Theravance Biopharma

Ampreloxetine KOL Event

December 8, 2025

Theravance Biopharma®

Medicines That Make a Difference®

Welcome and Opening Remarks

Rick Winningham
Chief Executive Officer

Forward Looking Statements

This presentation 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, Inc. (the “Company” or "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 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 or milestone payments, the ability to provide value to shareholders, the Company’s regulatory strategies and timing of clinical studies, possible ultimate safety, efficacy or differentiation of our investigational therapy, commercial opportunities, 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 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, the results of the patent infringement litigation initiated by the Company and its partner against certain generic companies in federal district courts, 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 November 12, 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.

Important Note

Ampreloxetine is an investigational product being studied for the treatment of symptomatic neurogenic orthostatic hypotension (nOH) in patients with multiple system atrophy (MSA). It has not been approved by the FDA or any other regulatory agency in the world and the safety and efficacy of ampreloxetine has not been established. This document is developed to share background information including current landscape of the disease state and stakeholders for purposes of investor communication only. The information are not intended to be promotional or commercial in nature. Per Theravance Biopharma policy, any implementation of commercial strategy or tactic are subject to internal review and approval.

Presenting KOL Disclosure

Dr. Kaufmann is a member of advisory committees supporting the CYPRESS clinical trial and paid consultant to Theravance Biopharma. The views and opinions expressed by Dr. Kaufmann are his own and do not necessarily reflect the views and opinions of Theravance Biopharma.

Agenda

10:30	Welcoming and Opening Remarks	**Rick Winningham:** Chief Executive Officer
10:35	Neurogenic Orthostatic Hypotension in Multiple System Atrophy and Ampreloxetine as a Potential Precision Medicine Therapy	**Dr. Horacio Kaufmann:** Felicia B. Axelrod Professor of Dysautonomia Research, Department of Neurology at NYU Grossman School of Medicine
10:55	Phase 3 CYPRESS Trial	**Dr. Áine Miller:** Senior Vice President, Head of Development
11:05	Commercial Opportunity	**Rhonda Farnum:** Senior Vice President, Chief Business Officer
11:20	Closing Remarks & Q&A	**Rick Winningham / All Presenters**

Commercial-Stage Biotech Focused on Respiratory and Neurological Diseases

Strong Financial Position and Cash-Generating YUPELRI® Set the Foundation for Near-Term Ampreloxetine Phase 3 Catalyst

Strong Financial Position

~$333M in cash and no debt; breakeven in Q3 2025[1], expected to remain at similar levels in Q4 2025

$175M in near-term, high probability TRELEGY[2] and YUPELRI sales-based milestones

Commitment to **return excess capital** to shareholders

YUPELRI®
Strong Cash Flow Generation

Launched in the U.S. in 2019; 35% U.S. profit share with Viatris[3]

Strong cash flow from U.S. profit share with **IP protection** in the U.S. into **2039**

Sizable addressable patient population remains[4]

Ampreloxetine
Upcoming Phase 3 Data

Completed **Phase 3 CYPRESS enrollment in Q3 2025; topline data in Q1 2026**

FDA Orphan Drug Designation

Targets **~40,000 underserved patients** in the U.S. with symptomatic nOH due to MSA[5,6]

Demonstrated Success in Advancing In-House Developed Assets through Approval and Successful Commercialization

FDA, U.S. Food and Drug Administration; MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension.
1. Cash balance of $332.7M as of 9/30/25; cash flow guidance excludes potential one-time milestones (and associated taxes). 2. Payments from Royalty Pharma (RP) will be triggered if RP receives certain minimum royalty payments from GSK based on TRELEGY global net sales. 3. In the U.S., Viatris is leading the commercialization of YUPELRI, and Theravance Biopharma co-promotes the product under a profit and loss sharing arrangement (65% to Viatris; 35% to Theravance Biopharma). Refer to our SEC filings for further information. 4. Addressable patient population quantifies the number of patients within the intended target profile. 5. Palma, Kaufmann. Epidemiology, Diagnosis, and Management of Neurogenic Orthostatic Hypotension; Kalra DK, et al. Clin Med Insights: Cardiol. 2020 14:1179546820953415. 6. Kaplan et al., Parkinsonism Relat Disord. 2023 Dec:117:105920; UCSD Dept. of Neurosciences : https://neurosciences.ucsd.edu/centers-programs/movement-disorders/community/disease-overview/msa.html; Internal claims analyses (IQVIA, Veeva, Real Chemistry), CD-10 Codes: G90.3, G23.2.

Neurogenic Orthostatic Hypotension in Multiple System Atrophy

Horacio Kaufmann, MD FAAN
The F. B. Axelrod Professor of Neurology and Professor of Medicine at NYU Grossman School of Medicine

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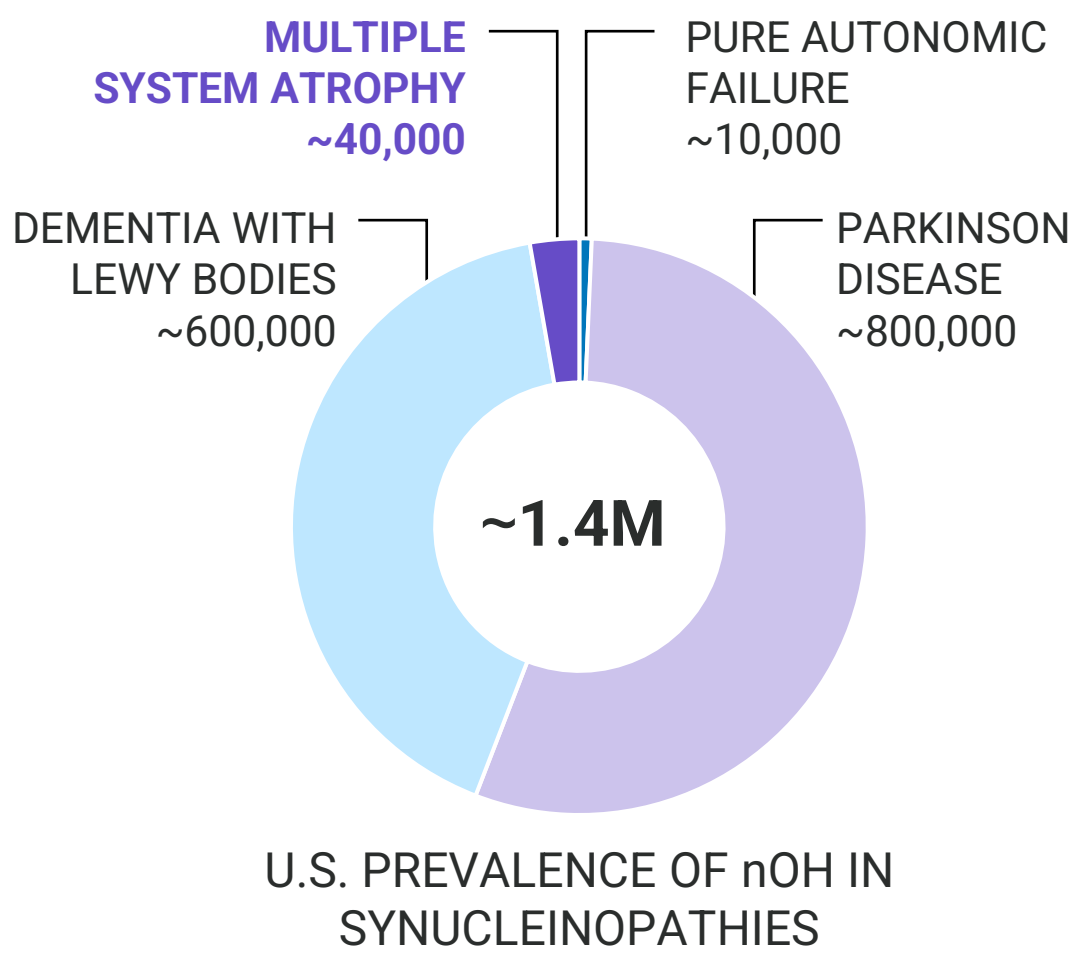
Neurogenic Orthostatic Hypotension (nOH)

- A sustained fall in blood pressure upon standing
- Chronic and disabling condition
- Present in diseases that damage or impair central and/or peripheral nerves that regulate blood pressure when standing
- Highly prevalent in the synucleinopathies



Kaplan et al., Parkinsonism Relat Disord. 2023 Dec:117:105920. Kaufmann et al., N Engl J Med 2020;382:163-178

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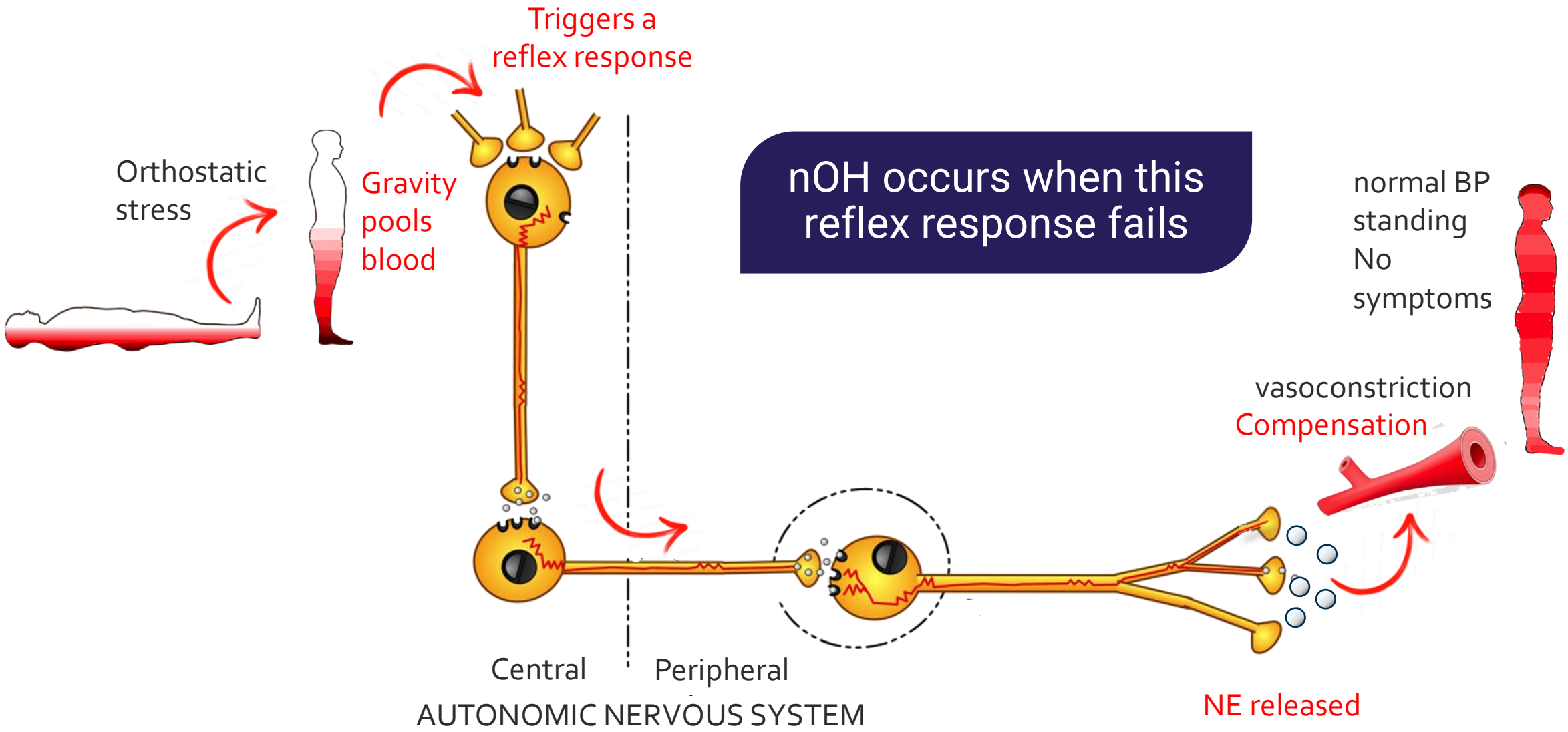
Blood pressure regulation by the autonomic nervous system



