Ampreloxetine in MSA: A pre-specified subgroup analysis of a phase 3, double-blind, placebo-controlled, randomized withdrawal trial

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DISCLOSURES

- LNK, RV, and TG have received personal compensation as employees and shareholders of Theravance Biopharma, Inc. HK, RF, IB, JJ and VI have received consultancy fees from Theravance Biopharma. HK and VI received funding through academic grants for research support from Theravance Biopharma

INTRODUCTION

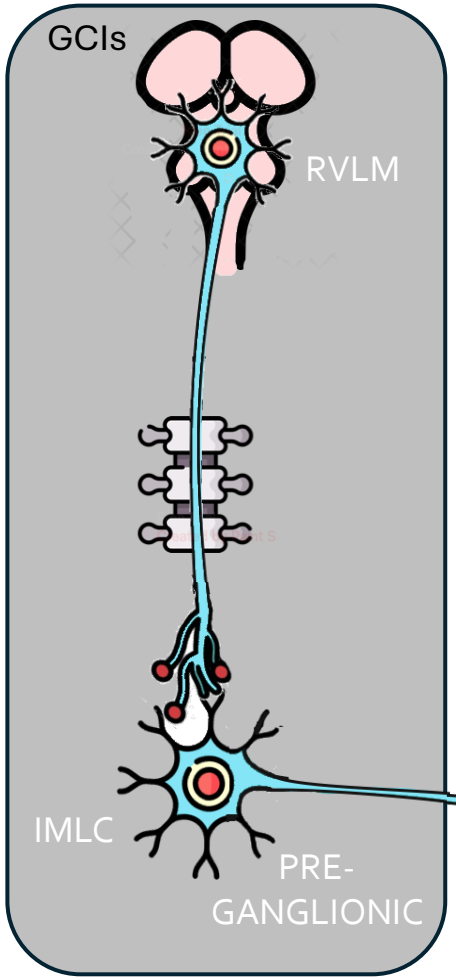
- 70-80% of patients with MSA will develop nOH in their lifetime[1]
- This adds significant disability, functional decline, and risk of early death from all-cause mortality
- Despite treatment with available pressor agents, 68% of MSA patients with nOH remain symptomatic[2]
- Ampreloxetine is a novel, long-acting, norepinephrine reuptake inhibitor being tested as a treatment for nOH in phase III trials

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

nOH

Underlying pathology in MSA

GCIs in the striatonigral & olivopontocerebellar systems, and central autonomic network



- This pathology is unique to MSA
- No drug has been developed for nOH specifically for patients intact peripheral autonomic neurons still capable of releasing NE

