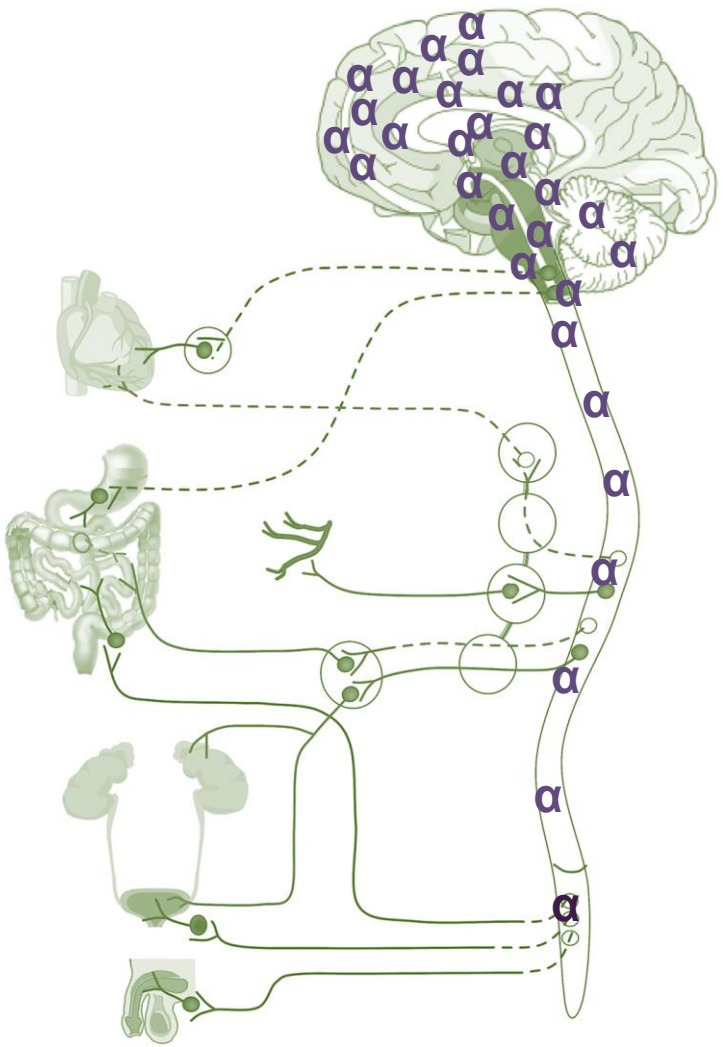
Pure autonomic failure



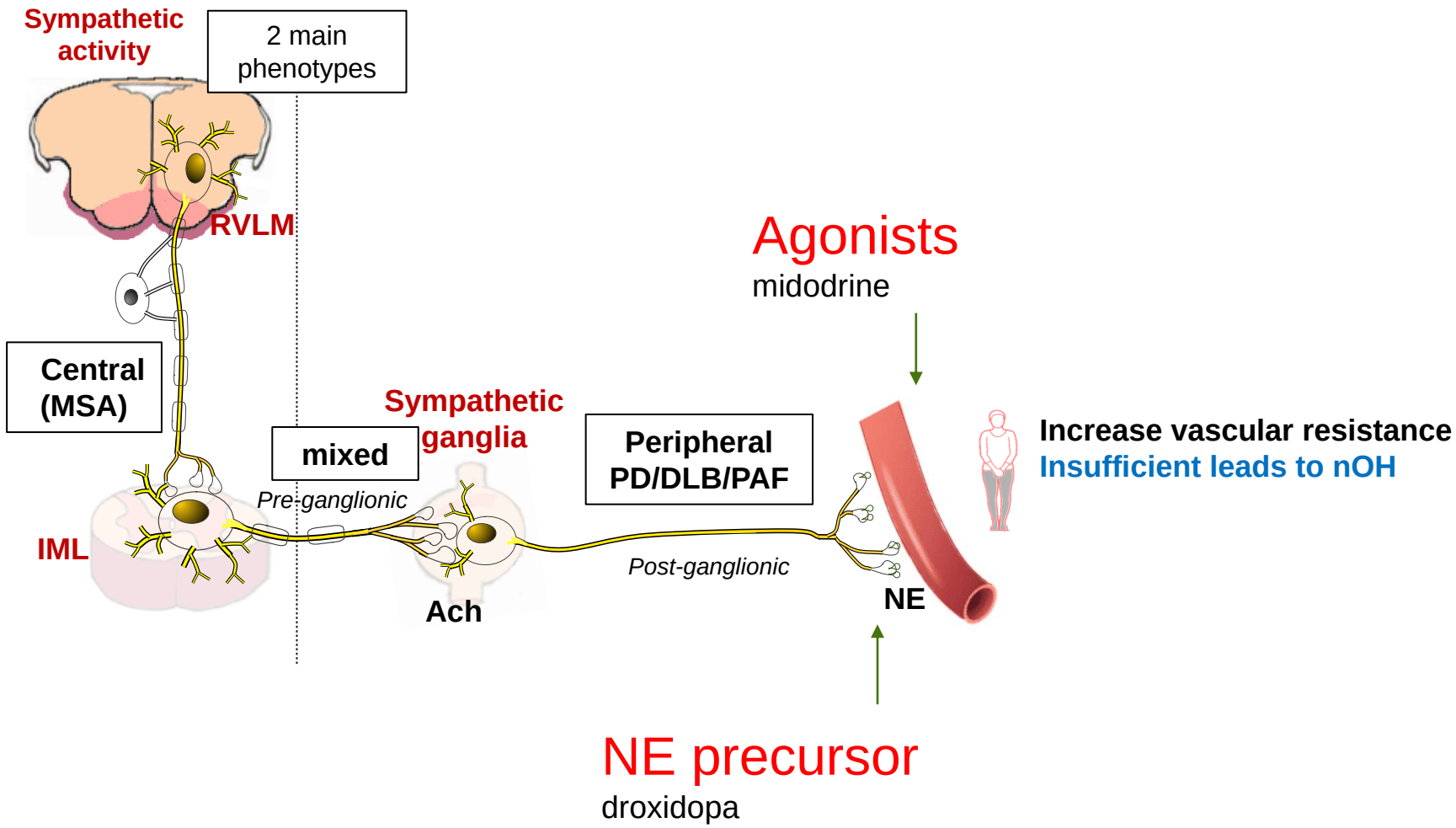
Parkinson's disease



Multiple system atrophy



Control of Sympathetic Activity to the Peripheral Vasculature

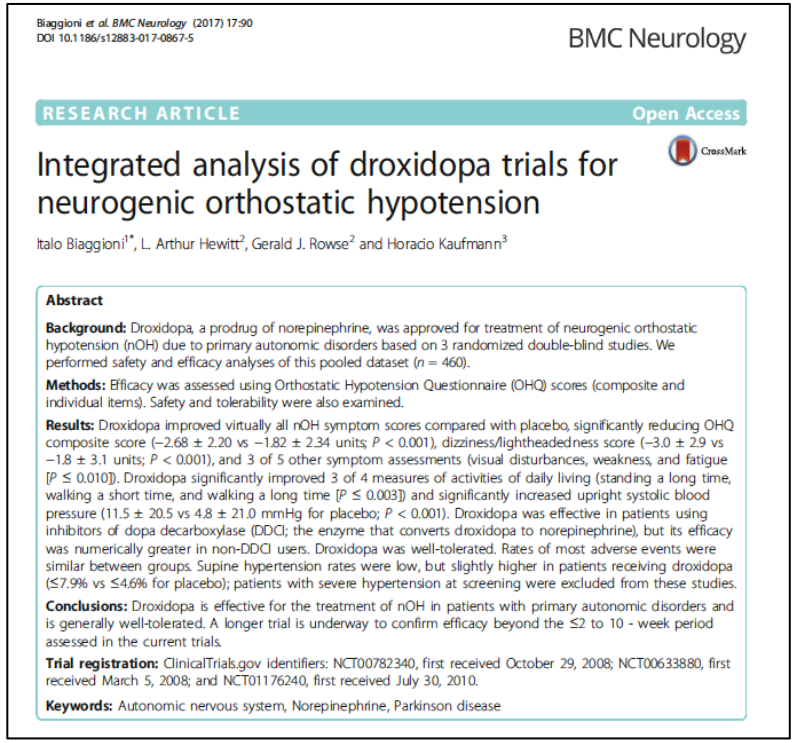


Ach, acetylcholine; DLB, dementia with Lewy bodies; IML, intermediolateral cell column; MSA, multiple system atrophy; NE, norepinephrine; nOH, neurogenic orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson's disease; RVLM, rostral ventrolateral medulla.

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.



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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.

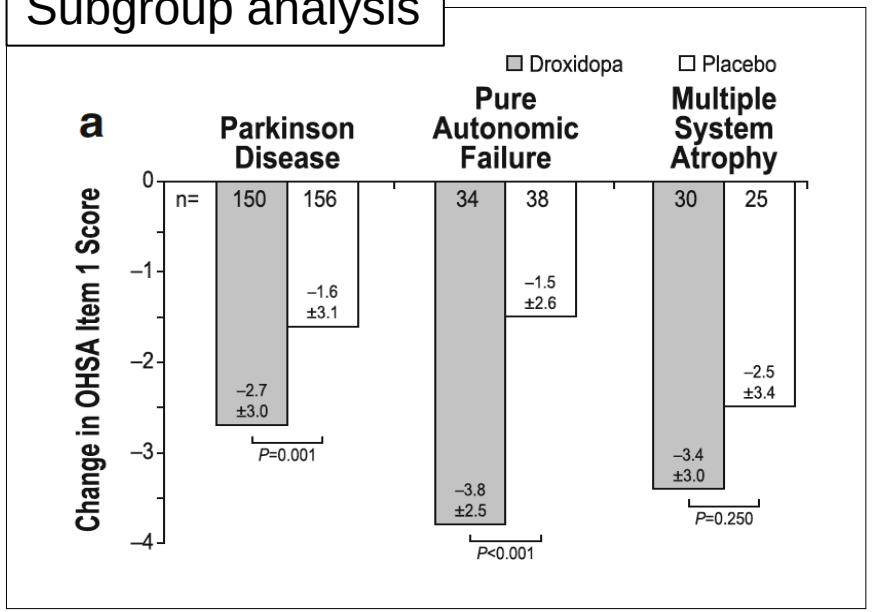
Results: Droxidopa improved virtually all nOH symptom scores compared with placebo, significantly reducing OHQ composite score (−2.68 ± 2.20 vs −1.82 ± 2.34 units; $P < 0.001$), dizziness/lightheadedness score (−3.0 ± 2.9 vs −1.8 ± 3.1 units; $P < 0.001$), and 3 of 5 other symptom assessments (visual 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 (DDCI; 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

