

SUPPLEMENTARY MATERIAL

Development and Validation of PARCOMS Composite Scales for Assessing Disease Progression and Treatment Effects in Parkinson's Disease

Gil L'Italien^a, Basia Rogula^b, Lauren Powell^b, Michele Potashman^a, Samuel P. Dickson^c, Nick Kozauer^{a*}, Patrick O'Keefe^c, Ellen Korol^b, Madeleine Crabtree^b, Fernanda Nagase^b, Vlad Coric^a, Jordan Dubow^d, Liana S. Rosenthal^c, Suzanne Hendrix^c

^a Biohaven Pharmaceuticals, Inc, 215 Church St, New Haven, CT, USA

^b Broadstreet HEOR, 343 Railway St, Vancouver, BC, Canada

^c Pentara Corporation, 2261 E 3300 S, Salt Lake City, UT, USA

^d Clintrex, 2 N Tamiami Trail #308, Sarasota, FL, USA

^e Johns Hopkins Medicine, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA

*at the time of study completion

Corresponding author:

Michele Potashman

michele.potashman@biohavenpharma.com

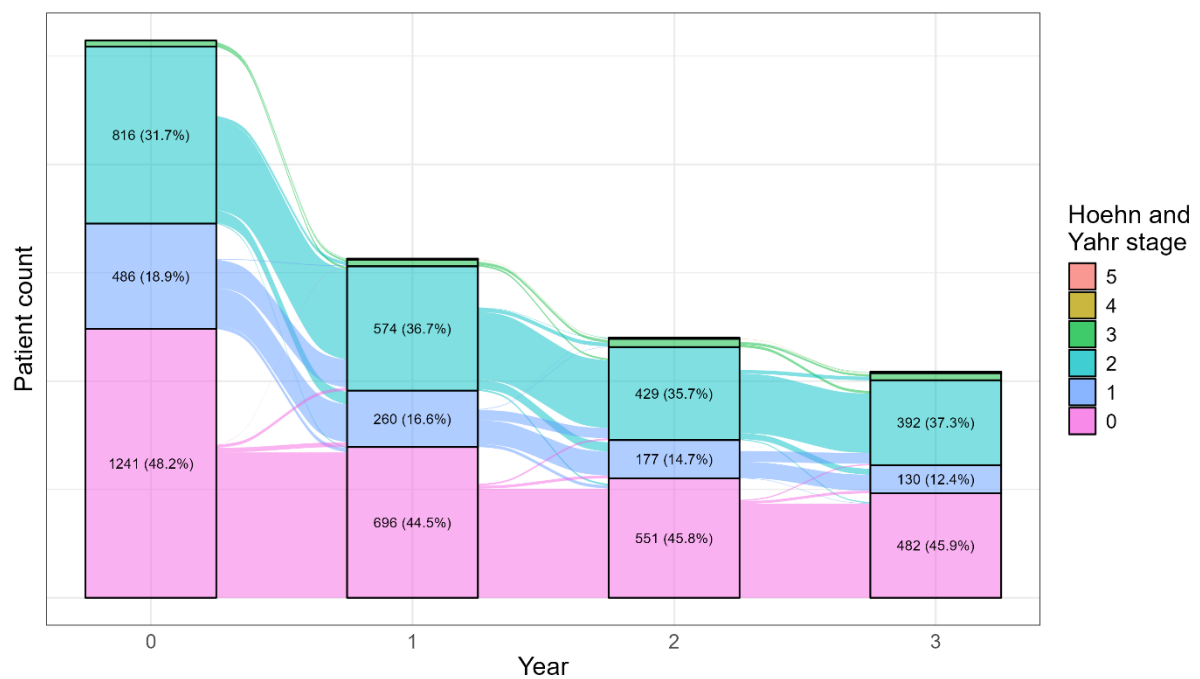
215 Church St, New Haven, CT, USA

Description of initial descriptive work on PPMI data

Prior to the development of motor and non-motor PARCOMS, an exploratory analysis was conducted to assess the characteristics of patients enrolled in PPMI and the availability and distribution of MDS-UPDRS data.

