Evaluating clinically meaningful changes in the Orthostatic Hypotension Symptom Assessment domain of the Orthostatic Hypotension Questionnaire

Horacio Kaufmann[1], Tadhg Guerin[2], David Lewin[3], Beiyao Zheng[2], Ross Vickery[2], David L Bourdet[2], Roy Freeman[4]

[1]NYU Langone Health, New York University School of Medicine, New York, NY, USA; [2]Theravance Biopharma US, Inc., South San Francisco, CA, USA; [3]Statistically Speaking Consulting, LLC, Venice, FL, USA; [4]Beth Israel Deaconess Medical Center, Boston, MA, USA

INTRODUCTION

- Neurogenic orthostatic hypotension (nOH) is a chronic, debilitating condition caused by autonomic dysfunction leading to reduced vasomotor sympathetic norepinephrine release[1]
- The Orthostatic Hypotension Questionnaire (OHQ) is an instrument developed to assess the symptomatic and functional impact of nOH and measure the treatment effect of therapeutic interventions in clinical trials[2]
- Determining clinically meaningful changes in endpoints derived from the OHQ is critical for the interpretation of clinical trial results in nOH[2]
- Anchor and distribution-based analyses represent commonly used methodologies to establish thresholds that help interpret the clinical meaningfulness of changes in patient-reported outcomes[2]
- These methods were applied to pooled data across treatment groups from two Phase 3 randomized controlled clinical trials, SEQUOIA and REDWOOD, which evaluated the efficacy of ampreloxetine in treating symptomatic nOH in patients with primary autonomic failure