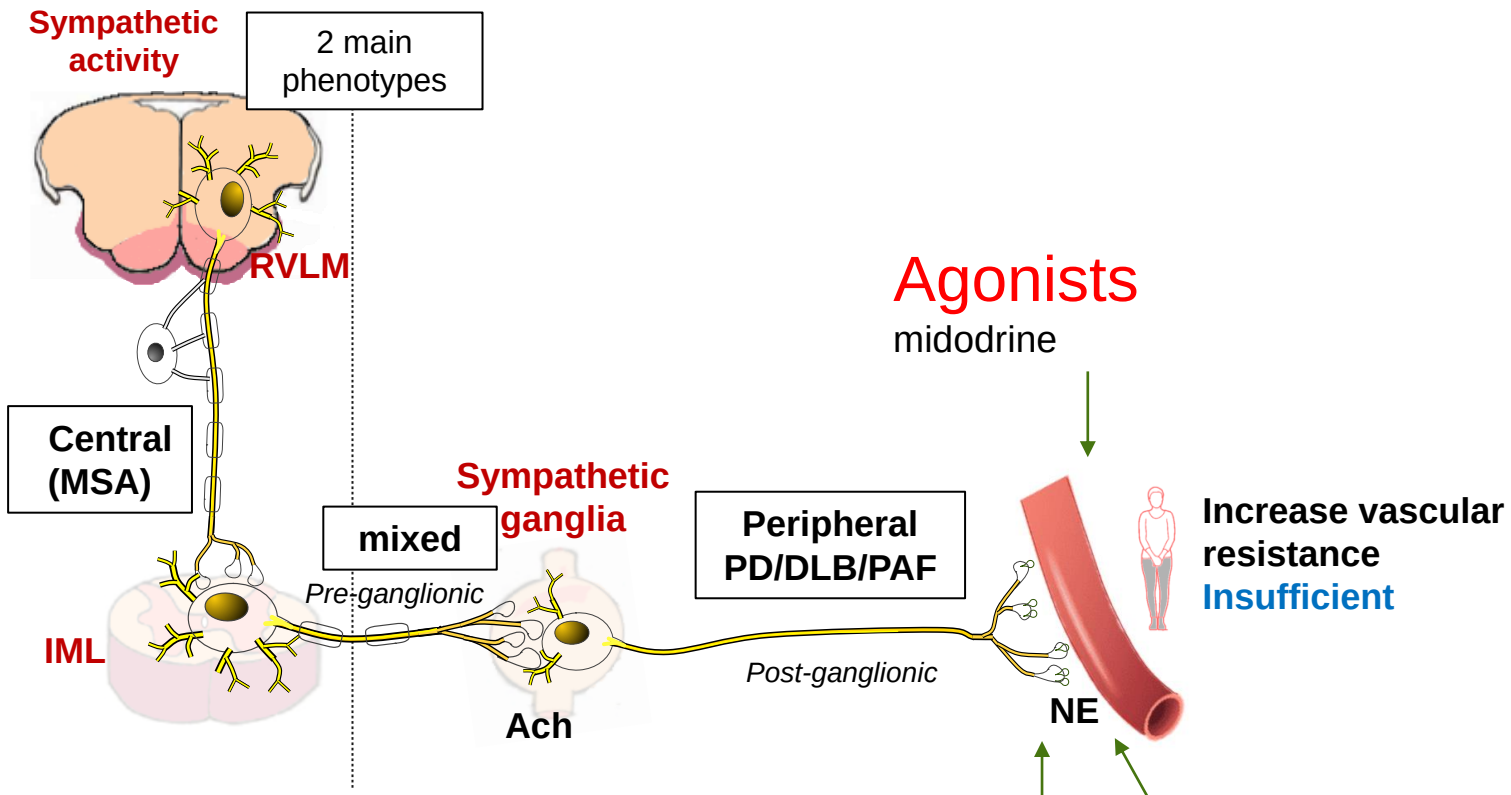


What determines the response to treatment?

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

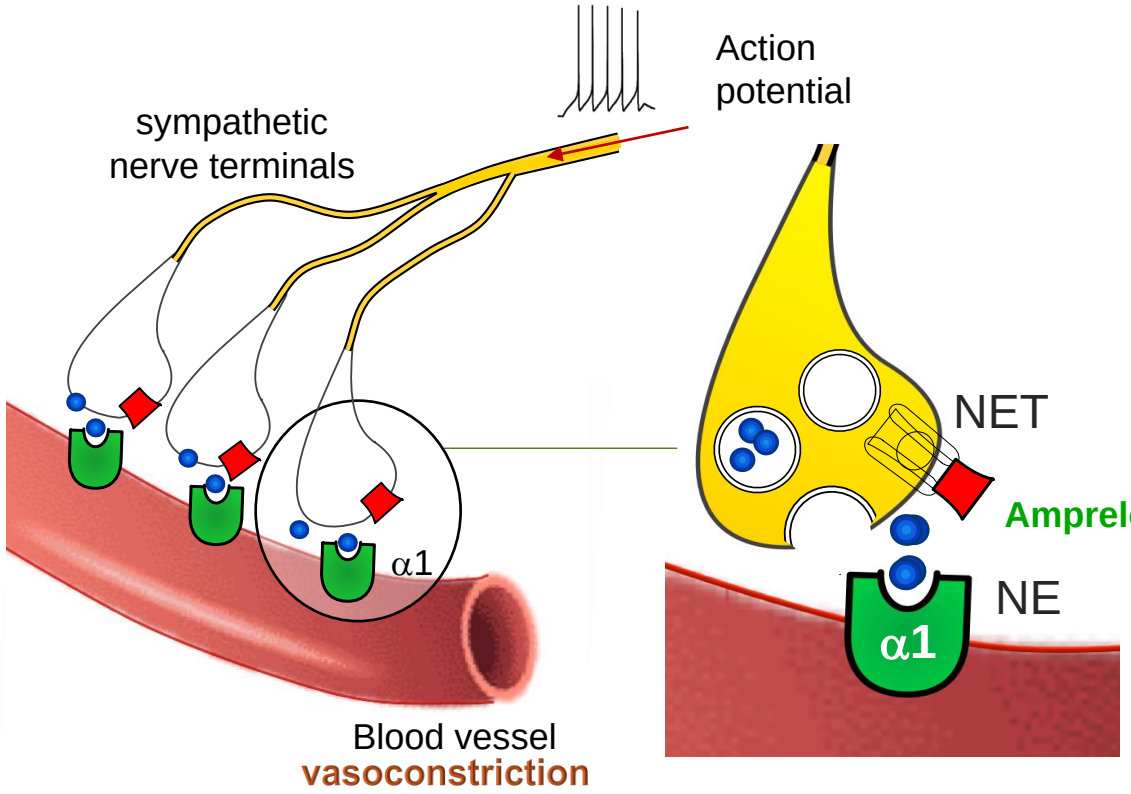
MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; OHSA, Orthostatic Hypotension Symptom Assessment.

Control of Sympathetic Activity to the Peripheral Vasculature



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 ventrolateral medulla.

Ampreloxetine: A Novel Pharmacological Strategy in nOH

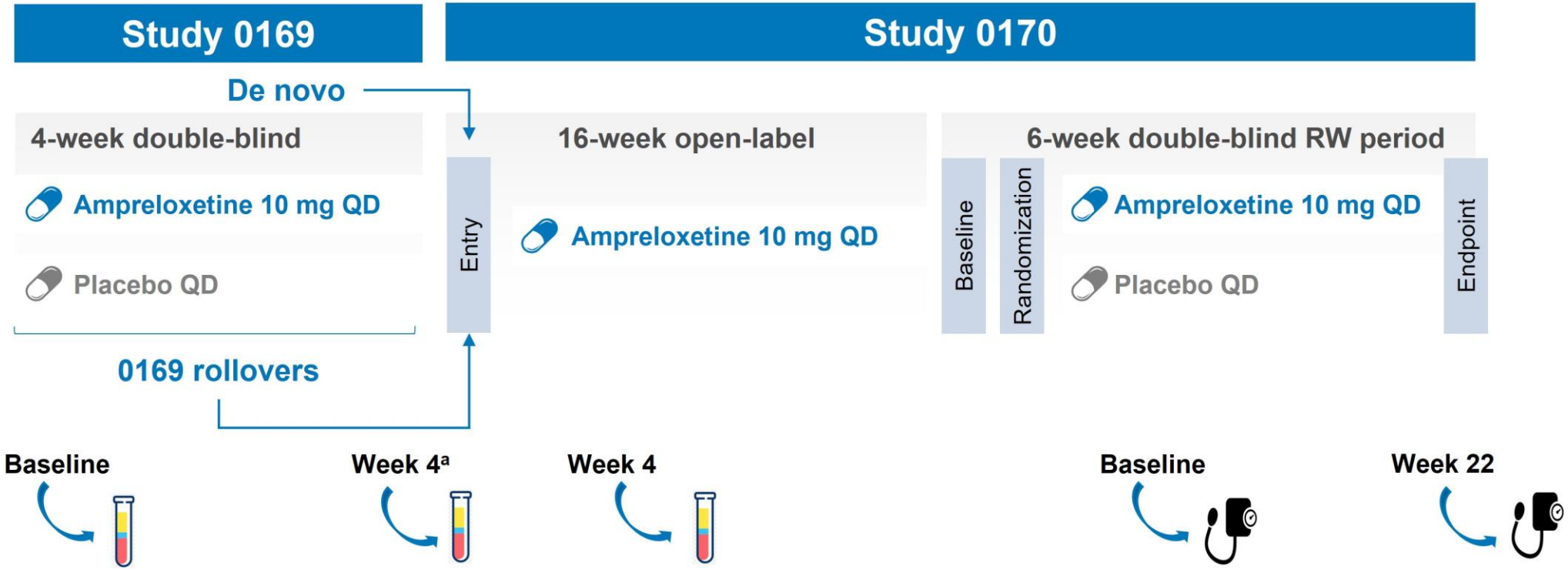


NE reuptake inhibition in nOH

- 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



Ampreloxetine 10 mg QD

Placebo QD

BP

Plasma NE, DHPG

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

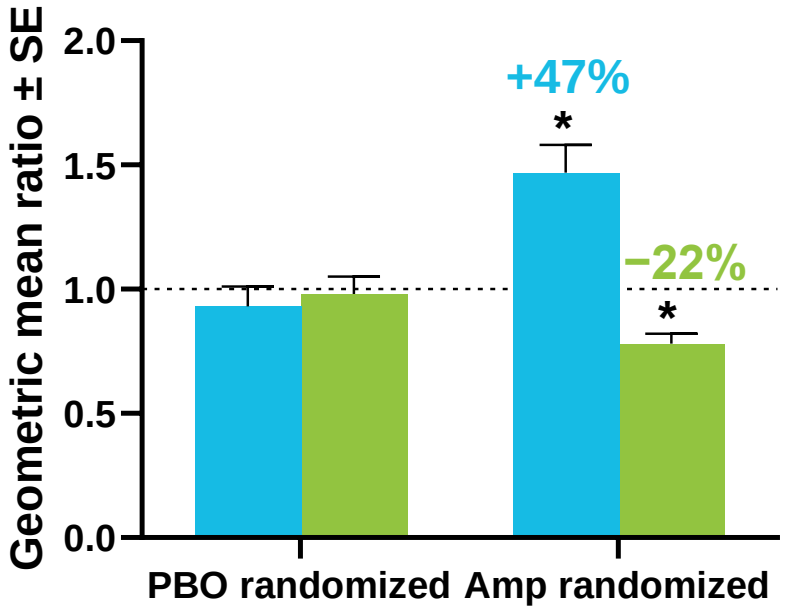
Study 0170
- Compliant with Study 0169 *or*
- De novo per same criteria as Study 0169

[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 a supine position as 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; PAF, pure autonomic failure; PD, Parkinson's disease; QD, once daily; RW, randomized withdrawal.

