American Academy of Neurology™

**Scientific Platform Session: Autonomic Disorders**
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# The impact of ampreloxetine on supine hypertension: An ambulatory blood pressure monitoring study

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# DISCLOSURES

*Prof. Norcliffe-Kaufmann has received personal compensation for serving as an employee & shareholder of Theravance Biopharma and has received personal compensation for serving as an employee of 23andMe.*

# INTRODUCTION

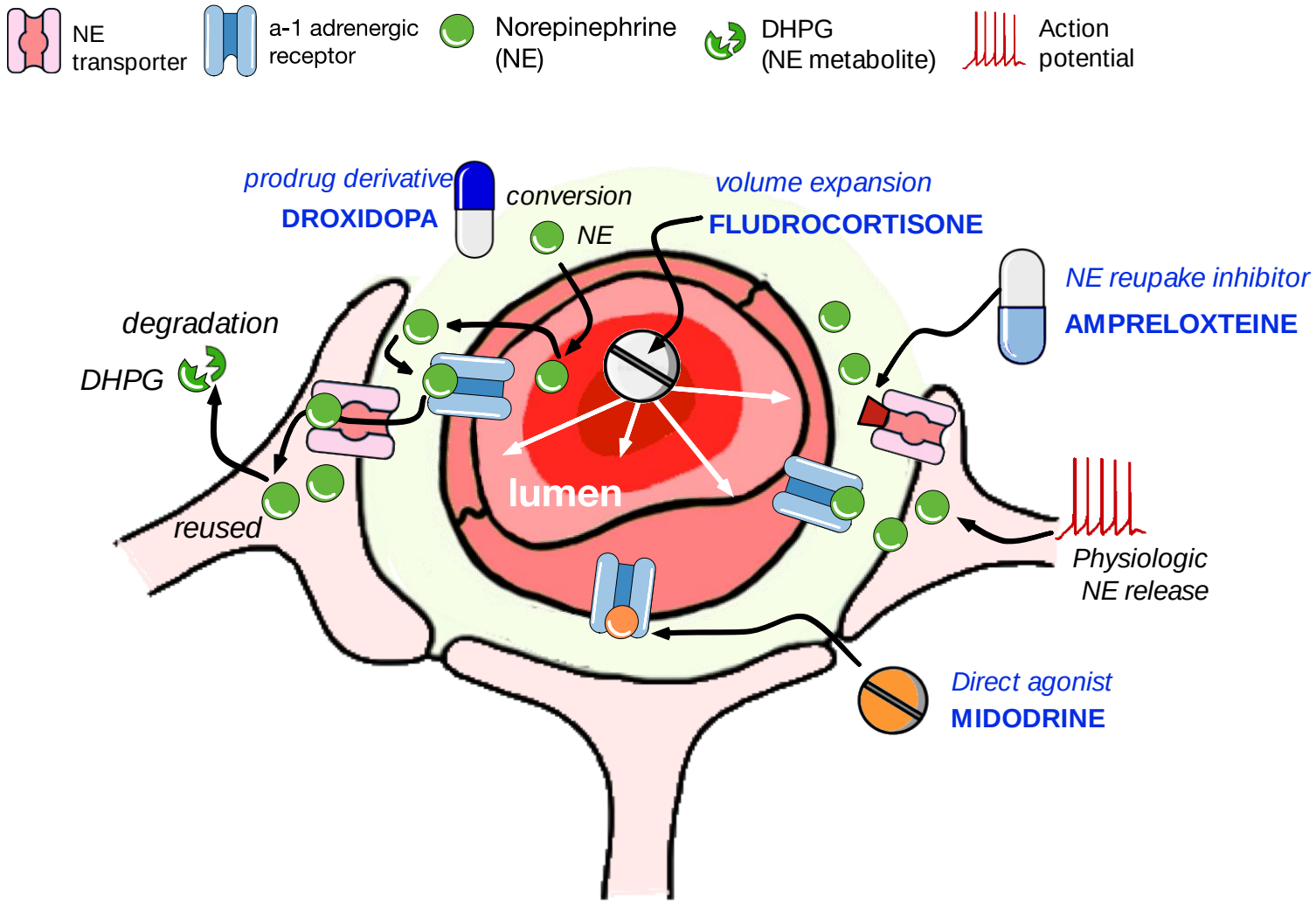
- In addition to neurogenic orthostatic hypotension (nOH), patients with α-synucleinopathies often have supine hypertension
- Currently, all FDA-approved pressor agents for nOH carry black-boxed warnings that these drugs may exacerbate supine hypertension
- The "double-edged sword" when treating autonomic failure