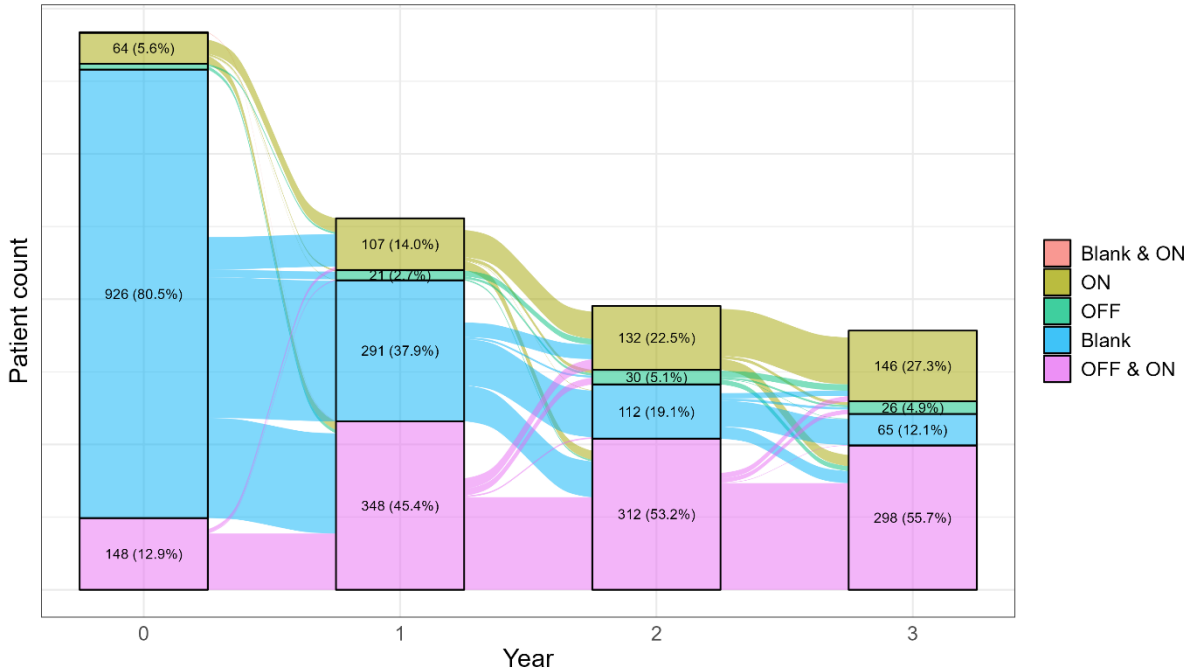
Descriptive summaries of the Parkinson's disease cohort of PPMI

Supplemental Figure 1. Hoehn and Yahr stage (at a blank or ON PD state) by year from PPMI baseline among all patients in the PD cohort



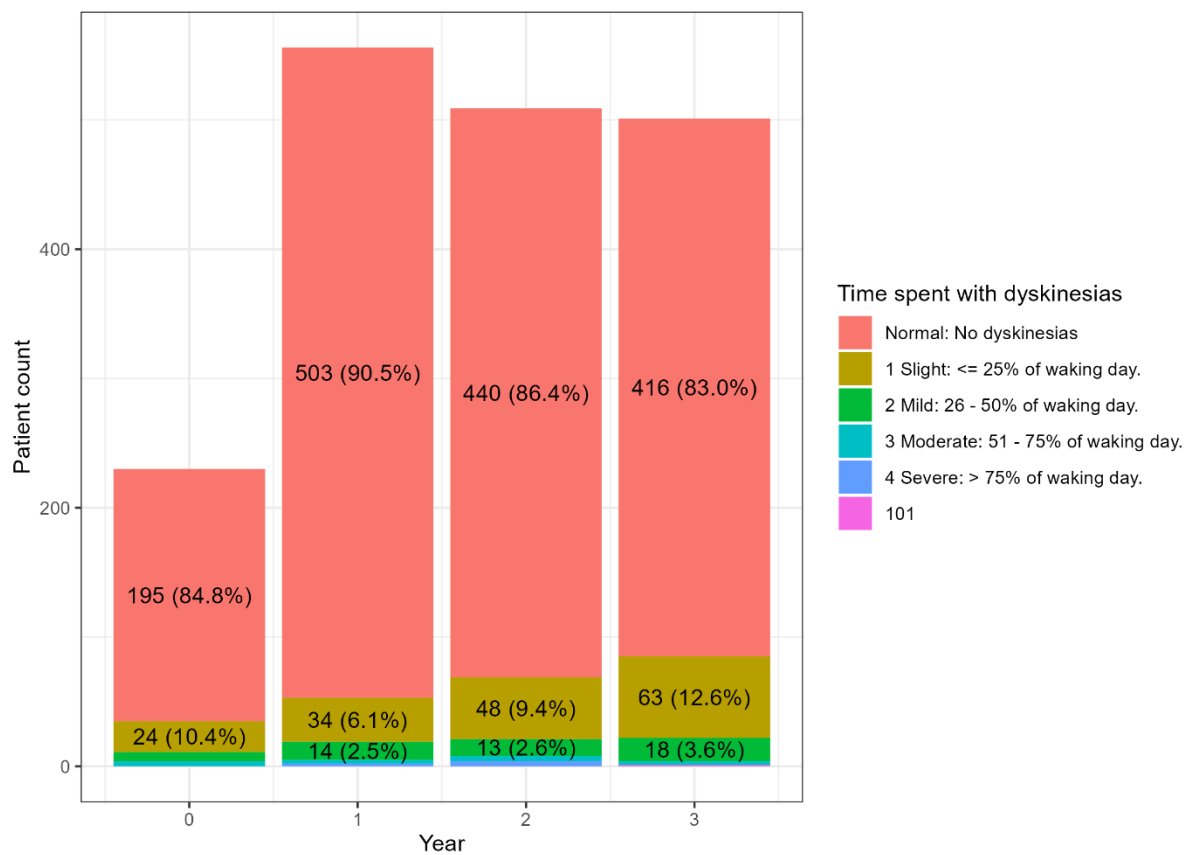
Abbreviations: PD – Parkinson's disease; PPMI - Parkinson's Progression Markers Initiative.