Ampreloxetine Elevates Plasma NE Levels in Patients With nOH

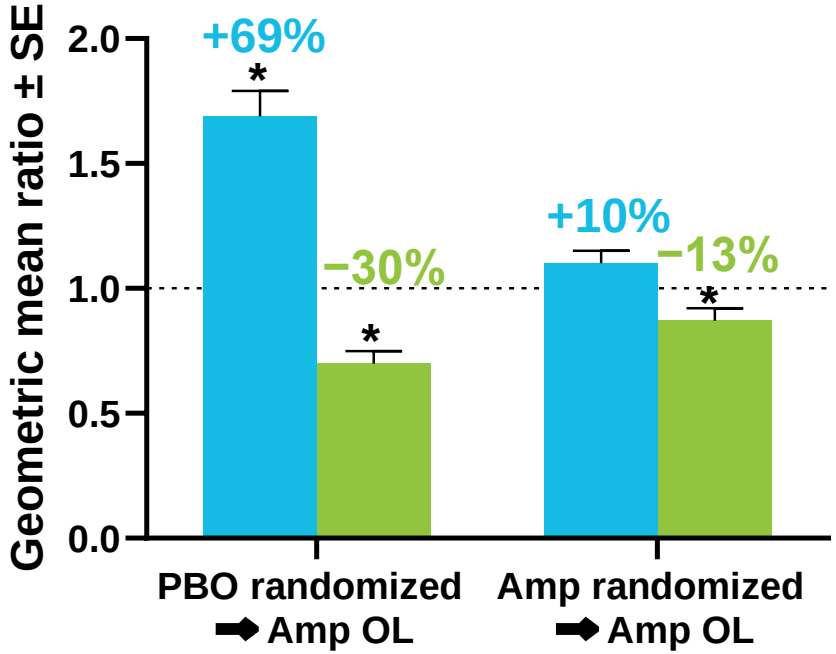
4 Weeks

(after 4 weeks randomized treatment)



8 Weeks

(after 4 weeks randomized treatment + 4 weeks open-label ampreloxetine)

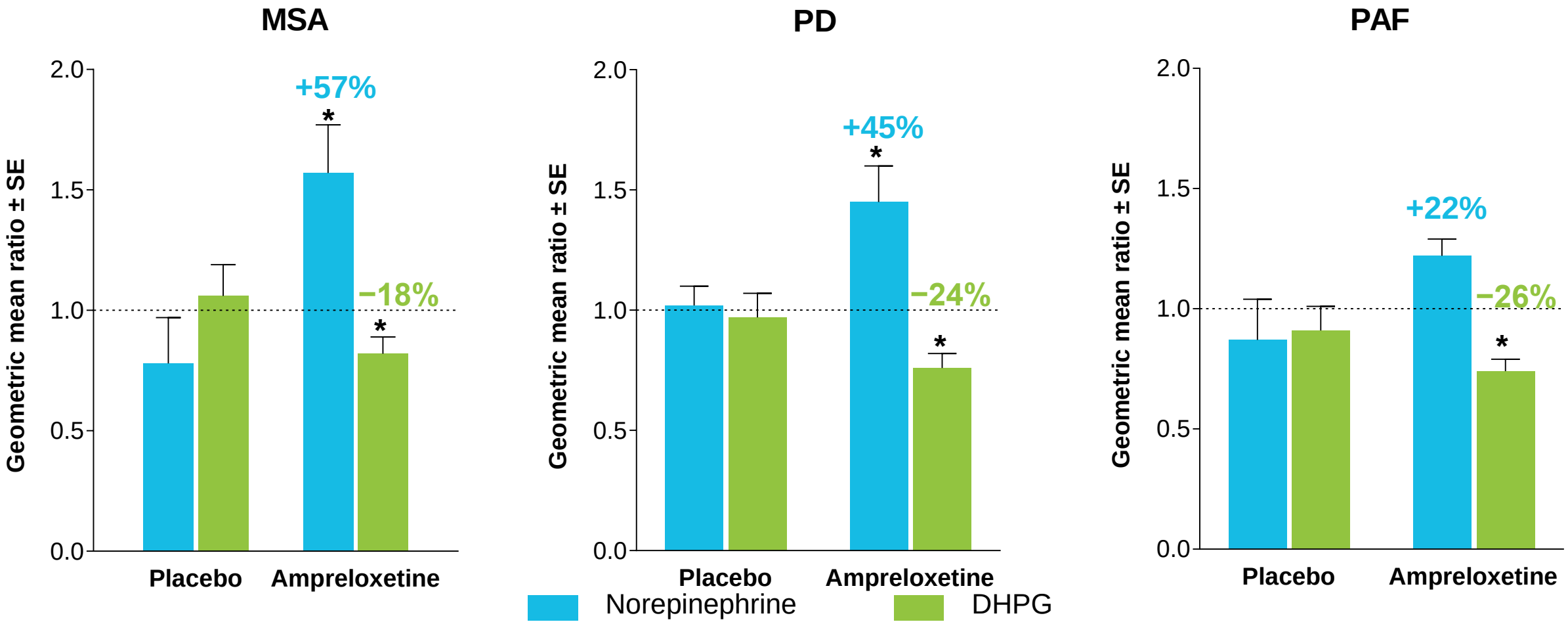


Norepinephrine DHPG

*P<0.05.

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

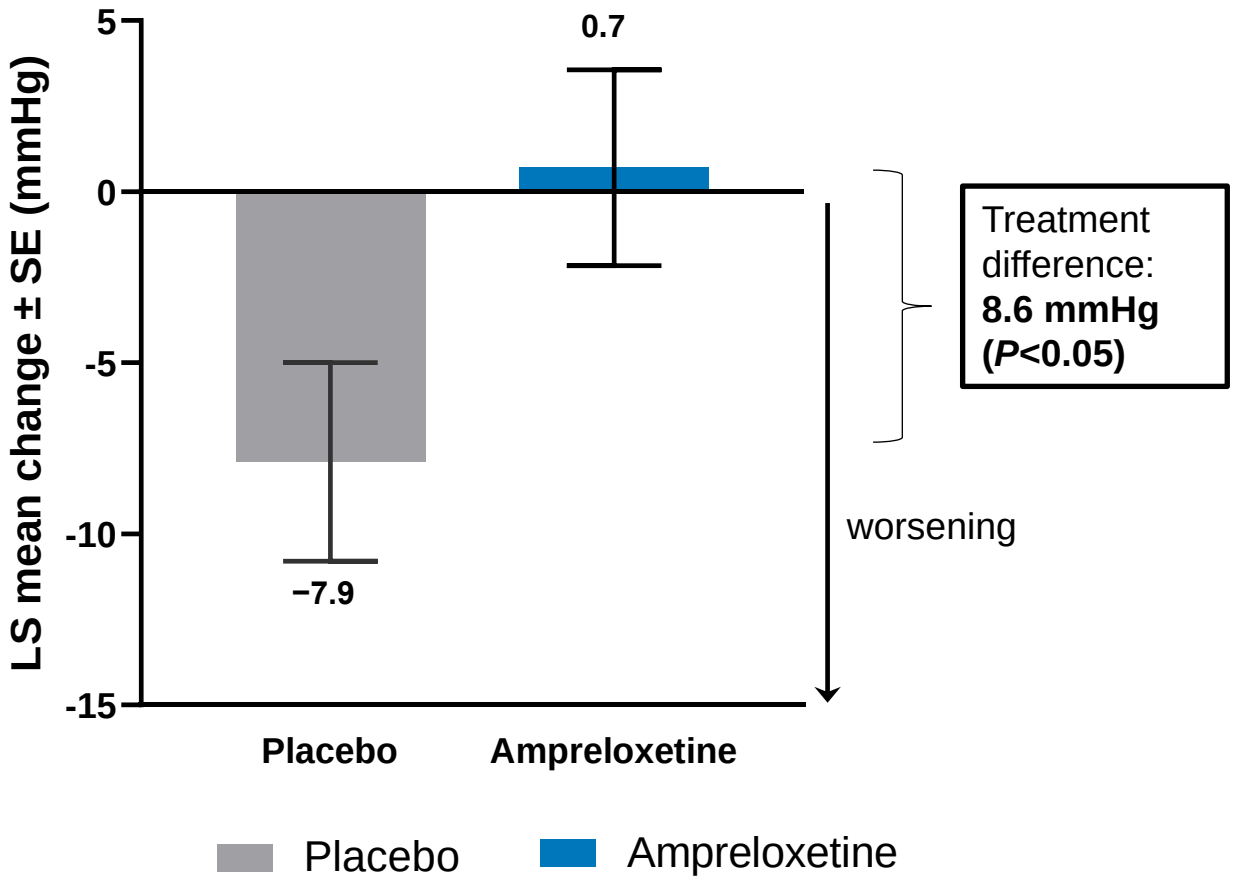
Greatest Improvements in Plasma NE Were Seen in Patients With MSA



*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.

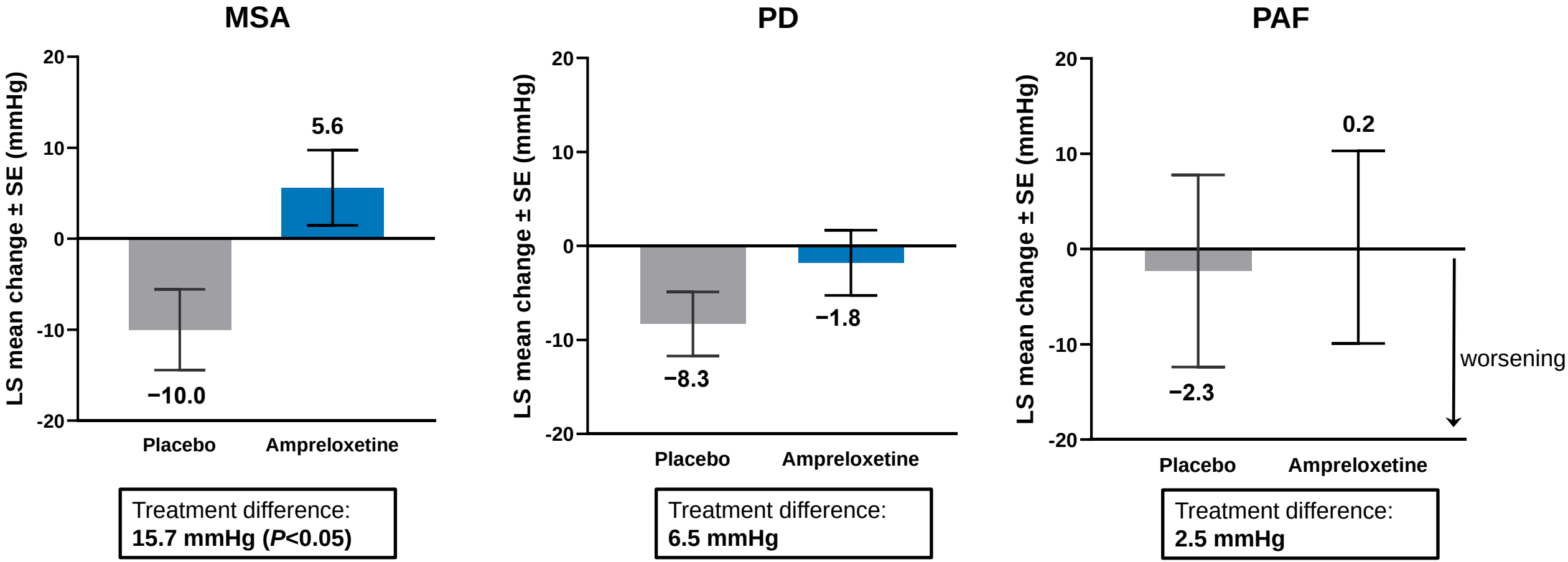
Patients Randomized to Placebo During the Withdrawal Period Had Worsening 3-Minute Standing SBP



