Re-Weighting MDS-UPDRS Part II and PDQ-39 Items to Detect Maximal Decline in Activities of Daily Living in Untreated Parkinson's Disease

Gil L'Italien[1], Sam Dickson[2], Basia Rogula[3], Jordan Dubow[4], Nick Kozauer[1*], Lauren Powell[3], Michele Potashman[1], Patrick O'Keefe[2], Ellen Korol[3], Madeleine Crabtree[3], Fernanda Nagase[3], Vlad Coric[1], Liana S. Rosenthal[5], Suzanne Hendrix[2]

[1]Biohaven Pharmaceuticals, Inc, 215 Church St, New Haven, CT, USA; [2]Pentara Corporation, 2261 E 3300 S, Salt Lake City, UT, USA; [3]Broadstreet HEOR, 343 Railway St, Vancouver, BC, Canada; [4]Clintrex, 2 N Tamiami Trail #308, Sarasota, FL, USA; [5] Johns Hopkins Medicine, Department of Neurology, Baltimore, MD, USA

*At the time of study completion

CONCLUSIONS

1. PARCOMS-Function is an optimized composite scale of two existing valid measures of patient function, with greater sensitivity to detect functional decline in early untreated patients with Parkinson's disease (PD), compared to the original scales.
2. This new scale includes items related to motor functioning, activities of daily living (ADL), and pain, all of which are particularly relevant for untreated PD patients.
3. Use of PARCOMS-Function could increase trial efficiency and power to detect meaningful delay in disease progression with disease modifying therapies (DMTs).

References:

1. L'Italien G, et al. Cerebellum. 2024;7(10):024-01697; 2. Dickson SP, et al. Neurology and Therapy. 2024 Dec;13(6):1627-39; 3. Wang J, et al. Journal of Neurology, Neurosurgery & Psychiatry. 2016 Sep 1;87(9):993-9; 4. Ha AD, Jankovic J. *Movement Disorders.* 2012;27(4):485-491; 5. Tai Y-C, Lin C-H. *Clinical Parkinsonism & Related Disorders.* 2020;2:1-8.

Disclosures:

GL, MP, NK and VC are employed by and own stock and stock options in Biohaven Pharmaceuticals, Inc. SD, PO, and SH are employees of Pentara of Pentara Corp, which received funding from Biohaven for conduct of this work. BR, LP, EK, MC, FN are employees of Broadstreet Health Economics and Outcomes Research, which received funding from Biohaven for conduct of this work. JD is an employee of Clintrex Research Corporation and own/ options in Revalesio Corporation. LR engaged in this research as a private consultant or advisor and not in her capacity as a Johns Hopkins faculty member; she was compensated for the consulting or advising service in income.

Data Acknowledgment:

CPP: data was downloaded on September 13, 2023

Poster originally presented at Alzheimer's and Parkinson's Diseases Conference (AD/PD™); April 1-5, 2025; Vienna, Austria & Virtual

To download a copy of this poster, scan QR code.

American Academy of Neurology (AAN) • April 5-9, 2025 • San Diego, US & Online

INTRODUCTION

- There are no DMTs available in PD, with current treatments focusing on symptom management.
- Progression of PD symptoms can occur at different rates over the course of the disease and can be related to background use of symptomatic therapy.
- Clinical trials assessing PD outcomes typically use scales designed to assess a broad spectrum of disease, of which the MDS-UPDRS and PDQ-39 are cornerstone measures. However, the heterogeneity of PD signs, symptoms, and progression rates limits these scales' ability to detect meaningful changes within a feasible study timeframe.
- To address this challenge, there is precedent for the development of composite scales optimized for sensitivity to clinical decline according to disease stage, treatment status, and symptom presentation.[1-3]

OBJECTIVE

To generate a composite scale, PARCOMS-Function, from MDS-UPDRS-Part II and PDQ-39 items optimized for sensitivity to detect functional decline over 1-year.