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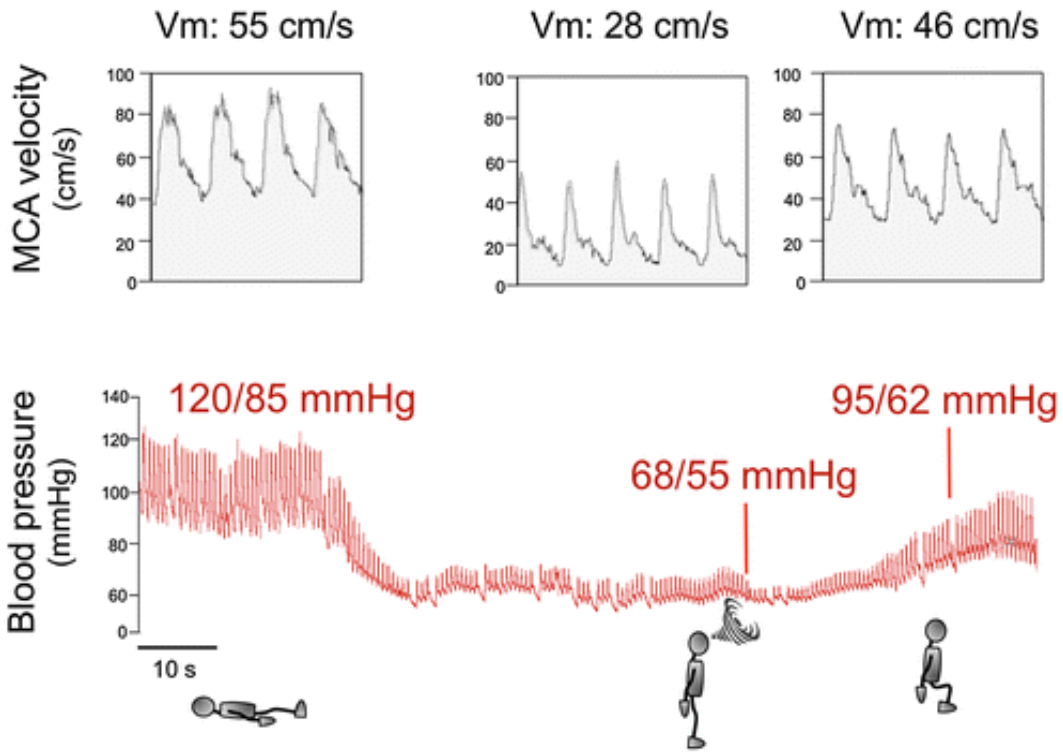
nOH: Failure to release norepinephrine and insufficient vasoconstriction

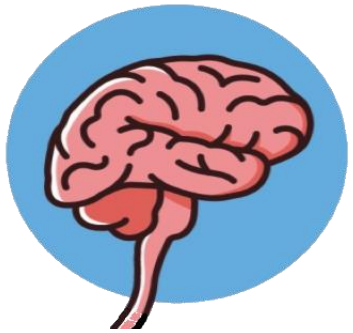
Impaired physiologic response to changes in posture



Disabling symptoms of postural hypotension

- Inability to adjust blood pressure to changes in posture
- Hypoperfusion of the vital organs and incapacitating symptoms of ischemia
- Persistent dizziness/lightheadedness on sitting and standing
- Inability to stand, walk, perform activities of daily living
- Can result in faints or falls
- Major reason for not being mobile
- Major impact on quality of life
- **Important to recognize and treat early**

Rapidly progressive features of MSA are distinct from Parkinson (PD)



Adult-onset neurodegenerative disease

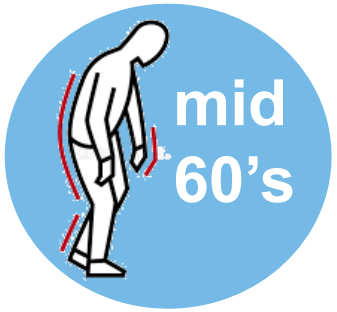
Toxic alpha-synuclein deposits

Similarities with PD

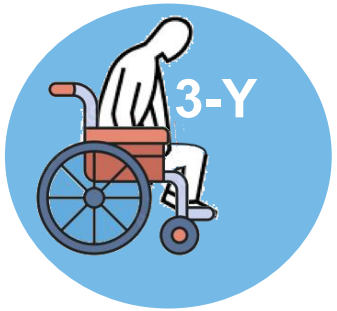
Rare disease

More rapidly progressive

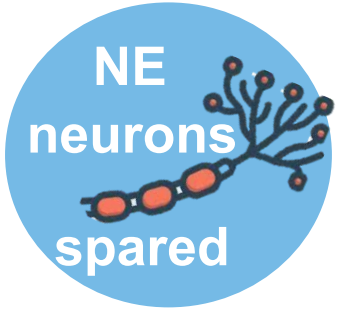
Frequently presents with severe nOH



Earlier age at onset



More severe motor deficits (Parkinsonism/ataxia)



Well-defined central autonomic pathology

Distinct differences

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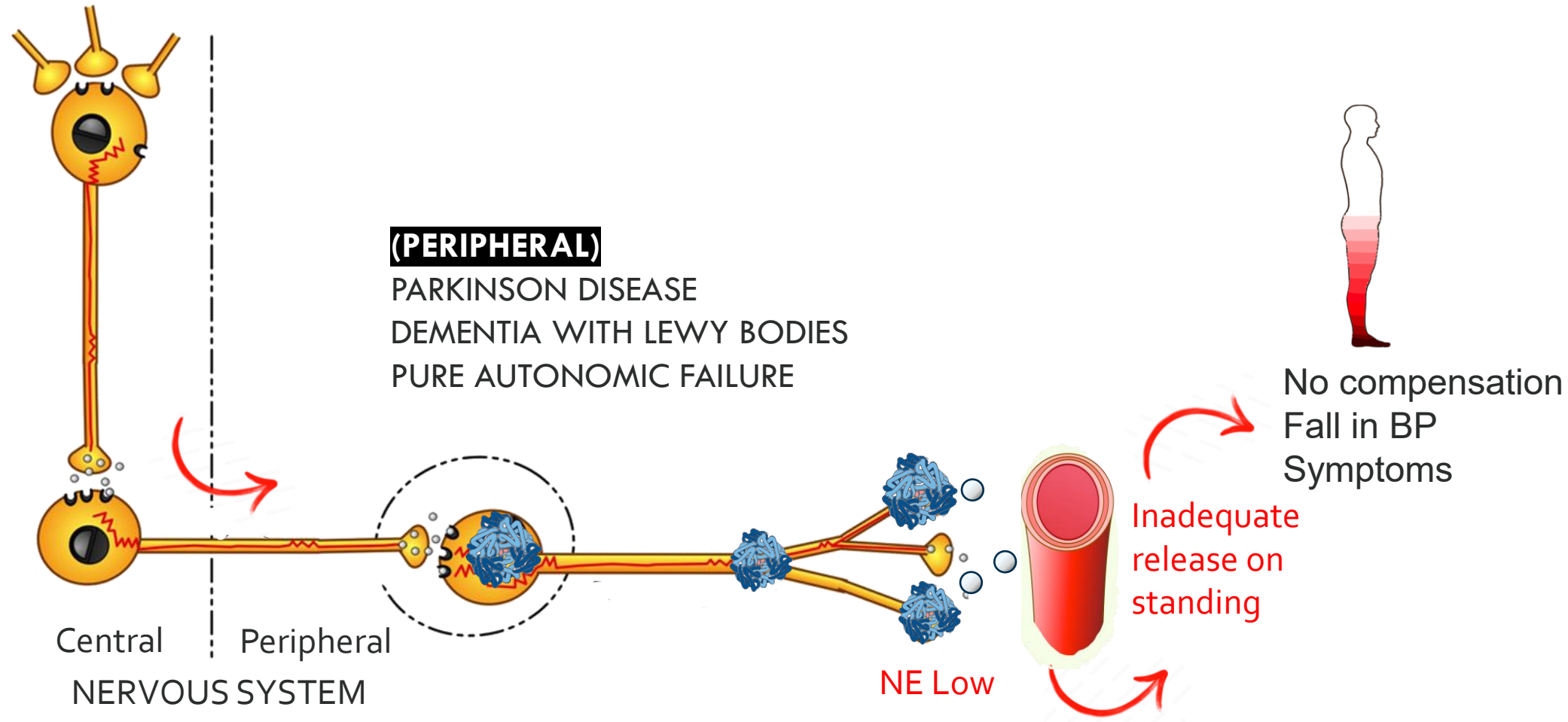
Crucial difference: Central vs. peripheral patterns of autonomic failure

Therapy could be tailored to the pathophysiological lesion



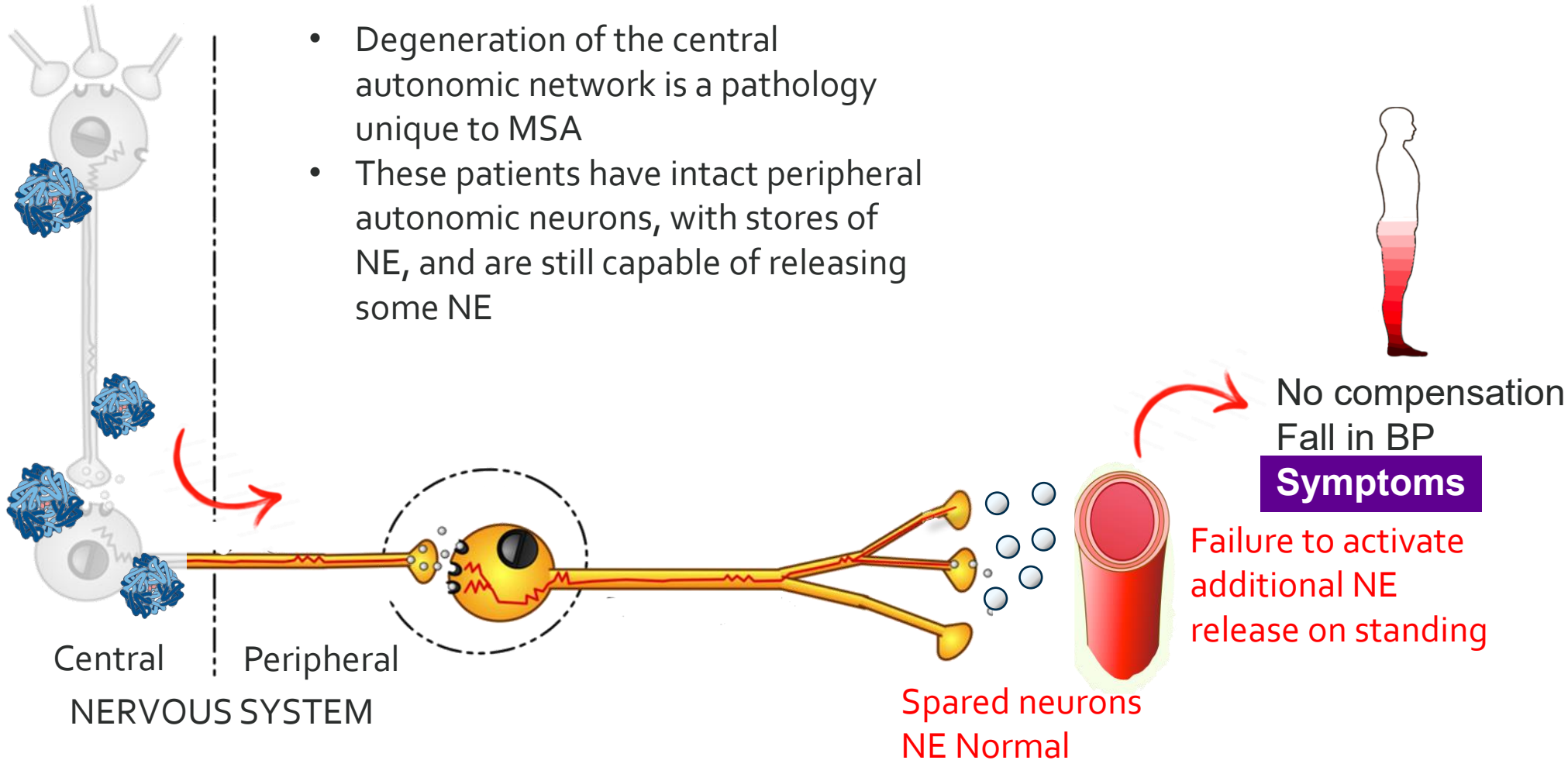
= alpha-synuclein deposits

Crucial difference: Central vs. peripheral patterns of autonomic failure

Therapy could be tailored to the pathophysiological lesion

(CENTRAL)
MULTIPLE SYSTEM ATROPHY

- Degeneration of the central autonomic network is a pathology unique to MSA
- These patients have intact peripheral autonomic neurons, with stores of NE, and are still capable of releasing some NE



= alpha-synuclein deposits

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nOH in MSA: A pressing need for effective pharmacotherapy options

70-80% of patients with MSA will develop nOH in their lifetime[1-3].

