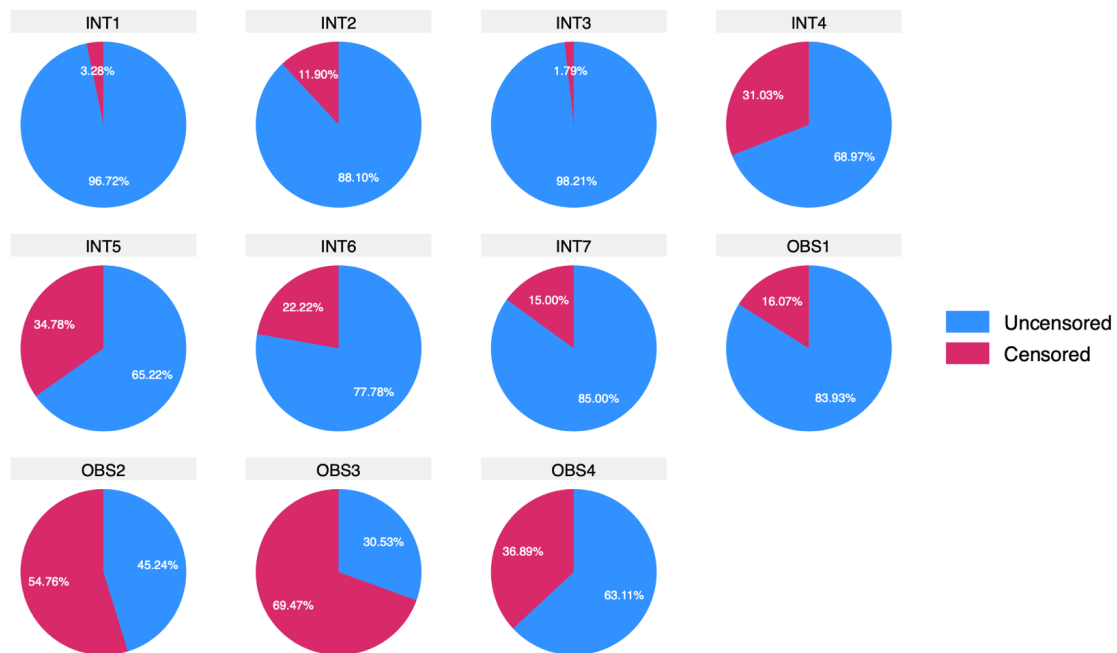


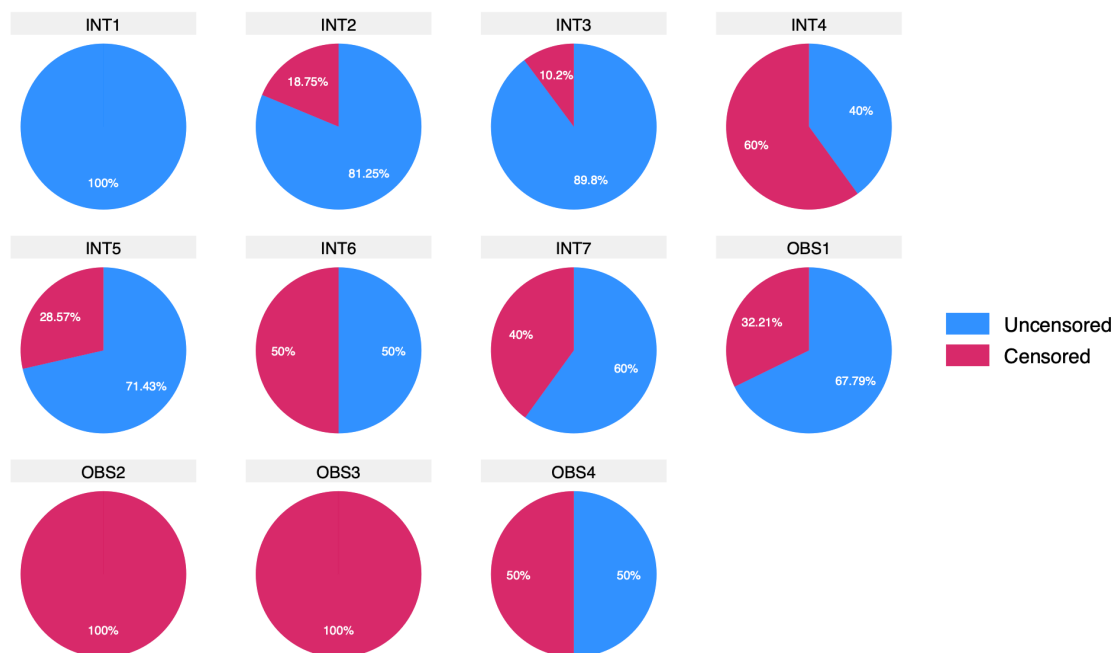
Exploring a milestone-based outcome measure for disease-modifying trials in Parkinson's disease – Supplementary Material

Supplementary Figure 1. Proportion of censors after milestone occurrence by study. 1A) After first milestone occurrence; 1B) After second milestone occurrence; 1C) After third milestone occurrence; 1D) After fourth milestone occurrence.

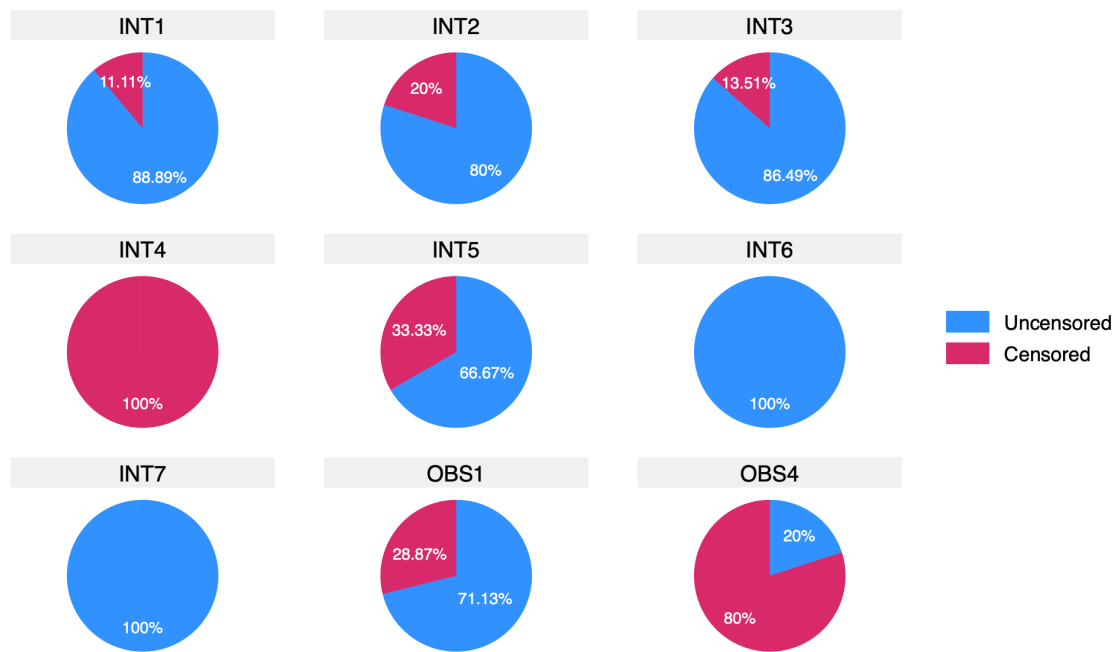
A)



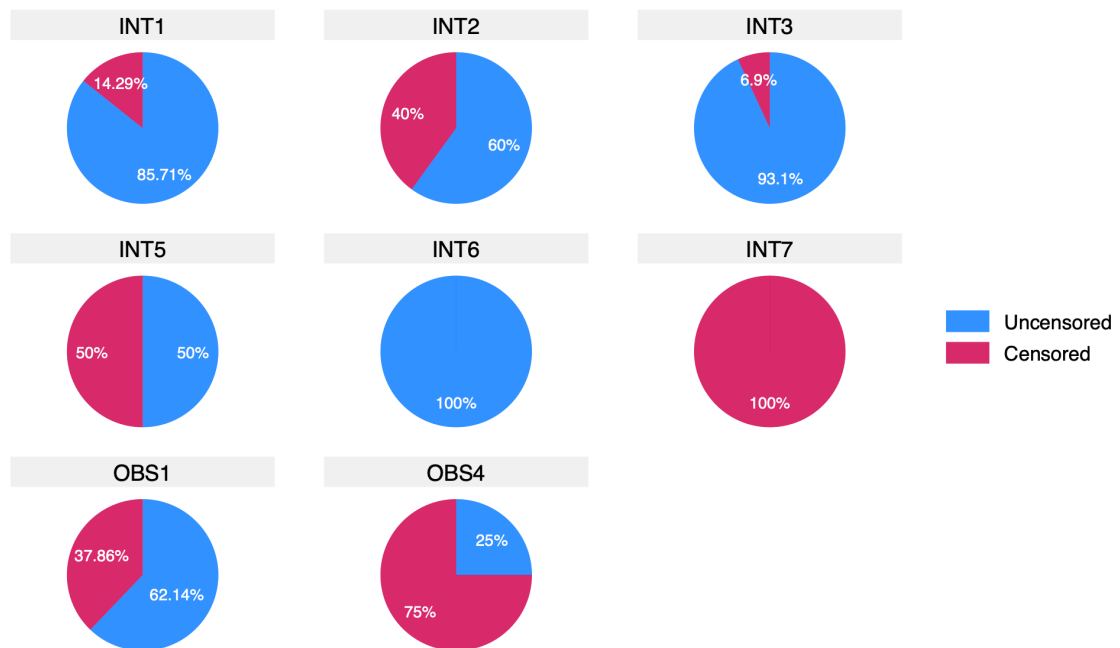
B)