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

The Effect of Ampreloxetine Treatment on 3-Minute Standing 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 NE metabolism (DHPG)
- Increases in standing BP after randomized withdrawal were most pronounced in patients with MSA
- Increasing bioavailability of NE with ampreloxetine may be particularly beneficial in patients with 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

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Poster #106

Presenting Author Disclosure

Dr. Italo Biaggioni reports the following conflicts of interest:

Related to this presentation:

- Theravance Biopharma: Consultant and institutional clinical trial support

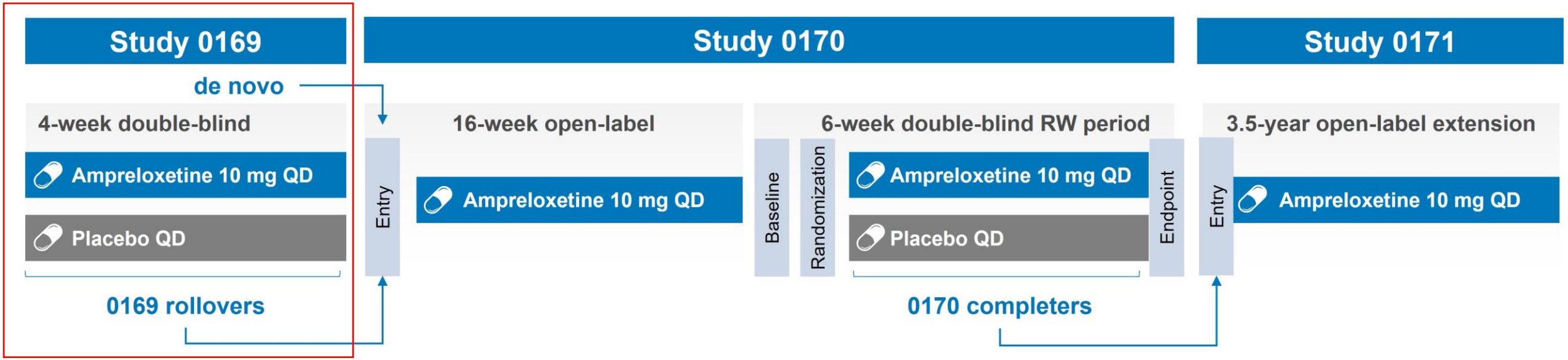
Unrelated to this presentation:

- 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



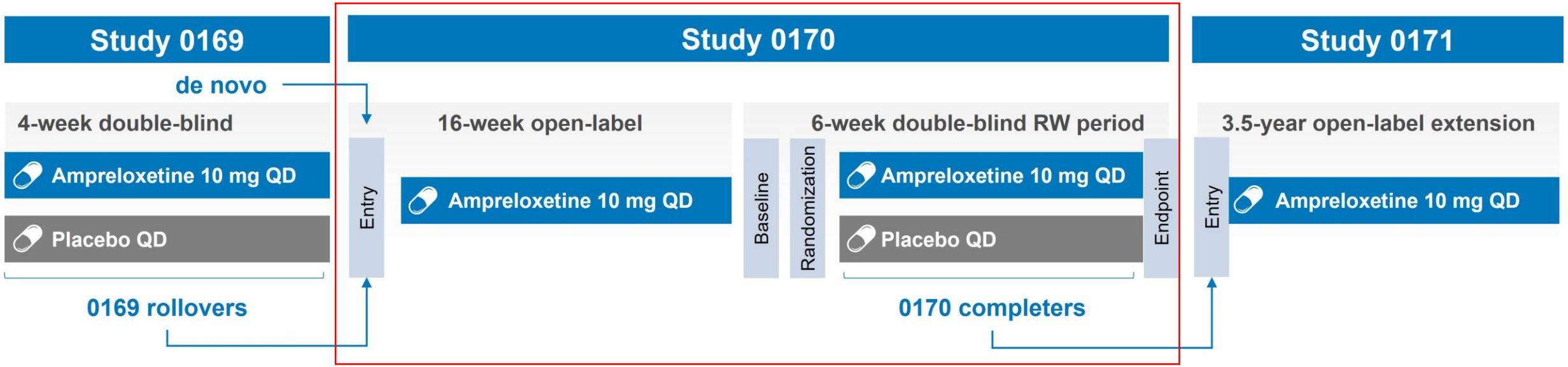
Study 0169 did not meet the primary endpoint based on reduction in OHSA#1

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; PAF, pure autonomic 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

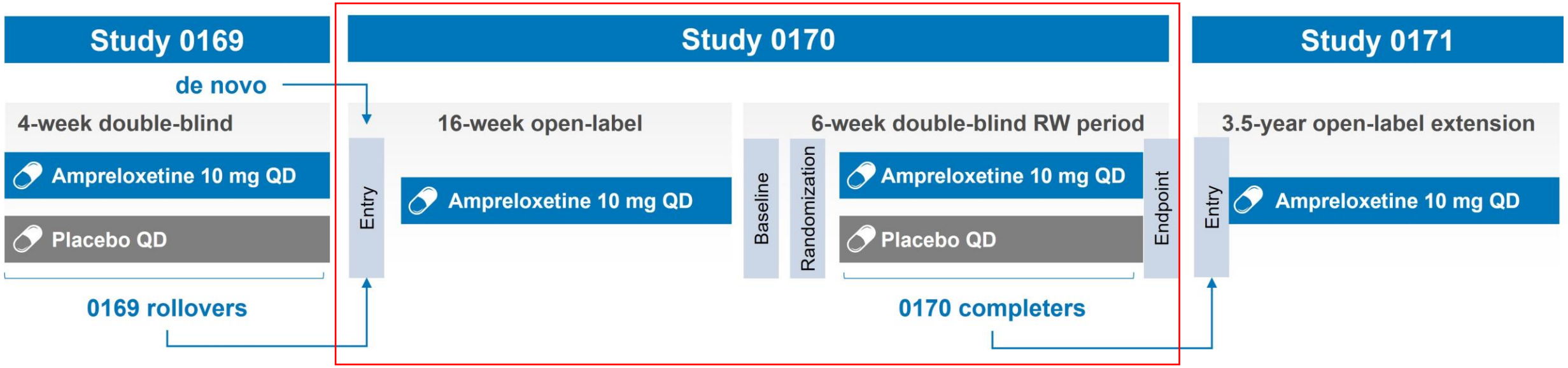
Treatment failure:
Worsening from baseline of both OHSA #1 (≥1 point) and PGI-S (≥1 point)

Key Secondary

Change from baseline in:
- OHSA #1
- OHSA composite score
- OHDAS composite score
- PGI-S

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; PAF, pure autonomic failure; PD, Parkinson's disease; PGI-S, Patient Global Impression of Severity; QD, once daily; RW, randomized withdrawal.

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)	Total (N = 128)
Male, n (%)	49 (76.6)	42 (65.6)	91 (71.1)
Age, mean ± SD, years	68.2 ± 8.1	67.5 ± 8.6	67.9 ± 8.3
White, n (%)	63 (98.4)	61 (95.3)	124 (96.9)
BMI, mean ± SD, kg/m^2	25.9 ± 4.7	25.4 ± 4.3	25.7 ± 4.5
Primary neurological diagnosis, n (%)			
MSA	20 (31.3)	20 (31.3)	40 (31.3)
PD	34 (53.1)	34 (53.1)	68 (53.1)
PAF	10 (15.6)	10 (15.6)	20 (15.6)
OHSA #1, mean ± SD	2.5 ± 1.8	3.1 ± 2.0	2.8 ± 1.9
OHSA #1 <4, n (%)	43 (67.2)	35 (54.7)	78 (60.9)
OHSA composite score, mean ± SD	2.2 ± 1.5	2.7 ± 1.7	2.4 ± 1.7
OHDAS composite score, mean ± SD	3.4 ± 2.3	3.3 ± 2.4	3.3 ± 2.4
PGI-S score, mean ± SD	2.4 ± 0.9	2.4 ± 0.8	2.4 ± 0.8

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 failure; PD, Parkinson's disease; PGI-S, Patient Global Impression of Severity; SD, standard deviation.

Study Disposition

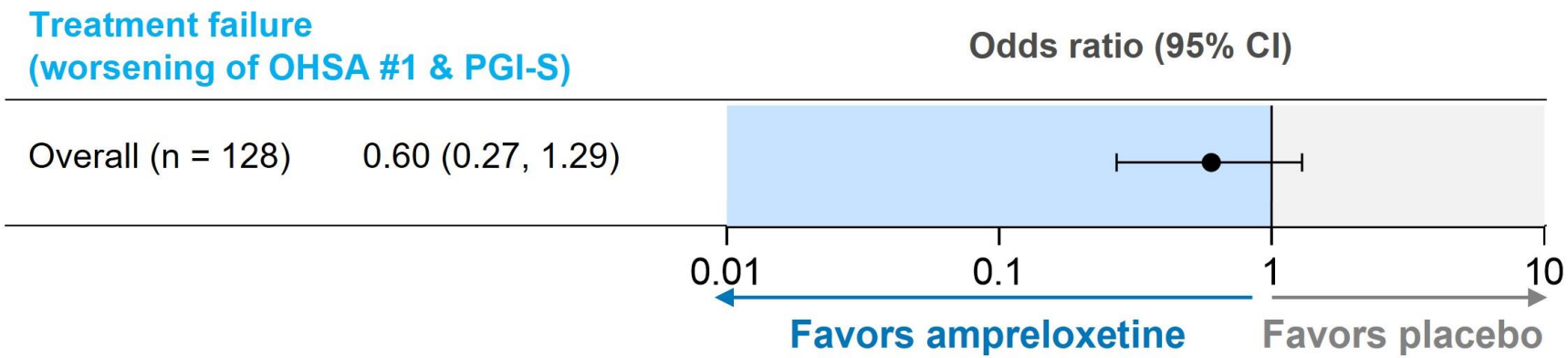
Randomized Withdrawal Period

	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 withdrawal)