This adds significant **disability, functional decline, and risk of early death** from all-cause mortality

Despite adherence to treatment with available pressor agents, **68% of MSA patients with nOH remain symptomatic**[4]

[1]Low PA, Lancet Neurol. 2015 May 27;14(7):710–719, [2]Vichayanrat Neurology. 2022 Sep 13;99(11):e1168–e1177; [3]Palma and Kaufmann. 2017. Mov Disord Clin Pract; 4 (3):298-308. [4] NYU MSA Database Statistics.

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Current landscape management of nOH in MSA

Clear opportunity to develop a targeted, effective, durable, safe treatment that targets blood pressure in the upright position, without worsening supine HTN, with a single daily dosing regimen

NON-PHARMACOLOGICAL

Approaches target improving venous return, increasing blood volume, and avoiding triggers

Rarely effective alone in MSA

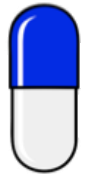
PHARMACOLOGICAL

Off-Label

Fludrocortisone
Expand volume

Approved
Pressor agents

Midodrine
(direct agonist)



Droxidopa
(NE precursor)

- Can require complex titration and 3X daily dosing
- Increase blood pressure in all positions
- Carry Box Warning for supine hypertension
- Effect may decrease over time
- Efficacy beyond 2 weeks has not been proven

HTN=hypertension.

nOH in MSA: A pressing need for effective pharmacotherapy options

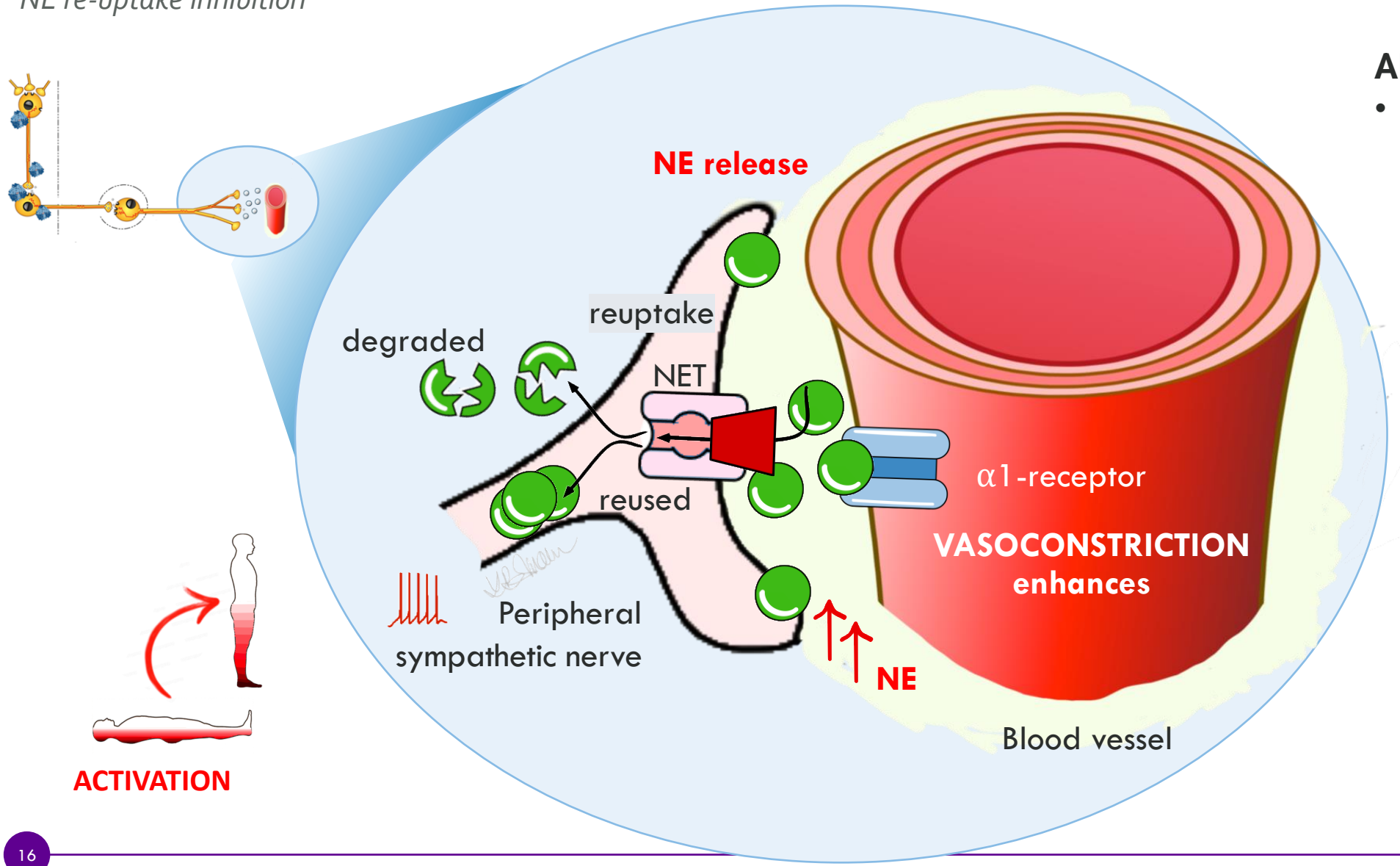
It has been over a decade since the FDA last approved a drug for nOH

- No drug has been developed for nOH specifically for patients with intact peripheral autonomic neurons still capable of releasing NE
- Ampreloxetine is a novel, long-acting, once-daily, norepinephrine reuptake inhibitor being tested as a treatment for nOH in patients with MSA in a phase III program

[1]Low PA. 2008. Clin Auton Res. 2008. Suppl 1:8-13. [2] NYU MSA Database Statistics.

Ampreloxetine: A precision medicine approach to nOH

NE re-uptake inhibition



AMPRELOXETINE

- Uniquely suited to MSA patients with relative sparing of peripheral sympathetic neurons

Reflects expectations for ampreloxetine. Ampreloxetine is in development and not approved for any indication. No conclusion can be drawn regarding its safety or efficacy.

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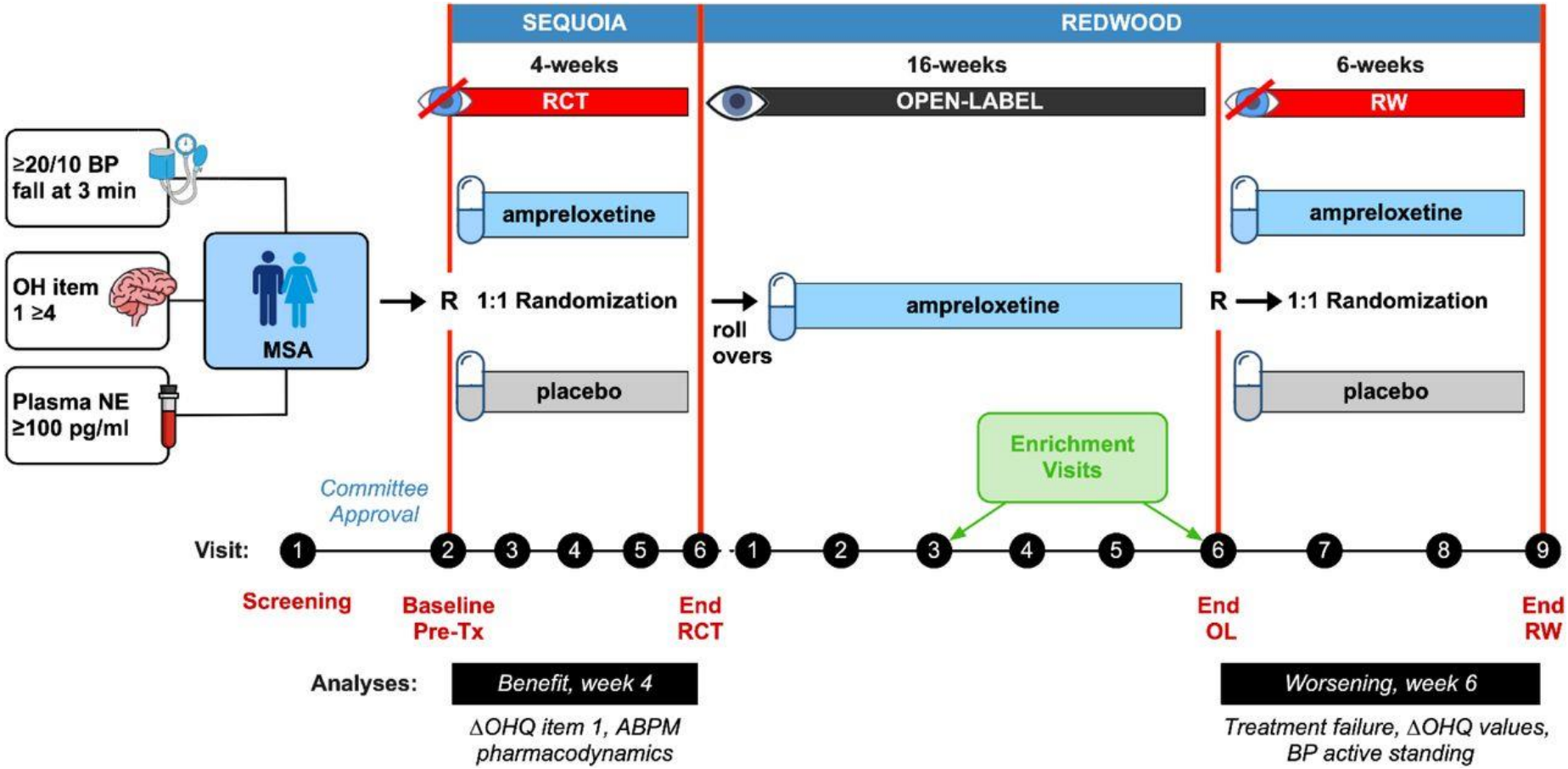
Initial Phase 3 program evaluating ampreloxetine

SAP included a hypothesis-driven, pre-specified subgroup analysis of MSA in the REDWOOD randomized withdrawal design study to determine the effect of ampreloxetine on symptoms, activity and blood pressure[1]



Full analysis set included 40 patients with MSA, 20 ampreloxetine, 20 placebo

Freeman R, et al. Precision therapy with ampreloxetine for neurogenic orthostatic hypotension in multiple system atrophy. MedRxiv. https://doi.org/10.1101/2025.08.12.25332833.