Supplemental Figure 2. Availability of MDS-UPDRS Part III data by PD state at each year from PPMI baseline among patients in the PD cohort with a Hoehn and Yahr stage of 1 or 2 at PPMI baseline



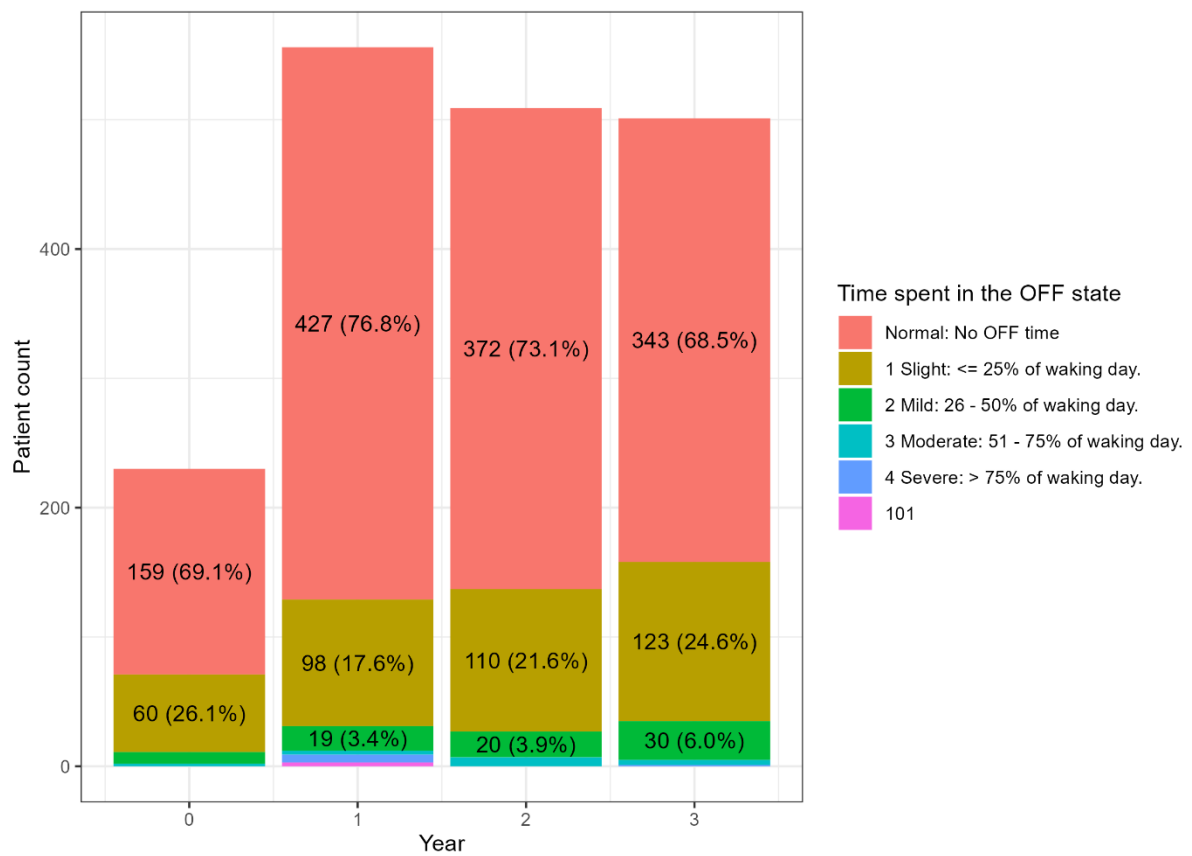
Abbreviations: MDS-UPDRS - International Parkinson and Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; Parkinson's disease; PPMI - Parkinson's Progression Markers Initiative.

Supplemental Figure 3. Time spent with dyskinesias by year among patients with a Hoehn and Yahr stage of 1 or 2 at PPMI baseline



Abbreviations: PPMI - Parkinson's Progression Markers Initiative.

Supplemental Figure 4. Time spent in the OFF state by year among patients with a Hoehn and Yahr stage of 1 or 2 at PPMI baseline



Abbreviations: PPMI - Parkinson's Progression Markers Initiative.

Cohort attrition tables and cohort overlap

Supplemental Table 1. Patient attrition based on eligibility criteria for the untreated cohort

Selection criteria	Untreated cohort (n)
PD patients in PPMI	1,580
Enrolment status one of 'Complete', 'Enrolled', 'Screened', 'Withdrew'	1,199
Hoehn and Yahr 1 and 2 at a blank or ON state at PPMI baseline	1,119
Less than 2 year since diagnosis at PPMI baseline	926
No previous or current use of levodopa or other dopaminergic medications at PPMI baseline	801
MDS-UPDRS Part I, II, or III values within three years post PPMI baseline	430

Abbreviations: MDS-UPDRS - International Parkinson and Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; PD – Parkinson's disease; PPMI – Parkinson's Progression Markers Initiative.