C)



D)



General

All studies

N° at risk (n° of events)

Follow-up time (months)	0	12	24	36	48	60	72	84	96	108	120
Observational	3491	3059	2274	2028	853	576	515	297	278	274	0
Clinical Trial	(50)	(70)	(43)	(126)	(51)	(11)	(31)	(7)	(3)	(10)	(0)

By study type

N° at risk (n° of events)

Follow-up time (months)	0	12	24	36	48	60	72	84	96	108	120
Observational	3320	2315	1839	1723	853	576	515	297	278	274	0
Clinical Trial	(0)	(62)	(25)	(126)	(51)	(11)	(31)	(7)	(3)	(10)	(0)

By study

N° at risk (n° of events)

Follow-up time (months)	0	12	24	36	48	60	72	84	96	108	120	
INT1	328	(2)	321	(0)	316	(0)	305	(0)	0	(0)	0	(0)
INT2	289	(5)	252	(5)	11	(0)	0	(0)	0	(0)	0	(0)
INT3	72	(32)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
INT4	113	(0)	113	(2)	108	(16)	0	(0)	0	(0)	0	(0)
INT5	204	(7)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
INT6	71	(1)	21	(0)	0	(0)	0	(0)	0	(0)	0	(0)
INT7	94	(3)	37	(1)	0	(0)	0	(0)	0	(0)	0	(0)
INT8	132	(0)	132	(6)	113	(6)	111	(7)	121	(1)	147	(4)
INT9	145	(0)	145	(0)	123	(2)	110	(13)	2	(1)	0	(0)
INT10	833	(0)	833	(0)	406	(3)	343	(23)	10	(0)	0	(0)
INT11	215	(0)	210	(1)	174	(4)	153	(19)	20	(9)	102	(6)
INT12	71	(4)	9	(1)	1	(0)	1	(0)	0	(0)	0	(0)

By age

All studies

N° at risk (n° of events)

Follow-up time (months)	0	12	24	36	48	60	72	84	96	108	120
Age ≤ 65	1559	1376	1062	958	422	293	271	177	170	167	0
Age > 65	1332	1163	1215	1070	431	283	244	120	108	107	0

Observational studies

N° at risk (n° of events)

Follow-up time (months)	0	12	24	36	48	60	72	84	96	108	120
Age ≤ 65	983	981	819	775	422	293	271	177	170	167	0
Age > 65	1337	1334	1020	948	431	283	244	120	108	107	0

Clinical trials

N° at risk (n° of events)

Follow-up time (months)	0	12	24	36	48	
Age ≤ 65	576	(20)	395	(3)	243	(8)
Age > 65	595	(30)	349	(5)	192	(10)

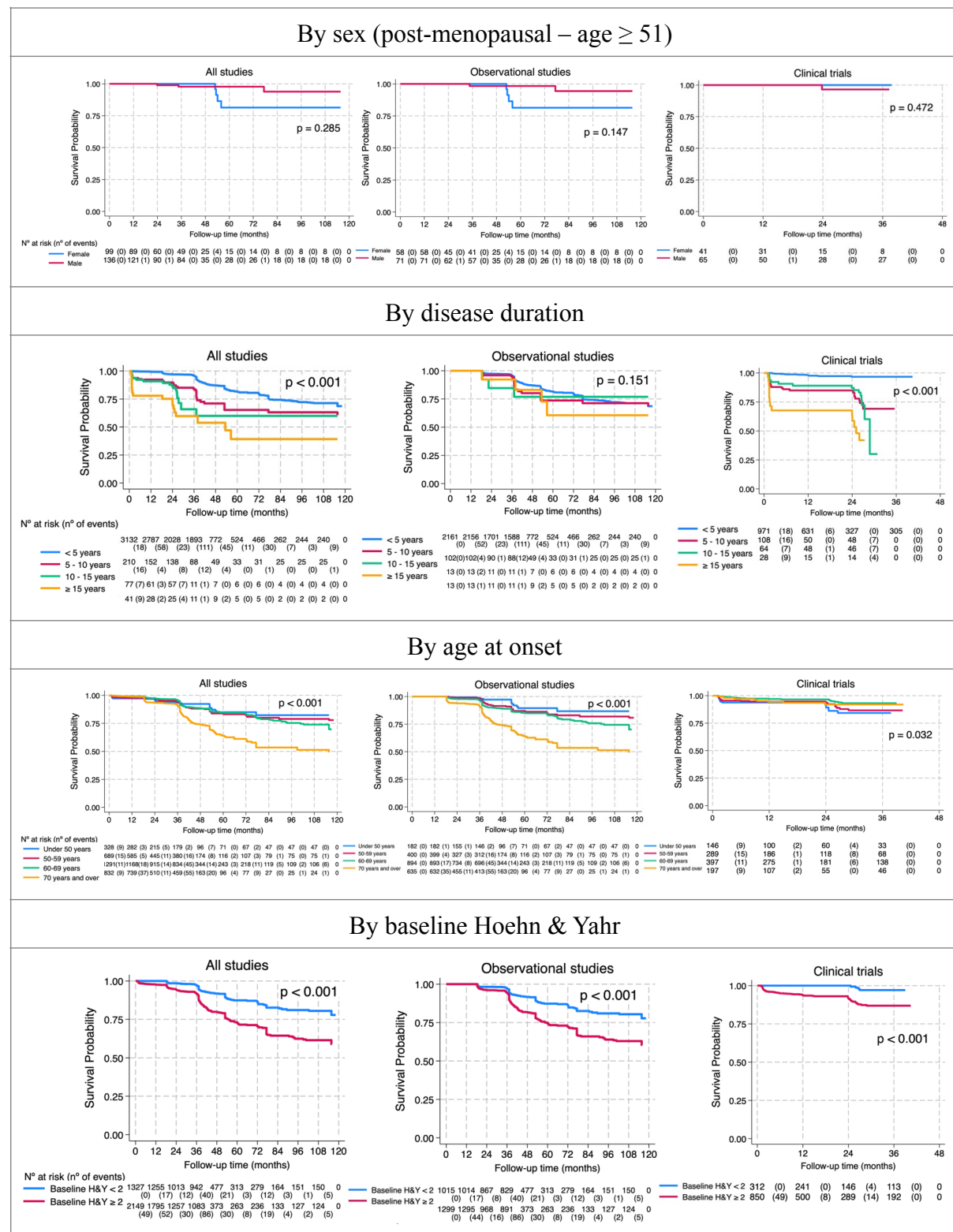
By sex (overall)