METHODS

Study Participants and Data

- Data were obtained from the Critical Path for Parkinson's (CPP), a collaboration of non-profit, academic, government and industry organizations with the aim to share research and advance drug development in early PD. Data available through 13 September 2023 were used in this study.
- Patients in the placebo group from three studies evaluating DMTs and that included both MDS-UPDRS and PDQ-39 measurements were selected in the analysis: STEADY PD3 (NCT02168842), SURE PD3 (NCT02642393), and Pasadena (NCT03100149).
- Patients were included if they were diagnosed within the previous two years, Hoehn and Yahr stage 1 or 2, and naïve to dopaminergic therapies.
- Patients were censored upon initiation of all dopaminergic therapies except for MAO-B inhibitors.
- The study cohort included data up to three years post baseline, although most clinical trials were of shorter duration, ranging from one to three years.
- In consultation with clinical experts, each item in both scales was mapped to clinical concepts to facilitate examination of underlying clinical PD progression.

Statistical Analysis

- Items were selected using partial least squares (PLS) regression applying a variable importance in projection (VIP) threshold of 0.5.[2,3]
- The sum of selected items weighted by their model coefficients created the composite scale. Weights reflected the contribution of the item, with higher weights attributed to the more progressive items.
- PARCOMS-Function's responsiveness to change was measured using a 1-year mean-to-standard-deviation ratio (MSDR), with higher values indicating better sensitivity.
- Sample sizes were calculated based off observed MSDRs, slowing of 30%, and power of 80% for an independent sample t-test. Changes in power were calculated using the initial N and the MSDR from the composite score.

RESULTS

- Baseline demographic and disease characteristics are presented in **Table 1.** Most patients were male, white, and had Hoehn and Yahr staging of 2. The average age at PD diagnosis was 63 years.
- The 1-year MSDR of PARCOMS-Function was 0.6534, reflecting increases in the ability to detect change of 12.3% compared to Part II alone, and 339.1% compared to PDQ-39 alone **(Table 2).**
- PARCOMS-Function retained 30% (15 of 44) items from the MDS-UPDRS Part II and PDQ-39. Of these items, eight were from the PDQ-39 and seven from the MDS-UPDRS Part II (**Figure 1**).
  - The items with the highest contribution from Part II were (indicating responsiveness to change in this population) hygiene (17.2%), speech (12.6%), and handwriting (11.2%)
  - The items with the highest contribution from the PDQ-39 were walking half a mile (8.7%), muscle cramps (8.3%), and buttons and shoelaces (6.3%).
- In PARCOMS-Function, ADL clinical concept items comprised most of the scale (60%), followed by oral dysfunction (20%; **Figure 2**). While a total of nine concepts were captured in the original scales, only four were captured in PARCOMS-Function.
- Use of PARCOMS-Function in place of MDS-UPDRS Part II alone would decrease sample size from 507 to 410 subjects per arm, corresponding to a 19.1% decrease that reflects a powering improvement of ~7.6%. (from 80 to 87.6% power with n=507)

Table 1. Demographic and baseline characteristics of the PARCOMS-function cohort

	PARCOMS-Function cohort (n=140)
Age in years, mean (SD)	63.4 (9.6)
Sex, n (%)	
Male	85 (61)
Female	55 (39)
Age at diagnosis (years), mean (SD)	62.9 (9.6)
Race, n (%)	
White	131 (94)
Multiracial	2 (1)
Black/African American	2 (1)
Asian	1 (1)
Native American	1 (1)
Not specified	3 (2)
Time since diagnosis (years), mean (SD)	0.6 (0.5)
Hoehn and Yahr stage, n (%)	
1	51 (36)
2	89 (64)
MDS-UPDRS Part II Score, mean (SD)	4.9 (4.1)