1. REDWOOD primary endpoint was not met.

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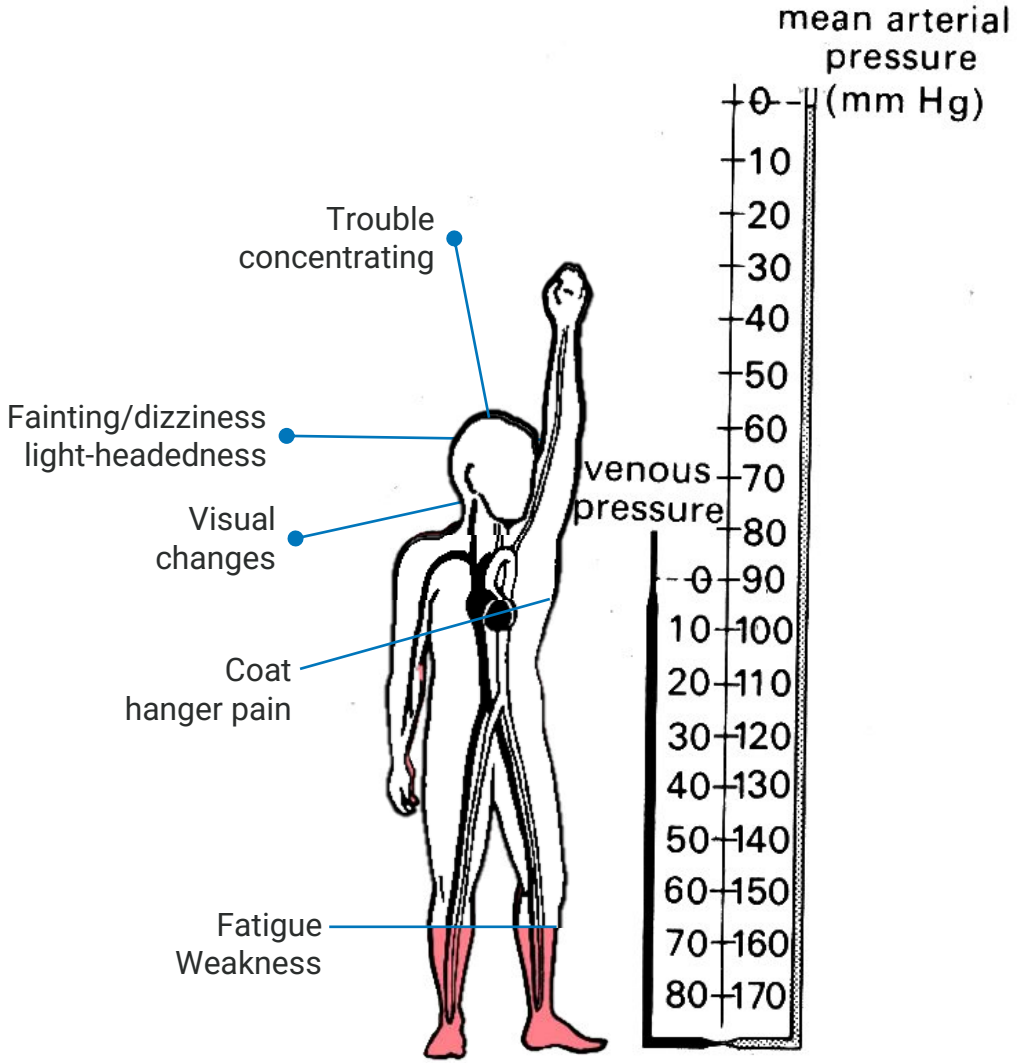
nOH Symptoms Assessment (OHQ)

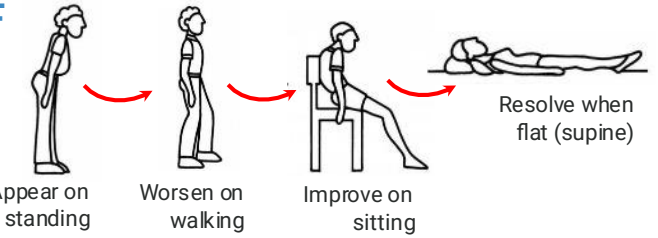
MEASURABLE OUTCOME



Orthostatic Hypotension Questionnaire (OHQ)

10 item -symptom, validated scale, accepted by the FDA for drug approvals

IMPACT OF POSTION



Orthostatic Hypotension Symptom Assessment (OHSA)

0 1 2 3 4 5 6 7 8 9 10

No Symptoms — Worst Possible

Orthostatic Hypotension Daily Activity Scale (OHDAS)

0 1 2 3 4 5 6 7 8 9 10

No interference — Complete interference

Kaufmann H, Malamut R, Norcliffe-Kaufmann L, Rosa K, Freeman R Clin Auton Res. 2012 Apr;22(2):79-90.

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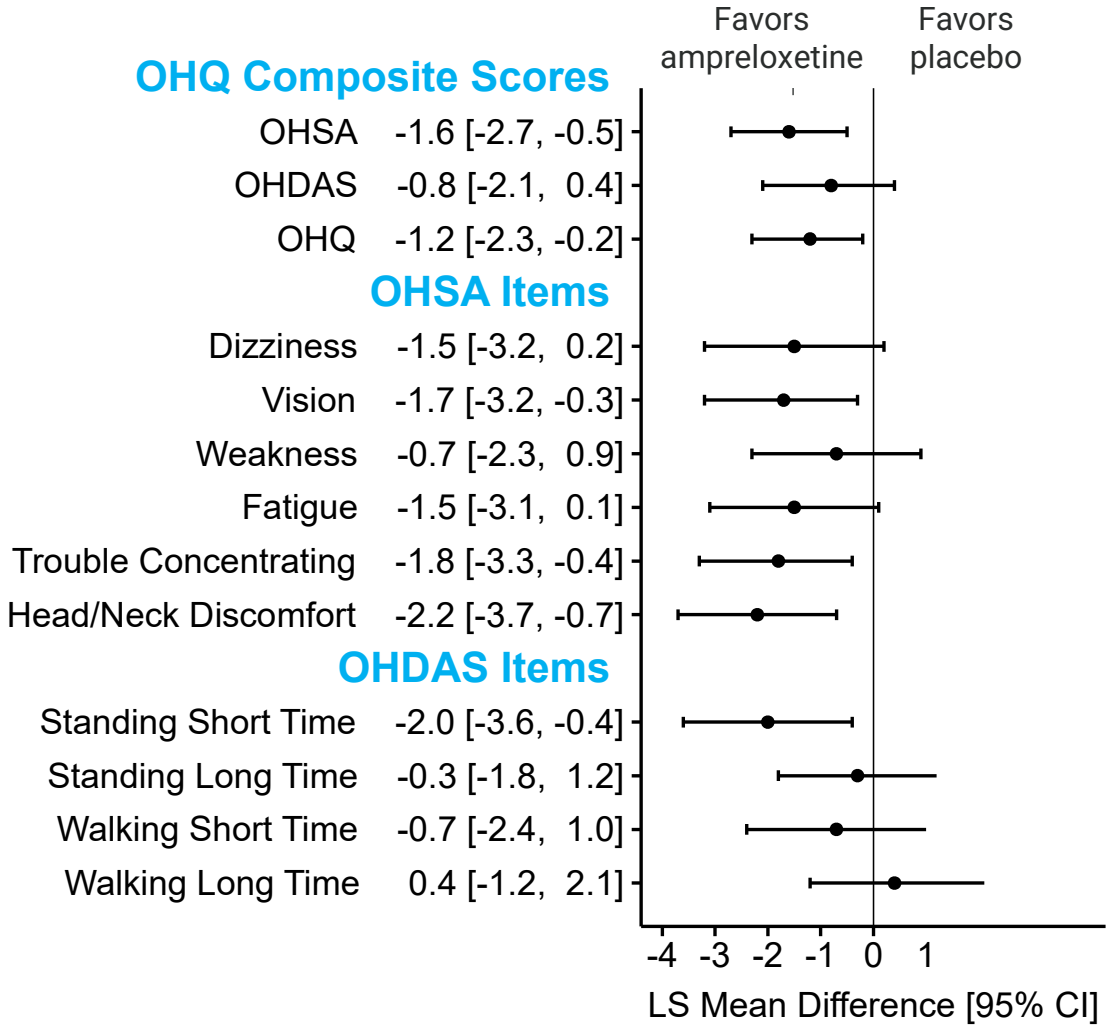
6-weeks

REDWOOD RWD

Results: Symptom burden and function

REDWOOD pre-specified MSA subgroup analysis, Full analysis set n=40



FINDINGS

- The greatest difference was observed in the 6-item OHSA composite score
- Most Individual items on the OHQ favor ampreloxetine over placebo

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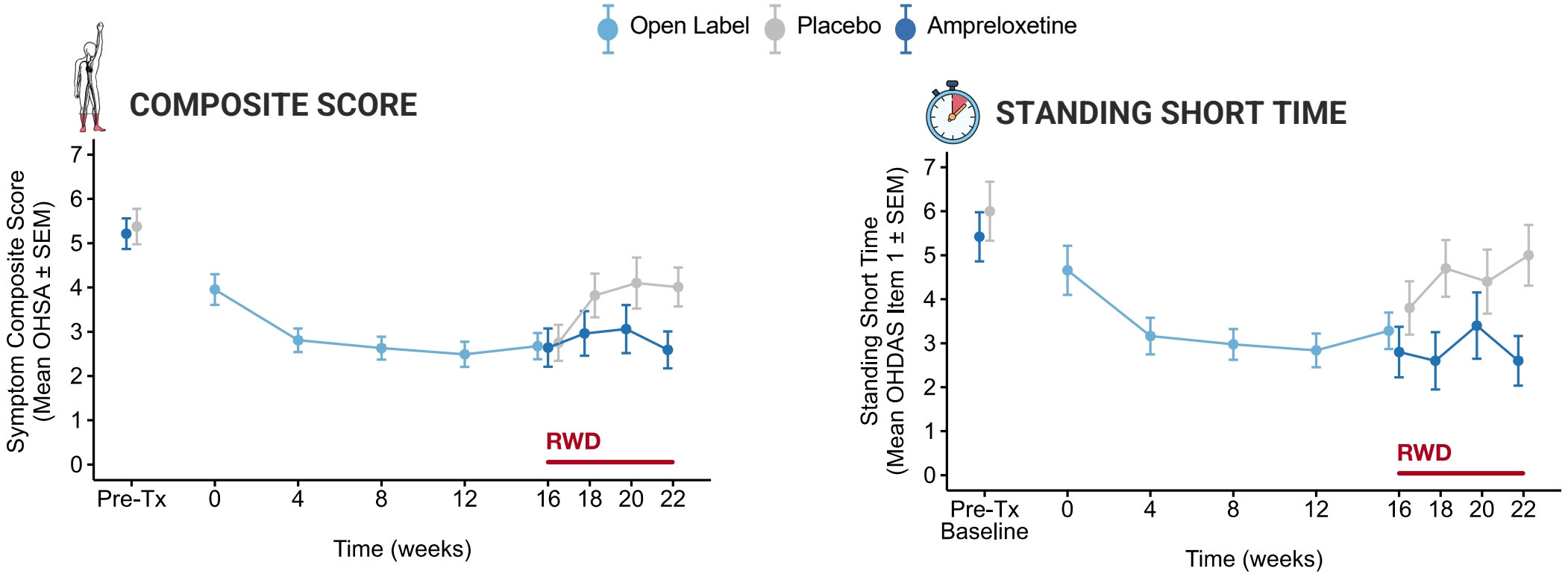
6-weeks

REDWOOD RWD

Results: Symptom burden and function

REDWOOD pre-specified MSA subgroup analysis, Full analysis set n=40



FINDINGS

- Self-reported scores showed symptomatic benefit with improvement in standing that was lost after ampreloxetine was withdrawn

FAS=full analysis set.