Supplemental Table 2. Patient attrition based on eligibility criteria for the Treated-w/o-MC cohort

Selection criteria	Treated-w/o-MC cohort (n)
PD in PPMI	1,580
Enrolment status one of ‘Complete’, ‘Enrolled’, ‘Screened’, ‘Withdrew’	1,199
One record of MDS-UPDRS Part III data at a visit considered for baseline, limiting to visits with a Hoehn and Yahr score of 1 and 2 at a blank or ON state	1,148
Taking levodopa or other dopaminergic medications for at least 1 month prior to the visit	826
No motor complications (no dyskinesias and no OFF time) at the visit and prior visits	613
MDS-UPDRS Part I, II, or III values within three years post the visit	426

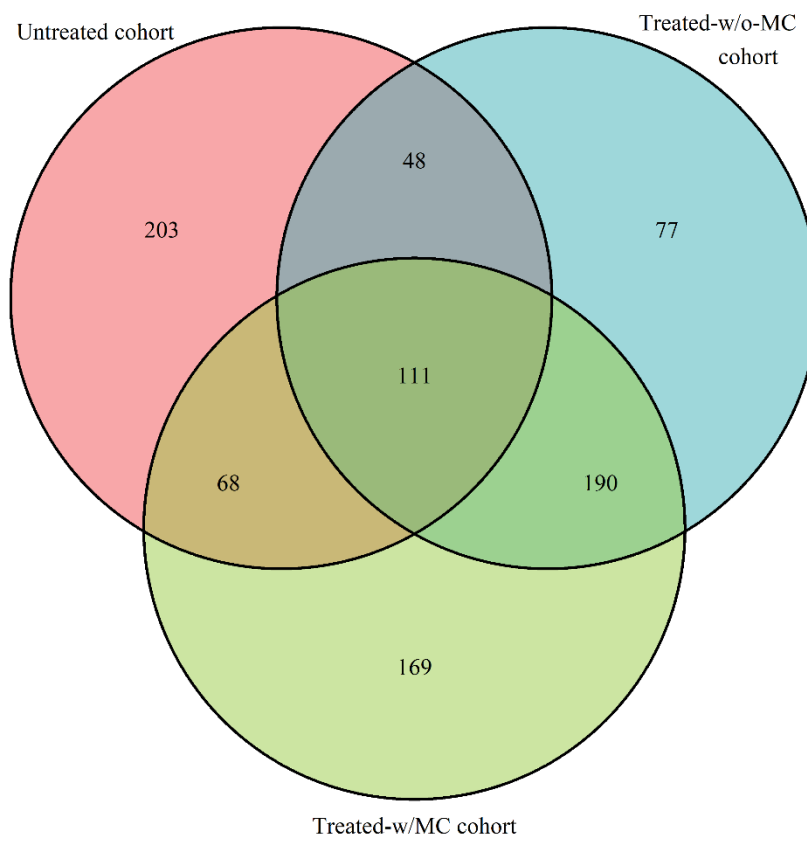
Abbreviations: MDS-UPDRS - International Parkinson and Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; PD – Parkinson's disease; w/o-MC – without motor complications.

Supplemental Table 3: Patient attrition based on eligibility for the Treated-w/MC cohort

Selection criteria	Treated-w/MC cohort (n)
PD patients in PPMI	1,580
Enrolment status one of ‘Complete’, ‘Enrolled’, ‘Screened’, ‘Withdrew’	1,199
One record of MDS-UPDRS Part I, II, or III data at the visit considered for baseline, excluding visits with a Hoehn and Yahr value of 0 at a blank or ON state	1,160
Taking levodopa or other dopaminergic medications for at least 1 month prior to the visit	775
Has motor complications (dyskinesias or OFF time) at the visit	604
MDS-UPDRS Part I, II, or III values within three years post the visit	538

Abbreviations: MDS-UPDRS - International Parkinson and Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; PD – Parkinson's disease; w/MC – with motor complications.

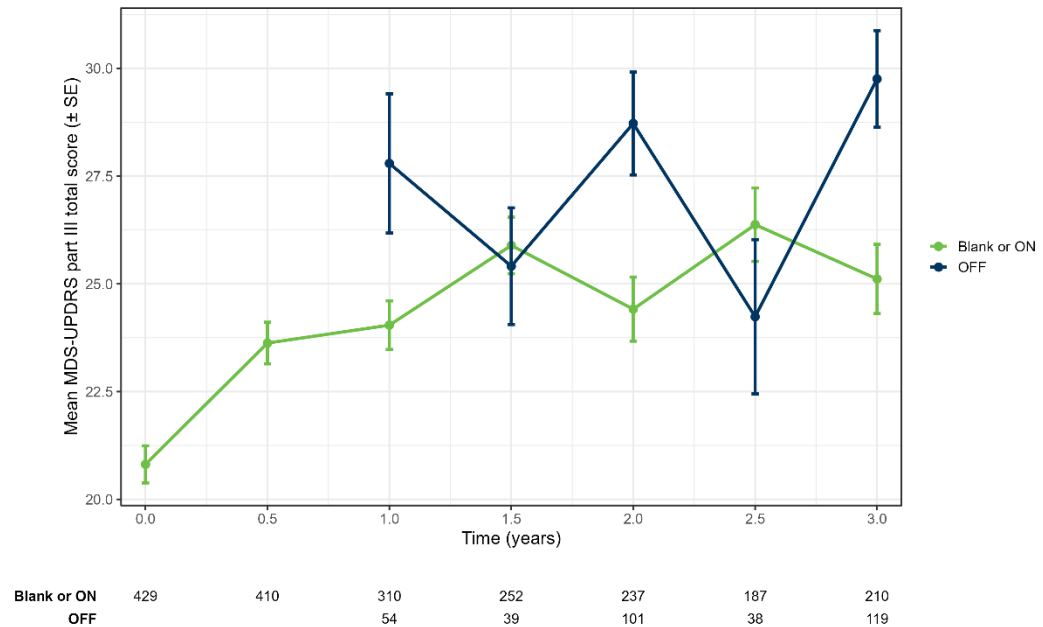
Supplemental Figure 5. Venn diagram of patient counts across cohorts



Abbreviations: w/MC – with motor complications; w/o-MC – without motor complications.