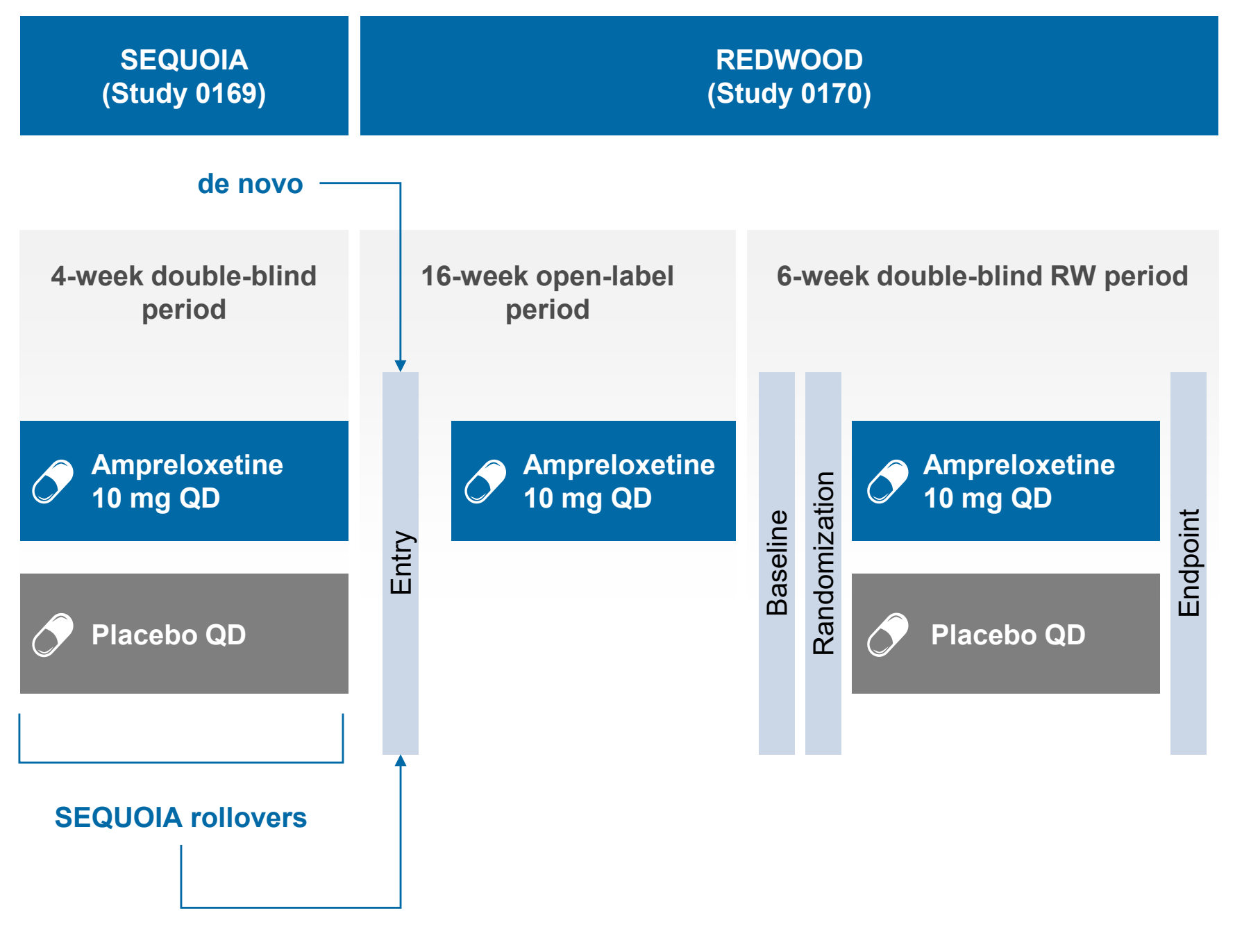
OBJECTIVE

- To establish thresholds for interpreting clinically meaningful improvements and deteriorations in the Orthostatic Hypotension Symptom Assessment (OHSA) composite score from the OHQ

METHODS

Study design and treatment

Figure 1. Phase 3 program study design



SEQUOIA (NCT03750552); REDWOOD (NCT03829657).
QD, once daily; RW, randomized withdrawal.

Study population

- SEQUOIA study
  - nOH: sustained reduction in blood pressure ≥20 mmHg (systolic) or ≥10 mmHg (diastolic) within 3 minutes of being tilted up ≥60° from a supine position as determined by a tilt-table test
  - Score of ≥4 on the OHSA item 1 (OHSA #1) at Visit 1
  - Diagnosis of multiple system atrophy, Parkinson's disease, or pure autonomic failure
- REDWOOD study
  - Open-label period
    - Completed the SEQUOIA study with ≥80% study medication compliance OR
    - Enrolled de novo and met eligibility criteria as outlined for SEQUOIA
  - Randomized withdrawal period
    - Reduction of ≥2 points from baseline in OHSA #1 at Week 4 of open-label period
    - OHSA #1 score ≤7 at Week 16 of open-label period

Assessments

- The OHQ consists of two parts: a 6-item symptom assessment scale (OHSA) and a 4-item daily activity scale (Orthostatic Hypotension Daily Activity Scale)
  - Each item is scored on an 11-point scale from 0 (no symptoms/interference) to 10 (worst symptoms/complete interference)
  - The OHSA composite score is the average of the 6 OHSA items and was collected throughout the SEQUOIA and REDWOOD studies
- SEQUOIA study
  - **Patient Global Impression of Change (PGI-C)** at Week 4 served as an anchor for evaluating the change in OHSA composite score
  - PGI-C uses a 5-category scale from "much better" to "much worse" to assess symptom change since starting the study medication
- REDWOOD study
  - For the randomized withdrawal period, the change in **Patient Global Impression of Severity (PGI-S)** was chosen as a more suitable anchor due to the study's increased complexity
  - PGI-S rates the current severity of nOH symptoms on a 5-category scale, from "none" to "very severe"

Statistical analysis

- Anchor-based analysis
  - Ampreloxetine and placebo data were combined for analysis to investigate clinically meaningful changes regardless of treatment
  - We assessed the relationship between each anchor and the change in OHSA composite score with a minimum Spearman's correlation of 0.3 required for a suitable anchor
  - The target anchor for a clinically meaningful change is a one category improvement or worsening from no change
  - Empirical cumulative distribution functions (eCDFs) were chosen as the primary anchor-based analysis, with the location where the target anchor reached the median (50%) on the y-axis chosen as an interpretable threshold
  - Categories with <10 patients were combined when possible; otherwise, categories with <10 patients were excluded
- Supportive anchor-based analysis
  - Receiver operating characteristic (ROC) curves were performed for predicting improvement (≥1-category decrease) and worsening (≥1-category increase) on the OHSA composite score
  - The threshold minimizing the sum of squares of 1-sensitivity and 1-specificity was selected
- Distribution-based analysis
  - The standard error of measurement (SEM) was calculated to determine the minimum detectable change for the OHSA composite score that can be reliably measured. Estimates for proposed thresholds from a given study were required to be above the SEM from that study
  - SEM was calculated as SD * $\sqrt{(1 - r)}$, where r represents the internal reliability estimated by Cronbach alpha for OHSA items 1 to 6 at baseline of the SEQUOIA study or randomized withdrawal baseline of the REDWOOD study
- All analyses were conducted using SAS v9.4 and SAS/STAT version 15.1 software (SAS Institute, Cary, NC, USA)