GANGLIA

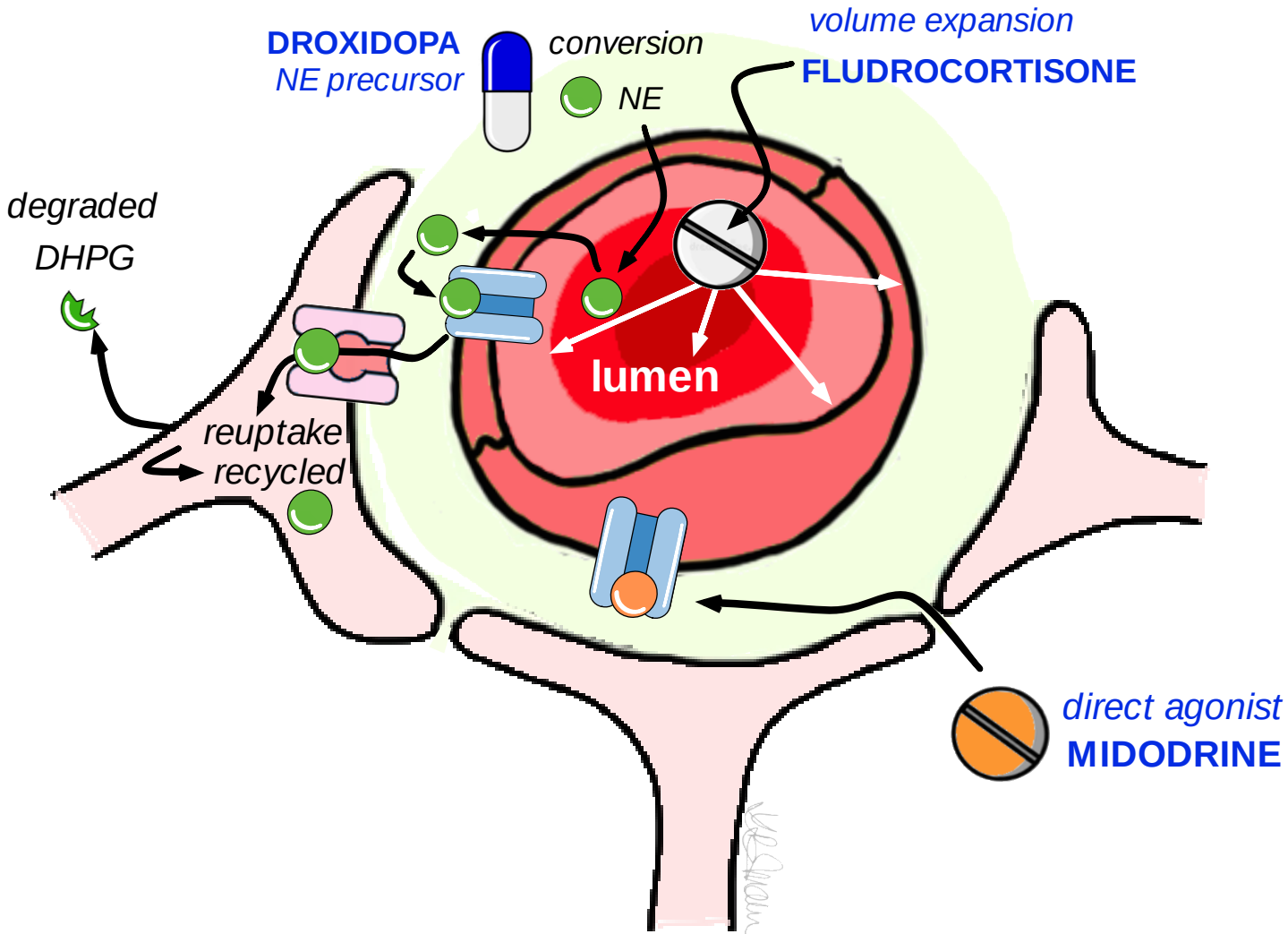
Relative sparing

PERIPHERAL
AUTONOMIC NEURONS

- Normal NE levels
- Impaired physiological release

Pharmacological strategies for nOH

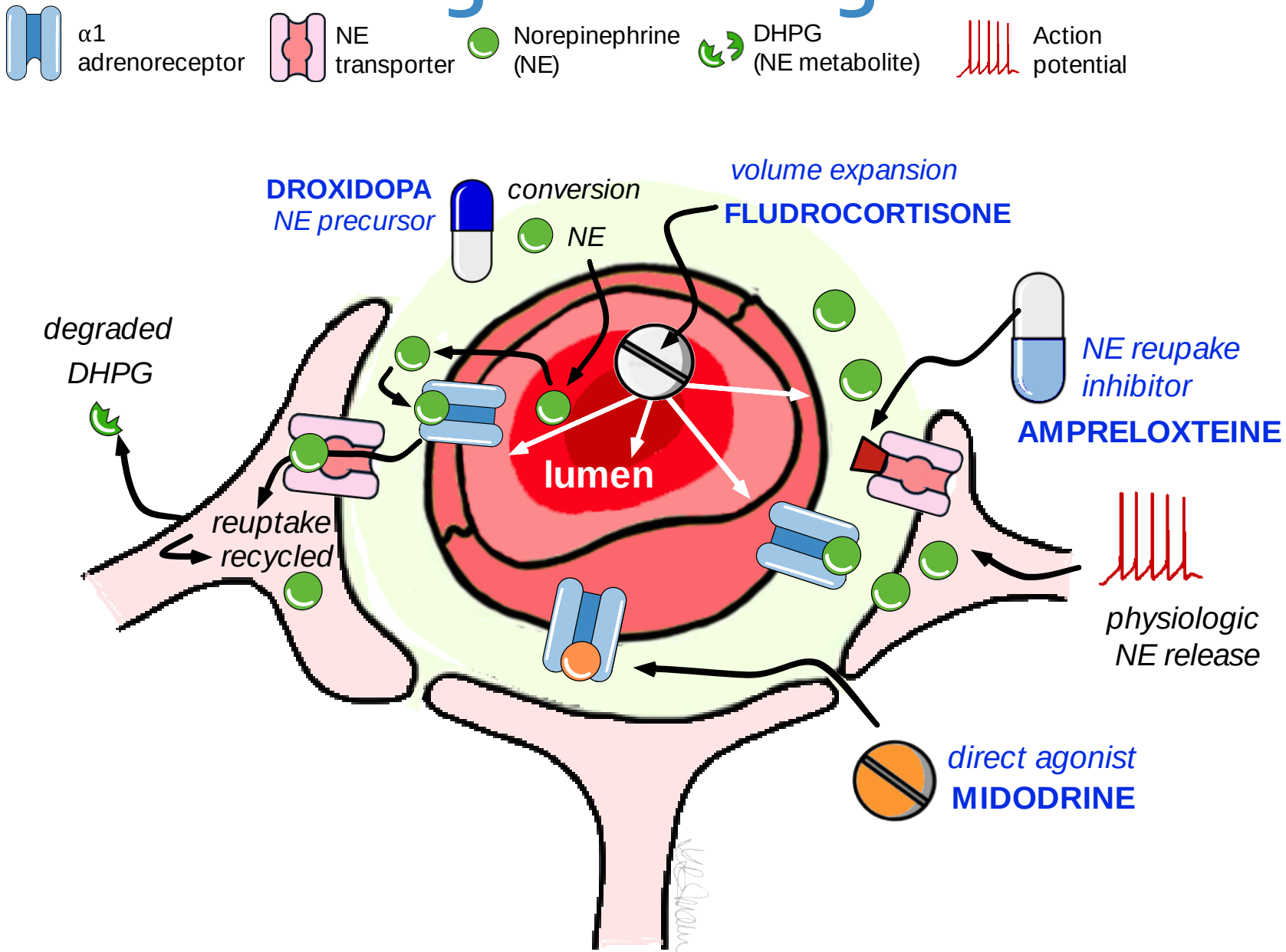
α1 adrenoreceptor | NE transporter | Norepinephrine (NE) | DHPG (NE metabolite) | Action potential



UNMET NEED

- Both FDA-approved pressor agents act on vascular α1-adrenoreceptors at the neurovascular junction
- Both approved agents carry Black-Box Warnings for supine hypertension
- Both can lead to tachyphylaxis with no effect