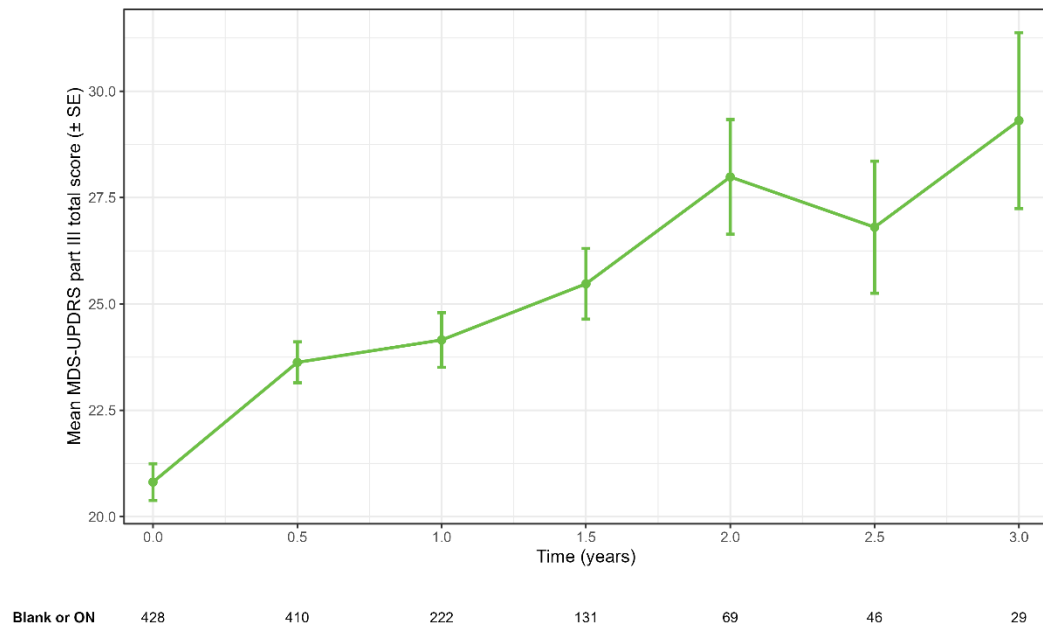
Summaries of MDS-UPDRS Part III scores by PD state in the study cohorts

Supplemental Figure 6. Mean MDS-UPDRS Part III score by PD state and half year from cohort-specific baseline among patients in the Untreated cohort, without censoring at PD treatment initiation



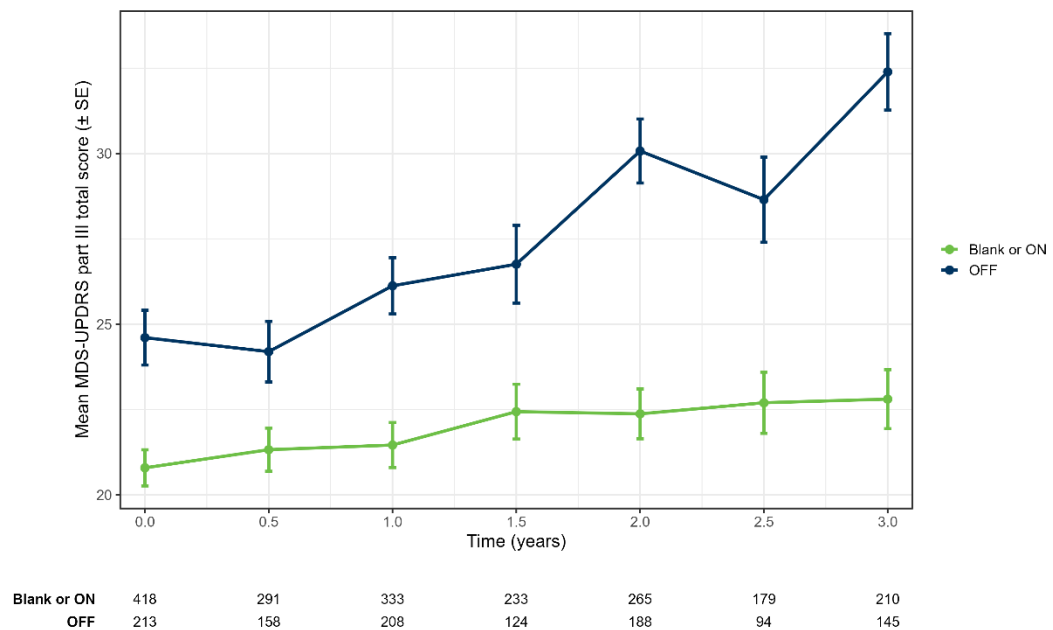
Abbreviations: MDS-UPDRS - International Parkinson and Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; PD - Parkinson's disease.