RESULTS

Patients

- In total, 184 and 128 patients were analyzed from the SEQUOIA study and the randomized withdrawal period of the REDWOOD study, respectively

SEQUOIA study

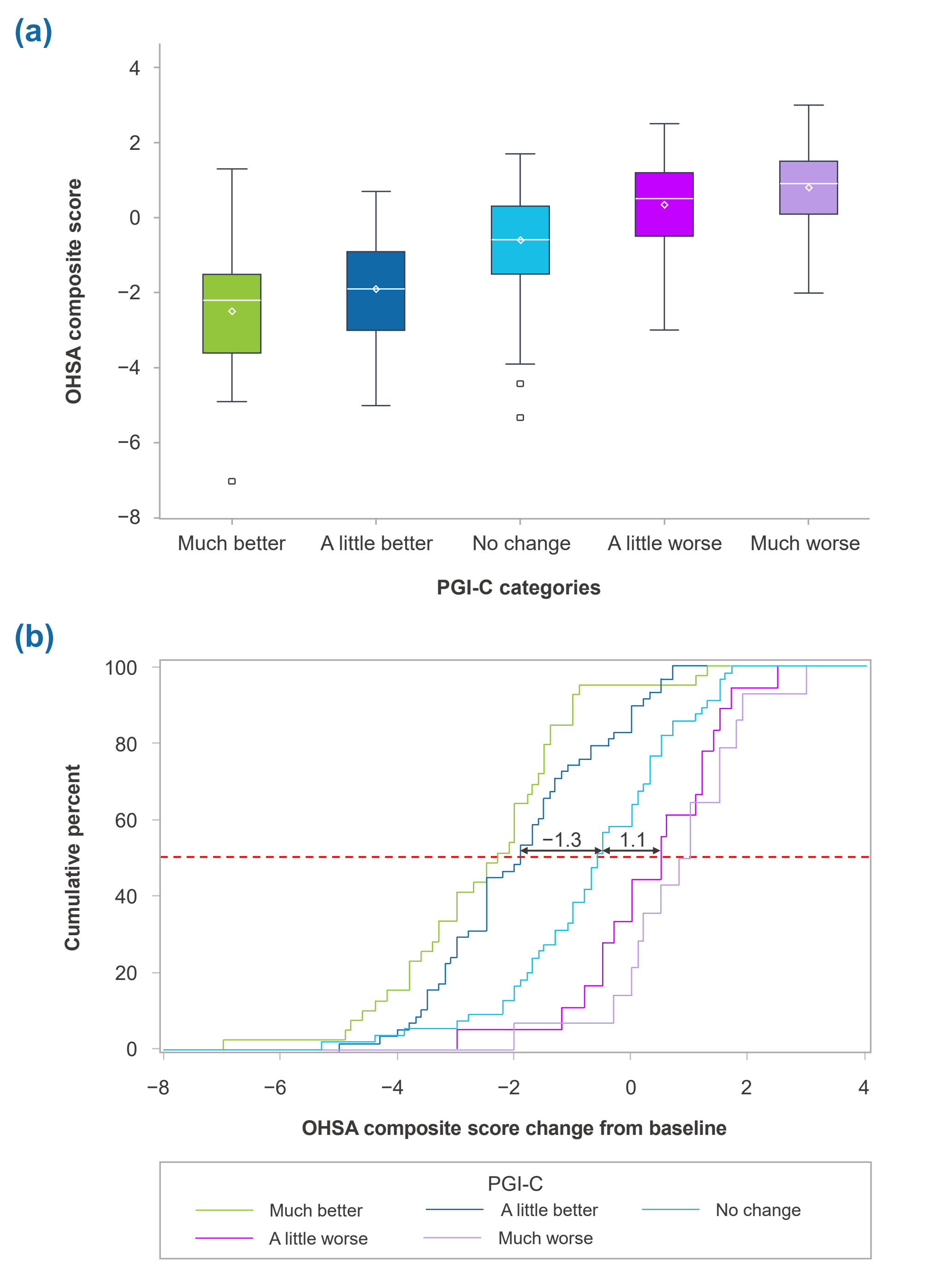
Table 1. Median change in OHSA composite score by PGI-C categories at Week 4