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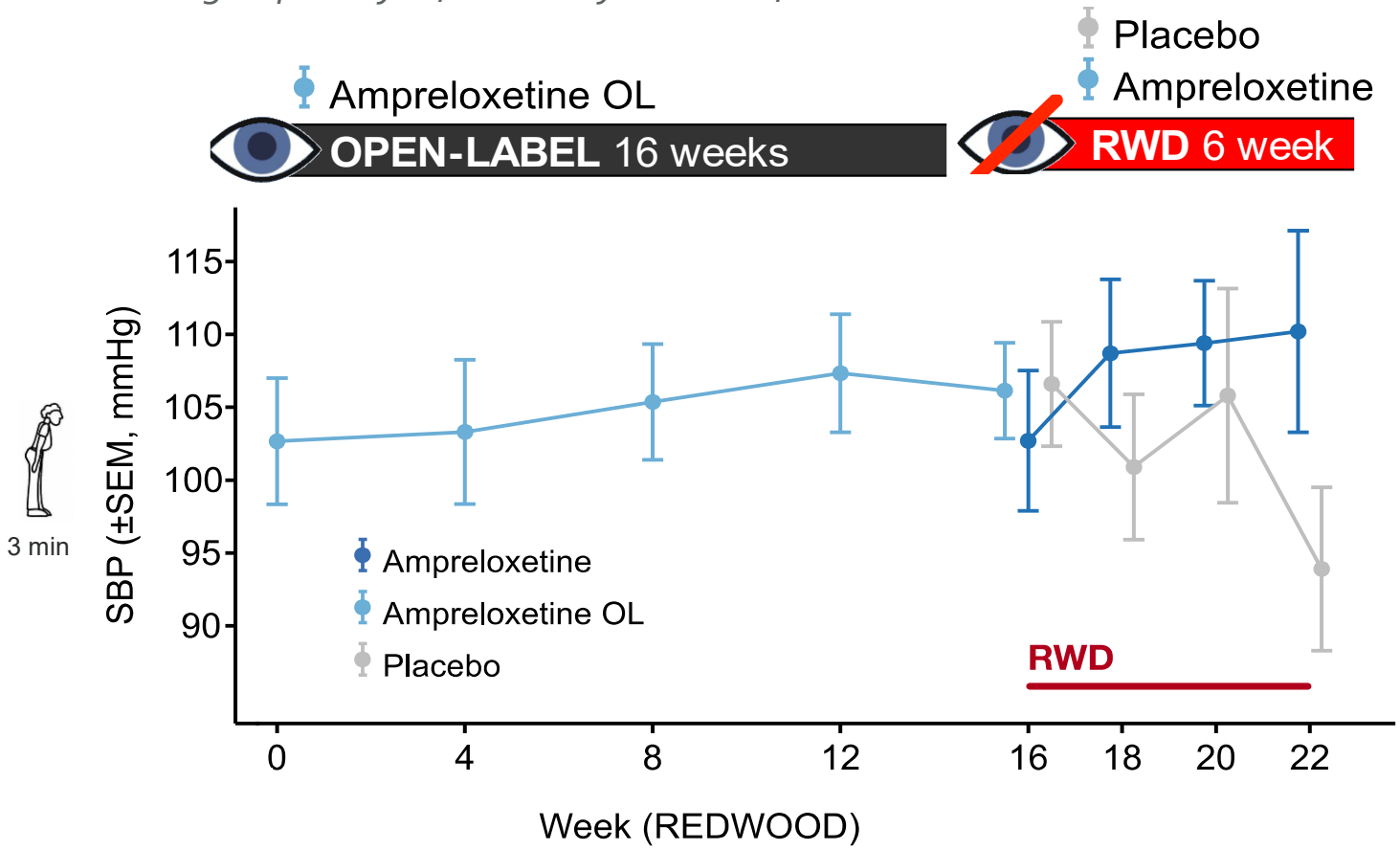
Results: Blood pressure over time

REDWOOD pre-specified MSA subgroup analysis, Full analysis set n=40



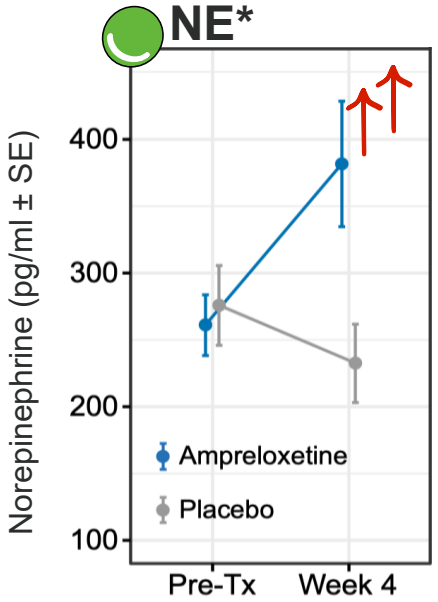
FINDINGS

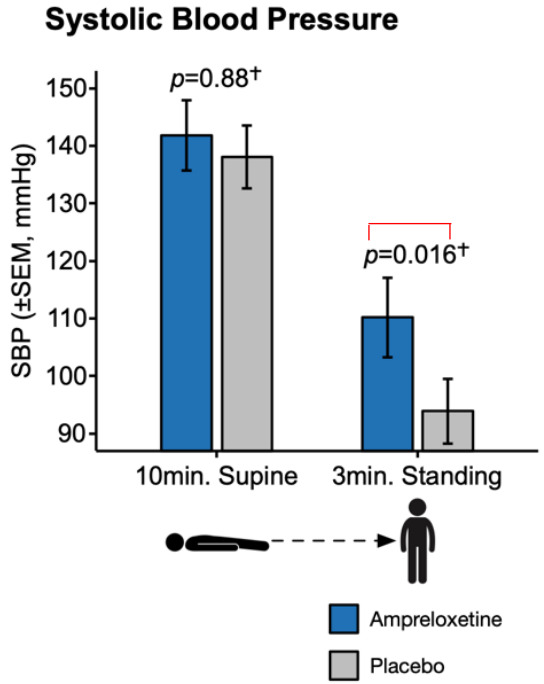
- A sustained improvement in orthostatic BP was observed over 16-weeks of open-label treatment, that was lost after 6-weeks of placebo withdrawal

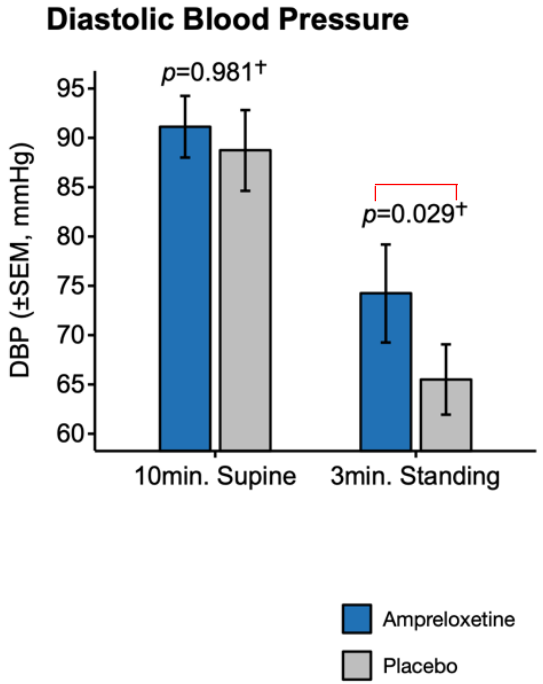
FAS=full analysis set.

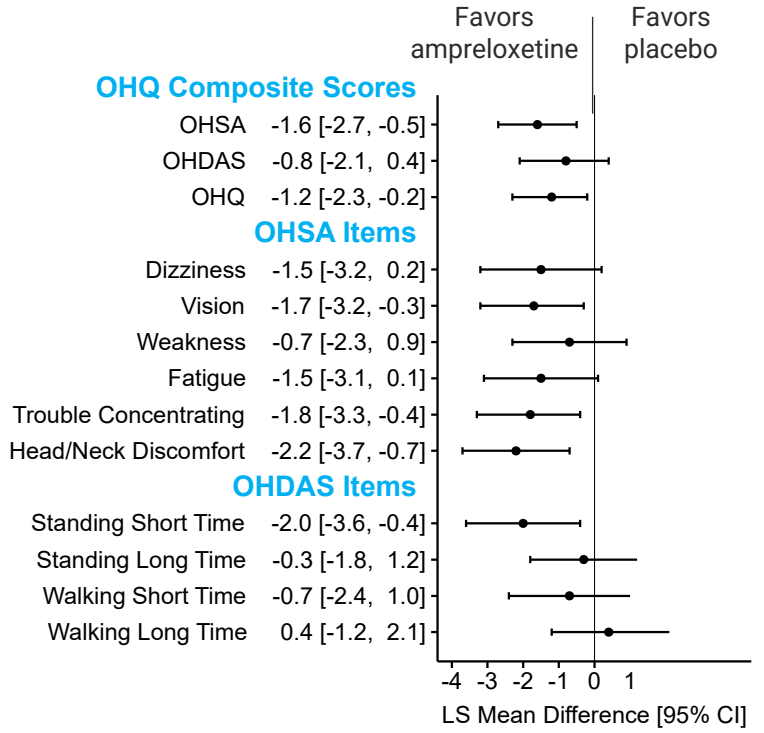
Results: NE, blood pressure and symptoms

REDWOOD pre-specified MSA subgroup analysis, Full analysis set n=40









FINDINGS

- Ampreloxetine increased NE and standing blood pressure, and reduced orthostatic symptoms

†P-values vs placebo are based on LS mean difference in change between the start and end of RW, *Norepinephrine data from baseline and at the end of the 4-week from SEQUOIA Study

Conclusions

The pre-specified subgroup analysis suggest that ampreloxetine could improve the ability to maintain an upright posture, lessen the functional burden of the disease, and could improve quality of life in MSA patients

The ampreloxetine CYPRESS study in patients with MSA (NCT05696717) nearing completion

If CYPRESS is positive, and the drug is approved, ampreloxetine would be the first example of a tailored treatment for nOH in this rare and fatal disease

Ampreloxetine: Discovery Through CYPRESS Design and Execution

Dr. Áine Miller
Theravance Biopharma SVP, Head of Development

Ampreloxetine: Intended to Address nOH in MSA

A potent high affinity NET inhibitor with a durable mechanism of action

Discovery/Early Development » Discovered and developed **in house** with a **desirable PK/PD profile that supports QD dosing**; demonstrated sustained, clinically meaningful symptom improvement in Phase 2

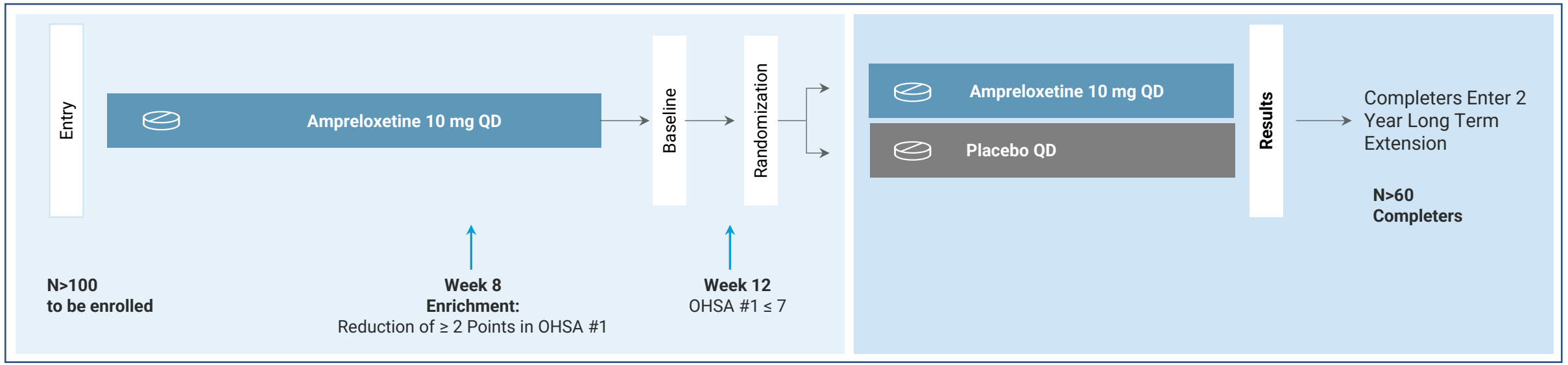
CYPRESS Design and Execution » Pivotal CYPRESS study **designed to confirm** the clinically meaningful results seen in REDWOOD (Study 0170) in patients with MSA

Regulatory Preparation » **Clear FDA regulatory path** forward; preparing for **expedited NDA submission** to capitalize rapidly and efficiently upon CYPRESS's potential success

FDA, U.S. Food and Drug Administration; MSA, multiple system atrophy; NDA, new drug application; NET, norepinephrine transporter; nOH, neurogenic orthostatic hypotension; PK/PD, pharmacokinetics/pharmacodynamics; QD, once daily.