Randomized Withdrawal Period

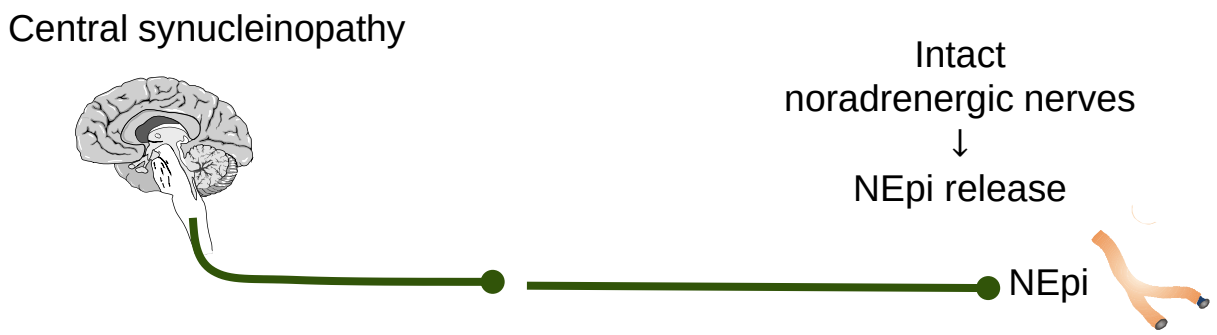


- Primary endpoint of reduction in treatment failure was not met
- …but, we had a **pre-specified** subgroup analysis planned based on diagnosis

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 Diagnosis

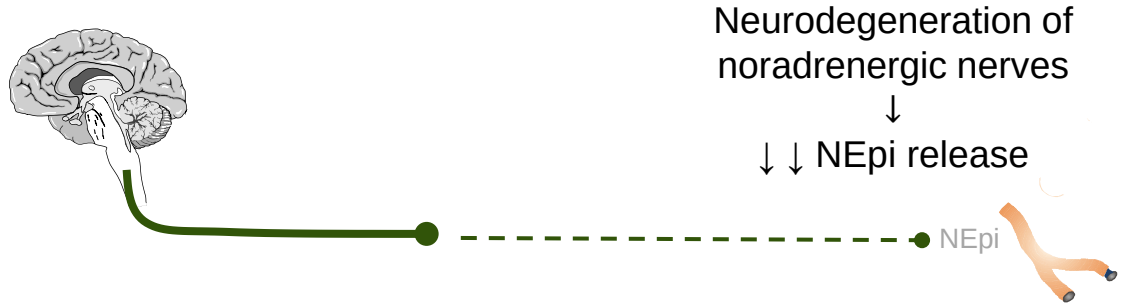
- NET inhibition with ampreloxetine potentiates **endogenously-released norepinephrine**
- **MSA**



Potentiation by NET Inhibition

✓

- **PAF/PD**



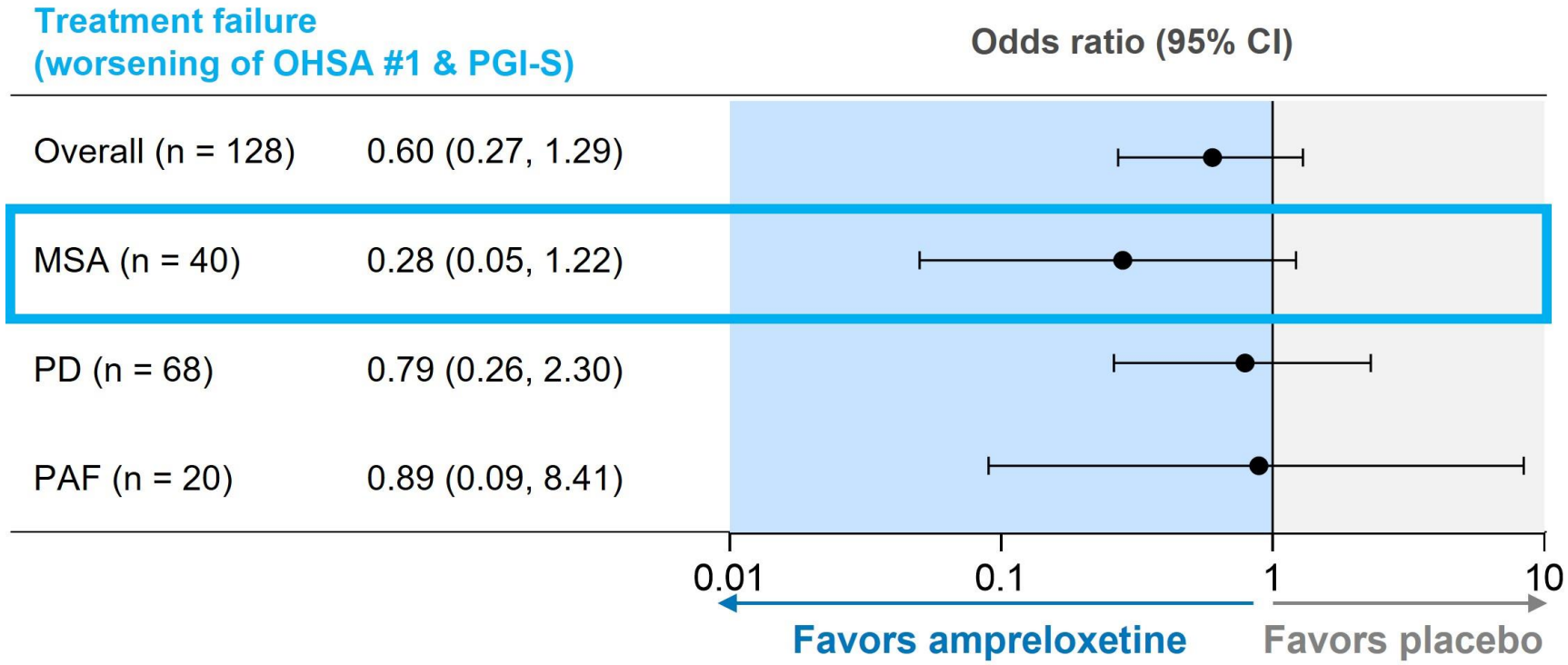
X

- ➔ 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 withdrawal)

Randomized Withdrawal Period

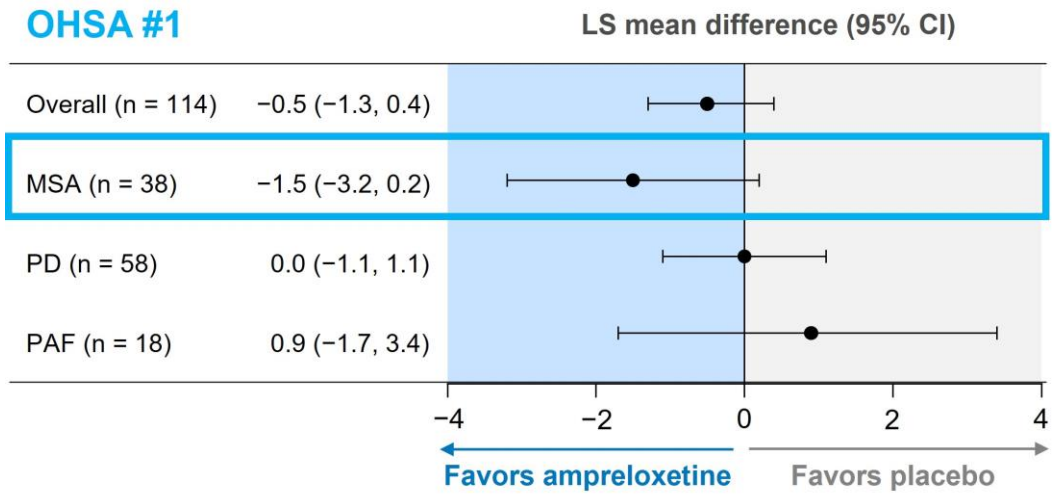


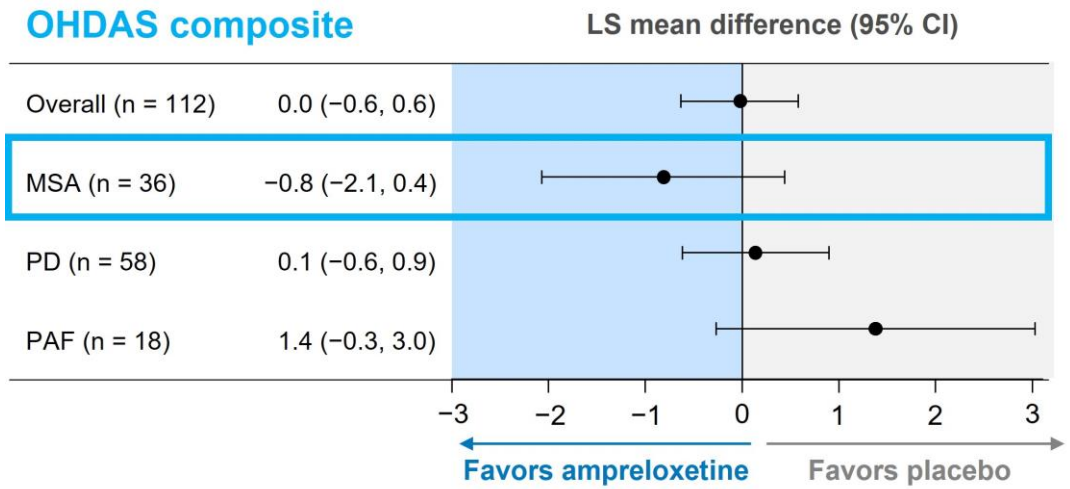
- Trend for benefit was observed in the MSA subpopulation based on prespecified subgroup analyses

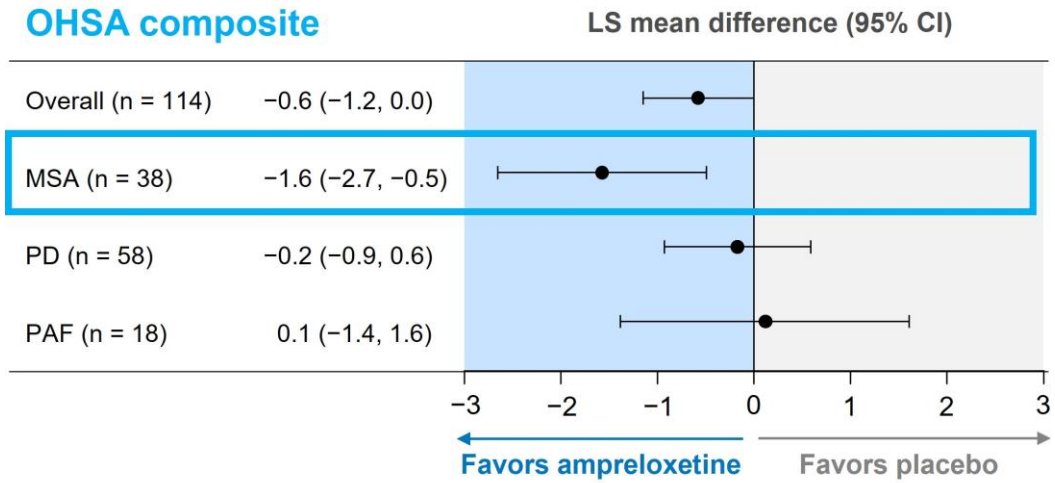
The logistic regression model for treatment failure included terms for treatment, baseline OHSA #1, baseline PGI-S, and disease type (MSA, PAF, or PD). Profile-likelihood CI is shown.
CI, confidence interval; MSA, multiple system atrophy; OHSA #1, Orthostatic Hypotension Symptom Assessment item 1; PAF,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

