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

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Introduction

- Neurogenic orthostatic hypotension (nOH) causes considerable disability in patients with multiple system atrophy (MSA)
- The underlying pathology involves degeneration of the central autonomic network with relative sparing of the peripheral autonomic neurons, which is unique to MSA
- Current FDA-approved pressor agents that target the vascular adrenergic receptors:
  1. Do not account for any residual peripheral autonomic neurons capable of releasing norepinephrine
  2. Are often ineffective long-term
  3. Carry Black Box warnings for supine hypertension

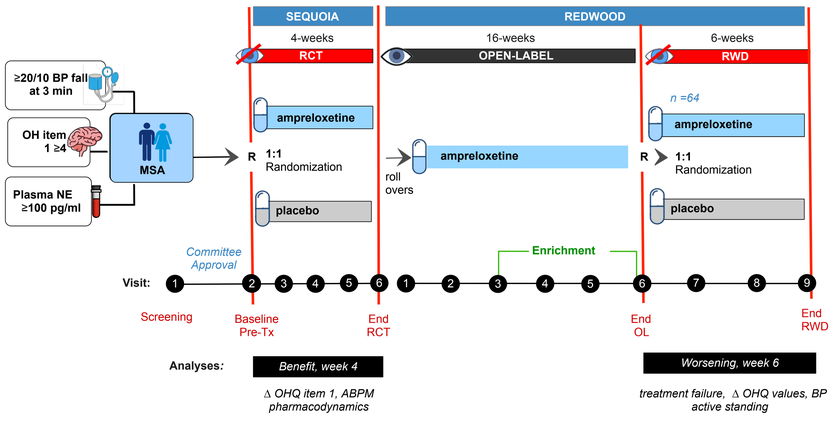
Objective

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

Methods

- REDWOOD was an international phase 3, placebo-controlled, double-blind, randomized withdrawal trial
- The design included a 16-week open-label enrichment and a 6-week 1:1 randomized withdrawal, planned to show worsening (i.e., higher odds of treatment failure) in those assigned to placebo
- Based in the hypothesis that a selective norepinephrine reuptake inhibitor that physiologically targets peripheral autonomic nerve activity would be ideally suited to patients with central autonomic lesions, we performed a pre-specified subgroup analysis including all randomly assigned MSA patients
- Outcome measures included symptom burden assessed by the 10-item OH-Questionnaire, blood pressures, and catecholamine profiles

Figure 1. Study design.



Note. BP=blood pressure; RCT=randomized controlled trial; OHQ=orthostatic hypotension questionnaire; NE=norepinephrine; RWD=randomized withdrawal; Tx=treatment; OL=open label; ABPM=ambulatory blood pressure monitor.

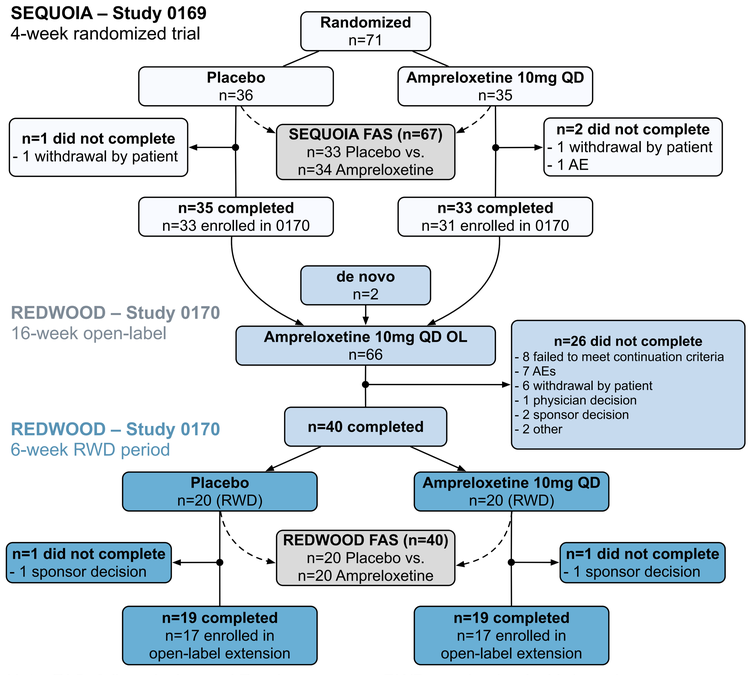
Results

Table 1. Demographics and clinical characteristics at pre-treatment baseline (SEQUOIA FAS).