Pivotal Phase 3 CYPRESS Trial was Informed by REDWOOD Study Results in Patients with nOH due to MSA

CYPRESS Study Design



Primary endpoint: OHSA composite score

Secondary endpoints:

- OHDAS Standing: Change from baseline in ability to stand for a short time (item 1)
- OHDAS Walking: Change from baseline in ability to walk for a short time (item 3)

Exploratory Endpoints:

- Standing blood pressure
- OHQ items score
- Composite OHDAS Score
- Hospital Anxiety and Depression Scale (HADS) score
- PGI-S and PGI-C
- PK/PD

MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; OHDAS, orthostatic hypotension daily activity scale; OHQ, orthostatic hypotension questionnaire; OHSA, orthostatic hypotension symptom assessment; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; PK/PD, pharmacokinetics/pharmacodynamics; QD, once daily; RW, randomized withdrawal. Completers to enter 2-year long-term extension.

CYPRESS Design and Execution Optimizes Probability of Success

Replicating the elements that led to the observed benefits in patients with MSA in the REDWOOD study

Protocol Design	CYPRESS protocol **leverages learnings** from REDWOOD (Study 0170) to **enhance the likelihood of reproducing benefits** observed in MSA patients through using the composite OHSA primary endpoint, the randomized withdrawal design, and the same enrichment criteria.
Investigators and Site Selection	Engagement with **leading KOLs, MSA centers of excellence, and top academic sites** from REDWOOD.
Patient Selection & Management	Using the **same external enrollment committee** as REDWOOD **ensures study integrity and patient quality** through consistent enrollment criteria and independent review of MSA diagnosis.
Study Conduct	**Direct study management** enables real-time oversight and agile execution, supported by training focused on study conduct, retention and **minimizing variability**.

KOL, key opinion leader; MSA, multiple system atrophy; OHSA, orthostatic hypotension symptom assessment.

Alignment with FDA on CYPRESS Design Derisks Regulatory Path

Ongoing collaborative interactions to ensure alignment on regulatory expectations

Successful Type C Meeting June 2022 → **CYPRESS Initiation March 2023** → **Successful Type C Meeting Dec 2024**

Aligned with FDA on CYPRESS design:

- RW design including the use of the OHSA composite as primary endpoint
- Successful outcome, with Study 170 results as supportive, would fulfill requirement for a full approval

Use of FDA-supported, Anchor-Based Analysis

- Established clinically meaningful thresholds for patient-reported outcomes measures
- **~1 point change in OHSA Composite identified as clinically meaningful[1]**

Aligned with FDA on key components to support full NDA:

- Addressed majority of pre-NDA topics and aligned on content of NDA
- Built on previous successful interactions where we aligned on other critical components of the NDA eg nonclinical, CMC and clinical pharmacology

CMC, chemistry, manufacturing and conrols; FDA, U.S. Food and Drug Administration; NDA, new drug application; OHSA, orthostatic hypotension symptom assessment; RW, randomized withdrawal.

1. Kaufmann H, et al. Establishing minimally clinically important differences for the orthostatic hypotension questionnaire (OHQ). *Clin Auton Res*. 2025 Oct 24. doi: 10.1007/s10286-025-01168-y.

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Comprehensive Safety Database Supporting Ampreloxetine Development

Safety profile established in >800 subjects

Phase 1

Phase 1 registration package

- Healthy volunteer studies
- Clinical pharmacology studies

Phase 2

Fibromyalgia

Adult ADHD

Symptomatic nOH

Phase 3

Symptomatic nOH

- 208 patients with MSA, PD & PAF exposed to ampreloxetine in initial P3 program
- 110 patients exposed to ampreloxetine for >6 months and 67 patients >12 months
- CYPRESS exposure will add to safety database

Safety Profile To Date

- Ampreloxetine was generally safe and well-tolerated
- No unexpected safety concerns occurred throughout the duration of the studies
- Safety profile for the MSA subgroup was also consistent with that of the overall nOH population
- No signal for worsening of supine hypertension

ADHD, attention-deficit/hyperactivity disorder; MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson disease.

CYPRESS Topline Readout will Provide an Extensive Data Set

Population

- Patient disposition: status during OL and RW
- Baseline characteristics: demography, clinical characteristics and OHQ scores

Efficacy

- Primary endpoint: OHSA composite score
- Secondary endpoints: OHDAS1 and OHDAS3
- Exploratory endpoint: blood pressure (seated, supine and standing)
- Forest plot of OHQ compositions score and individual items (e.g., dizziness, etc.), longitudinal analysis

Safety

Adverse events and serious adverse events

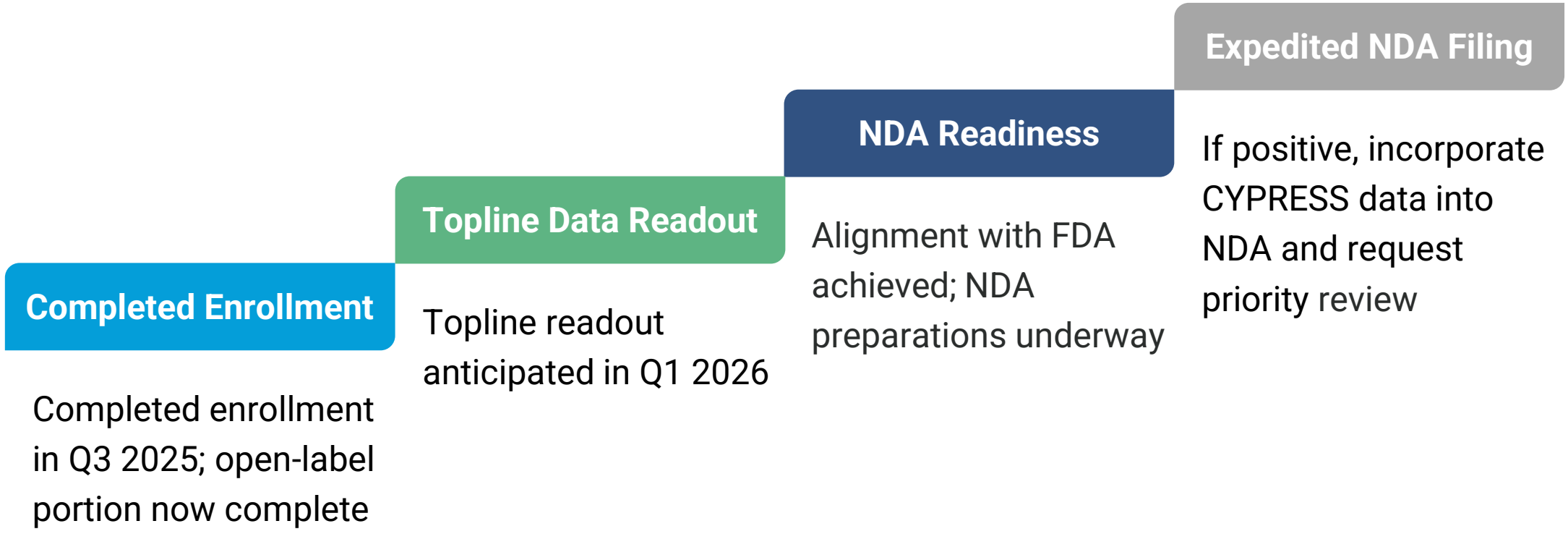
Clinical meaningfulness

Meaningful change thresholds for OHSA composite score

CYPRESS study replicated the elements that led to the observed benefits in patients with MSA in the REDWOOD study

OHDAS, orthostatic hypotension daily activity scale; OHQ, orthostatic hypotension questionnaire; OHSA, orthostatic hypotension symptom assessment; OL, open-label; RW, randomized withdrawal.

Positioned to Capitalize Rapidly Upon Potential Positive Readout from Pivotal Phase 3 CYPRESS Trial



FDA, U.S. Food and Drug Administration; NDA, new drug application.

Commercial Opportunity

Rhonda Farnum
Senior Vice President,
Chief Business Officer

Concentrated, Rare Neurology Market with Potential Therapeutic Breakthrough

Concentrated rare neuro market + high unmet need globally + rare disease economics =

Blockbuster Potential

KOL, key opinion leader, MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension.

1. Palma, Kaufmann. Epidemiology, Diagnosis, and Management of Neurogenic Orthostatic Hypotension; Kalra DK, et al. Clin Med Insights: Cardiol. 2020 14:1179546820953415. 2. Kaplan et al., Parkinsonism Relat Disord. 2023 Dec:117:105920; UCSD Dept. of Neurosciences : https://neurosciences.ucsd.edu/centers-programs/movement-disorders/community/disease-overview/msa.html; Internal claims analyses (IQVIA, Veeva, Real Chemistry), CD-10 Codes: G90.3, G23.2.

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Significant Commercial Opportunity for Ampreloxetine Given Available Treatments

Only ~34% of patients are treated, current therapies limited in this patient population[1]

	Ampreloxetine (investigational)[2]	Current Treatment Landscape[3]	
		Midodrine	Droxidopa
Indication	Symptomatic nOH in patients with MSA	Symptomatic OH	Symptomatic nOH
Efficacy-Primary Endpoint	OHSA Composite Score	Increase in systolic blood pressure	OHSA Item #1
Durability of Response	20 weeks (CYPRESS Study Design)	Effectiveness not studied beyond 3-4 weeks	Effectiveness beyond 2 weeks has not been established
Dosing	1x/day *No titration or dose adjustment*	3x/day	3x/day *Requires titration*
Supine Hypertension	No worsening of supine hypertension observed in clinical studies to date	Boxed warning for increased risk of supine hypertension	

Fludocortisone is used off-label as volume expander, despite limited evidence, with 1x/day dosing (requires titration). Adverse events include hypertension, edema and congestive heart failure; requires strict monitoring of blood pressure and potassium

MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; OHSA, orthostatic hypotension symptom assessment.
1. Veeva Compass patient-level claims data, MSA patients (G90.3) with at least 1 Rx from 2020-2023. Product share defined as total "days supplied" in this patient population.
MSA, multiple system atrophy; nOH neurogenic orthostatic hypotension. . 2. Reflects Theravance Biopharma's expectations for ampreloxetine. Ampreloxetine is in development and not approved for any indication. No conclusion can be drawn regarding its safety or efficacy. Data on file. 3. The information in the table presents factual information gathered from approved product prescribing information and are not intended to make comparisons of available therapies and investigational drug as there are no head-to-head comparative studies or data supporting any such comparisons.