# 101: Supine Hypertension

- Cause is multifactorial: Depends on site of lesion, degree of volume expansion, vascular aging, and underlying vasoconstrictor tone [2]
- Consequences include sleep fragmentation (nocturia arousals), target organ damage, cardiovascular events, and increased mortality risk [3]
- Guidelines exist for staging severity (>140 mmHg)[1]

[1] { Fanciulli et al., *Clin Auton Res*. 2018; 28(4):355-362 PMID: 29766366 } [2] { Biaggioni. *Pharmacol Rev*. 2017; 69(1):53-62 PMID: 28011746 } [2] { Palma et al., *Parkinsonism Relat Disord.* 2020; 75: 97-104 PMID: 32516630 }

# Pharmacological strategies for nOH




## UNMET NEED

- Midodrine + droxidopa do **not account for residual peripheral autonomic neurons that are still capable of releasing NE**
- Increase BP in all positions
- Exacerbate supine HTN

## AMPRELOXETINE

- Once-daily, highly selective, NE re-uptake inhibitor
- Mechanism of action is ideally suited to patients who have a central pattern of degeneration
- Precisely targets residual peripheral autonomic neurons on **physiological arousal**

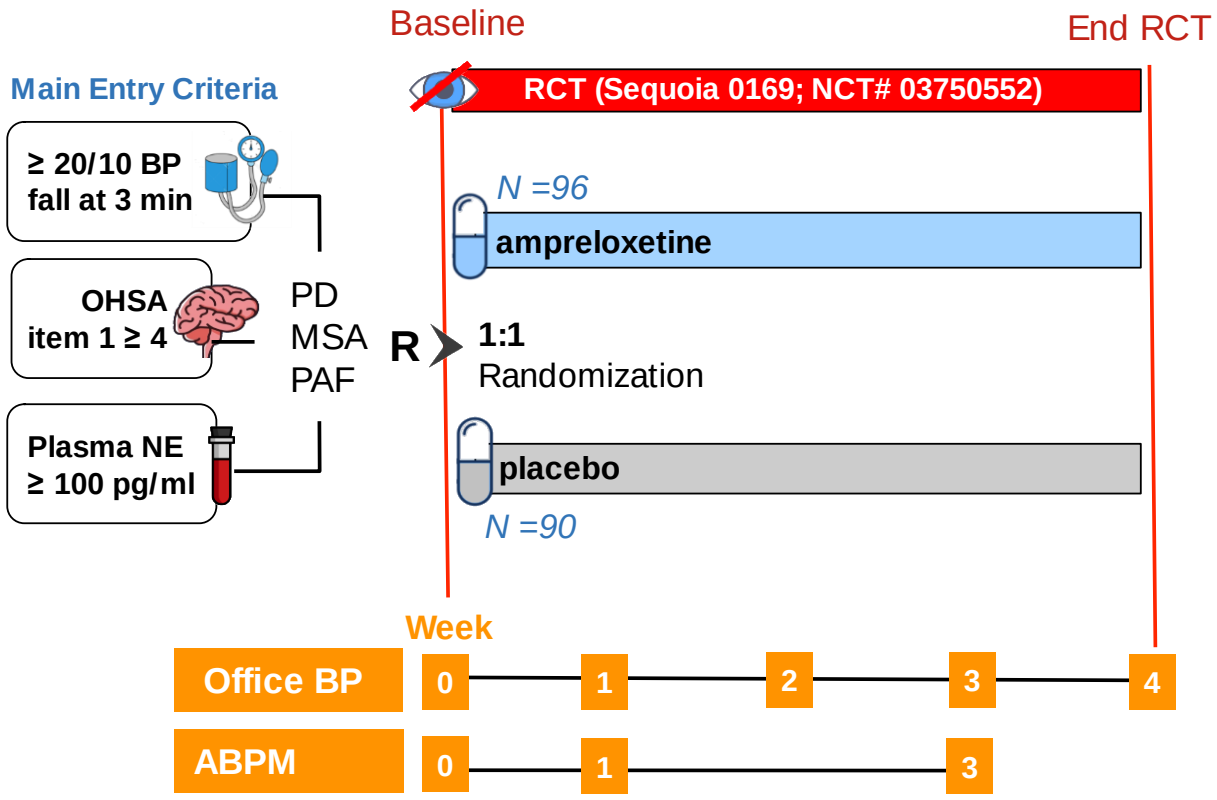
*NE= norepinephrine, DHPG = dihydroxyphenylglycol, HTN = hypertension*