All studies

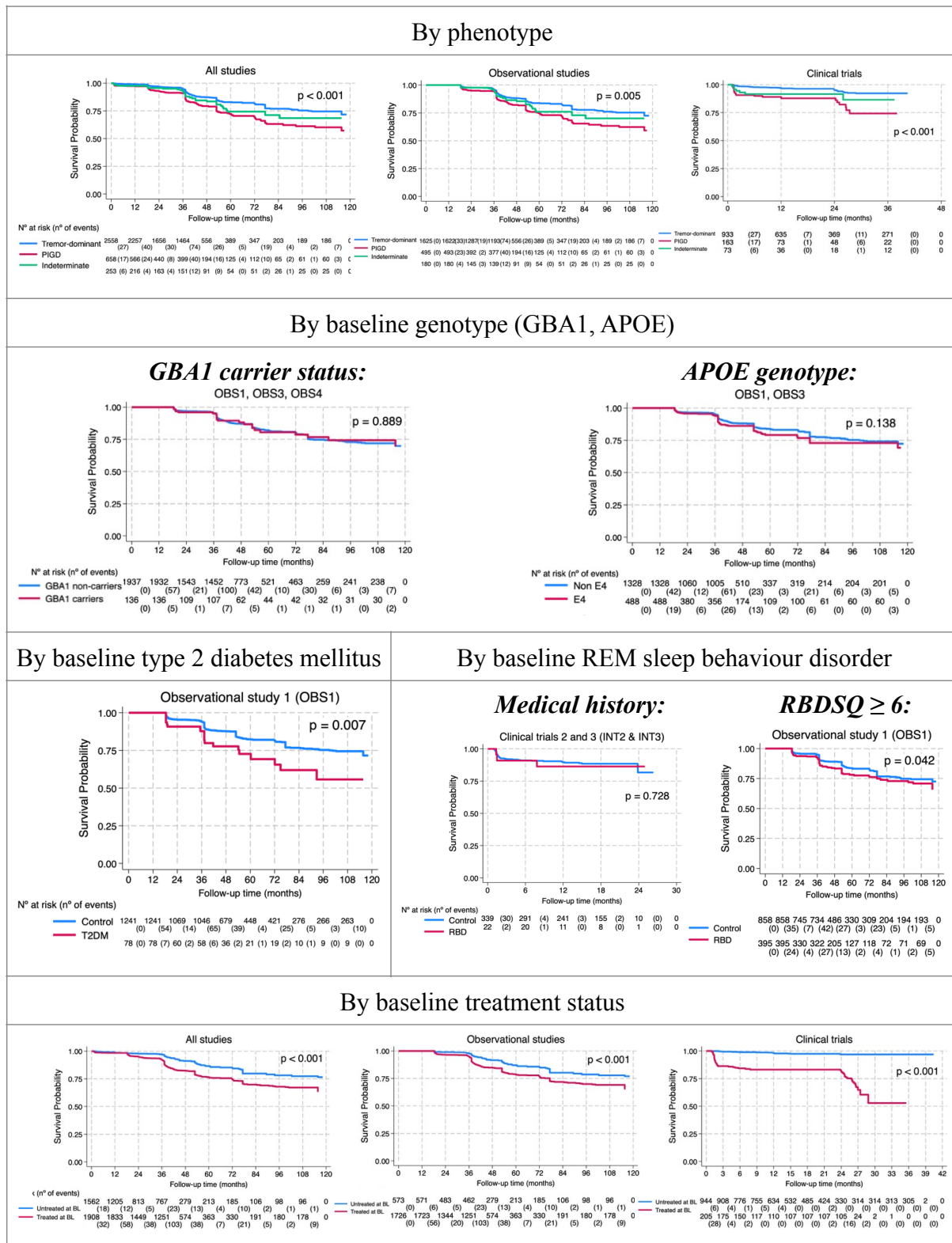
N° at risk (n° of events)

Follow-up time (months)	0	12	24	36	48	60	72</
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Supplementary Figure 2 (continued). Survival curves for composite milestone occurrence in two consecutive visits.

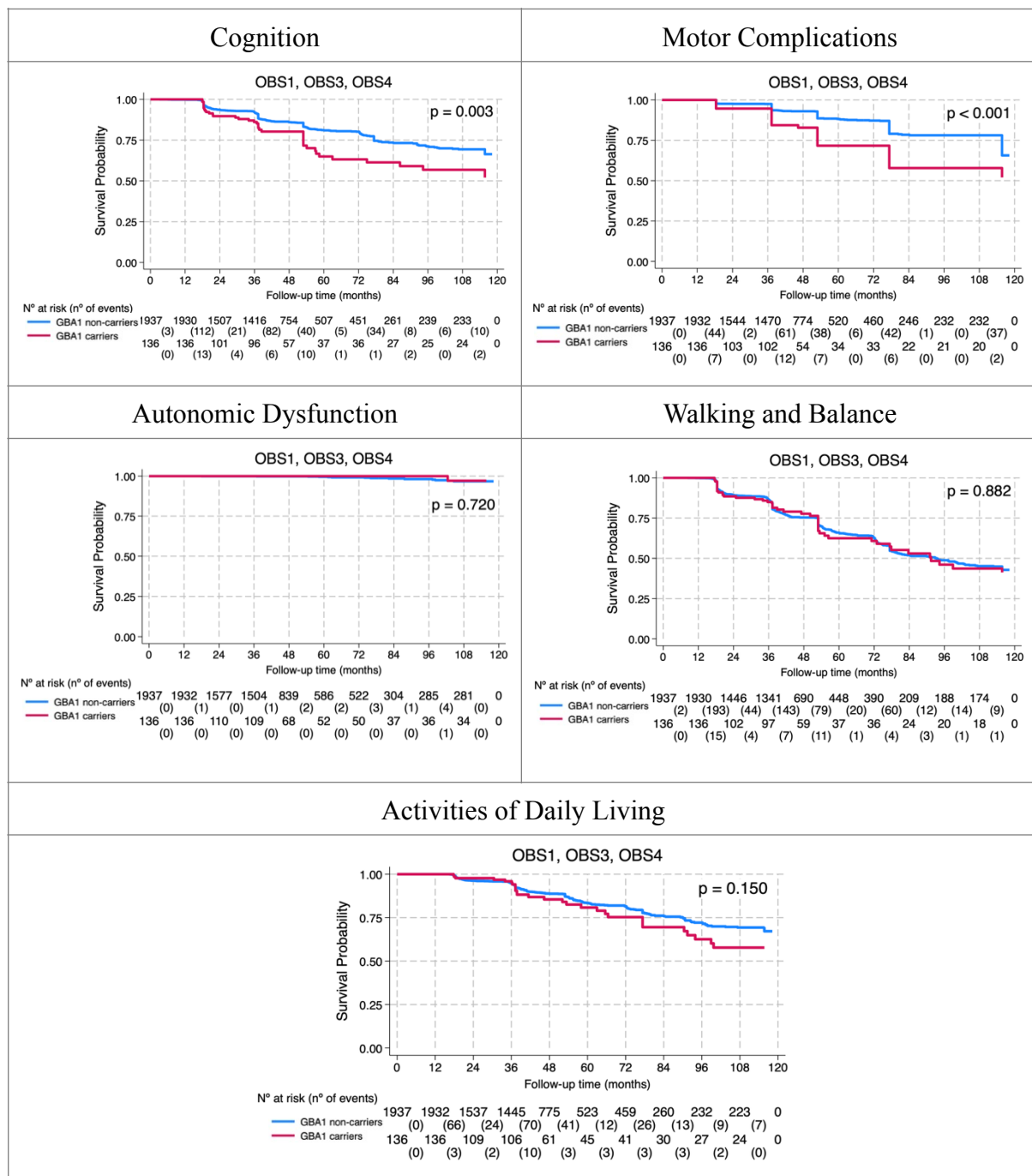


Supplementary Figure 2 (continued). Survival curves for composite milestone occurrence in two consecutive visits.



H&Y: Hoehn & Yahr; N.S.: not significant (i.e. $p > 0.05$); PIGD: postural instability-gait disorder; RBD: rapid eye movement (REM)-sleep behaviour disorder; RBDSQ: RBD screening Questionnaire; T2DM: type 2 diabetes mellitus.

Supplementary Figure 3. Time to each composite milestone domain by GBA1 carrier status.



No data available to assess the “Functional Dependence” domain.

Supplementary Table 1. Baseline data – Observational studies.