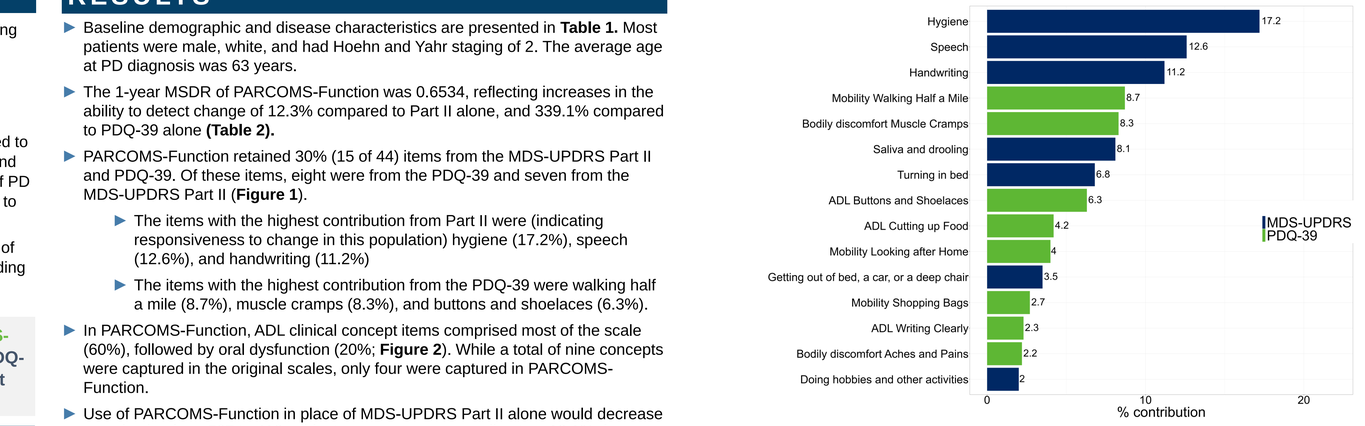
Abbreviations: MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease rating scale; SD, standard deviation.

Table 2. Change in MSDR for PARCOMS-function from the original scales

Scale	MSDR of original scale	MSDR of composite	% change from original
MDS-UPDRS Part II	0.5817	0.6534	12.3
PDQ-39	0.1488		339.1

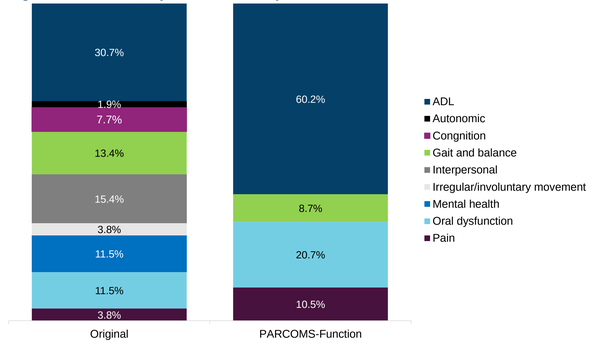
Abbreviations: MSDR, mean-to-standard-deviation ratio; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease rating scale; PDQ- 39, Parkinson's Disease Questionnaire.

Figure 1. Percent contributions of items in PARCOMS-Function (MDS-UPDRS Part 2 and PDQ-39)



Abbreviations: ADL, Activities of daily living; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease rating scale; PDQ- 39, Parkinson's Disease Questionnaire

Figure 2. Impact of re-weighting MDS-UPDRS Part 2 and PDQ-39 items based on PARCOMS-Function PLS regression results, by clinical concepts



Abbreviations: ADL, Activities of daily living; CPP, Critical Path for Parkinson's; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease rating scale; PDQ- 39, Parkinson's Disease Questionnaire; PLS, Partial least square

DISCUSSION

- PARCOMS-Function resulted in an increased sensitivity to detect progression and a 30% reduction in the number of items from the combined original scales.
- PARCOMS-Function represents a more responsive measure of ADL abilities as compared to each scale alone and is thought to be of highest relevance to patients, clinicians, and regulators.
- PARCOMS-Function includes items related to both motor-complications and ADL impacts that are particularly relevant to untreated PD patients. Notably, it also includes PD patients experience of pain, which can be particularly distressing, and have an impact on patients' mental health and their ability to perform daily activities.[4,5]
- As a scale derived from patients enrolled in PD trials, PARCOMS-Function may be particularly suitable for measuring treatment efficacy in clinical trials.
- The use of composite scales optimizes current validated measures by improving the sensitivity of the original scale(s) to progression. This, in turn, decreases the number of patients required to detect statistically significant changes in clinical trials, thus improving their efficiency.