Supplemental Figure 7. Mean MDS-UPDRS Part III score by PD state and half year from cohort-specific baseline among patients in the Untreated cohort, censoring at PD treatment initiation



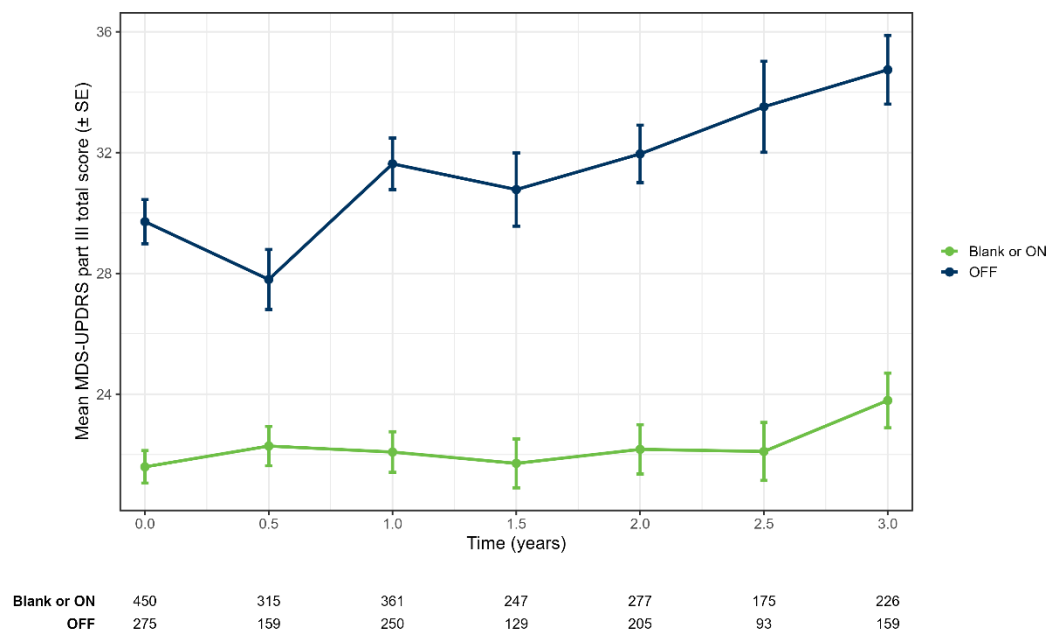
Abbreviations: MDS-UPDRS - International Parkinson and Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; PD - Parkinson's disease.

Supplemental Figure 8. Mean MDS-UPDRS Part III score by PD state and half year from cohort-specific baseline among patients in the Treated-w/o-MC cohort



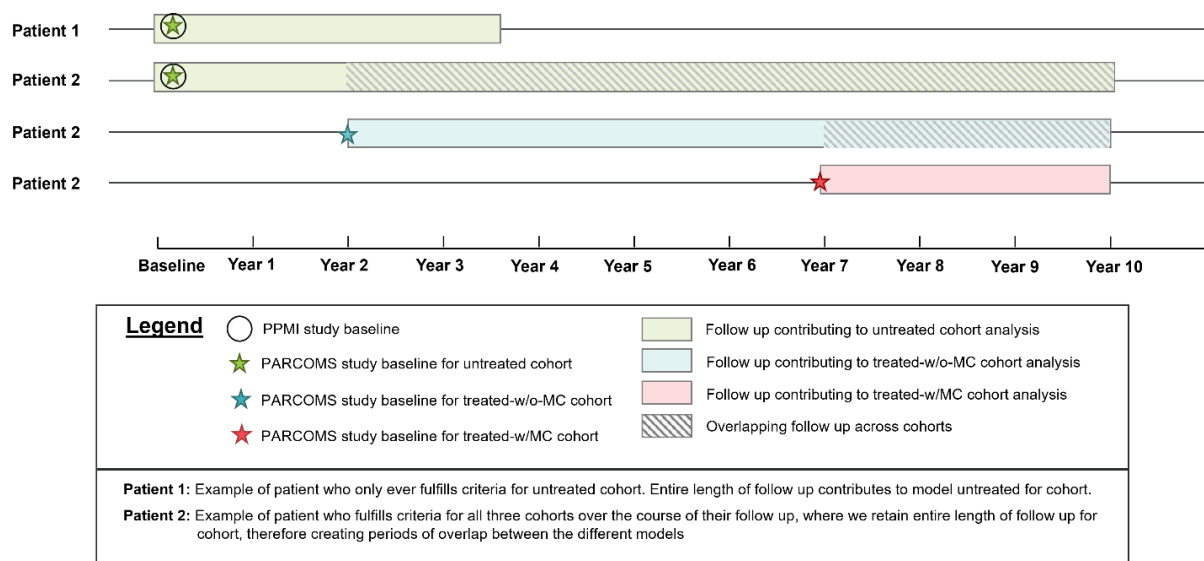
Abbreviations: MDS-UPDRS - International Parkinson and Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; PD - Parkinson's disease; w/o-MC – without motor complications.

Supplemental Figure 9. Mean MDS-UPDRS Part III score by PD state and half year from cohort-specific baseline among patients in the Treated-w/MC cohort



Abbreviations: MDS-UPDRS - International Parkinson and Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; PD - Parkinson's disease; w/MC – with motor complications.