PGI-C value	n	Median change in OHSA composite score
(1) Much better	36	−2.20
(2) A little better	57	−1.90
(3) No change	51	−0.60
(4) A little worse	18	0.50
(5) Much worse	14	0.90

A Spearman correlation of 0.6 was observed, validating PGI-C as a viable anchor.
SEM of 0.85 was calculated at study baseline.
OHSA, Orthostatic Hypotension Symptom Assessment; PGI-C, Patient Global Impression of Change; SEM, standard error of the mean.

- **Thresholds of −1.3 points for improvement (a little better minus no change) and 1.1 points for worsening (a little worse minus no change) were identified**

Figure 2. Change in OHSA composite score at Week 4 in PGI-C categories from SEQUOIA study



OHSA, Orthostatic Hypotension Symptom Assessment; PGI-C, Patient Global Impression of Change.

REDWOOD study

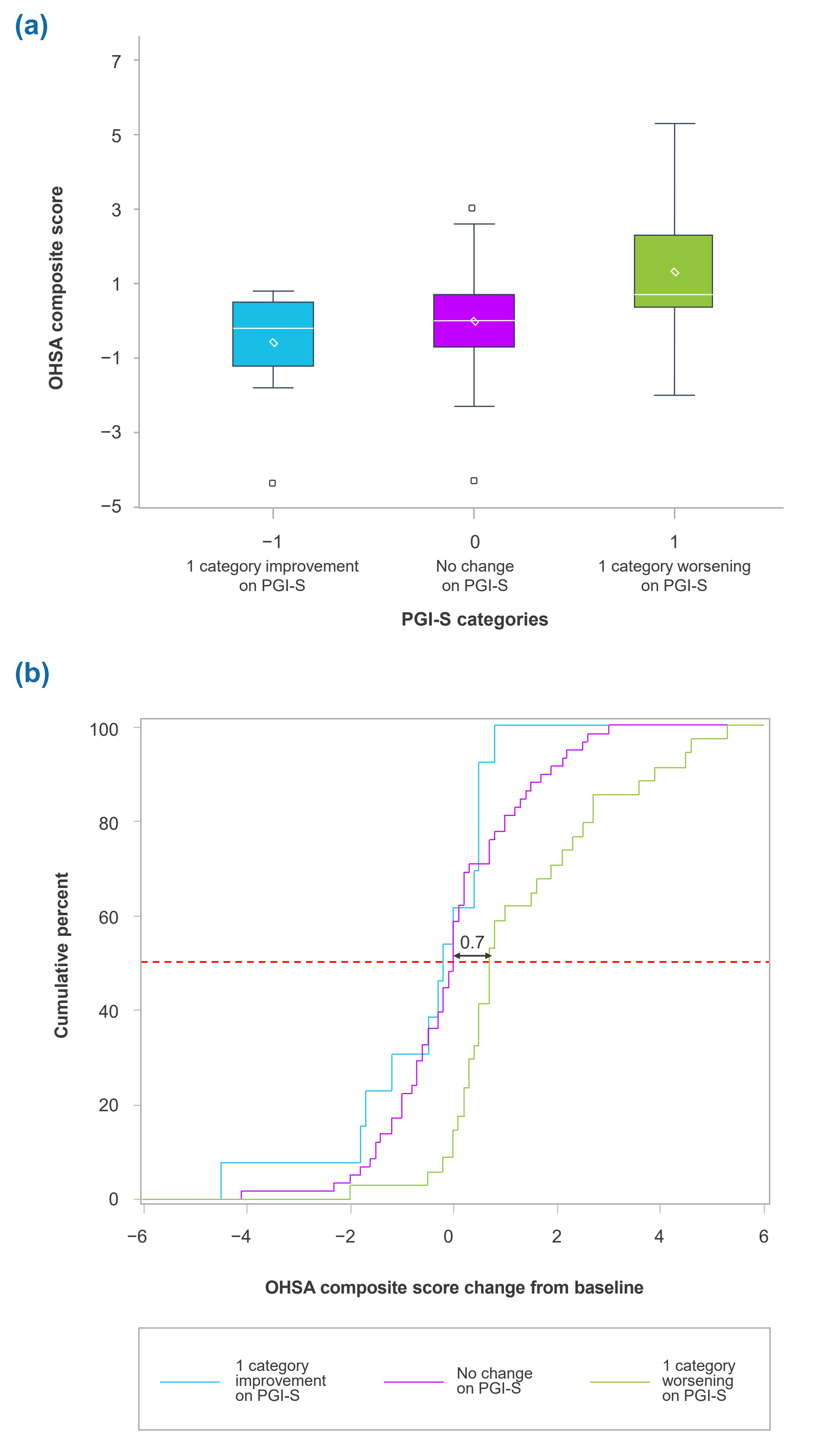
Table 2. Median change in OHSA composite score by change in PGI-S at Week 6 from REDWOOD study