Study Variables	Original (PPMI) (N = 376)	CPP – Observational studies			
		OBS1 (N = 1327)	OBS2 (N = 145)	OBS3 (N = 633)	OBS4 (N = 215)
Age (years)	61.5 (9.8)	66.2 (8.9)	65.0 (9.1)	66.3 (9.0)	67.0 (9.1)
Sex (females)	127 (33.8)	465 (35.0)	52 (35.9)	222 (35.1)	75 (34.9)
Age at PD onset (years)	NA	63.2 (9.5)	64.6 (9.1)	65.1 (9.0)	66.7 (9.1)
Disease duration (months)	6.7 (6.5)	36.6 (36.6)	5.3 (5.3)	14.7 (11.4)	3.1 (3.8)
On dopaminergic treatment	0 (0)	1012 (76.3)	85 (58.6)	521 (85.1)	108 (50.2)
Race					
American Indian or Alaska Native	NA	NA			NA
Asian	8 (2.1)	5 (0.4)			1 (0.5)
Black or African- American	6 (1.6)	1 (0.1)			NA
Multiracial	6 (1.6)	4 (0.3)	NA	NA	NA
Native Hawaiian or Other Pacific Islander	NA	NA			NA
Other	NA	2 (0.2)			1 (0.5)
White	355 (94.7)	1303 (98.2)			213 (99.1)
Unknown	NA	12 (0.9)			NA
Ethnicity					
Hispanic or Latino	5 (1.3)	NA	NA	NA	NA
Not Hispanic or Latino	371 (98.7)				
Unknown	–				
GBA1 variant carriers	NA	108 (8.4)	NA	13 (2.3)	15 (7.1)
APOE genotype					
ε2/ε2 / ε2/ε3	NA	177 (14.3)	NA	84 (14.6)	NA
ε3/ε3		719 (58.0)		348 (60.3)	
ε4		343 (27.7)		145 (25.1)	
Body mass index (kg/m²)	27.2 (4.7)	26.8 (4.3)	26.9 (4.5)	NA	NA
Type 2 DM	NA	78 (5.9)	NA	NA	NA
RBD	NA	395 (31.5)	NA	NA	NA
UPSIT score	NA	19.9 (6.8)	NA	NA	NA
MDS-UPDRS total score	31.5 (12.8)	35.7 (15.2)	NA^	NA^	43.1 (14.9)
H&Y stage	1.6 (0.5)	1.6 (0.5)	1.7 (0.5)	1.8 (0.4)	1.6 (0.6)
S&E ADL score	93.5 (5.6)	NA	NA	NA	NA
MoCA score	27.2 (2.2)	26.0 (2.4)	26.1 (2.5)	NA	26.3 (2.2)
GDS-15 score	NA	NA	2.6 (2.4)	NA	4.8 (2.3)
SCOPA-AUT score	9.0 (5.5)	NA	NA	NA	NA
ESS score	NA	6.2 (4.1)	6.2 (4.2)	NA	NA
RBDSQ score	NA	4.5 (3.1)	NA	NA	NA
DAT-SPECT mean striatum SBR	1.40 (0.39)	NA	NA	NA	NA
DAT-SPECT mean putamen SBR	NA	NA	NA	NA	NA
Serum urate (mg/dL)	5.4 (1.3)	NA	NA	5.2 (1.2)	NA
Serum CRP (mg/L)	NA	NA	NA	2.7 (7.9)	NA
Serum APOA1 (g/L)	NA	NA	NA	1.6 (0.2)	NA
CSF t-tau/β-A₁₋₄₂	NA	NA	NA	NA	NA
CSF α-synuclein (ng/L)	NA	NA	NA	NA	NA

^No MDS-UPDRS part I data so MDS-UPDRS total score (I+II+III) could not be calculated.

Supplementary Table 2. Baseline data – Interventional studies.

Study Variables	Original (PPMI) (N = 376)	CPP – Interventional studies						
		INT1 (N = 328)	INT2 (N = 289)	INT3 (N = 72)	INT4 (N = 113)	INT5 (N = 204)	INT6 (N = 71)	INT7 (N = 94)
Age (years)	61.5 (9.8)	62.1 (8.9)	63.1 (9.6)	64.6 (7.3)	65.7 (8.3)	65.9 (9.2)	59.5 (8.7)	NA
Sex (females)	127 (33.8)	105 (32.0)	145 (50.2)	22 (30.6)	71 (62.8)	108 (52.9)	15 (21.1)	25 (26.6)
Age at PD onset (years)	NA	61.3 (8.9)	62.3 (9.6)	54.6 (8.0)	55.0 (8.7)	64.3 (9.4)	58.6 (8.7)	NA
Disease duration (months)	6.7 (6.5)	9.6 (8.8)	10.3 (8.1)	119.6(58.0)	128.4(49.1)	18.9 (20.1)	9.7 (6.5)	22.9 (23.5)
On dopaminergic treatment	0 (0)	0 (0)	0 (0)	72 (100)	113 (100)	0 (0)	0 (0)	0 (0)
Race								
American Indian or Alaska Native	–	1 (0.3)	–	–	–	–	–	–
Asian	8 (2.1)	10 (3.1)	3 (1.0)	–	–	204 (100)	1 (1.4)	–
Black or African-American	6 (1.6)	8 (2.4)	2 (0.7)	–	–	–	–	–
Multiracial	6 (1.6)	5 (1.5)	2 (0.7)	2 (2.8)	–	–	–	–
Native Hawaiian or Other Pacific Islander	–	1 (0.3)	–	–	–	–	–	–
Other	–	3 (0.9)	–	–	–	–	–	1 (1.1)
White	355 (94.7)	299 (91.2)	279 (96.5)	68 (94.4)	113 (100)	–	60 (84.5)	90 (95.7)
Unknown	–	1 (0.3)	3 (1.0)	2 (2.8)	–	–	10 (14.1)	3 (3.2)
Ethnicity								
Hispanic or Latino	5 (1.3)	10 (3.1)	9 (3.1)	2 (2.8)	–	–	3 (4.2)	–
Not Hispanic or Latino	371 (98.7)	318 (97.0)	275 (95.2)	70 (97.2)	NA	NA	62 (87.3)	NA
Unknown	–	–	5 (1.7)	–	–	–	6 (8.5)	–
GBA1 variant carriers	NA	NA	NA	NA	NA	NA	NA	NA
APOE genotype	NA	NA	NA	NA	NA	NA	NA	NA
Body mass index (kg/m²)	27.2 (4.7)	27.0 (4.5)	26.5 (4.9)	26.5 (4.5)	26.4 (4.2)	22.5 (3.0)	NA	26.2 (3.9)
Type 2 DM*	NA	NA	NA	2 (2.8)	NA	NA	6 (8.5)	NA
RBD**	NA	NA	NA	NA	NA	NA	NA	NA
UPSIT score	NA	NA	NA	NA	NA	NA	NA	NA
MDS-UPDRS total score	31.5 (12.8)	32.3 (11.7)	32.5 (12.3)	66.4 (19.6)	46.3 (14.6)	36.3 (15.0)	32.2 (12.4)	31.3 (12.0)
H&Y stage	1.6 (0.5)	1.6 (0.5)	1.7 (0.5)	3.0 (0.3)	1.8 (0.6)	2.0 (0.5)	1.8 (0.4)	1.7 (0.5)

Supplementary Table 2 (continued). Baseline data – Interventional studies.

Study Variables	Original (PPMI) (N = 376)	CPP – Interventional studies						
		INT1 (N = 328)	INT2 (N = 289)	INT3 (N = 72)	INT4 (N = 113)	INT5 (N = 204)	INT6 (N = 71)	INT7 (N = 94)
S&E ADL score	93.5 (5.6)	94.2 (6.1)	94.2 (4.8)	89.5 (7.6)	NA	NA	91.7 (6.1)	92.6 (6.2)
MoCA score	27.2 (2.2)	28.1 (1.4)	27.6 (1.8)	27.1 (2.3)	27.6 (2.2)	NA	27.8 (2.0)	27.0 (2.0)
GDS-15 score	NA	NA	NA	NA	NA	NA	NA	NA
SCOPA-AUT score	9.0 (5.5)	NA	NA	NA	NA	NA	NA	9.3 (6.0)
ESS score	NA	NA	NA	NA	NA	NA	NA	4.7 (3.5)
RBDSQ score	NA	NA	NA	NA	NA	NA	NA	NA
DAT-SPECT mean striatum SBR	1.40 (0.39)	NA	1.58 (0.44)	NA	NA	NA	1.52 (0.41)	NA
DAT-SPECT mean putamen SBR	NA	NA	0.95 (0.31)	NA	NA	NA	0.96 (0.26)	NA
Serum urate (mg/dL)	5.4 (1.3)	NA	NA	NA	NA	NA	5.3 (1.2)	NA
Serum urate (mg/dL)	NA	NA	NA	NA	NA	NA	NA	NA
Serum CRP (mg/L)	NA	NA	NA	NA	NA	NA	NA	NA
Serum APOA1 (g/L)	NA	NA	NA	NA	NA	NA	NA	NA
CSF t-tau/β-A42	NA	NA	NA	NA	NA	NA	0.2 (0.1)	NA
CSF α-synuclein (ng/L)	NA	NA	NA	NA	NA	NA	207.2 (178.4)	NA

Results are means (SD) for continuous variables and counts (%) for categorical variables. *In medical history. **Defined as RBDSQ score ≥ 6 . APOA1: Apolipoprotein A1; APOE: Apolipoprotein E (gene); β -A₁₋₄₂: Beta amyloid 1-42; BMI: Body Mass Index; CRP: C-reactive protein; CSF: cerebrospinal fluid; DAT-SPECT: Dopamine Transporter Single-Photon Emission Computed Tomography; DM: Diabetes mellitus; ESS: Epworth Sleepiness Scale; GBA1: Glucosylceramidase beta 1 (gene); GDS-15: 15-item Geriatric Depression Scale; MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; NA: Not available; PD: Parkinson's disease; RBD: REM sleep behaviour disorder; RBDSQ: REM sleep Behaviour Disorder Screening Questionnaire; S&E ADL: Schwab & England Activities of Daily Living scale; SBR: Specific Binding Ratio; SCOPA-AUT: Scales for Outcomes in Parkinson's disease - Autonomic Dysfunction.; t-tau: Total tau protein; UPSIT: University of Pennsylvania Smell Identification Test.