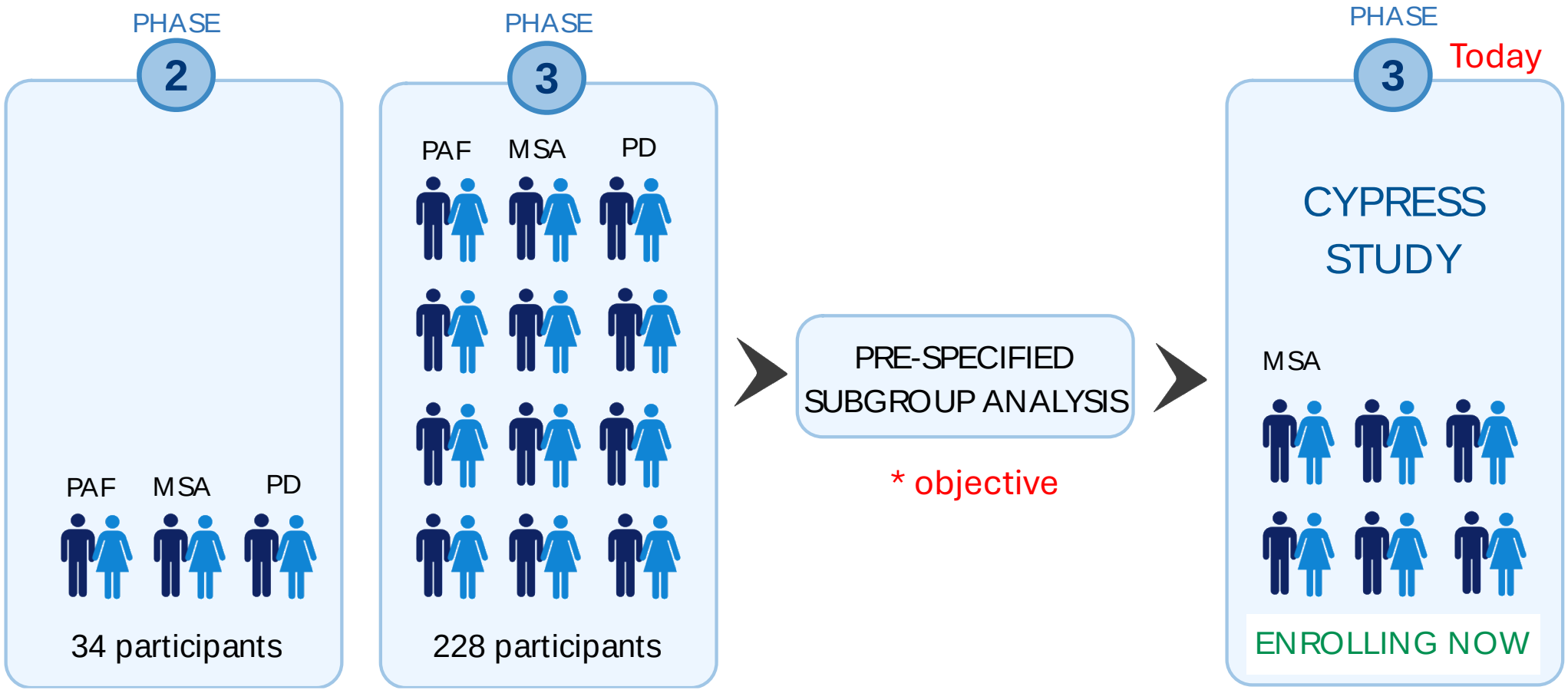
Pharmacological strategies for nOH



AMPRELOXETINE

- Ampreloxetine in MSA targets the right treatment to the right patient at the right time
- Enhances NE availability on standing
- This precise mechanism of action is ideally suited to patients with MSA and central degeneration