# OBJECTIVE

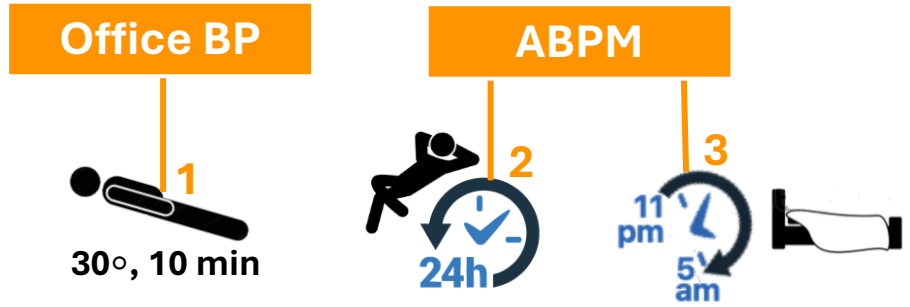
To determine the impact of ampreloxetine (oral, 10 mg/once-daily) on supine hypertension as assessed by in-office and ambulatory blood pressure monitoring

# METHODS

## A) Protocol design




## B) Measures of supine HTN




## C) Analysis plan

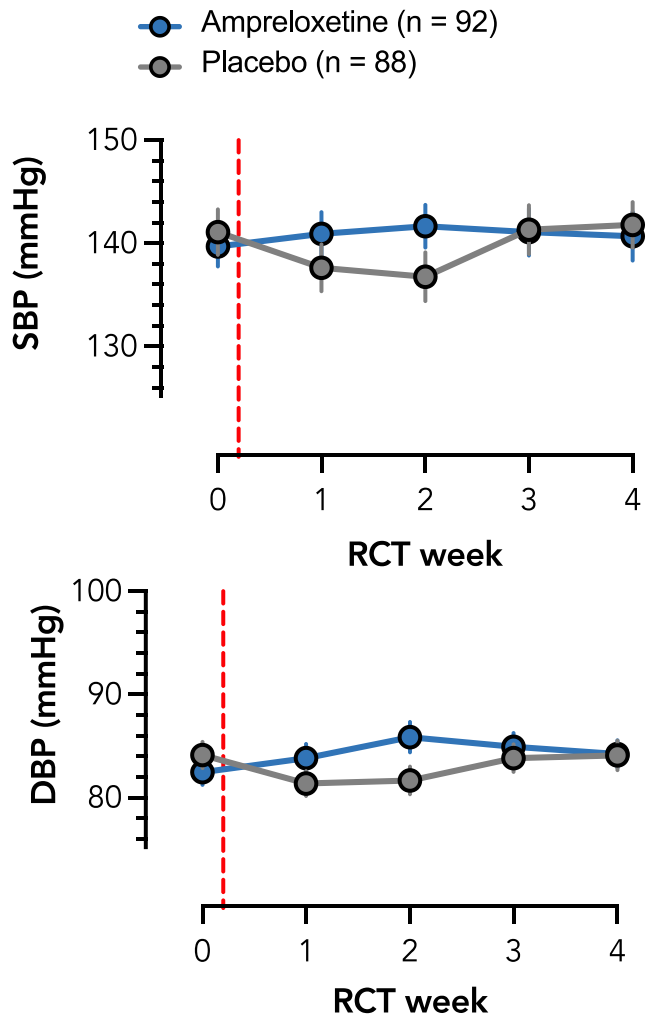
- Post hoc, prioritizing 24-h dataset
- Descriptive statistics
- Absolute values, change from baseline, shift tables (stage HTN)