Supplementary Table 3. Baseline characteristics of the sample by milestone occurrence at baseline visit.

Variable	Milestone occurrence at baseline		Total*	<i>p</i> ***
	No	Yes		
Number of subjects (%)	3505 (83.3%)	704 (16.7%)	4209 (100.0%)	—
Sex, females (%)	1,311 (37.4%)	305 (43.3%)	1616 (38.4%)	0.003
Age, years	65.4 (9.1)	70.4 (9.0)	66.2 (9.3)	<0.001
Age at onset, years	63.1 (9.6)	66.4 (10.2)	63.6 (9.8)	<0.001
Disease duration, months	27.7 (38.4)	48.0 (55.5)	31.0 (42.3)	<0.001
BMI, kg/m2	26.4 (4.5)	27.2 (5.2)	26.6 (4.6)	<0.001
Race				0.214
<i>American Indian or Alaska Native</i>	1 (0.0%)	0 (0.0%)	1 (0.0%)	
<i>Asian</i>	224 (8.3%)	48 (8.3%)	272 (8.3%)	
<i>Black</i>	11 (0.4%)	6 (1.0%)	17 (0.5%)	
<i>Native Hawaiian or Other Pacific Islander</i>	1 (0.0%)	0 (0.0%)	1 (0.0%)	
<i>White</i>	2439 (90.5%)	526 (90.7%)	2965 (90.5%)	
<i>Mixed / Multiple</i>	13 (0.5%)	0 (0.0%)	13 (0.4%)	
<i>Other</i>	7 (0.3%)	0 (0.0%)	7 (0.2%)	
Ethnicity				0.630
<i>Not Hispanic or Latino</i>	725 (96.8%)	7 (100.0%)	732 (96.8%)	
<i>Hispanic or Latino</i>	24 (3.2%)	0 (0.0%)	24 (3.2%)	
MDS-UPDRS total score (I+II+III)	36.7 (15.7)	58.1 (21.3)	40.5 (18.7)	<0.001
H&Y stage	1.7 (0.6)	2.3 (0.7)	1.8 (0.6)	<0.001
S&E ADL score	93.4 (6.0)	87.1 (6.9)	93.3 (6.0)	<0.001
MoCA score	26.4 (3.0)	22.8 (4.8)	25.6 (3.7)	<0.001
SCOPA-AUT score	9.3 (6.0)	16.1 (6.7)	9.662 (6.2)	0.017
DAT-SPECT – Striatum SBR	1.55 (0.43)	1.32 (0.27)	1.55 (0.43)	0.445
Serum urate, mg/dL	5.15 (1.20)	4.93 (1.45)	5.15 (1.23)	0.167

*Total includes subjects with no follow-up visits beyond baseline, since the interest of comparison here is on baseline data. **Milestone-free at baseline vs. milestone occurrence at baseline. BMI: Body Mass Index; DAT-SPECT: Dopamine Transporter Single-Photon Emission Computed Tomography; MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; S&E ADL: Schwab & England Activities of Daily Living; SBR: Specific Binding Ratio; SCOPA-AUT: Scales for Outcomes in Parkinson's disease - Autonomic Dysfunction.

Supplementary Table 4. Baseline characteristics of the sample by withdrawal from study after first milestone occurrence.

Variable	Withdrew after first milestone occurrence		Total*	<i>p</i> **
	No	Yes		
Number of subjects (%)	967 (75.8%)	309 (24.2%)	1276 (100.0%)	-
Age, years	67.2 (9.3)	67.5 (9.1)	67.2 (9.3)	0.530
BMI, kg/m2	26.9 (4.5)	27.1 (4.5)	26.9 (4.5)	0.561
Disease duration, months	39.0 (45.9)	27.8 (33.5)	36.3 (43.5)	<0.001
Age at onset, years	63.8 (10.2)	65.2 (9.8)	64.2 (10.1)	0.036
MDS-UPDRS total score (I+II+III)	43.2 (16.6)	42.0 (15.7)	43.0 (16.5)	0.384
H&Y stage	1.8 (0.6)	1.8 (0.5)	1.8 (0.6)	0.507
S&E ADL score	90.7 (7.9)	90.7 (5.6)	90.7 (7.8)	0.970
MoCA score	26.2 (2.4)	26.0 (2.6)	26.2 (2.4)	0.216
SCOPA-AUT score	13.9 (7.1)	8.7 (6.1)	13.2 (7.0)	0.245
DAT-SPECT striatum SBR	1.59 (0.46)	1.19 (0.25)	1.50 (0.46)	0.037
Serum urate, μmol/L	5.38 (1.17)	5.34 (1.24)	5.36 (1.21)	0.883
Sex, females (%)	333 (34.4%)	102 (33.0%)	435 (34.1%)	0.645
Race				
<i>Asian</i>	19 (2.0%)	9 (2.9%)	28 (2.2%)	0.217
<i>Black</i>	3 (0.3%)	1 (0.3%)	4 (0.3%)	
<i>White</i>	871 (90.1%)	181 (58.6%)	1052 (82.4%)	
<i>Mixed / Multiple</i>	4 (0.4%)	2 (0.6%)	6 (0.5%)	
<i>Other</i>	2 (0.2%)	0 (0.0%)	2 (0.2%)	
Ethnicity				
<i>Not Hispanic or Latino</i>	156 (16.1%)	12 (100.0%)	168 (96.0%)	0.464
<i>Hispanic or Latino</i>	7 (0.7%)	0 (0.0%)	7 (4.0%)	
Dopaminergic treatment status				
<i>Untreated</i>	299 (30.9%)	82 (26.6%)	381 (29.9%)	0.151
<i>Treated</i>	668 (69.1%)	226 (73.4%)	894 (70.1%)	

*Total includes participants ever reaching a milestone. **Withdrawers vs. non-withdrawers.

Supplementary Table 5. Baseline characteristics of the sample by milestone reversal profile.

Variable	Milestone reversal profile*			Total**	<i>p</i>
	Non-reverters	Temporary	Permanent		
Number of subjects (%)	402 (41.6%)	263 (27.2%)	302 (31.2%)	967 (100.0%)	-
Age, years	69.3 (8.2)	66.2 (9.6)	65.1 (9.9)	67.2 (9.3)	<0.001
BMI, kg/m2	26.9 (4.5)	27.0 (4.5)	26.8 (4.6)	26.9 (4.5)	0.816
Disease duration, months	45.2 (56.5)	38.5 (34.0)	31.2 (37.3)	39.0 (45.9)	<0.001
Age at onset, years	65.5 (9.8)	63.0 (10.0)	62.4 (10.5)	63.8 (10.2)	<0.001
MDS-UPDRS total score (I+II+III)	47.8 (17.5)	42.2 (16.0)	38.2 (14.4)	43.2 (16.6)	<0.001
H&Y stage	2.0 (0.6)	1.8 (0.6)	1.7 (0.5)	1.8 (0.6)	<0.001
S&E ADL score	87.8 (10.5)	89.8 (7.4)	92.8 (5.8)	90.7 (7.9)	0.001
MoCA score	26.0 (2.5)	26.2 (2.4)	26.5 (2.3)	26.2 (2.4)	0.028
SCOPA-AUT score	13.6 (12.8)	13.4 (3.8)	14.6 (6.2)	13.9 (7.1)	0.955
DAT-SPECT Striatum SBR	1.60 (0.62)	1.43 (0.71)	1.62 (0.41)	1.59 (0.46)	0.827
Serum urate, μmol/L	5.14 (1.29)	4.81 (.)	5.63 (1.04)	5.38 (1.17)	0.354
Sex, female (%)	140 (34.8%)	85 (32.3%)	108 (35.8%)	333 (34.4%)	0.676
Race					
<i>Asian</i>	8 (2.2%)	2 (0.8%)	9 (3.2%)	19 (2.1%)	0.050
<i>Black</i>	0 (0.0%)	0 (0.0%)	3 (1.1%)	3 (0.3%)	
<i>White</i>	347 (97.2%)	254 (98.1%)	270 (95.4%)	871 (96.9%)	
<i>Mixed / Multiple</i>	2 (0.6%)	1 (0.4%)	1 (0.4%)	4 (0.4%)	
<i>Other</i>	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.2%)	
<i>Unknown</i>	45 (11.2%)	4 (1.5%)	19 (6.3%)	68 (7.0%)	
Ethnicity					
<i>Not Hispanic or Latino</i>	42 (93.3%)	37 (94.9%)	77 (97.5%)	156 (95.7%)	0.527
<i>Hispanic or Latino</i>	3 (6.7%)	2 (5.1%)	2 (2.5%)	7 (4.3%)	
<i>Unknown</i>	357 (88.8%)	224 (85.2%)	223 (73.8%)	804 (83.1%)	
Dopaminergic treatment status					
<i>Untreated</i>	89 (22.1%)	69 (26.2%)	141 (46.7%)	299 (30.9%)	<0.001
<i>Treated</i>	313 (77.9%)	194 (73.8%)	161 (53.3%)	668 (69.1%)	

*Temporary: no milestone occurrence at the following visit; Permanent: no milestone recurrence overall during follow-up.. **Total only includes subjects who ever met milestones and did not drop out after first milestone occurrence (n = 967). BMI: Body Mass Index; DAT-SPECT: Dopamine Transporter Single-Photon Emission Computed Tomography; MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; S&E ADL: Schwab & England Activities of Daily Living scale; SBR: Specific Binding Ratio; SCOPA-AUT: Scales for Outcomes in Parkinson's disease - Autonomic Dysfunction.