Value	n	Median
(−3) 3-category improvement	1	−1.60
(−2) 2-category improvement	1	−0.30
(−1) 1-category improvement	13	−0.20
(0) No change	58	0.00
(+1) 1-category worsening	34	0.70
(+2) 2-category worsening	6	1.50
(+3) 3-category worsening	1	5.50

A Spearman correlation of 0.5 was observed, validating PGI-S as a viable anchor.
SEM of 0.65 was calculated during the randomized withdrawal baseline period.
OHSA, Orthostatic Hypotension Symptom Assessment; PGI-S, Patient Global Impression of Severity; SEM, standard error of the mean.

- **A threshold of 0.7 points for worsening (1 category worsening minus no change) was identified**
  - A 1-category improvement of −0.2 was within the SEM and not considered

Figure 3. Change in OHSA composite score at Week 6 in PGI-S categories from the REDWOOD study

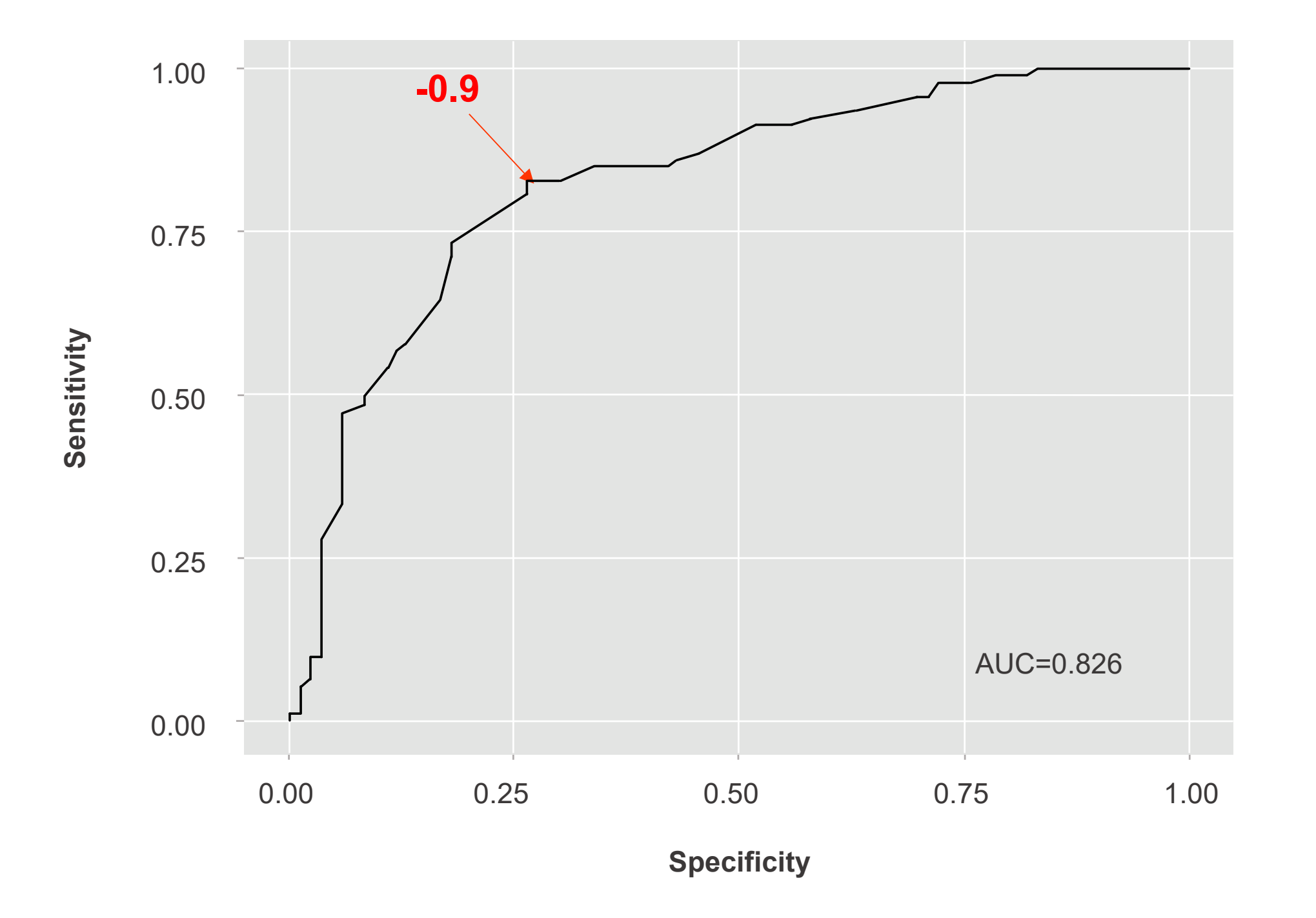


Only changes in PGI-S of −1, 0, and 1 are shown due to insufficient data in other categories to combine groups to a sample size of ≥10 patients.
OHSA, Orthostatic Hypotension Symptom Assessment; PGI-S, Patient Global Impression of Severity.

ROC curve from the SEQUOIA study

- ROC curve for a ≥1-category improvement from the SEQUOIA study is shown in **Figure 4**
  - The only viable threshold identified was from this analysis, all other thresholds were within the SEM

Figure 4. ROC curve for ≥1-category improvement in PGI-C at Week 4 of the SEQUOIA study vs change in OHSA composite score



−0.9 is the proposed threshold minimizing the sum of squares of 1-sensitivity and 1-specificity.
AUC, area under the curve; OHSA, Orthostatic Hypotension Symptom Assessment; PGI-C, Patient Global Impression of Change; ROC, receiver operating characteristic.

Table 3. Derived thresholds indicative of clinically meaningful changes within patients