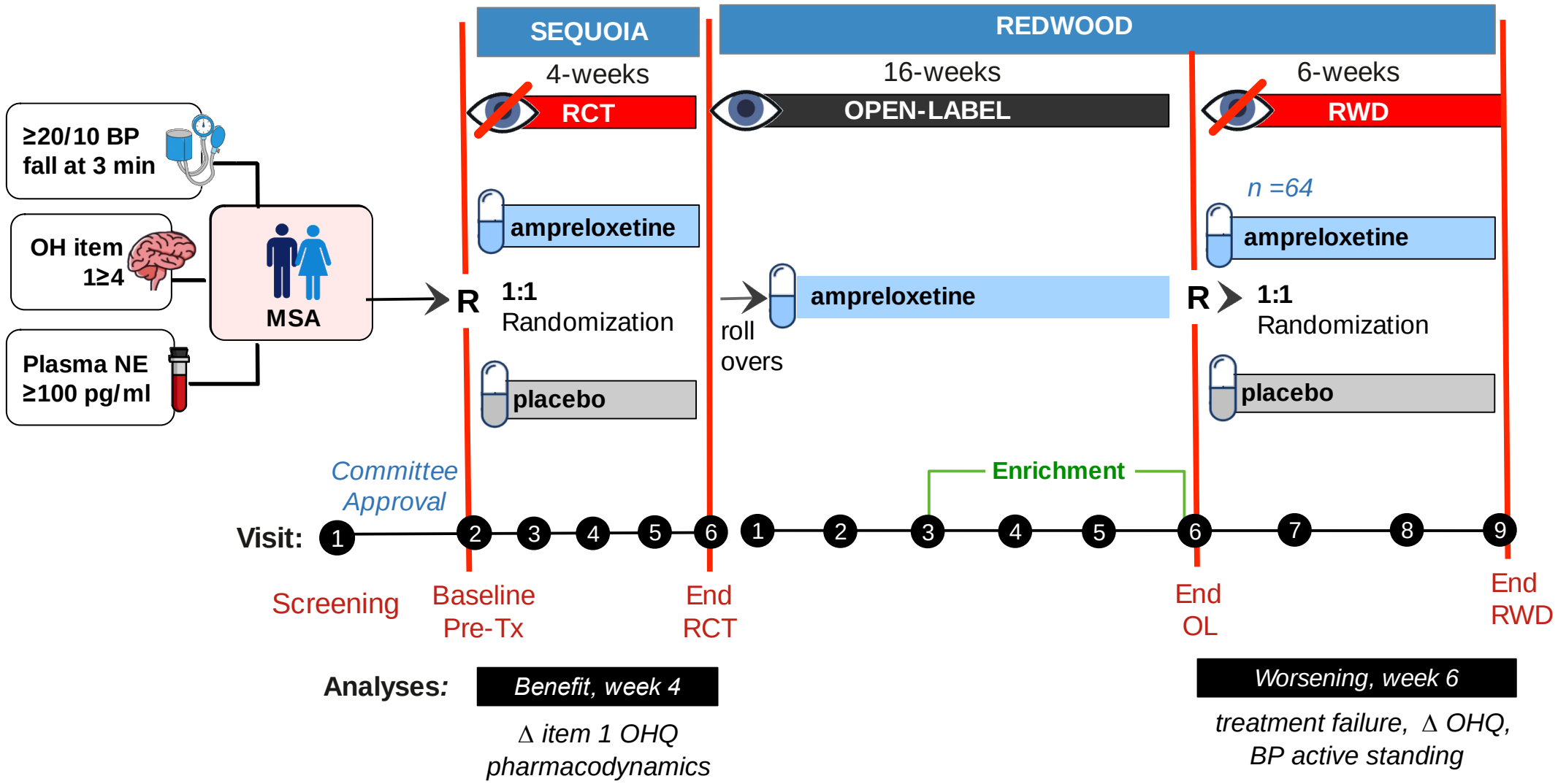
AMPRELOXETINE nOH PROGRAM



OBJECTIVE

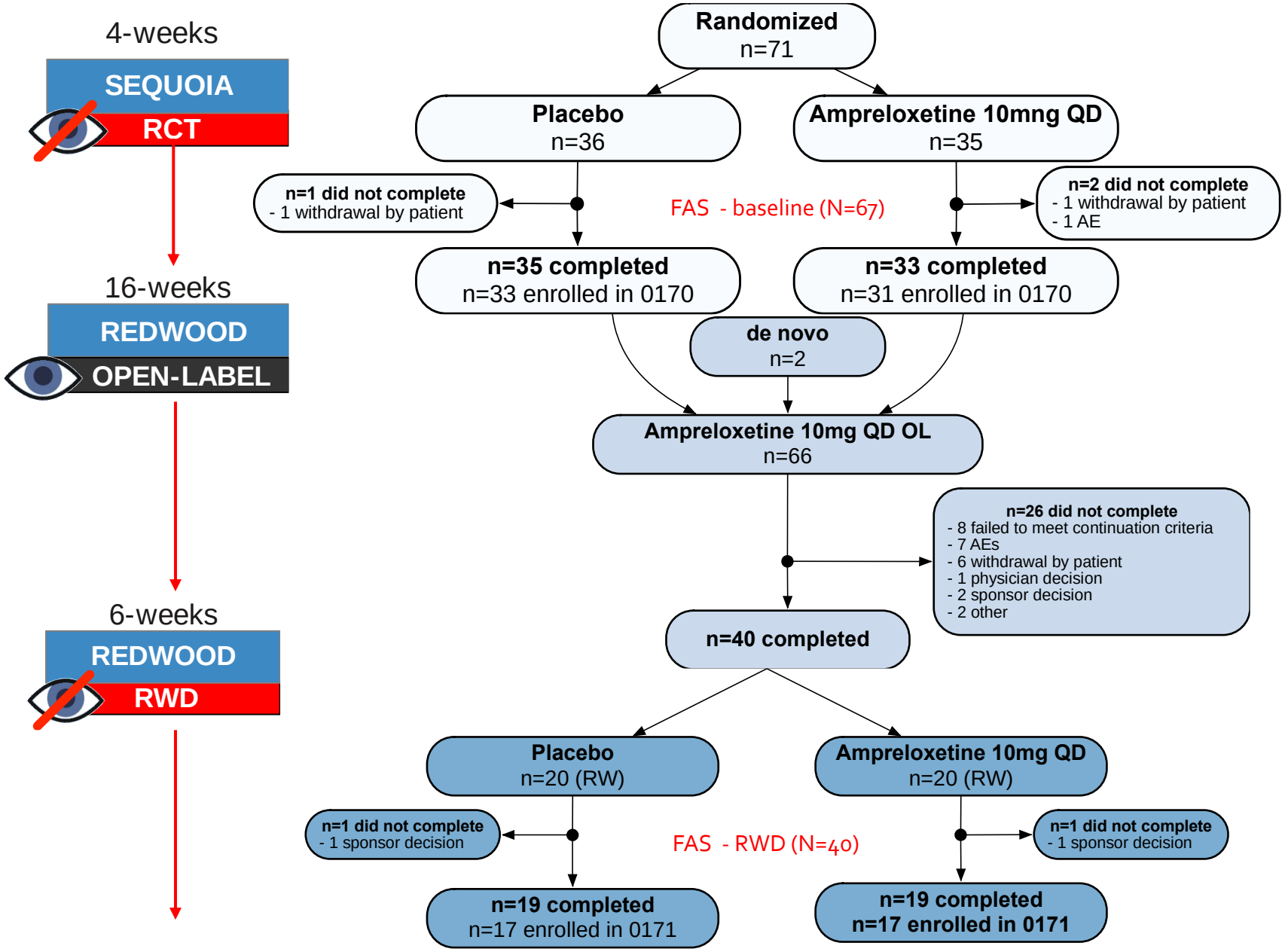
- A pre-specified subgroup analysis of ampreloxetine (oral, 10 mg/once-per-day) for neurogenic orthostatic hypotension (nOH) in patients with multiple system atrophy (MSA)

METHODS: Protocol Design and procedures



RESULTS

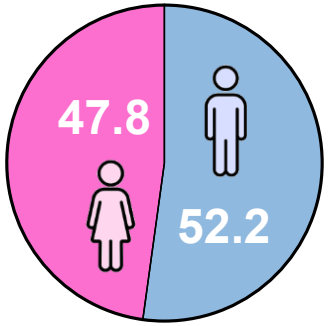
PATIENT FLOW



RESULTS: Baseline (pre-treatment) Characteristics

Well-balanced between groups (FAS, SEQUOIA)