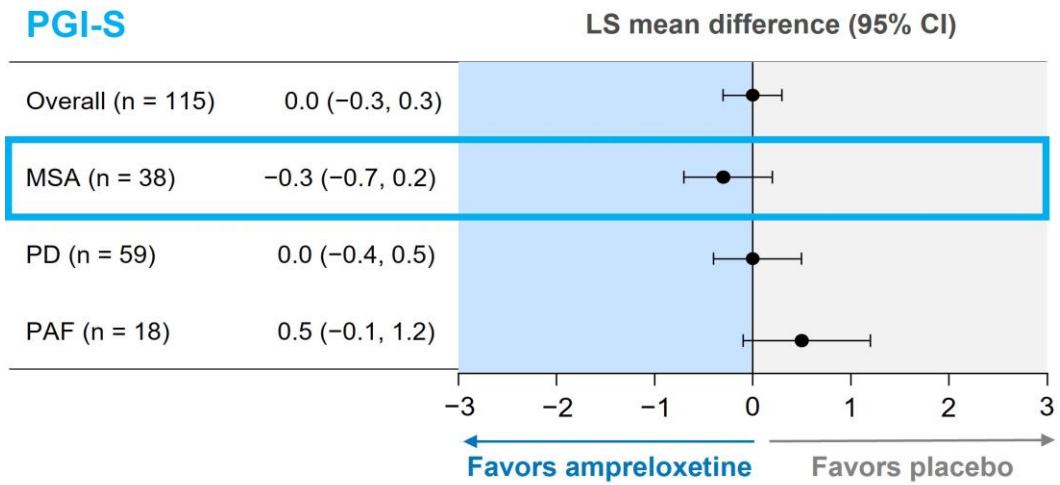
Key Secondary Endpoints: Trend for Benefit in MSA Subgroup

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, pure autonomic failure; 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 monitoring, 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 endpoints in the prespecified MSA subgroup
- Ampreloxetine was generally well tolerated
- These results encouraged us to perform a longitudinal analysis in the subset of patients with MSA

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

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

MSA, multiple system atrophy.

AMERICAN AUTONOMIC SOCIETY

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Poster #4

Presenting Author Disclosure

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

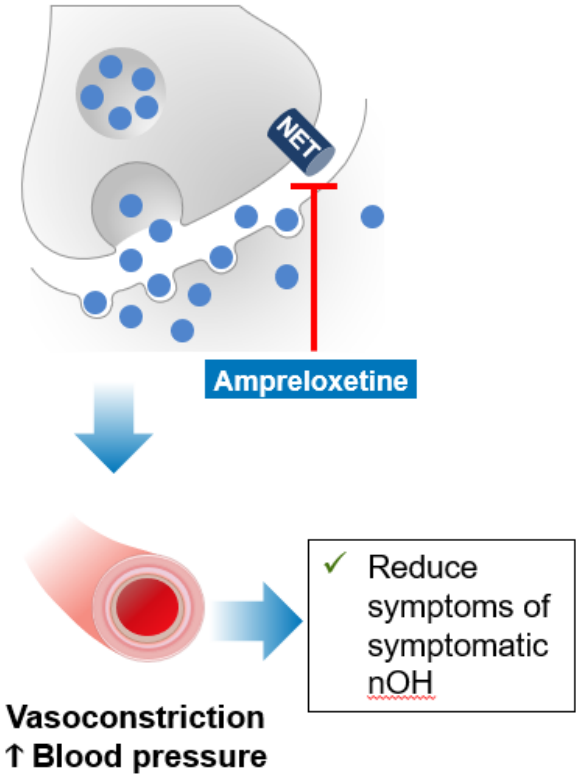
Ampreloxetine Phase 3 Program Results

- Ampreloxetine failed to meet its primary endpoint in two pivotal trials for the treatment of nOH in patients with MSA, PD, and PAF
- However, a prespecified subgroup analysis by primary disease type suggested a consistent benefit for ampreloxetine over placebo in patients with MSA across multiple endpoints in a randomized withdrawal period
- These results prompted an in-depth analysis across Phase 3 clinical studies of all patients with 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 prespecified subgroup of patients with MSA

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

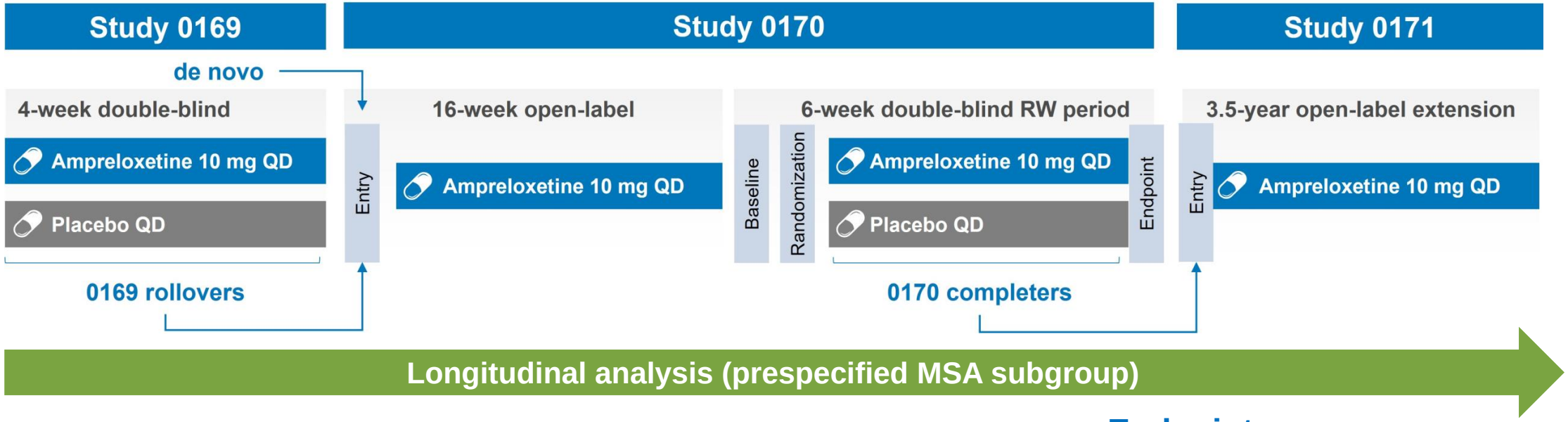
Neurogenic Orthostatic Hypotension in MSA and Ampreloxetine

- 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]



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 events

[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 of being tilted-up to ≥60° 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 Symptom Assessment item 1; OL, open-label; PAF, pure autonomic failure; PD, Parkinson's disease; QD, once daily; RW, randomized withdrawal; SBP, systolic blood pressure.