Method	Improvement in OHSA composite score	Worsening in OHSA composite score
SEQUOIA study – PGI-C	−1.3	1.1
REDWOOD study – PGI-S	NA	0.7
SEQUOIA study – ROC	−0.9	NA
Range	−0.9 to −1.3	0.7 to 1.1

NA, not assessed; OHSA, Orthostatic Hypotension Symptom Assessment; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

CONCLUSIONS

- The OHSA composite score is correlated with changes in patient clinical status and is an appropriate endpoint for evaluating nOH symptoms
- Clinically meaningful changes in the OHSA composite score included improvements of 0.9 to 1.3 points and worsening of 0.7 to 1.1 points
- Future nOH clinical trials should consider prospectively applying the thresholds identified here to assess clinically meaningful effects

References:

1. Kalra DK, et al. *Clin Med Insights: Cardiol.* 2020;14:1179546820953415.
2. Kaufmann H, et al. *Clin Auton Res.* 2012;22:79-90.

Acknowledgments:

Medical writing and editorial support were provided by Hilary Durbano, PhD, of AlphaBioCom, a Red Nucleus company, and were funded by Theravance Biopharma Ireland Limited.

Disclosures:

HK received consulting fees from Theravance Biopharma US, Inc. related to this presentation. **TG, BZ, RV,** and **DLB** employees and shareholders of Theravance Biopharma US, Inc. **DL** is a contractor for Theravance Biopharma US, Inc. **RF** has received personal compensation and/or stock options for serving on scientific advisory boards of AlgoRx, Applied Therapeutics, Clexio, Cutaneous NeuroDiagnostics, Eli Lilly, Glaxo-Smith Kline, Glenmark, GW Pharma, Inhibikase, Maxona, NeuroBo, Novartis, Regenacy, Theravance Biopharma US, Inc., 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.

American Autonomic Society Annual Meeting | Rio Mar, Puerto Rico | November 15–18, 2023