Supplementary Table 6. Stability of the composite milestone and its domains (**pooled cohort, n = 3491**).

Variable	Domain first reached							
	<i>Overall (any domain)</i>	<i>Cognition</i>	<i>Functional dependence</i>	<i>Autonomic dysfunction</i>	<i>Walking and balance</i>	<i>Motor complications</i>	<i>ADL</i>	<i>Multiple*</i>
Met criteria by last visit , n (%)**	1276 (36.6%)	443 (12.7%)	47 (1.3%)	24 (0.7%)	776 (22.2%)	386 (11.1%)	386 (11.1%)	—
Milestone domain first met , n***	—	234	26	7	479	200	141	189
Time to each domain (months), Median (IQR)****	—	36.9 (18.4-54.1)	9.3 (3.7-24.4)	54.5 (11.1-87.6)	37.3 (18.4-55.1)	37.3 (18.4-77.3)	37.3 (18.8-65.6)	—
Withdrew before next visit, n (%)	309/1276 (24.2%)	54/234 (23.1%)	2/26 (7.7%)	1/7 (14.3%)	115/479 (24.0%)	42/200 (21.0%)	40/141 (28.4%)	55/189 (29.1%)
N subsequent visits completed, mean (SD)**** Median (min, max)****	3.2 (2.3) 3 (1, 12)	3.2 (2.3) 3 (1, 11)	5.1 (3.0) 4.5 (1, 12)	4.5 (4.0) 3.5 (1, 11)	3.0 (2.2) 3 (1, 10)	3.2 (2.1) 2 (1, 9)	3.3 (2.6) 3 (1, 12)	3.0 (2.2) 2 (1, 9)
Met any domain at any visit , n (%)****	665/967 (68.8%)	111/180 (61.7%)	11/24 (45.8%)	3/6 (50.0%)	272/364 (74.7%)	100/158 (63.3%)	58/101 (57.4%)	110/134 (82.1%)
Met any domain at next visit , n (%)****	402/967 (41.6%)	60/180 (33.3%)	3/24 (12.5%)	2/6 (33.3%)	177/364 (48.6%)	51/158 (32.3%)	35/101 (34.7%)	74/134 (55.2%)
Met same domain at next visit , n (%)****	—	40/180 (22.2%)	2/24 (8.3%)	1/6 (16.7%)	144/364 (39.6%)	29/158 (18.4%)	17/101 (16.8%)	—

Multiple**: more than one domain simultaneously met at the initial event. **Indicates how many participants ever met that domain during follow-up. ***Indicates how many participants met the corresponding criteria at the initial event. *Calculations only include individuals ever meeting the composite milestone (n = 1276), and each cell refers to the whole cohort (n = 1276) regardless of which milestone domain was reached first. *****Calculations exclude anyone who withdrew before completing another follow-up. ADL: Activities of daily living; IQR: Interquartile range.

Supplementary Table 7. Stability of the composite milestone and its domains (**all participants treated at baseline, n= 1908**).

Variable	Domain first reached							
	<i>Overall (any domain)</i>	<i>Cognition</i>	<i>Functional dependence</i>	<i>Autonomic dysfunction</i>	<i>Walking and balance</i>	<i>Motor complications</i>	<i>ADL</i>	<i>Multiple*</i>
Met criteria by last visit , n (%)**	894 (46.9%)	306 (16.0%)	15 (0.8%)	13 (0.7%)	596 (31.2%)	294 (15.4%)	281 (14.7%)	—
Milestone domain first met , n***	—	139	1	3	363	150	91	147
Time to each domain (months), Median (IQR)****	—	37.3 (19.2-58.4)	3.5 (1.1-3.7)	75.9 (36.9-98.2)	37.3 (18.4-55.0)	37.3 (18.4-77.3)	40.9 (30.5-72.8)	—
Withdrew before next visit, n (%)	226/894 (25.3%)	35/139 (25.2%)	0/1 (0.0%)	0/3 (0.0%)	90/363 (24.8%)	28/150 (18.7%)	33/91 (36.3%)	40/147 (27.2%)
N subsequent visits completed, mean (SD)***** Median (min, max)*****	3.0 (2.1) 2 (1, 9)	3.0 (2.2) 2 (1, 9)	6	2.7 (2.1) 2 (1, 5)	3.0 (2.1) 3 (1, 9)	3.2 (2.1) 2 (1, 9)	3.0 (2.4) 2 (1, 9)	2.9 (2.1) 2 (1, 9)
Met any domain at any visit , n (%)*****	507/668 (75.9%)	71/104 (68.3%)	1/1 (100%)	2/3 (66.7%)	217/273 (79.5%)	84/122 (68.9%)	39/58 (67.2%)	93/107 (86.9%)
Met any domain at next visit , n (%)*****	313/668 (46.9%)	35/104 (33.7%)	0/1 (0.0%)	1/3 (33.3%)	144/273 (52.7%)	44/122 (36.1%)	24/58 (41.4%)	65/107 (60.7%)
Met same domain at next visit , n (%)*****	—	20/104 (19.2%)	0/1 (0.0%)	0/3 (0.0%)	118/273 (43.2%)	27/122 (22.1%)	12/58 (20.7%)	—

"Multiple": more than one domain simultaneously met at the initial event. **Indicates how many participants ever met that domain during follow-up. *Indicates how many participants met the corresponding criteria at the initial event. ****Calculations only include individuals ever meeting the composite milestone (n = 114), and each cell refers to the whole cohort (n = 114) regardless of which milestone domain was reached first.

*****Calculations exclude anyone who withdrew before completing another follow-up. ADL: Activities of daily living; IQR: Interquartile range.

Supplementary Table 8. Predictors of time to two consecutive milestones.

Variable	Univariable HR(95% CI)	<i>p</i>	Multivariable HR (95% CI)	<i>p</i>
Age, years	1.07 (1.06, 1.09)	<0.001	1.06 (1.05, 1.08)	<0.001
Sex (male vs. female)	1.06 (0.86, 1.30)	0.599	0.84 (0.65, 1.07)	0.157
Age at onset, years	1.06 (1.04, 1.07)	<0.001	NI*	–
Disease duration, months	1.00 (1.00, 1.01)	<0.001	1.00 (1.00, 1.01)	0.070
GBA1 pathogenic variant carrier	1.02 (0.66, 1.56)	0.939	NA**	–
APOE ε4 genotype	1.22 (0.93, 1.60)	0.147	NA**	–
Phenotype (vs. tremor-dominant) <i>PIGD</i>	1.63 (1.31, 2.04)	<0.001	1.48 (1.15, 1.92)	0.003
<i>Indeterminate</i>	1.34 (0.95, 1.89)	0.100	1.64 (1.12, 2.40)	0.012
Dopaminergic treatment at baseline	1.95 (1.48, 2.57)	<0.001	NI*	–
Dopaminergic treatment (whole study duration)	1.92 (1.02, 3.60)	0.042	1.23 (0.55, 2.75)	0.609
T2DM	1.84 (1.17, 2.88)	0.008	NI***	–
MDS-UPDRS score (I+II+III) (per 5-point increase)	1.21 (1.18, 1.25)	<0.001	1.18 (1.14, 1.22)	<0.001
H&Y stage	2.48 (2.05, 3.02)	<0.001	1.44 (1.12, 1.85)	0.004
S&E ADL score (per 10-unit decrease)	2.25 (1.54, 3.29)	<0.001	NA**	–
MoCA score (per 1-unit decrease)	1.12 (1.07, 1.17)	<0.001	1.04 (0.99, 1.10)	0.091
ESS score	1.05 (1.02, 1.08)	<0.001	NA**	–
GDS-15 score	1.34 (1.15, 1.56)	<0.001	NA**	–

*Not included due to being redundant. **Not available (i.e. missing in multiple studies, precluding shared frailty multivariable Cox analysis). ***Not included to maximise number of studies and individuals included in multivariable analysis. The multivariable model included 2103 subjects (OBS1: 1213, OBS4: 23, INT1: 327, INT2: 287, INT3: 72, INT4: 112, INT6: 69). ESS: Epworth Sleepiness Scale; GDS-15: 15-item Geriatric Depression Scale; H&Y: Hoehn & Yahr; MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; PIGD: Postural Instability-Gait Disorder; S&E ADL: Schwab & England Activities of Daily Living; T2DM: Type 2 Diabetes Mellitus.