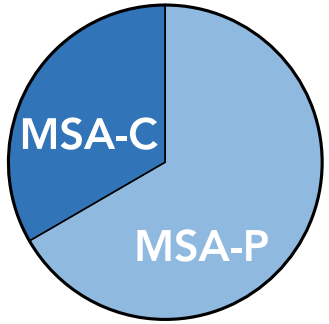
DEMOGRAPHICS



94%
WHITE

63.5Y
AGE

FEATURES OF MSA



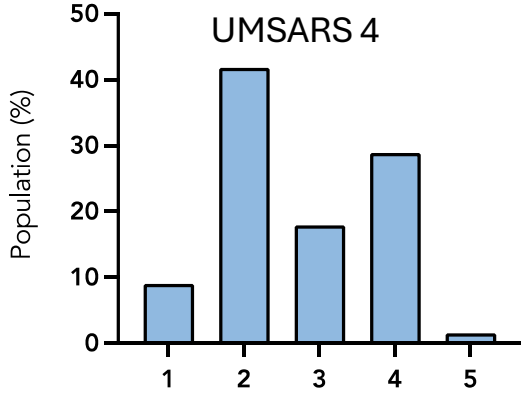
UMSARS
PART 1
20.9

PART 2
22.5

40.3%
IMBALANCE/FALLS

1.6Y
SINCE DIAGNOSIS

67.2%
DOPAMINERGIC MEDICATIONS



70.2%
USED A WALKING AID

NEUROGENIC OH

SYSTOLIC 142.0
DIASTOLIC mmHg 85.6

HEART RATE
70.2
bpm

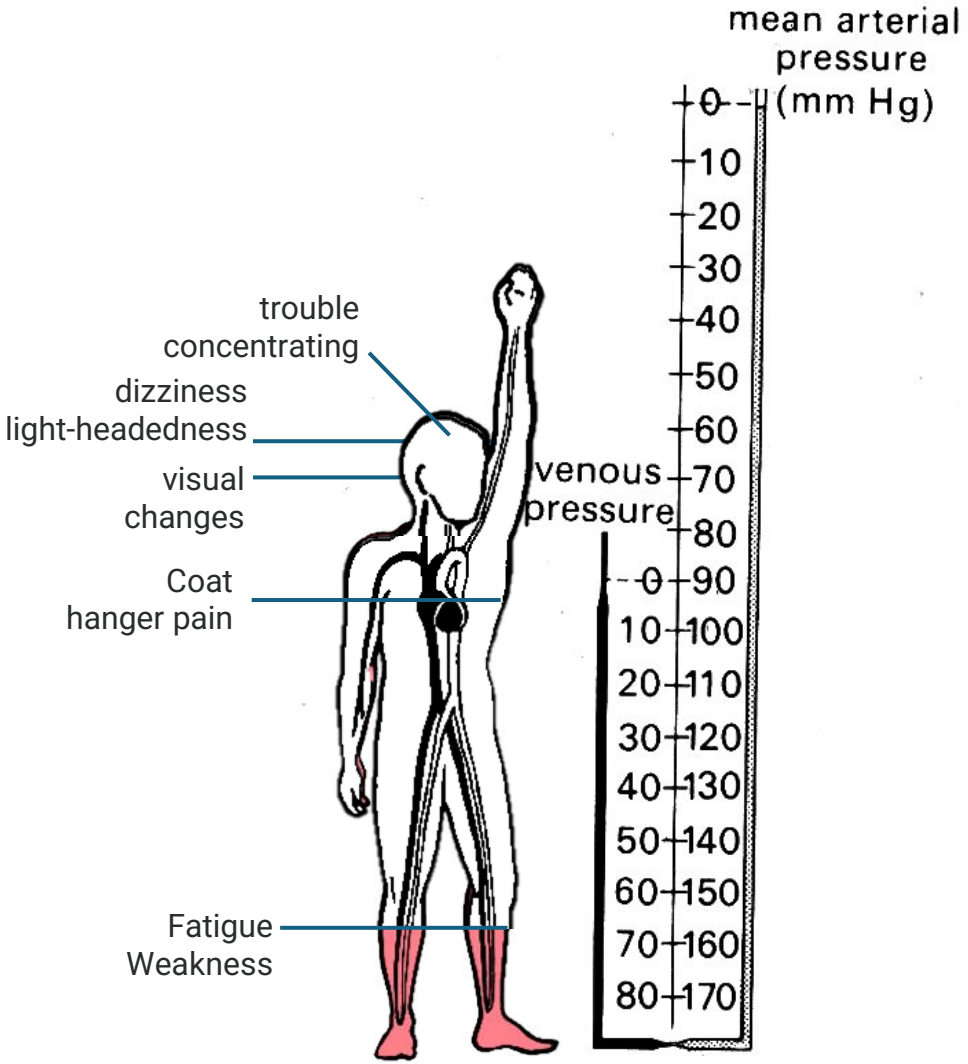