# RESULTS:

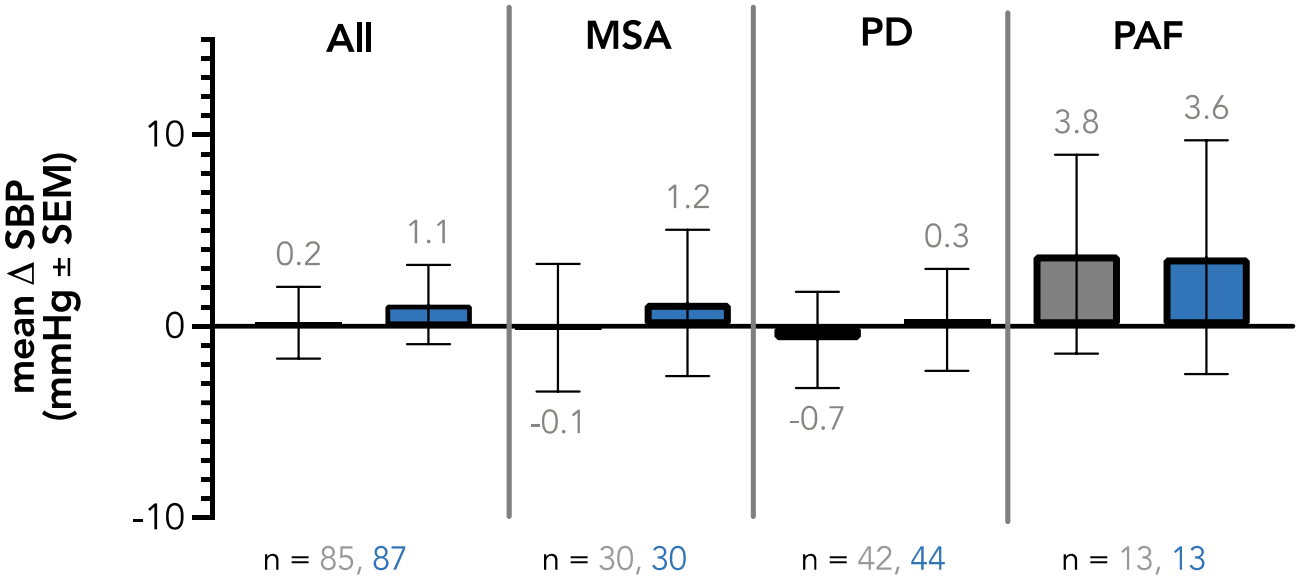
Supine 10 min BP obtained in clinic

# **RESULTS:** Office supine BP in the 4-week RCT


## A) Absolute values



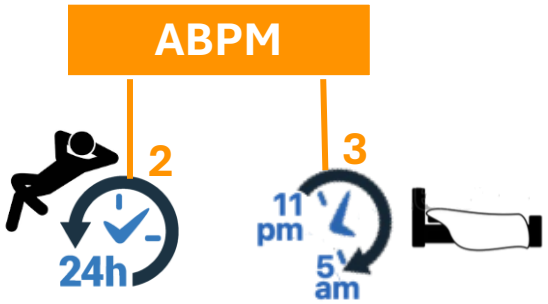

## B) Week 4 △ from pre-treatment baseline stratified by diagnosis




No signal for sustained worsening of supine HTN on office BP readings after 4 weeks on ampreloxetine across diagnostic groups