Appendix.

Separate Cox models for each CPP study.

Time to one milestone:

OBS1 (707 subjects, 386 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, BMI (kg/m²), T2DM, GBA1 carrier status (yes vs. no), APOE genotype (E4 vs. non-E4), UPSIT score (per 1-point decrease) , motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS parts I+ II+III (per 5-point increase), H&Y stage, MoCA score (per 1-point decrease), ESS score (per 1-point increase), RBDSQ score (per 1-point increase)

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Age (per 1-year increase)	1.023048	.0069928	3.33	0.001	1.009433	1.036845
UPSIT score (per 1-point decrease)	1.02153	.0087068	2.50	0.012	1.004607	1.038738
MoCA score (per 1-point decrease)	1.062089	.0239439	2.67	0.008	1.016181	1.11007
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.196405	.0210477	10.19	0.000	1.155855	1.238377
Motor phenotype						
PIGD	1.848379	.2046174	5.55	0.000	1.48786	2.296253

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.196405	.0210477	10.19	0.000	1.155855	1.238377
Motor phenotype						
PIGD	1.848379	.2046174	5.55	0.000	1.48786	2.296253
Age (per 1-year increase)	1.023048	.0069928	3.33	0.001	1.009433	1.036845

MoCA score (per 1-point decrease)	1.062089	.0239439	2.67	0.008	1.016181	1.11007
UPSIT score (per 1-point decrease)	1.02153	.0087068	2.50	0.012	1.004607	1.038738

OBS2 (111 subjects, 28 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, BMI (kg/m²), motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS part III (per 5-point increase), H&Y stage, MoCA score (per 1-point decrease), GDS-15 score (per 1-point increase), ESS score (per 1-point increase)

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf. interval]
MoCA score (per 1-point decrease)	1.217451	.0905896	2.64	0.008	1.052239 1.408604
GDS-15 score	1.234695	.0814102	3.20	0.001	1.085014 1.405025

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf. interval]
GDS-15 score	1.234695	.0814102	3.20	0.001	1.085014 1.405025
MoCA score (per 1-point decrease)	1.217451	.0905896	2.64	0.008	1.052239 1.408604

OBS3:

Variables included (380 subjects, 82 events): age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, GBA1 carrier status (yes vs. no), APOE genotype (E4 vs. non-E4), motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS part III (per 5-point increase), H&Y stage, plasma urate, serum CRP (mg/L), plasma lipoprotein A1 (per decile decrease)

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Age (per 1-year increase)	1.060592	.0163416	3.82	0.000	1.029042	1.093109
MDS-UPDRS part III (per 5-point increase)	1.134726	.0613392	2.34	0.019	1.020653	1.261548
Motor phenotype						
Indeterminate	3.142611	1.882863	1.91	0.056	.9711853	10.16902
Serum CRP (mg/L)	1.017992	.0081067	2.24	0.025	1.002227	1.034006

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Age (per 1-year increase)	1.060003	.0163498	3.78	0.000	1.028437	1.092537
MDS-UPDRS part III (per 5-point increase)	1.125419	.0607279	2.19	0.029	1.012473	1.250965
Serum CRP (mg/L)	1.017326	.008108	2.16	0.031	1.001558	1.033342

Alternative model excluding CRP, urate and apolipoprotein A1 (571 subjects, 120 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Age (per 1-year increase)	1.058905	.0137544	4.41	0.000	1.032287	1.086209
Sex (male vs. female)	.6103741	.1204354	-2.50	0.012	.4146121	.8985663
Motor phenotype						
PIGD	1.854098	.4502707	2.54	0.011	1.151906	2.984341

Indeterminate	3.319025	1.435254	2.77	0.006	1.422078	7.74636
MDS-UPDRS part III (per 5-point increase)	1.201814	.0574288	3.85	0.000	1.094366	1.319812

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Age (per 1-year increase)	1.058905	.0137544	4.41	0.000	1.032287	1.086209
MDS-UPDRS part III (per 5-point increase)	1.201814	.0574288	3.85	0.000	1.094366	1.319812
Sex (male vs. female)	.6103741	.1204354	-2.50	0.012	.4146121	.8985663
Motor phenotype						
PIGD	1.854098	.4502707	2.54	0.011	1.151906	2.984341
Indeterminate	3.319025	1.435254	2.77	0.006	1.422078	7.74636

OBS4 (209 subjects, 98 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, GBA1 carrier status (yes vs. no), motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS parts I+ II+III (per 5-point increase), H&Y stage.

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Age (per 1-year increase)	1.032707	.0145612	2.28	0.022	1.004558	1.061644
Dopaminergic treatment initiation	.4425379	.2172951	-1.66	0.097	.1690415	1.158531

Hoehn & Yahr stage	1.698232	.4089484	2.20	0.028	1.059304	2.722534
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.195103	.0487746	4.37	0.000	1.10323	1.294627

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.181703	.0476359	4.14	0.000	1.091932	1.278855
Age (per 1-year increase)	1.031649	.014407	2.23	0.026	1.003795	1.060277
Hoehn & Yahr stage	1.677756	.4026933	2.16	0.031	1.048152	2.68555

INT1 (318 subjects, 59 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, BMI (kg/m²), motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS parts I+ II+III (per 5-point increase), H&Y stage, MoCA score (per 1-point decrease), S&E ADL score (per 10-point decrease).

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MoCA score (per 1-point decrease)	1.364107	.1376533	3.08	0.002	1.119317	1.662432
S&E ADL score (per 10-point decrease)	2.039443	.4433928	3.28	0.001	1.331843	3.122988
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.26879	.0771298	3.92	0.000	1.126277	1.429336
Motor phenotype						
PIGD	2.77195	1.129386	2.50	0.012	1.247318	6.160184
Hoehn & Yahr stage	.642433	.1717678	-1.65	0.098	.3804008	1.084961

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.238596	.0741019	3.58	0.000	1.10155	1.392691
MoCA score (per 1-point decrease)	1.378031	.1413085	3.13	0.002	1.127129	1.684785
S&E ADL score (per 10-point decrease)	1.998198	.4309448	3.21	0.001	1.309371	3.0494
Motor phenotype						
PIGD	2.816371	1.146327	2.54	0.011	1.268328	6.253861

INT2 (286 subjects, 42 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, BMI (kg/m²), motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS parts I+ II+III (per 5-point increase), H&Y stage, MoCA score (per 1-point decrease), S&E ADL score (per 10-point decrease).

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
BMI (kg/m ²)	1.056862	.0334227	1.75	0.080	.9933441	1.124442
Motor phenotype						
Indeterminate	2.757243	1.473795	1.90	0.058	.9671477	7.86063
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.45816	.0930276	5.91	0.000	1.286768	1.652381

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.423715	.0869481	5.78	0.000	1.263104	1.604749

INT3 (71 subjects, 55 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, BMI (kg/m²), motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS parts I+ II+III (per 5-point increase), H&Y stage, MoCA score (per 1-point decrease), S&E ADL score (per 10-point decrease).

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Motor phenotype						
PIGD	3.000018	.9111742	3.62	0.000	1.654224	5.440681
Indeterminate	4.030265	1.939405	2.90	0.004	1.569375	10.35
Hoehn & Yahr stage	3.327993	1.808001	2.21	0.027	1.147492	9.651954
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.118229	.0456545	2.74	0.006	1.032234	1.211387

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Hoehn & Yahr stage	3.327993	1.808001	2.21	0.027	1.147492	9.651954
Motor phenotype						
PIGD	3.000018	.9111742	3.62	0.000	1.654224	5.440681
Indeterminate	4.030265	1.939405	2.90	0.004	1.569375	10.35
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.118229	.0456545	2.74	0.006	1.032234	1.211387

INT4 (112 subjects, 57 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, BMI (kg/m²), motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS parts I+ II+III (per 5-point increase), H&Y stage, MoCA score (per 1-point decrease).