Supplemental Figure 10. Re-baseline of patients as cohort criteria are met over time



Abbreviations: MDS-UPDRS - International Parkinson and Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; PD - Parkinson's disease; PPMI – Parkinson's Progression Markers Initiative; w/MC – with motor complications.

Supplemental Table 4. VIP score and PLS coefficients for PARCOMS motor PPMI untreated population

Item	MSDR	VIP	PLS weight	% contribution
2.9 Turning in bed	0.3498	0.8853	0.7619	9.4
3.1 Speech	0.3683	0.9706	0.6261	7.7
3.17b Rest tremor amplitude - LUE	0.3329	1.0614	0.5510	6.8
3.8b Leg agility - Left leg	0.3061	1.3672	0.5328	6.6
3.17a Rest tremor amplitude - RUE	0.2711	1.0651	0.5075	6.3
2.11 Getting out of bed, a car, or a deep chair	0.2208	0.9876	0.4674	5.8
3.6b Pronation-Supination - Left Hand	0.3842	1.3425	0.4484	5.5
2.10 Tremor	0.2322	0.8414	0.3556	4.4
2.12 Walking and balance	0.2723	0.6476	0.3358	4.2
3.13 Posture	0.1708	0.7745	0.3251	4.0
3.2 Facial expression	0.2019	1.0356	0.3164	3.9
2.1 Speech	0.2420	0.6893	0.3144	3.9
3.5b Hand movements - Left Hand	0.3332	1.4373	0.3107	3.8
2.7 Handwriting	0.2456	1.1884	0.3042	3.8
3.3e Rigidity - LLE	0.1430	1.1031	0.2782	3.4
3.7a Toe tapping - Right foot	0.1784	1.3510	0.2586	3.2
2.2 Saliva and drooling	0.2288	0.8720	0.2335	2.9
3.18 Constancy of rest tremor	0.3316	1.5598	0.2289	2.8
2.4 Eating tasks	0.2947	0.7090	0.2227	2.8

Item	MSDR	VIP	PLS weight	% contribution
3.3b Rigidity - RUE	0.1834	0.8314	0.2116	2.6
3.14 Global spontaneity of movement	0.2734	0.9049	0.1519	1.9
3.3c Rigidity - LUE	0.3370	1.0914	0.0694	0.9
3.7b Toe tapping - Left foot	0.2227	1.3155	0.0597	0.7
2.5 Dressing	0.3113	0.7396	0.0599	0.7
3.5a Hand movements - Right Hand	0.2268	1.1942	0.0464	0.6
3.3a Rigidity - Neck	0.2428	0.9632	0.0521	0.6
3.4b Finger Tapping Left Hand	0.3876	1.3037	0.0279	0.3
3.4a Finger Tapping Right Hand	0.2000	1.1148	0.0240	0.3
Overall MSDR	0.8612			

Abbreviations: LLE – left lower extremity; LUE – left upper extremity; MSDR – mean standard deviation ratio; PLS – partial least squares regression; RLE – right lower extremity; RUE – right upper extremity; VIP – variable importance of projection

Note: items with negative coefficients and VIP<0.5 were not retained in the model and are not shown in the table.

Supplemental Table 5. VIP score and PLS coefficients for PARCOMS motor PPMI treated-w/o-MC population

Item	MSDR	VIP	PLS weight	% contribution
2.9 Turning in bed	0.3638	1.5536	0.8935	19.7
2.1 Speech	0.2604	1.2813	0.5285	11.6
3.13 Posture	0.3552	1.0020	0.5066	11.1
2.11 Getting out of bed, a car, or a deep chair	0.2949	1.3994	0.4962	10.9
3.10 Gait	0.3484	0.9891	0.2938	6.5
3.12 Postural stability	0.2699	0.7502	0.2776	6.1
2.2 Saliva and drooling	0.1813	1.1020	0.2601	5.7
3.7a Toe tapping – Right foot	0.2448	1.0175	0.2571	5.7
2.5 Dressing	0.2291	1.1374	0.2562	5.6
3.7b Toe tapping – Left foot	0.3122	1.0918	0.1859	4.1
2.8 Doing hobbies and other activities	0.3245	1.4530	0.1584	3.5
2.12 Walking and balance	0.2903	1.0150	0.1260	2.8
2.13 Freezing	0.1717	0.6581	0.1267	2.8
2.7 Handwriting	0.1722	1.1114	0.0884	1.9
3.8b Leg agility – Left leg	0.2118	0.8348	0.0462	1.0
2.4 Eating tasks	0.1566	0.7096	0.0189	0.4
3.6b Pronation-Supination – Left Hand	0.1441	0.6013	0.0124	0.3
3.1 Speech	0.1604	0.5357	0.0109	0.2
Overall MSDR	0.6117			

Abbreviations: LLE – left lower extremity; LUE – left upper extremity; MSDR – mean standard deviation ratio; PLS – partial least squares regression; RLE – right lower extremity; RUE – right upper extremity; VIP – variable importance of projection.

Note: items with negative coefficients and $VIP < 0.5$ were not retained in the model and are not shown in the table.