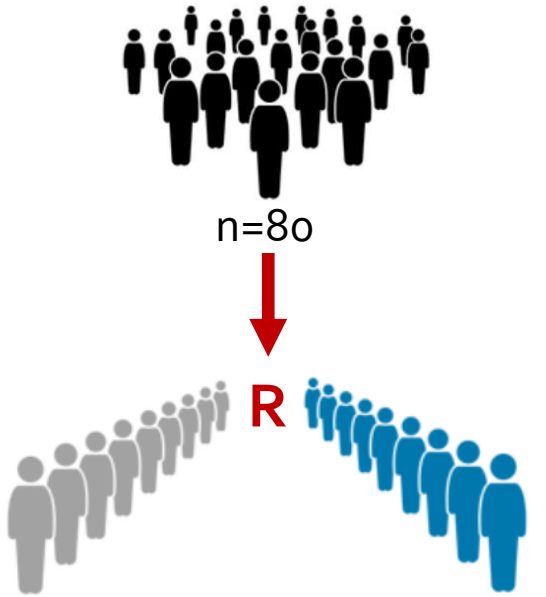
# RESULTS:

Ambulatory blood pressure monitoring [ABPM]

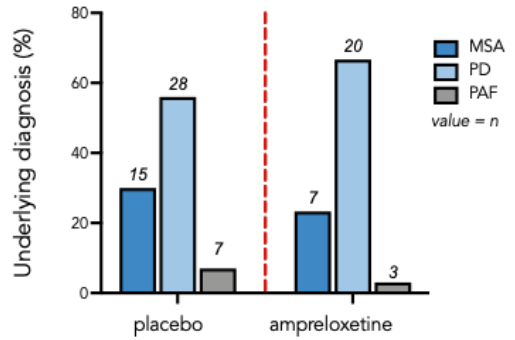


# **RESULTS:** Clinical Characteristics 24h ABPM Set

## A) 24h ABPM Cohort

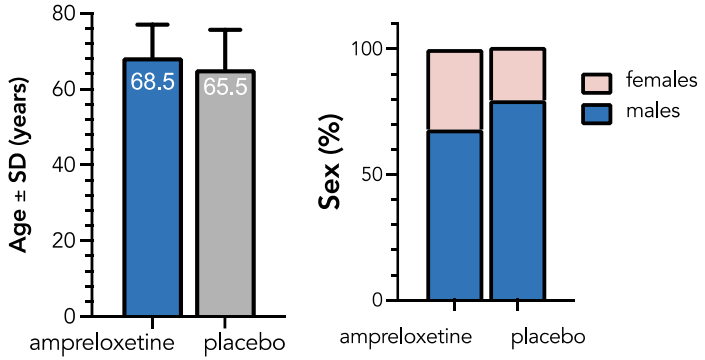



## B) Underlying Diagnosis



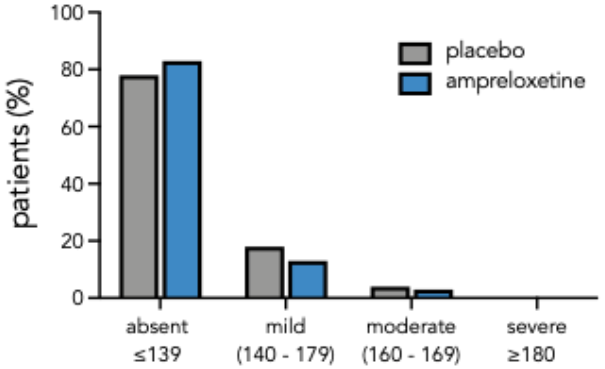

Disease diagnosis equally distributed

## C) Age/Sex



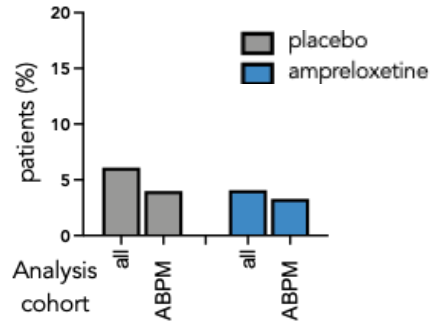