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
PD duration (per 1-year increase)	1.072041	.0346925	2.15	0.032	1.006157	1.14224
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.155109	.0510086	3.27	0.001	1.059338	1.259538

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.155109	.0510086	3.27	0.001	1.059338	1.259538
PD duration (per 1-year increase)	1.072041	.0346925	2.15	0.032	1.006157	1.14224

INT5 (204 subjects, 23 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, BMI (kg/m²), motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS parts I+ II+III (per 5-point increase), H&Y stage.

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
BMI (kg/m ²)	1.22286	.0881071	2.79	0.005	1.061812	1.408335
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.178268	.068624	2.82	0.005	1.05116	1.320746

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.178268	.068624	2.82	0.005	1.05116	1.320746
BMI (kg/m ²)	1.22286	.0881071	2.79	0.005	1.061812	1.408335

INT6 (69 subjects, 18 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS parts I+ II+III (per 5-point increase), H&Y stage, MoCA score (per 1-point decrease), S&E ADL score (per 10-point decrease), DaT-SPECT striatal SBR (per 0.1-unit decrease).

Backward stepwise (global significance of the model: $p \leq 0.0662$):

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.192911	.1111906	1.89	0.058	.9937291	1.432017

Forward stepwise:

No variables included (likely due to too few events ($n = 18$)).

INT7 (86 subjects, 16 events):

Variables included: age (per 1-year increase), sex (male vs. female), PD duration (per 1-year increase), dopaminergic treatment initiation, BMI (kg/m²), motor phenotype (PIGD and indeterminate vs. tremor-dominant), MDS-UPDRS parts I+ II+III (per 5-point increase), H&Y stage, MoCA score (per 1-point decrease), S&E ADL score (per 10-point decrease), ESS score, SCOPA-AUT score.

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	2.026473	.3262487	4.39	0.000	1.478097	2.778297
MoCA score (per 1-point decrease)	1.649634	.2505853	3.30	0.001	1.224862	2.221714
S&E ADL score (per 10-point decrease)	.1098993	.0756227	-3.21	0.001	.0285283	.4233643
Motor phenotype						
PIGD	9.216895	6.104203	3.35	0.001	2.516793	33.75374

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MoCA score (per 1-point decrease)	1.649634	.2505853	3.30	0.001	1.224862	2.221714
MDS-UPDRS parts I+ II+III (per 5-point increase)	2.026473	.3262487	4.39	0.000	1.478097	2.778297
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Motor phenotype						
PIGD	9.216895	6.104203	3.35	0.001	2.516793	33.75374

Time to two consecutive milestones:

Variables included in each study are the same as for time to one milestone.

OBS1 (707 subjects, 120 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Age (per 1-year increase)	1.078847	.0136593	5.99	0.000	1.052405	1.105954
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.164759	.0362626	4.90	0.000	1.09581	1.238045
BMI (kg/m2)	1.040974	.0230603	1.81	0.070	.9967433	1.087167
Hoehn & Yahr stage	1.422119	.2712497	1.85	0.065	.9785454	2.066764
Motor phenotype						
PIGD	1.731854	.3297561	2.88	0.004	1.192441	2.515275

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.194287	.0341089	6.22	0.000	1.129271	1.263046
Age (per 1-year increase)	1.077268	.0133294	6.02	0.000	1.051457	1.103712
Motor phenotype						
PIGD	1.68338	.3194209	2.74	0.006	1.160558	2.441729

OBS2 (111 subjects, 10 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
GDS-15 score	1.624371	.2382714	3.31	0.001	1.218503	2.165429
Sex (male vs. female)	17.74296	20.1092	2.54	0.011	1.924448	163.5859

MoCA score (per 1-point decrease)	1.978053	.4840594	2.79	0.005	1.224436	3.195507
Hoehn & Yahr stage	17.33737	17.42798	2.84	0.005	2.417315	124.3464
BMI (kg/m2)	1.147883	.0907267	1.74	0.081	.9831509	1.340217
MDS-UPDRS part III (per 5- point increase)	.5213742	.1225278	-2.77	0.006	.3289344	.8263991

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf. interval]
GDS-15 score	1.379766	.1296993	3.42	0.001	1.147603 1.658896
BMI (kg/m2)	1.169262	.0767018	2.38	0.017	1.028193 1.329687
MoCA score (per 1-point decrease)	1.400442	.2062974	2.29	0.022	1.049242 1.869195

OBS3:

Model including wet biomarkers (380 subjects, 17 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf. interval]
Age (per 1-year increase)	1.123477	.0434227	3.01	0.003	1.041514 1.21189
Sex (male vs. female)	.3508964	.1739847	-2.11	0.035	.1327786 .92732

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf. interval]
Age (per 1-year increase)	1.123477	.0434227	3.01	0.003	1.041514 1.21189
Sex (male vs. female)	.3508964	.1739847	-2.11	0.035	.1327786 .92732

Model excluding wet biomarkers (571 subjects, 23 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf. interval]
Age (per 1-year increase)	1.106984	.0364308	3.09	0.002	1.037835 1.18074
Sex (male vs. female)	.2772146	.1188051	-2.99	0.003	.1196793 .6421157
MDS-UPDRS part III (per 5-point increase)	1.185311	.1199243	1.68	0.093	.9721014 1.445283

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf. interval]
Age (per 1-year increase)	1.118175	.0377924	3.30	0.001	1.046504 1.194756
Sex (male vs. female)	.2968654	.1263966	-2.85	0.004	.1288673 .6838744

OBS4 (209 subjects, 41 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf. interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.267354	.0617203	4.87	0.000	1.151978 1.394285

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf. interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.267354	.0617203	4.87	0.000	1.151978 1.394285

INT1 (318 subjects, 2 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	2.381798	.8581601	2.41	0.016	1.175486	4.826055

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	2.381798	.8581601	2.41	0.016	1.175486	4.826055

INT2 (286 subjects, 10 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Age (per 1-year increase)	1.07564	.0463296	1.69	0.090	.9885628	1.170387
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.299879	.1565781	2.18	0.029	1.026528	1.646021

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.369594	.1619334	2.66	0.008	1.086301	1.726765

INT3 (71 subjects, 31 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.161899	.0639804	2.73	0.006	1.043029	1.294315
Hoehn & Yahr stage	6.972401	4.185857	3.23	0.001	2.149643	22.61509
Motor phenotype						
PIGD	2.765028	1.14429	2.46	0.014	1.228669	6.22249
Indeterminate	6.378064	3.70549	3.19	0.001	2.042504	19.91658

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
Hoehn & Yahr stage	6.972401	4.185857	3.23	0.001	2.149643	22.61509
Motor phenotype						
PIGD	2.765028	1.14429	2.46	0.014	1.228669	6.22249
Indeterminate	6.378064	3.70549	3.19	0.001	2.042504	19.91658
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.161899	.0639804	2.73	0.006	1.043029	1.294315

INT4 (112 subjects, 20 events):

Backward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.191323	.0987073	2.11	0.035	1.012752	1.40138
PD duration (per 1- year increase)	1.14732	.0534095	2.95	0.003	1.047273	1.256925

Forward stepwise:

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
PD duration (per 1-year increase)	1.14732	.0534095	2.95	0.003	1.047273	1.256925
MDS-UPDRS parts I+ II+III (per 5-point increase)	1.191323	.0987073	2.11	0.035	1.012752	1.40138

INT5 (204 subjects, 7 events):

Backward stepwise:

Variable	Haz. Ratio	Std. err.	Z	P>z	[95% conf.	interval]
BMI (kg/m2)	1.347719	.1641706	2.45	0.014	1.061478	1.711147

Forward stepwise:

Variable	Haz. Ratio	Std. err.	Z	P>z	[95% conf.	interval]
BMI (kg/m2)	1.347719	.1641706	2.45	0.014	1.061478	1.711147

INT6 (69 subjects, 1 event):

Backward stepwise:

No significant models derived from the initial list of potential predictors.

Forward stepwise:

No significant models derived from the initial list of potential predictors.

INT7 (86 subjects, 3 events)

Backward stepwise (global significance, $p = 0.0192$; only 3 events):

Variable	Haz. ratio	Std. err.	z	P>z	[95% conf.	interval]
SCOPA-AUT score	1.185464	.1101367	1.83	0.067	.9881131	1.422231
S&E ADL score (per 10-point decrease)	24.35603	39.95284	1.95	0.052	.9779643	606.5825
ESS score	.5208808	.1998201	-1.70	0.089	.2455844	1.10478

Forward stepwise:

No significant models derived from the initial list of potential predictors.