SYSTOLIC mmHg 99.4
DIASTOLIC 67.2

HEART RATE
83.1
bpm

2.1Y
nOH DURATION

44.8%
PRIOR nOH DRUG

nOH SYMPTOMS ASSESSMENT

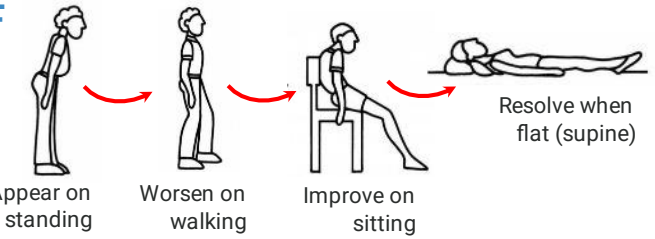


MEASURABLE OUTCOME

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

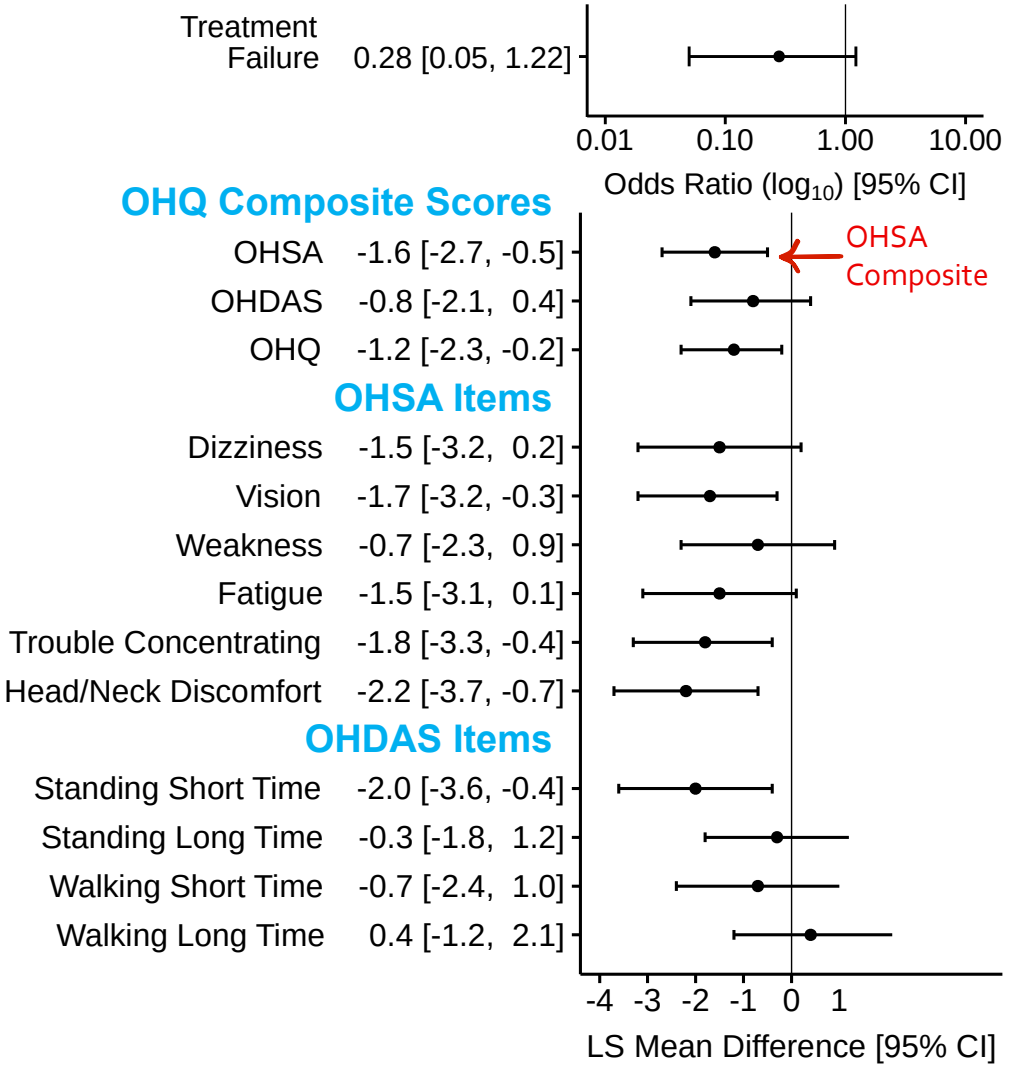
Kaufmann H, Malamut R, Norcliffe-Kaufmann L, Rosa K, Freeman R Clin Auton Res. 2012 Apr;22(2):79-90.