Expected age and sex distribution

## D) Stage HTN at Entry




20% had pre-existing supine HTN

## E) Anti-HTN use

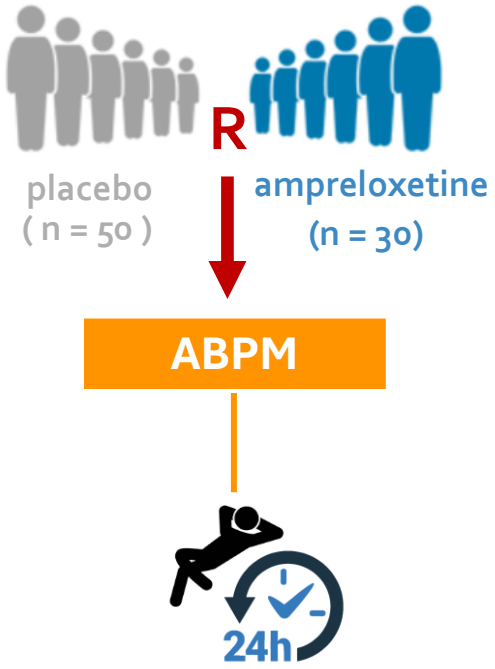



Infrequent pharmacological treatment

24hr Analysis Set; not predefined subset, subjects with satisfactory ambulatory recordings at 2 or more time points; TD-9855, ad-hoc study analysis

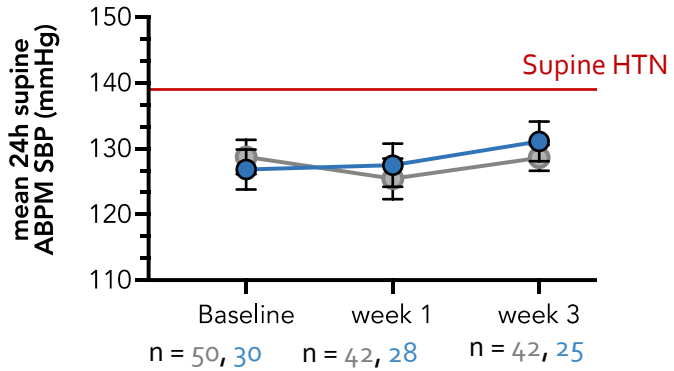
# RESULTS: Supine ABPM values captured over 24h