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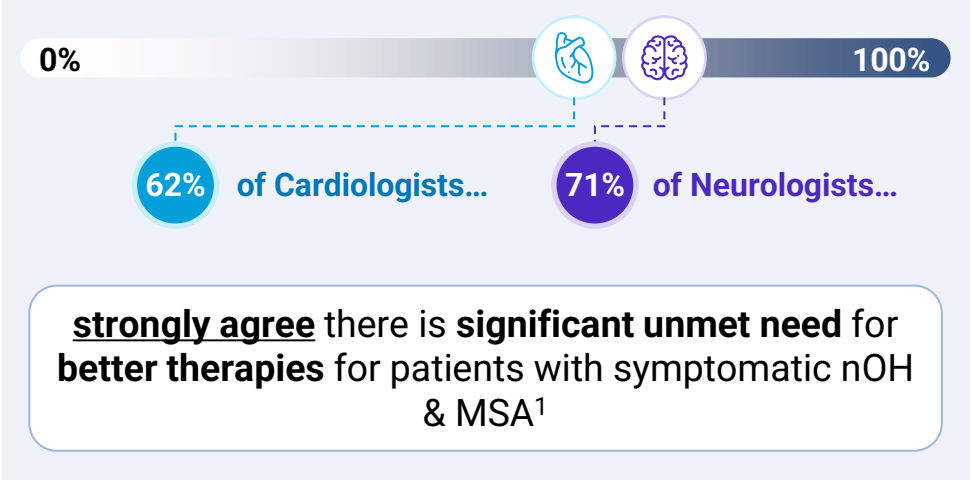
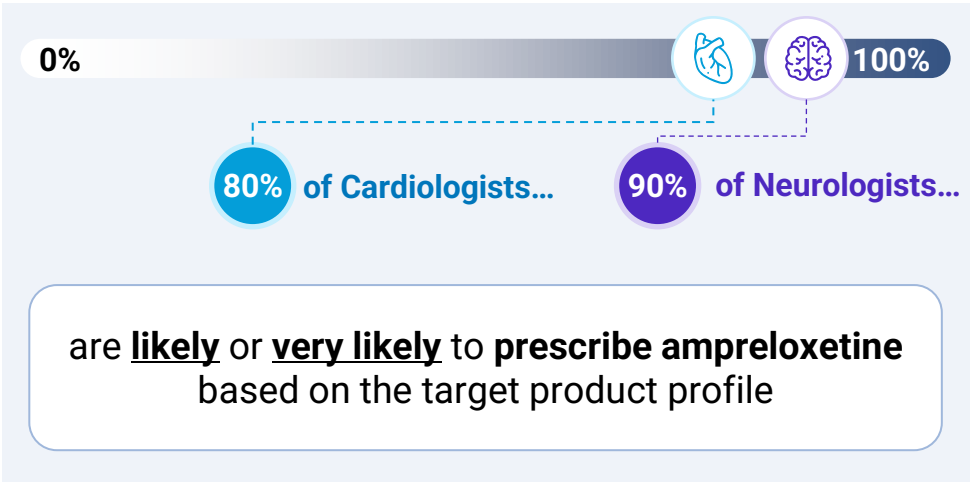
Ampreloxetine has an Opportunity to Address the Significant Unmet Need In nOH Treatment with its Unique Target Product Attributes

Majority of HCPs acknowledge significant unmet need for better nOH treatments in MSA



> ***Options are generally limited** to begin with. But **given the efficacy, lack of supine hypertension and convenience of dosing, it would be a no-brainer**.*
>
> Neurologist

Majority of HCPs have favorable reactions to ampreloxetine's target product profile



> *Easier to use with **less side effects. Once daily** is very attractive. Also, **no dosage adjustments** needed for multiple medical conditions is attractive.*
>
> Cardiologist

HCP, healthcare professional; MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension.
1. N=200 board certified neurologists (n=150) and cardiologists (n=50) treating MSA patients and familiar with nOH diagnosis and treatment.
Survey Questions: Based on your experience in managing MSA patients with symptomatic nOH, please indicate your level of agreement with the following statements. Please use a 7-point scale where 1=Do not agree at all and 7=Strongly agree. Assuming coverage and cost to the patient is on par with existing treatments, and assuming full FDA approval, how likely would you be to prescribe Product X [ampreloxetine] in the future?

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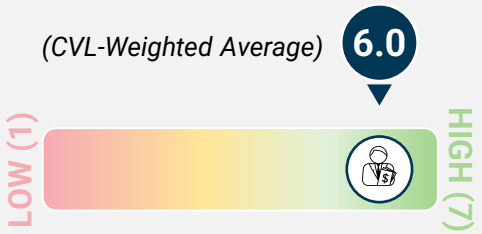
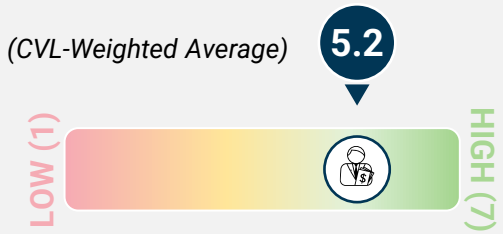
Payers Acknowledge its High Burden and Large Unmet Need for Novel Treatments

Disease Burden



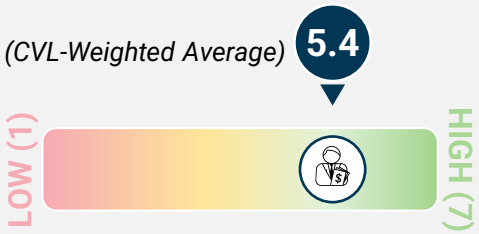
Payers recognize **high disease burden of MSA,** driven by mortality, disability, and **nOH's impact on daily living**

Economic Burden



Payers acknowledge the **economic burden of MSA-related nOH** is **driven mainly by indirect / medical costs**, such as hospitalizations from falls

Perceptions of Unmet Need



Payers are aware of unmet **need for novel nOH treatments**

Enhanced symptomatic agents that improve quality of life and avoid costly complications would be valued

> *I think [nOH] is a **major consideration** because that **immediately impacts activities of daily living, functionality**, etc. You're completely debilitated to a certain extent.*
>
> Payer

> *…the **syncope related to nOH is a problem** because this is an older population and **falls put patients at this age in the hospital**.*
>
> Payer

CVL, covered lives; MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension.
Source: Trinity Pre-Topline Ampreloxetine Pricing and Demand Opportunity Assessment June 2025 (N=10 Payers).

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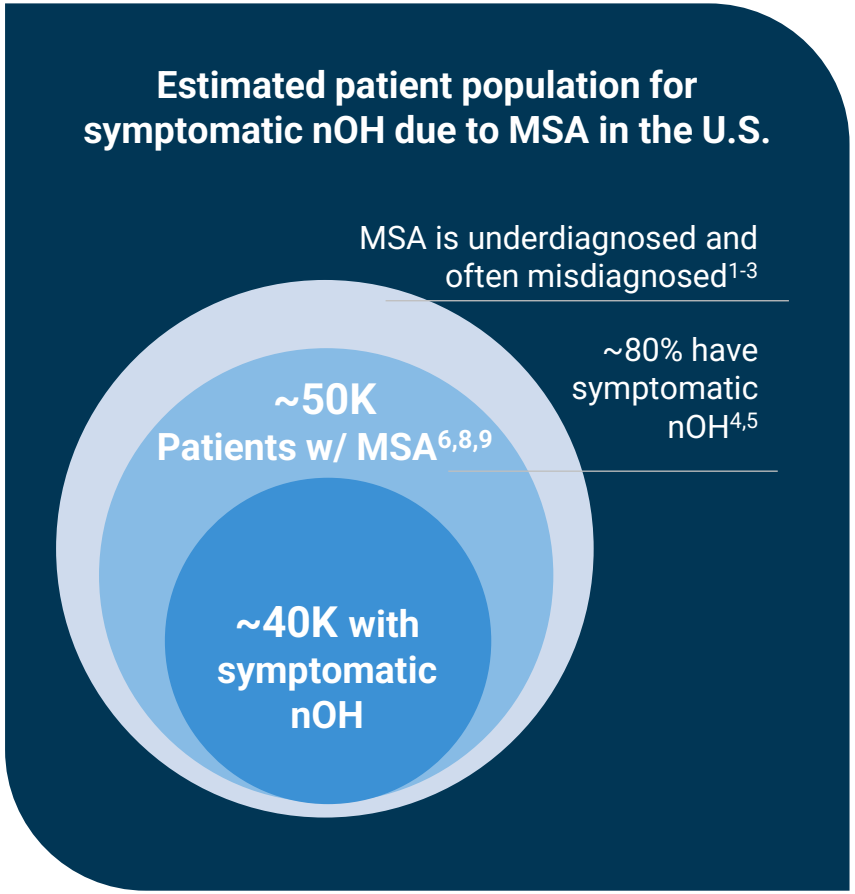
~40,000 Patients with MSA Suffer from Symptomatic nOH in the U.S.

Epidemiology supported by detailed claims analysis, substantiated by several leading institutions



Claims level analysis supports epidemiology assumptions:

- U.S. patient-level claims data using ICD-10 codes most commonly associated with MSA[6]
- Coding practices validated through external experts[7]
- Similar claims-based analysis published in 2023[8]
- Leading institutions support estimated epidemiology (e.g., UCSD[9], NIH)

Linking patients to treating specialists:

- Initial targeting efforts suggest treating physicians are highly concentrated within **autonomic and movement disorder centers, large neurology groups, and select academic institutions**
- Approach enables efficient deployment of commercial and medical resources across a **small, specialized physician universe**

MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension.
1. Krismer F, et al. Lancet Neurol. nOH2024;23(12):1252-1266. 2. DeRight J. Multiple System Atrophy. In: Essential Neuropsychology: A Concise Handbook for Adult Practitioners. Springer; 2021. 3. Goolla M, et al. Frontiers in Neurology. 2023;14:1210220. 4. Palma, Kaufmann. Epidemiology, Diagnosis, and Management of Neurogenic Orthostatic Hypotension. 5. Kalra DK, et al. Clin Med Insights: Cardiol. 2020 14:1179546820953415. 6. Internal claims analyses (IQVIA, Veeva, Real Chemistry); ICD-10 Codes: G90.3, ~90% of patients, and G23.2, ~10%. 7. Medical coding consultant, as well as primary market research with EHR specialists, billing & coding specialists, neurologists, and movement disorder specialists. 8. Estimating the prevalence and incidence of multiple system atrophy in the USA: Insights from a national claims database, Parkinsonism and Related Disorders 11/4/2023. 9. UCSD Dept. of Neurosciences (25K-75K): https://neurosciences.ucsd.edu/centers-programs/movement-disorders/community/disease-overview/msa.html.