Measure	Placebo (n=33)	Ampreloxetine (n=34)	All (n=67)
Age (years)	63.7 (9.61)	63.3 (8.45)	63.5 (9.04)
Male	20 (60.6%)	15 (44.1%)	35 (52.2%)
White	31 (93.9%)	32 (94.1%)	63 (94.0%)
Not Hispanic or Latino	31 (93.9%)	30 (88.2%)	61 (91.0%)
Never Smoker	23 (69.7%)	24 (70.6%)	47 (70.1%)
NE (pg/ml)*	275.7 (30.05)	261.0 (22.57)	268.1 (18.47)
Body Mass Index (kg/m^2)	24.34 (3.92)	25.47 (4.62)	24.91 (4.29)
OHSA #1 Score	6.55 (1.52)	6.65 (1.63)	6.60 (1.58)
OHSA Composite Score	5.27 (1.64)	5.35 (1.75)	5.31 (1.7)
OHDAS Composite Score	6.44 (1.98)	6.44 (2.48)	6.44 (2.24)
OHQ Total	5.84 (1.61)	5.79 (1.96)	5.81 (1.8)
Supine SBP 10 min (mmHg)	142.9 (22.83)	141.24 (20.08)	142.04 (21.46)
Supine DBP 10 min (mmHg)	87.1 (12.76)	84.29 (14.84)	85.63 (13.89)
Supine HR 10 min (beats/min)	69.52 (10.23)	70.85 (9.6)	70.22 (9.9)
Standing SBP 3 min (mmHg)	101.97 (27.03)	96.84 (22.98)	99.36 (25.05)
Standing DBP 3 min (mmHg)	69.57 (16.53)	64.91 (17.12)	67.16 (16.84)
Standing HR 3min (beats/min)	82.83 (14.5)	83.44 (13.14)	83.14 (13.81)
Weekly falls because of fainting	7 (21.2%)	12 (35.3%)	19 (28.4%)

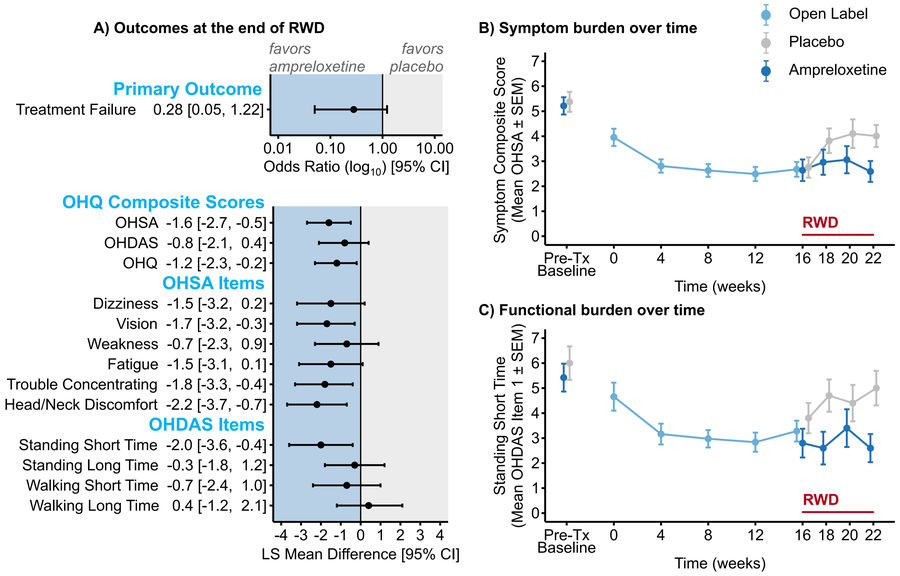
Note. Continuous measures are presented *M (SD)* and categorical *N* (%); *geometric *M* (*SEM*); NE=norepinephrine; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; OHQ=orthostatic hypotension questionnaire; OHSA=OH symptom assessment; OHDAS=OH daily activity scale.

Figure 2. CONSORT diagram of participant flow.



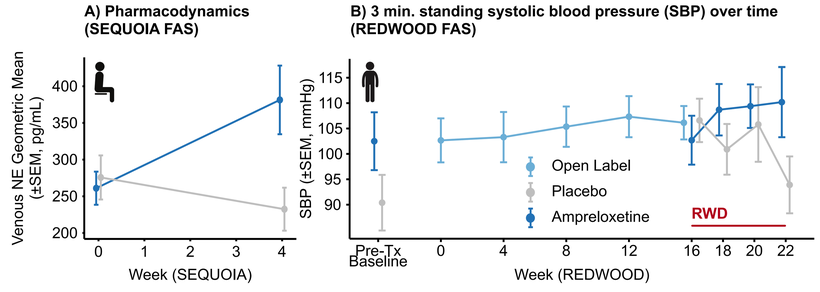
Note. FAS=full analysis set; AE=adverse event; RWD=randomized withdrawal.

Figure 3. Primary and reported outcome measures from MSA subgroup (REDWOOD FAS).



Note. RWD=randomized withdrawal; OHQ=orthostatic hypotension questionnaire; OHSA=OH symptom assessment; OHDAS=OH daily activity scale; Tx=treatment.

Figure 4. Norepinephrine and blood pressure outcomes.



Note. NE=norepinephrine; RWD=randomized withdrawal; Tx=treatment.

Conclusion

- This pre-specified MSA population analysis shows discontinuation of ampreloxetine leads to relapse of nOH symptoms and functional decline
- Ampreloxetine shows target engagement of residual peripheral autonomic neurons, a sustained pressor effect, and improvement in orthostatic symptoms
- If the ongoing phase 3 study confirms the safety and efficacy, ampreloxetine would be the first example of precision medicine in autonomic neurology