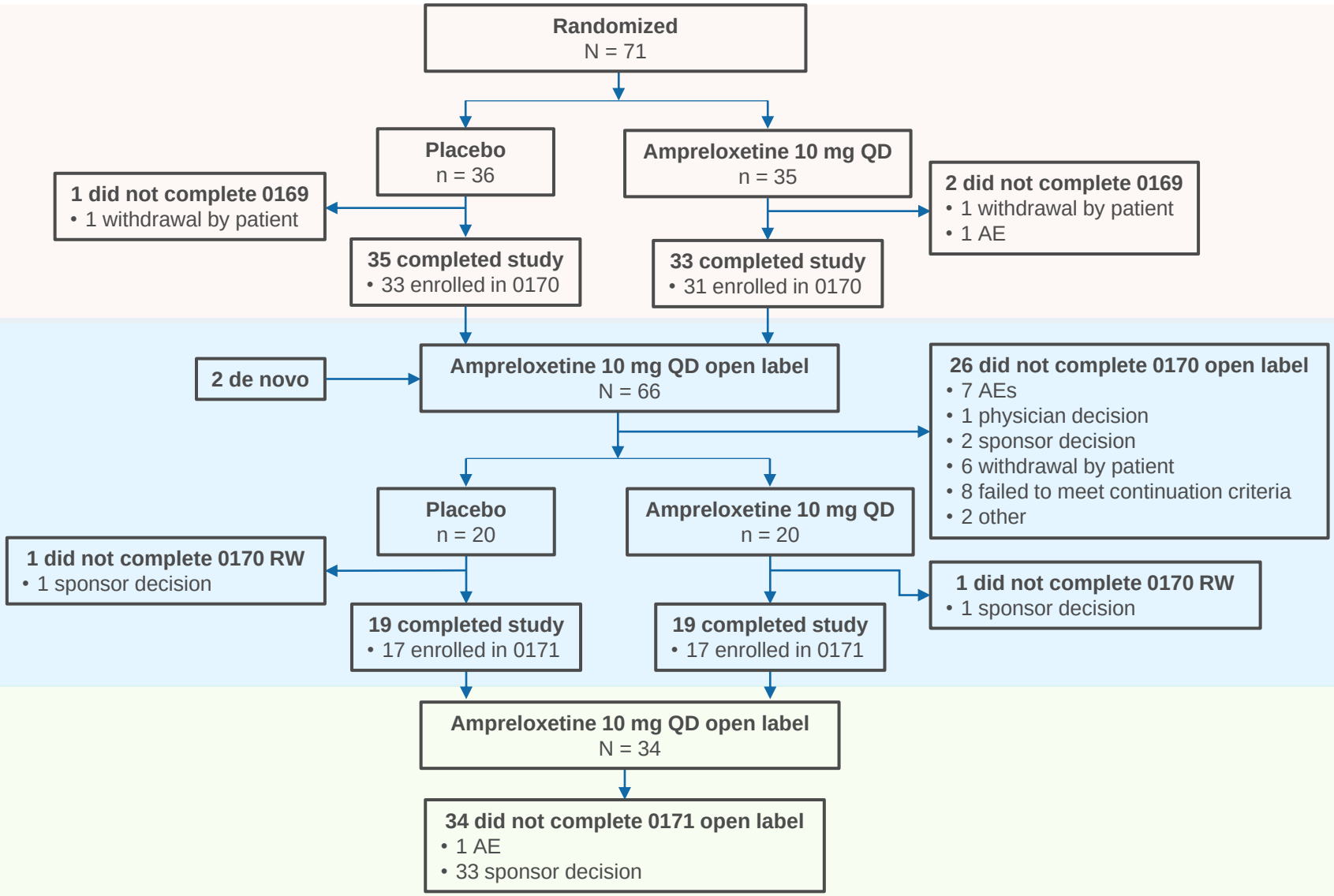
Study Disposition

MSA Subgroup

Study 0169

Study 0170

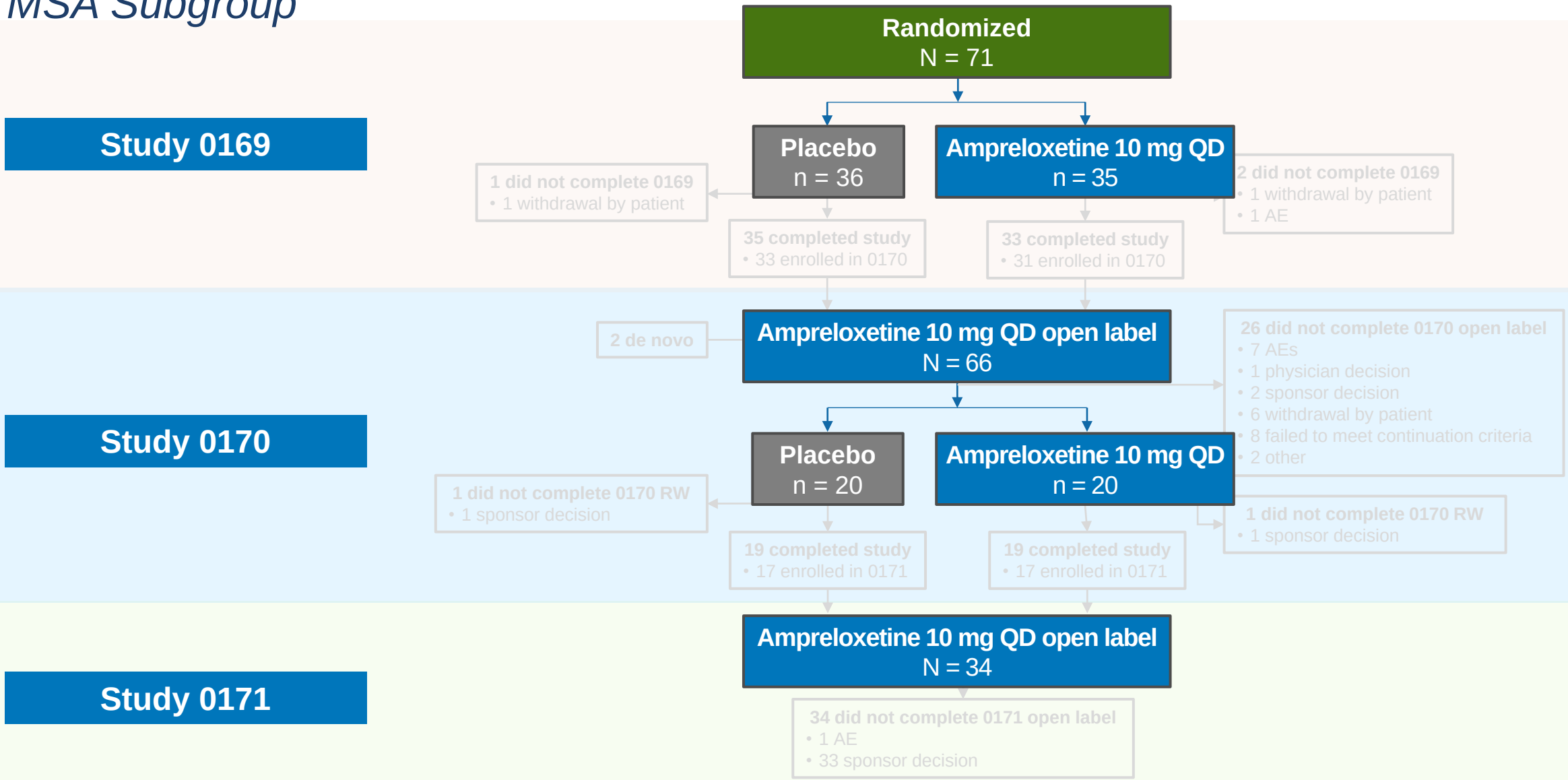
Study 0171



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 period		
	Placebo (n = 33)	Ampreloxetine (n = 34)	Total (N = 67)	Placebo (n = 20)	Ampreloxetine (n = 20)	Total[a] (N = 40)
Male, n (%)	20 (60.6)	15 (44.1)	35 (52.2)	13 (65.0)	8 (40.0)	21 (52.5)
White, n (%)	31 (93.9)	32 (94.1)	63 (94.0)	19 (95.0)	17 (85.0)	36 (90.0)
Age, years	63.7 (9.6)	63.3 (8.5)	63.5 (9.0)	62.6 (6.7)	63.6 (9.0)	63.1 (7.8)
OHSA #1 score	6.6 (1.5)	6.7 (1.6)	6.6 (1.6)	3.2 (2.1)	2.8 (2.2)	3.0 (2.1)
OHSA composite score	5.3 (1.6)	5.4 (1.8)	5.3 (1.7)	2.8 (1.8)	2.6 (1.9)	2.7 (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)	4.3 (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)	3.5 (1.9)
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)	138.7 (21.4)
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)	104.5 (19.8)

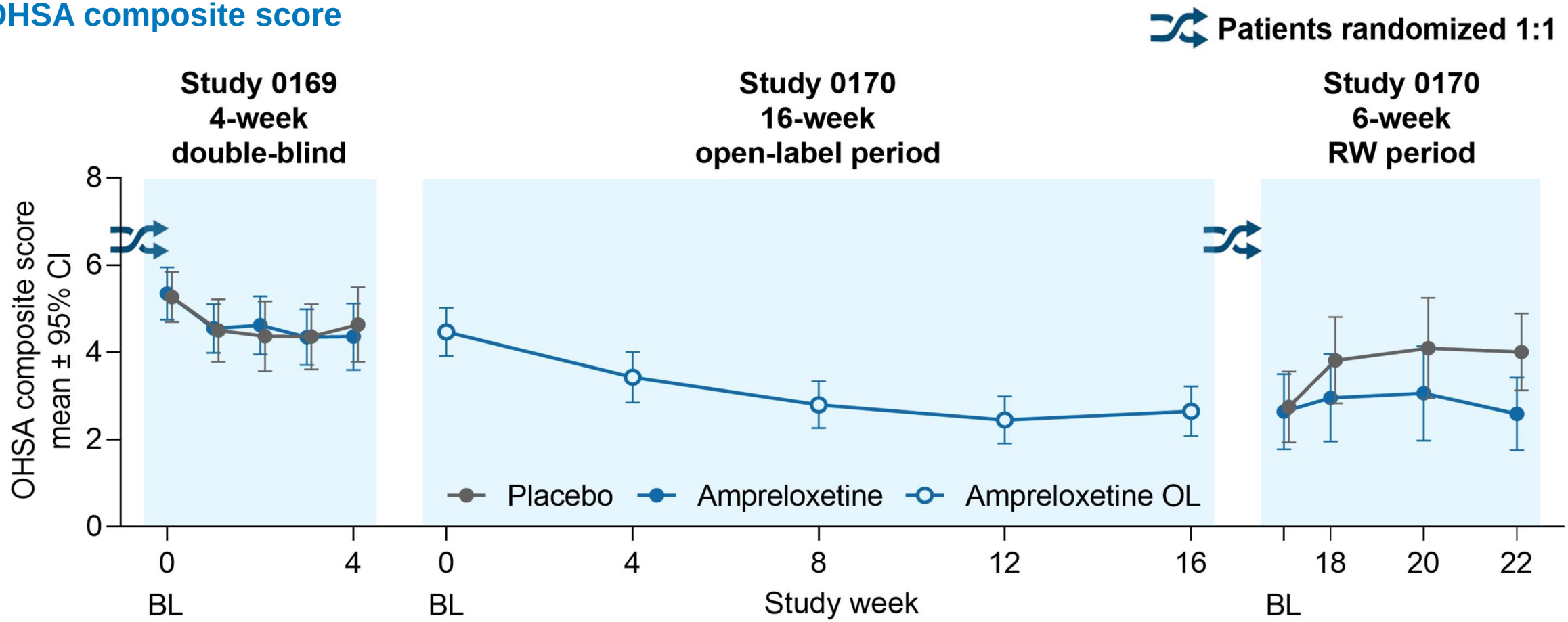
Data are presented as mean (SD) unless otherwise indicated.

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

[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 Over Time and Maintained Effect During RW in Patients With MSA

OHSA composite score

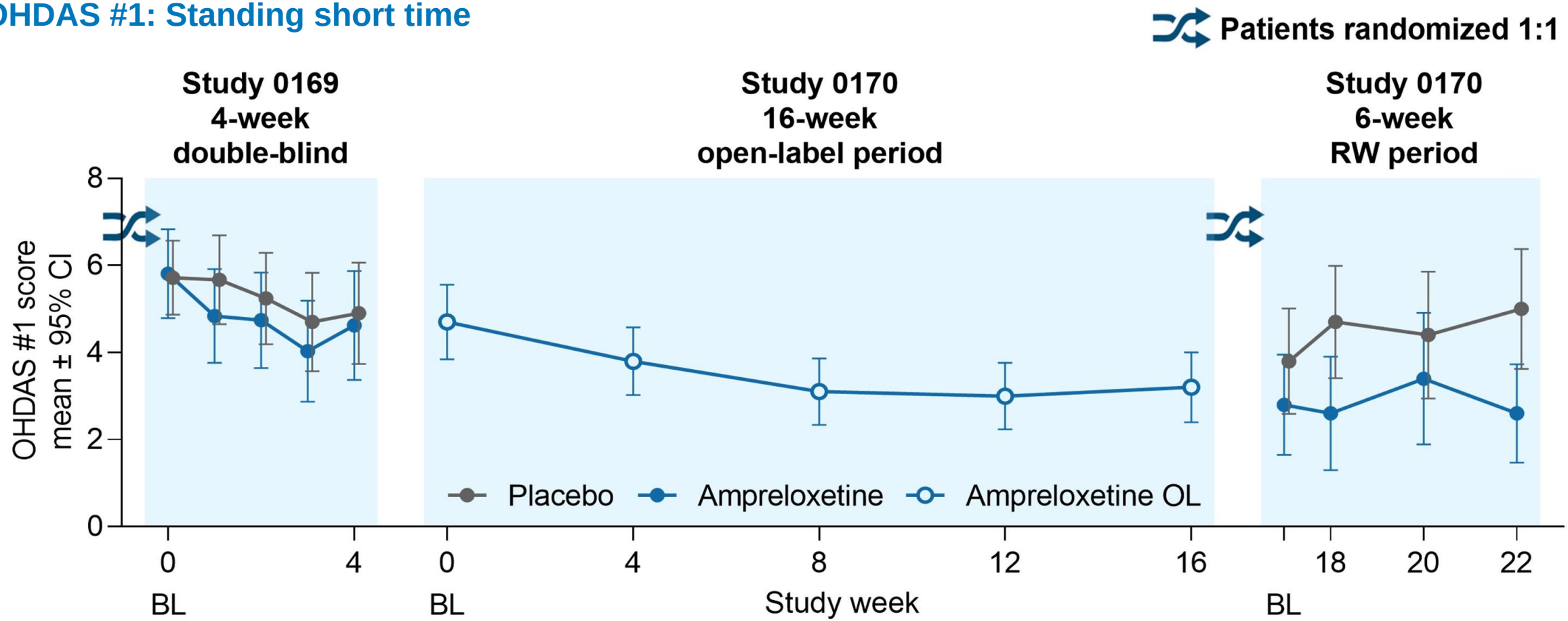


Placebo, n =	33	31				20	18
Ampreloxetine, n =	34	32	64		42	20	20

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 and Maintained Effect During RW in Patients With MSA