## A) 24h ABPM Cohort

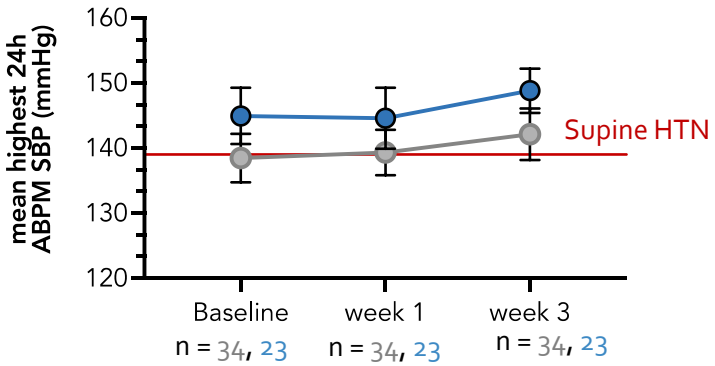



Successful 24h recordings identifying supine position **[n = 80]**

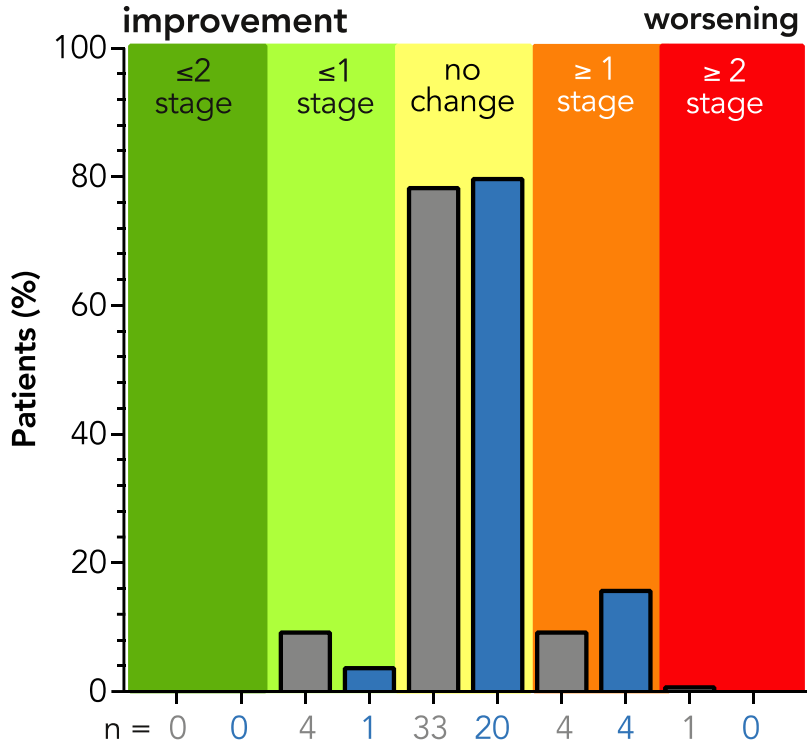
## B) Mean supine SBP 24h[1]




## C) Max SBP excursion 24h[2]




## C) Shift Table Analysis[3]

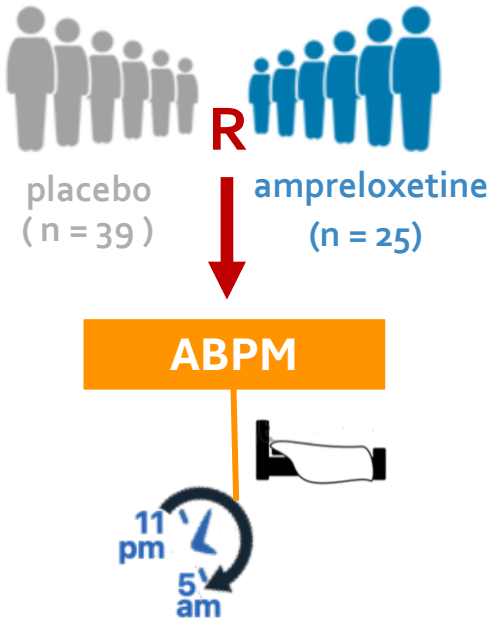



No worsening of supine HTN captured over 24h period of ABPM

*[1] All available subject supine SBP data captured at all ABPM visits. [2] Subset with successful supine SBP AMBP datasets at all 3 visits. [3]Systolic Supine HTN = absent (≤139), mild (140-159), moderate (160-179); severe (≥ 180) mmHg. Shift = change in stage. Ambulatory BP readings corresponding with supine position 24hr Analysis Set week 3; TD-9855, ad-hoc study analysis*