RESULTS: Symptom burden and function

6-weeks

REDWOOD RWD

REDWOOD, FAS n=40



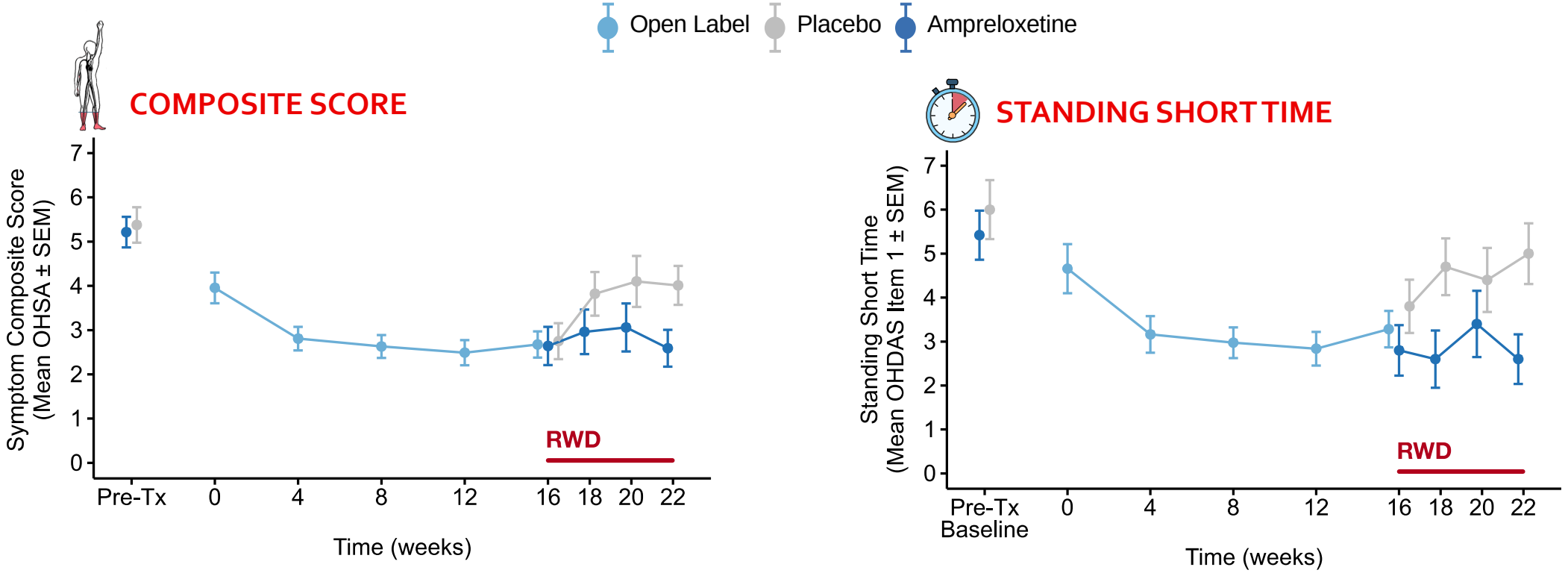
FINDINGS

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

RESULTS: Symptom burden and function

6-weeks
REDWOOD
RWD

REDWOOD, FAS n=40



FINDINGS

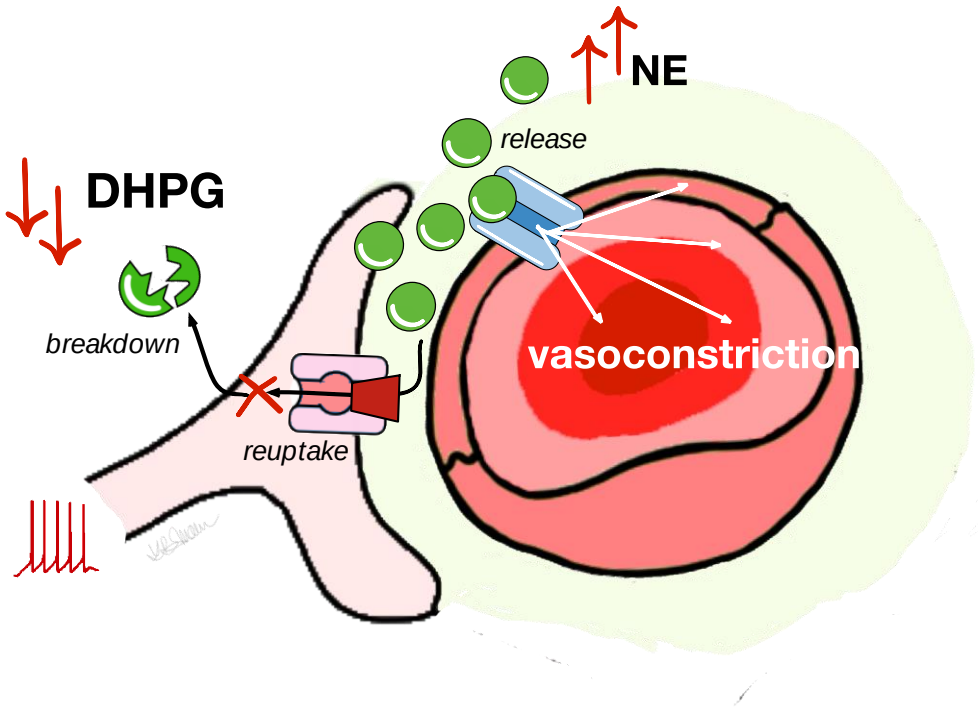
- Self-reported scores show symptomatic benefit with improvement in activities of daily living that was lost after ampreloxetine was withdrawn