Supplemental Table 6. VIP score and PLS coefficients for PARCOMS motor PPMI treated-w/MC population

Item	MSDR	VIP	PLS weight	% contribution
2.1 Speech	0.3167	1.4345	0.5181	12.5
2.9 Turning in bed	0.2109	1.3310	0.4491	10.8
2.13 Freezing	0.1575	1.1370	0.4309	10.4
3.13 Posture	0.1412	1.0633	0.4045	9.7
3.12 Postural stability	0.2390	0.9694	0.3623	8.7
2.5 Dressing	0.2122	1.1682	0.3581	8.6
3.3a Rigidity – Neck	0.1197	0.7939	0.3098	7.5
2.7 Handwriting	0.2034	1.4687	0.2982	7.2
2.3 Chewing and swallowing	0.0871	0.6425	0.2477	6.0
3.1 Speech	0.1129	0.6375	0.2013	4.9
2.12 Walking and balance	0.2347	1.1613	0.1440	3.5
3.4a Finger Tapping Right Hand	0.0904	0.7356	0.1339	3.2
2.2 Saliva and drooling	0.0906	0.8345	0.1205	2.9
3.3d Rigidity – RLE	0.1066	0.5248	0.0742	1.8
3.3e Rigidity – LLE	0.1001	0.5044	0.0470	1.1
2.8 Doing hobbies and other activities	0.1598	1.4098	0.0258	0.6
3.7b Toe tapping – Left foot	0.0647	1.0041	0.0211	0.5
3.9 Arising from chair	0.1760	0.7869	0.0012	0.0
3.8b Leg agility – Left leg	0.0913	0.8381	0.0007	0.0

Item	MSDR	VIP	PLS weight	% contribution
3.5a Hand movements – Right Hand	0.0910	0.6346	0.0004	0.0
Overall MSDR	0.3905			

Abbreviations: LLE – left lower extremity; LUE – left upper extremity; MSDR – mean standard deviation ratio; PLS – partial least squares regression; RLE – right lower extremity; RUE – right upper extremity; VIP – variable importance of projection.

Note: items with negative coefficients and VIP<0.5 were not retained in the model and are not shown in the table.

PARCOMS non-motor tables:

Supplemental Table 7. VIP score and PLS coefficients for PARCOMS non-motor PPMI untreated population

Item	MSDR	VIP	PLS weight	% contribution
1.13 Fatigue	0.1229	1.6209	0.5670	23.9
1.11 Constipation problems	0.1002	0.7585	0.4023	17.0
1.1 Cognitive impairment	0.0315	0.5925	0.3709	15.7
1.10 Urinary problems	0.1748	1.1277	0.3641	15.4
1.9 Pain and other sensations	0.2082	1.6078	0.3436	14.5
1.8 Daytime sleepiness	0.0684	1.1553	0.3204	13.5
Overall MSDR	0.2589			

Abbreviations: MSDR – mean standard deviation ratio; PLS – partial least squares regression; VIP – variable importance of projection

Note: items with negative coefficients and VIP<0.5 were not retained in the model and are not shown in the table.

Supplemental Table 8. VIP score and PLS coefficients for PARCOMS non-motor PPMI treated-w/o-MC population

Item	MSDR	VIP	PLS weight	% contribution
1.1 Cognitive impairment	0.3450	1.2817	0.6357	18.2
1.10 Urinary problems	0.2133	1.3281	0.5053	14.5
1.2 Hallucinations and psychosis	0.2067	0.5001	0.4107	11.8
1.12 Light headedness on standing	0.1897	0.9123	0.3920	11.2
1.13 Fatigue	0.2847	1.3293	0.3425	9.8
1.4 Anxious mood	0.1730	0.9093	0.2752	7.9
1.11 Constipation problems	0.1292	0.6242	0.2588	7.4
1.3 Depressed mood	0.1568	0.9675	0.2299	6.6
1.5 Apathy	0.2383	0.8635	0.1447	4.1
1.9 Pain and other sensations	0.1826	0.8550	0.1141	3.3
1.7 Nighttime sleep problems	0.1397	1.1218	0.1118	3.2
1.8 Daytime sleepiness	0.1526	0.9254	0.0720	2.1
Overall MSDR	0.4854			

Abbreviations: MSDR – mean standard deviation ratio; PLS – partial least squares regression; VIP – variable importance of projection; w/o-MC – without motor complications.

Note: items with negative coefficients and VIP<0.5 were not retained in the model and are not shown in the table.

Supplemental Table 9. VIP score and PLS coefficients for PARCOMS non-motor PPMI treated-w/-
MC population

Item	MSDR	VIP	PLS weight	% contribution
1.1 Cognitive impairment	0.2037	1.7485	0.7322	37.6
1.10 Urinary problems	0.1479	1.1411	0.3452	17.7
1.11 Constipation problems	0.2211	1.0229	0.2513	12.9
1.5 Apathy	0.0293	0.7445	0.1891	9.7
1.12 Light headedness on standing	0.1359	0.7149	0.1583	8.1
1.7 Nighttime sleep problems	0.1698	1.2799	0.1493	7.7
1.13 Fatigue	0.1370	0.9497	0.0804	4.1
1.9 Pain and other sensations	0.0653	0.8421	0.0412	2.1
Overall MSDR	0.3248			

Abbreviations: MSDR – mean standard deviation ratio; PLS – partial least squares regression; VIP – variable importance of projection; w/MC – with motor complications.

Note: items with negative coefficients and VIP<0.5 were not retained in the model and are not shown in the table.