OHDAS #1: Standing short time

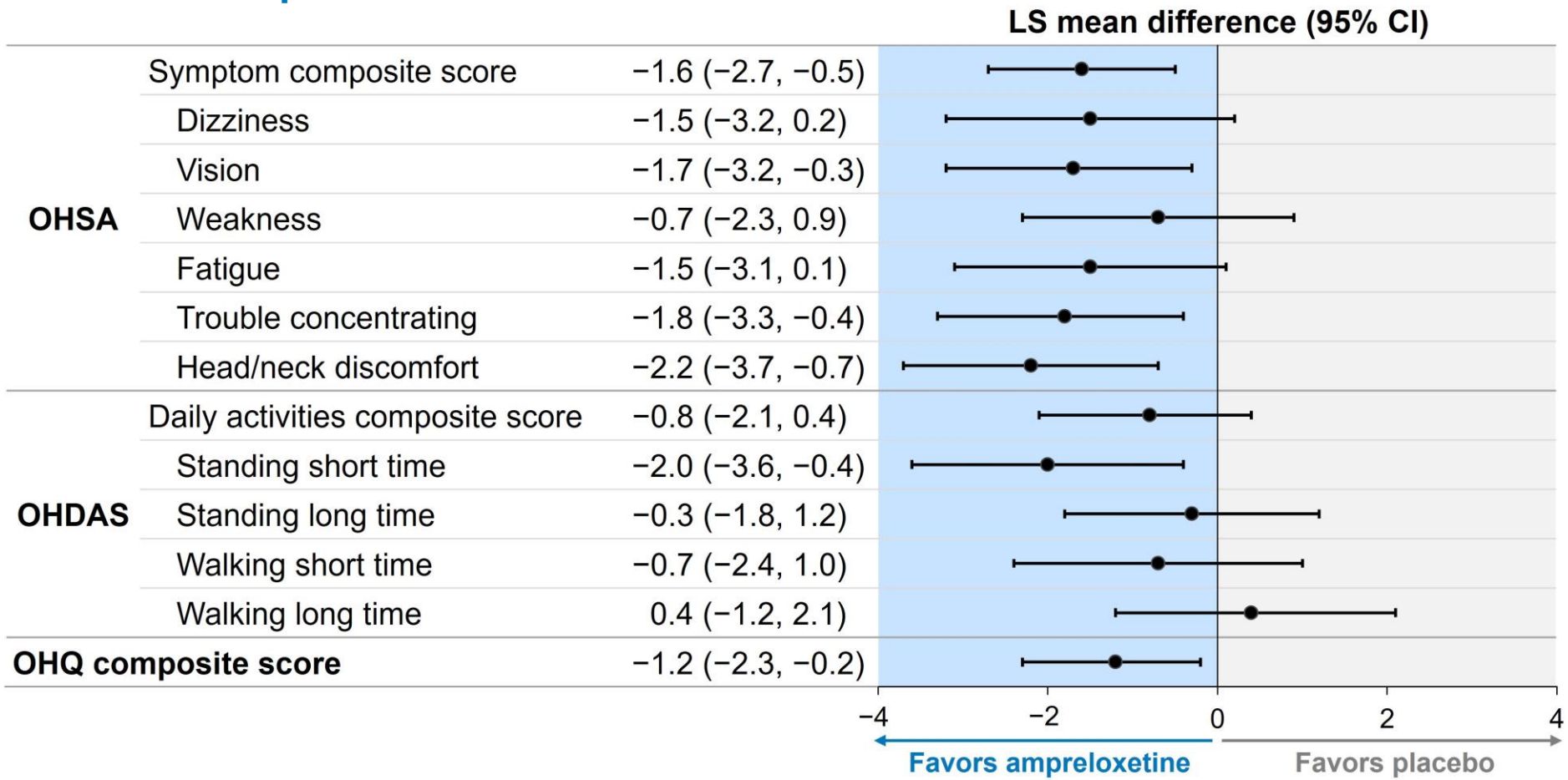


Placebo, n =	32	30				19	16
Ampreloxetine, n =	32	29	60		41	20	20

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 of Ampreloxetine in MSA Subgroup

Randomized withdrawal period

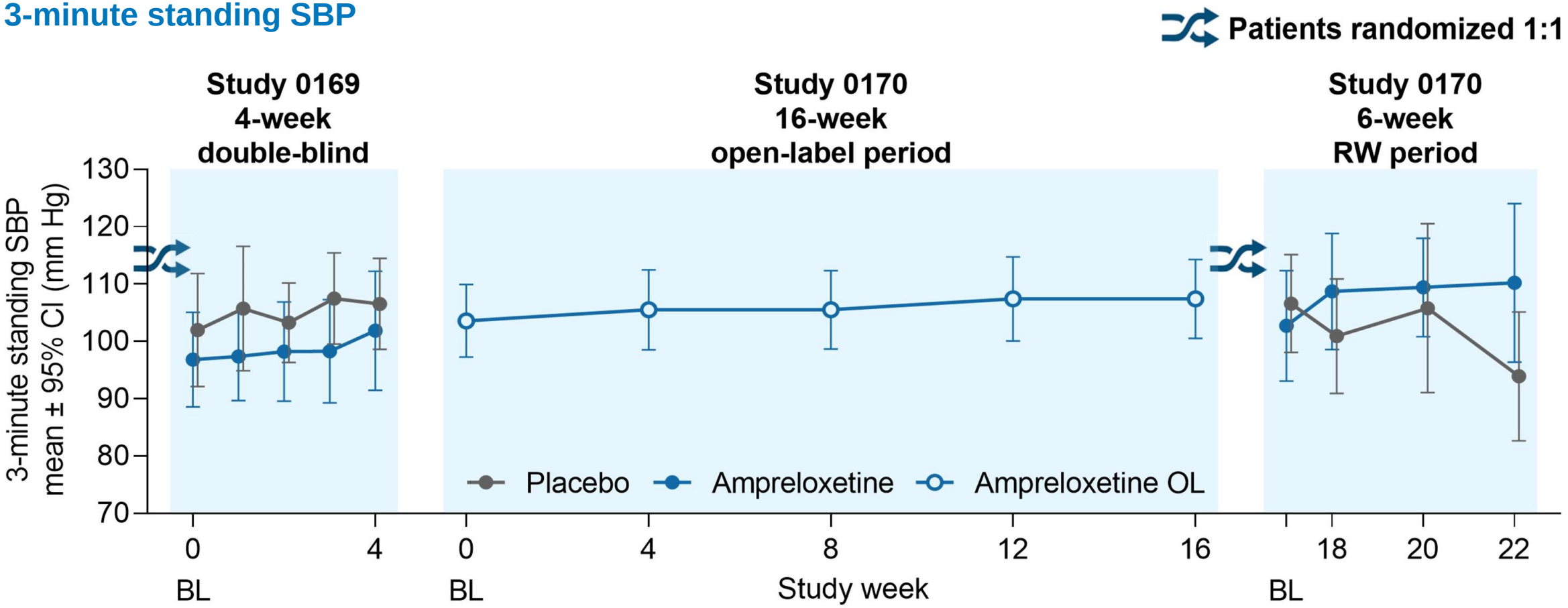


- Benefits observed in OHSA composite score and ability to stand for a short time

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

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

3-minute standing SBP



Placebo, n =	30	29					18	15
Ampreloxetine, n =	31	29	58			38	20	18

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 Phases

MSA Subgroup

	Study 0169		Study 0170 RW period	
	Placebo (n = 33)	Ampreloxetine (n = 35)	Placebo (n = 20)	Ampreloxetine (n = 20)
Any TEAEs	19 (57.6)	19 (54.3)	7 (35.0)	4 (20.0)
TEAEs related to study drug	5 (15.2)	5 (14.3)	1 (5.0)	1 (5.0)
SAEs	2 (6.1)	4 (11.4)	1 (5.0)	2 (10.0)
SAEs related to study drug	0	0	1 (5.0)	1 (5.0)
TEAEs leading to permanent study drug discontinuation	0	1 (2.9)	0	0
Deaths during study	0	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 randomized 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 consistent improvement in nOH symptoms over time
- Worsening of nOH symptoms and SBP was observed in patients with MSA upon randomized withdrawal of ampreloxetine to placebo
  - Broad symptomatic impact across each OHSA component: dizziness, vision, weakness, fatigue, trouble concentrating, head/neck discomfort
- The safety profile of ampreloxetine was similar to that of placebo during randomized controlled phases
- Patients with MSA may benefit from ampreloxetine treatment due to the presence of central autonomic pathway degeneration and intact peripheral postganglionic fibers

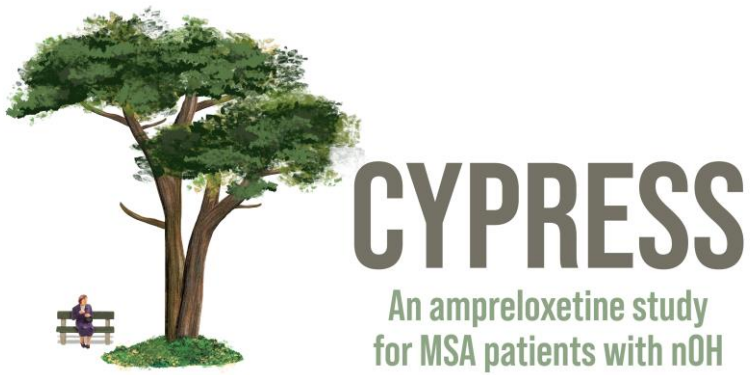
MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; OHSA, Orthostatic Hypotension Symptom Assessment; SBP, systolic blood pressure.

New Ampreloxetine Study in Patients With MSA

Phase 3 registrational study

Study 0197: 20 weeks

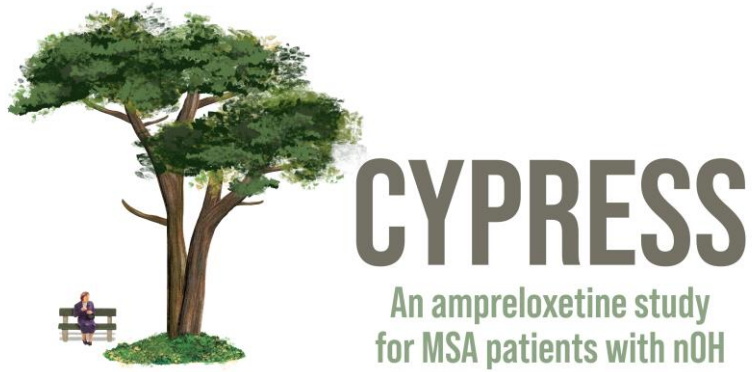
12-week, open-label; 8-week, randomized, double-blind, placebo-controlled, withdrawal



Long-term extension

Study 0197: 2 years

Long-term, open-label



- CYPRESS study initiation planned for first quarter of 2023

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