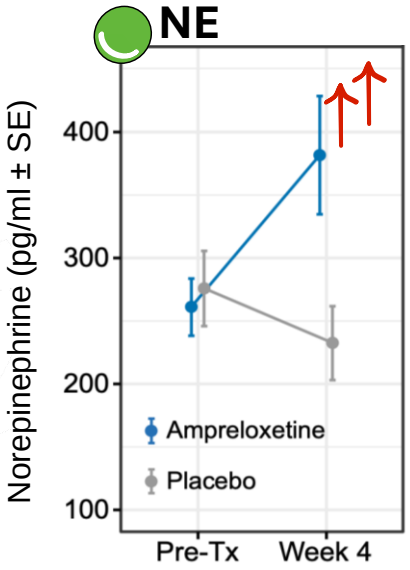
RESULTS: Pharmacodynamics

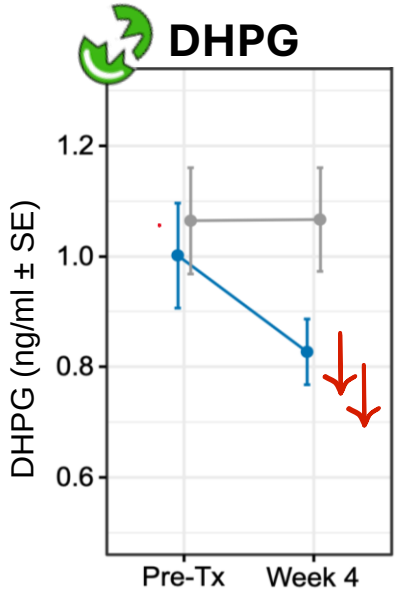
4-weeks

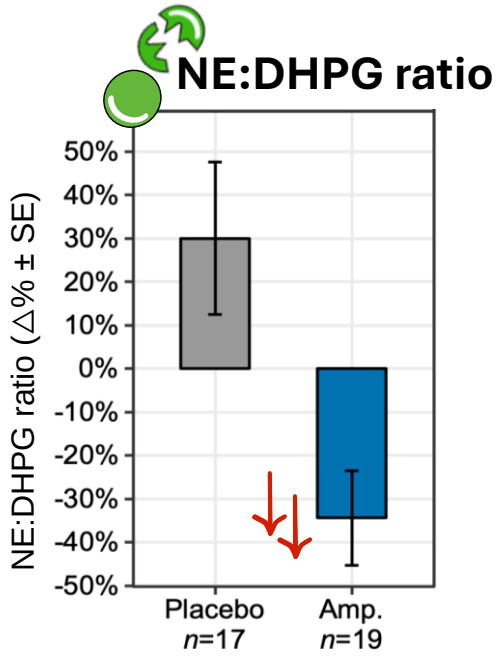
SEQUOIA RCT

Catecholamines, seated, HPLC analysis, SEQUOIA FAS n=67







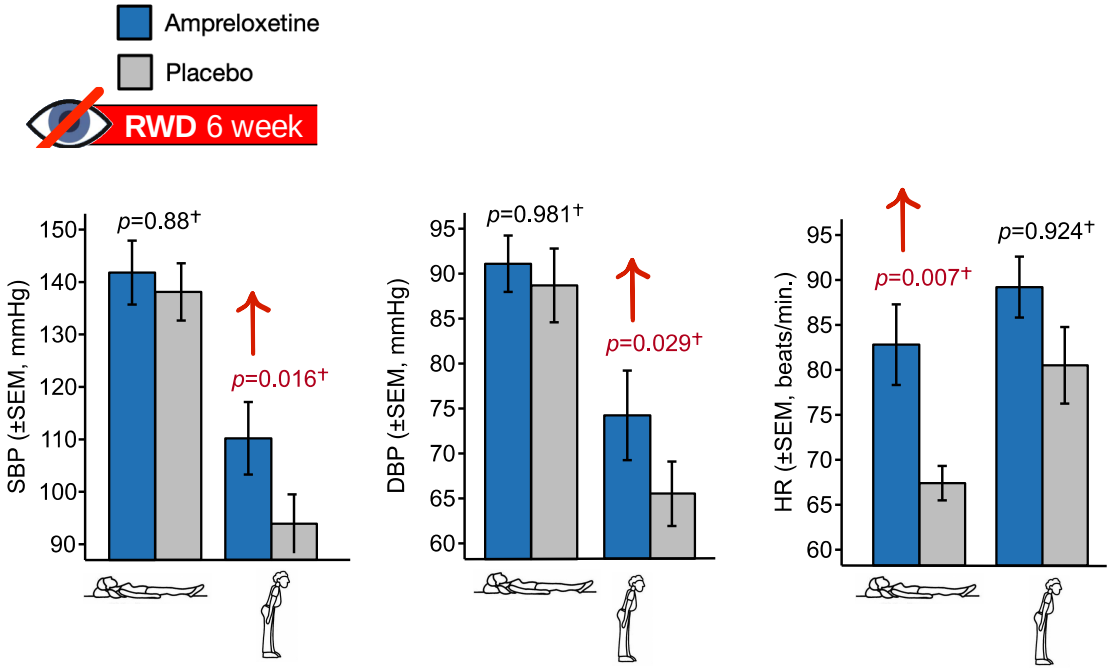


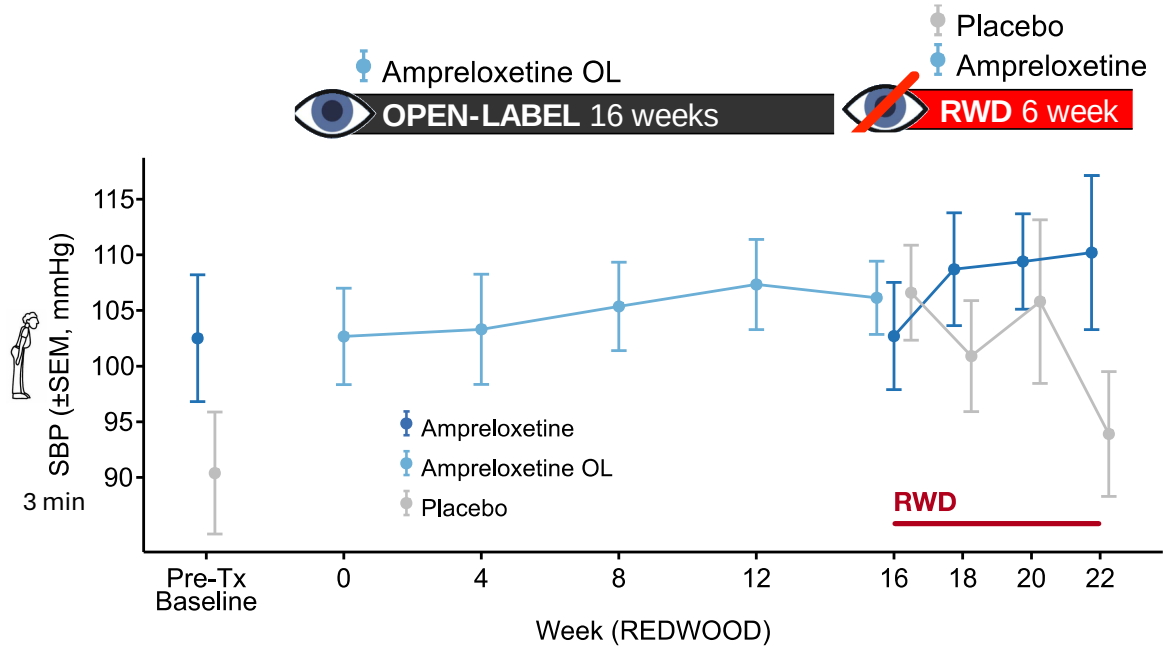
FINDINGS

- Profile was consistent with the activity of a highly selective peripheral NE transporter inhibitor

RESULTS: BP and HR

BP and HR, REDWOOD FAS n=40





FINDINGS

- A pressor effect was observed over 16-weeks of open-label treatment, that was lost after 6-weeks of placebo withdrawal

CONCLUSIONS

- This pre-specified subgroup analysis of MSA patients entering the ampreloxetine RW trial show a durable symptomatic benefit with improvement in activities of daily living that was lost after ampreloxetine was withdrawn
- The pharmacodynamic profile of ampreloxetine was consistent with the activity of a peripheral NE transporter inhibitor, and a sustained improvement in orthostatic BP, through a pressor effect mediated by increased venous NE levels

FUTURE DIRECTIONS

- This targeted therapy is ideally suited to patients with intact peripheral autonomic neurons and uses a highly specific NE re-uptake inhibitor to restore residual peripheral autonomic nerve function on standing
- We are now nearing completion of the ampreloxetine CYPRESS study, which is dedicated to patients with MSA (NCT # 05696717).
- If these findings are reproducible, ampreloxetine would be the first example of precision medicine in autonomic neurology, with a targeted treatment for nOH in the rare fatal disease MSA