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Launch Strategy to Focus on Establishing Ampreloxetine as the Standard of Care for Patients with nOH Due to MSA

Insights from Rare Disease Launches

- Centers of excellence are critical
- Peer-to-peer influence
- Early engagement with payers builds understanding
- Patient advocacy groups serve as “disease authority”
- Patients and caregivers are highly connected knowledge seekers

Strategic Priorities for Ampreloxetine Successful Launch

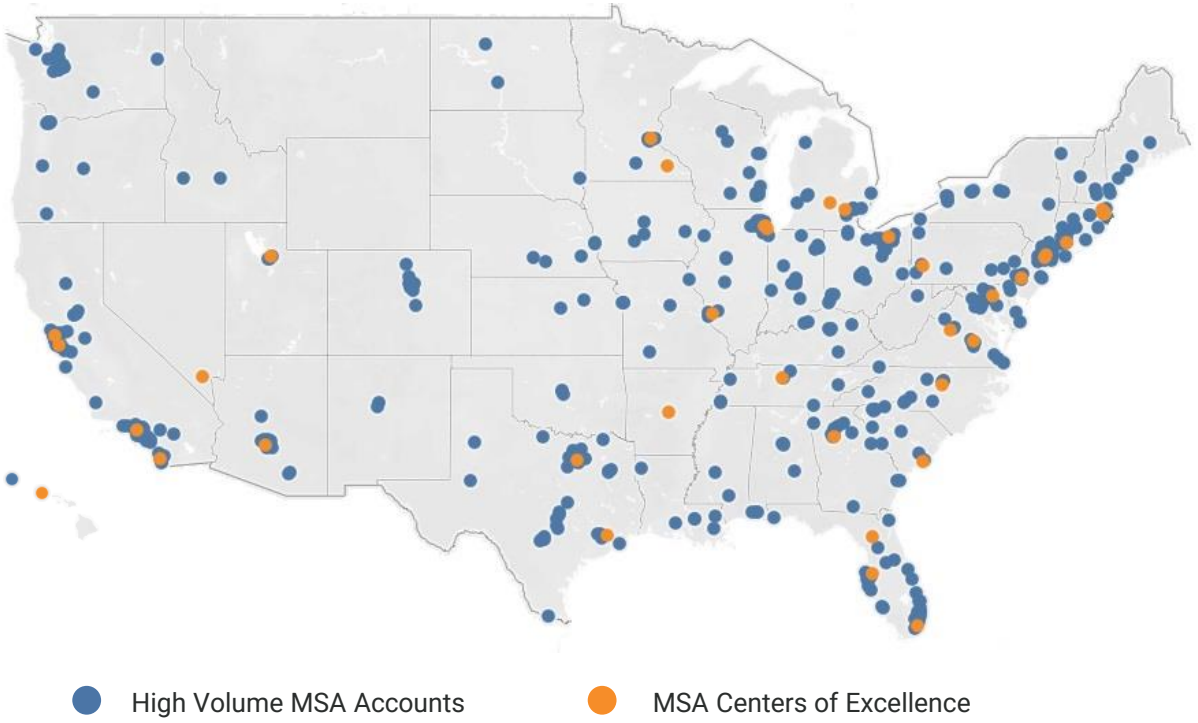
1. Drive urgency to improve outcomes in patients with nOH due to MSA
2. Establish ampreloxetine as the only treatment studied and approved for patients with nOH due to MSA
3. Create a seamless, positive customer experience with ampreloxetine

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

Targeted Launch Plan Leverages Concentrated MSA Treatment Landscape

Lean commercial infrastructure required for focused execution

High Volume MSA Accounts[1] and Centers of Excellence[2]



~550
High Volume MSA Accounts[1]

~90
MSA Specialists with 10+ Patients[1]

40
MSA Centers of Excellence

26
CYPRESS Trial Sites (U.S.)

Investment plans aligned with lean, rare-disease industry benchmarked spend

MSA, multiple system atrophy.
1. Veeva Compass patient-level claims data, MSA patients (G90.3), 2022-2024. 2. Centers of Excellence: https://missionmsa.org/resource-library/centers-of-excellence-overview/, https://www.psp.org/centers-of-care, accessed Nov 5, 2024.

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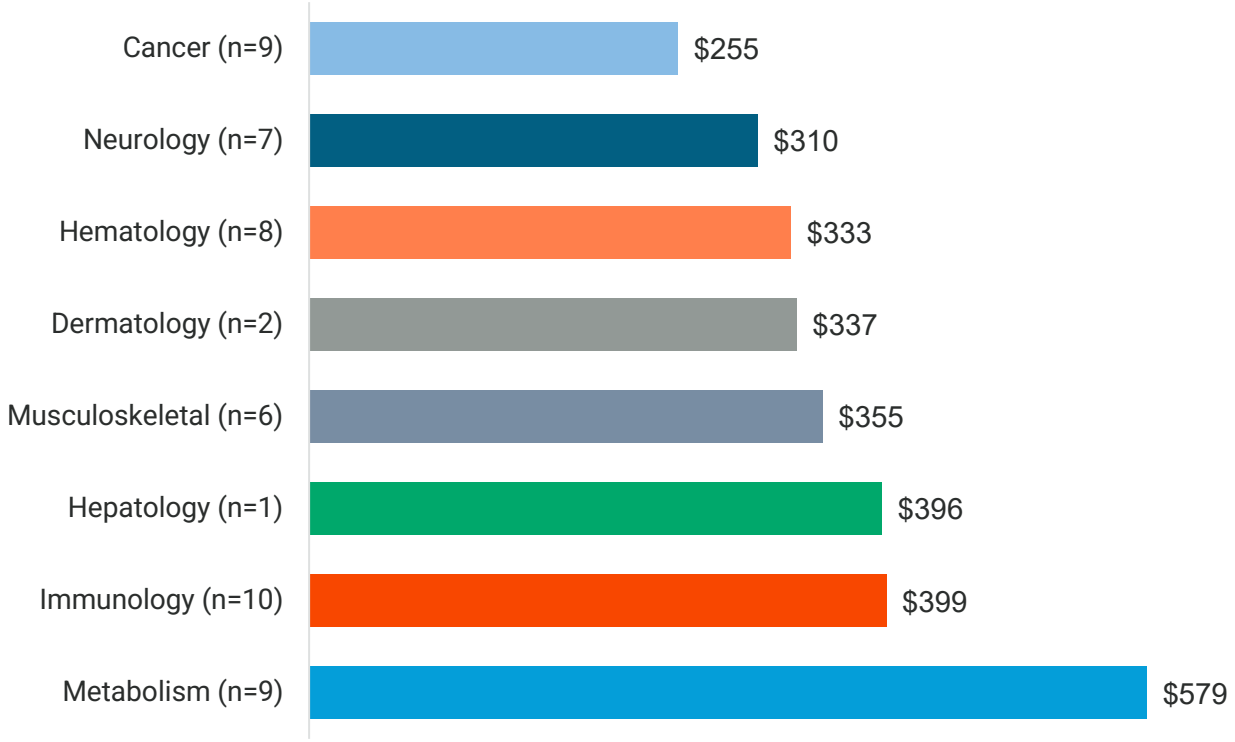
Premium Value Opportunity Driven by Unmet Need and Clinical Impact

Pricing Expectations Consistent with Recent Rare Disease Approvals

Rare Disease Launches ('21-'24)[1]

Average launch price ($K) for chronic therapies by therapeutic area (n=52)



Ampreloxetine is well positioned to redefine expectations for patients with nOH due to MSA

Serious disorder with negative consequences
For ~80% of patients with MSA, nOH is a driver of morbidity, mortality, and healthcare burden

Value for patients and caregivers
Treating nOH equates to functional benefit — reducing dependency and the burden of the constellation of symptoms patients experience

Targeted, Orphan Drug Opportunity
Overall low total budget impact; potential ~40K patients in the U.S.[2,3]

MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension.
1. Cantor Fitzgerald, Biotechnology Equity Research, April 11, 2024. Includes 63 drugs approved in the US between 1/22/2021-3/21/2024; average launch price based on WAC (wholesale acquisition cost).
2. Palma, Kaufmann. Epidemiology, Diagnosis, and Management of Neurogenic Orthostatic Hypotension; Kalra DK, et al. Clin Med Insights: Cardiol. 2020 14:1179546820953415. 3. Kaplan et al., Parkinsonism Relat Disord. 2023 Dec:117:105920; UCSD Dept. of Neurosciences : https://neurosciences.ucsd.edu/centers-programs/movement-disorders/community/disease-overview/msa.html; Internal claims analyses (IQVIA, Veeva, Real Chemistry), CD-10 Codes: G90.3, G23.2.

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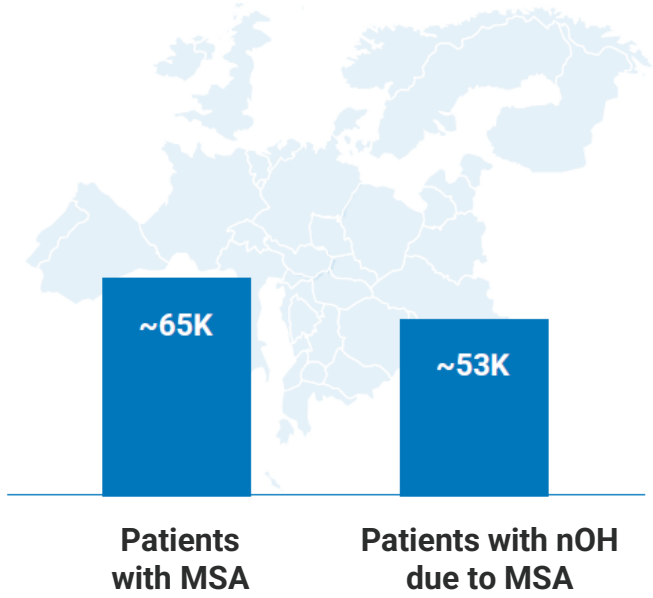
Meaningful Market Opportunity for Ampreloxetine Exists in Europe and Asia

Prevalence in Europe[1,2]

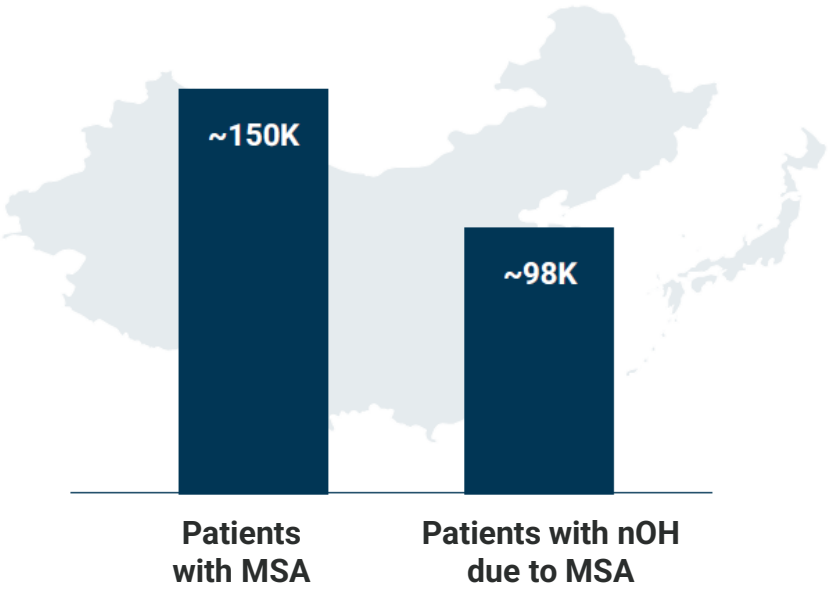
45-60K MSA Patients with nOH



- 28 CYPRESS study sites in EU
- Existing relationships with KOLs and patient advocacy groups
- Will seek EMA scientific advice/ marketing authorization following CYPRESS readout

Prevalence in China & Japan[1]

90-105K MSA Patients with nOH



- nOH included in medical treatment guidelines for patients with MSA
- Specialist networks in place
- Droxidopa is the only approved medication in Japan

EMA, European Medicines Agency; EU, European Union; KOL, key opinion leader; MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension.

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Ampreloxetine: Potential to Transform Care in a Rare and Debilitating Disease

- Rare disease neurology market with **blockbuster potential**
- **De-risked Phase 3 program** designed FDA with alignment
- **Potential to become standard of care** for symptomatic nOH in MSA
- **Lean commercial model** enabled by concentrated treatment landscape
- **Meaningful ex-U.S. opportunity**
- **Near-term catalyst:** Phase 3 data expected Q1 2026

FDA, U.S. Food and Drug Administration; MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension.


Questions?
Answers.