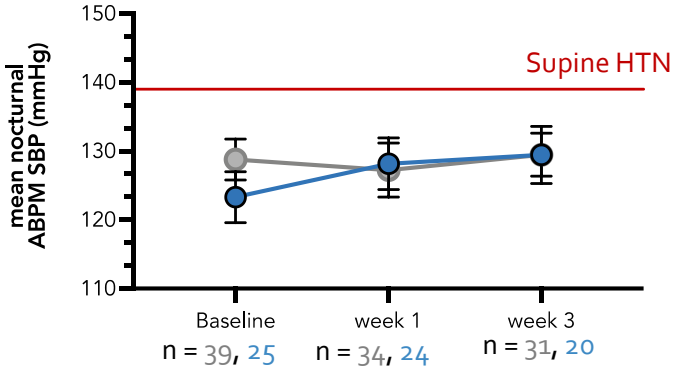
# RESULTS: Supine nocturnal ABPM values

## A) Nocturnal Cohort

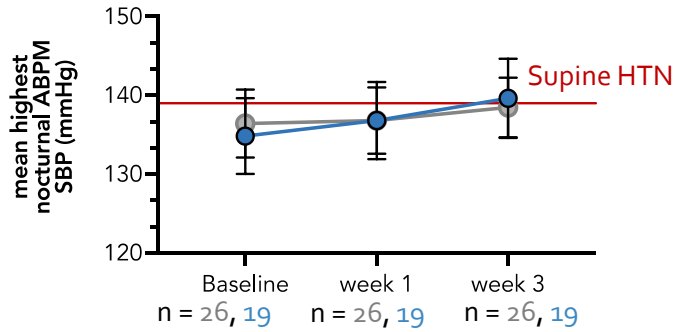



Successful nocturnal recordings **[n = 64, 80%]**

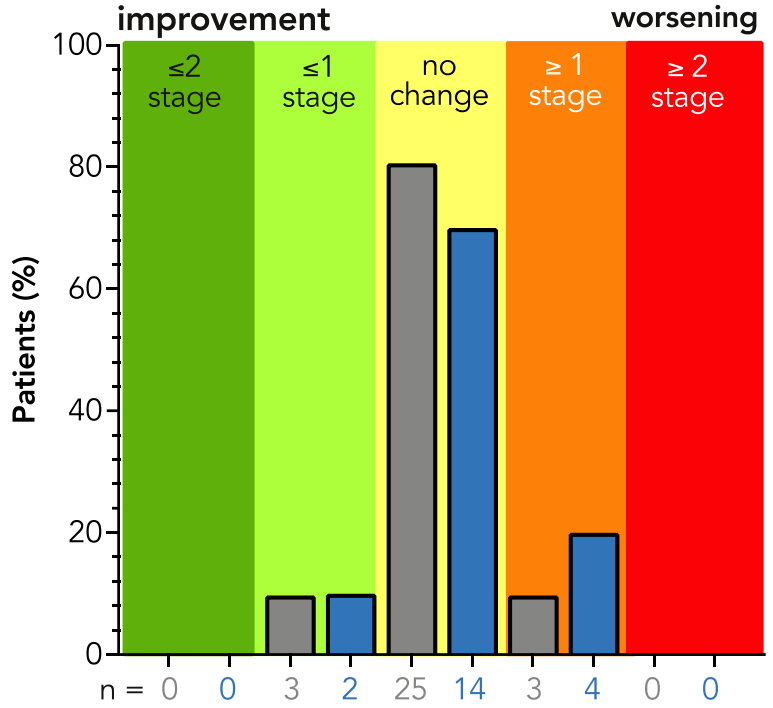
## B) Mean supine SBP nocturnal[1]




## C) Max SBP excursion 24h[2]




## C) Shift Table Analysis [1]




No worsening of nocturnal HTN on ABPM

*[1] All available subject supine SBP data captured at all ABPM visits. [2] Subset with successful supine SBP AMBP datasets at all 3 visits. [3]Systolic Supine HTN = absent (≤139), mild (140-159), moderate (160-179); severe (≥ 180) mmHg. Shift = change in stage. Ambulatory BP readings corresponding with supine position 24hr Analysis Set week 3; TD-9855, ad-hoc study analysis*

# CONCLUSIONS

- We saw no signal for worsening of supine HTN in office or on 24h ambulatory BP monitoring on ampreloxetine in patients with α-synucleinopathies and nOH
- This suggests that, if the ongoing phase 3 study confirms safety and efficacy, ampreloxetine may be the first drug to treat nOH without exacerbating supine hypertension
- This should not worsen intravascular volume loss overnight or add to the risk of target organ damage

# ACKNOWLEGDEMENTS

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