Table e-1. Baseline characteristics and random allocation to treatment.

Pt No.	Baseline characteristics									Randomised treatment allocation					
	Gender	Age (ys)	Body weight (kg)	Duration of PD (ys)	Duration of motor fluctuations (ys)	UPDRS-III (OFF)	H&Y stage (OFF)	Levodopa dose weight-adjusted [a] (mg/kg/day)	Total LEDD [a,b] (mg/day)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1	M	61	52	9	5	61	4	34.3	1783	D	B	C	E	A	F
2	M	66	70	14	7	51	3	10.7	750	B	A	F	D	C	E
3	M	55	80	9	6	36	2.5	49.0	3920	A	F	D	B	E	C
4	F	61	66	14	5	33	2.5	18.6	1530	C	E	A	F	D	B
5	M	68	84	14	10	29	2	39.5	3315	F	A	E	B	C	D
6	M	52	94	7	3	33	2	4.0	675	D	C	F	E	B	A
7	M	67	76	8	5	30	4	13.2	1000	E	F	B	A	C	D
8	F	68	54	17	15	51	3	18.5	1000	A	C	B	D	E	F
9	M	49	85	8	6	51	2.5	13.2	1425	B	D	C	F	A	E
10	F	74	47	9	4	36	2.5	11.5	750	E	B	D	A	F	C
11	M	53	96	10	3	33	2.5	15.6	1800	A	D	C	B	E	F
12	M	65	74	7	2	44	2	15.2	1125	F	C	E	D	B	A
13	M	79	49	6	4	20	2	23.0	1125	B	D	F	C	E	A
14	M	53	79	10	7	38	2.5	18.4	1450	A	C	E	D	F	B
15	M	45	68	9	3	42	2.5	14.8	1000	D	E	A	F	B	C
16	F	67	66	8	2	40	3	21.4	1425	C	B	D	A	F	E
17	F	69	66	7	4	22	2.5	15.8	1050	E	F	B	C	A	D
18	M	61	111	10	6	30	2	9.9	1100	C	E	A	F	D	B

Abbreviations: **H&Y**, Hoehn and Yahr stage; **LEDD**, Levodopa equivalent daily dose; **UPDRS-III**, Unified PD Rating Scale motor score; **PD,** Parkinson's disease.

[a] Including Levodopa/DDCI and Levodopa contained in *Mucuna pruriens.*

[b] Levodopa/DDCI + Levodopa contained in *Mucuna pruriens* + DA agonist daily dose in LEDD (Tomlinson et al., 2010).

Table e-2. Motor response according to the treatment arm.

Features	Treatment Arm						Statistical Analysis (P-value) [a]									
							MP High-dose				*MP Low-dose*			*MP+DDCI*		*LD-DDCI*
	LD+DDCI	**MP-Hd**	**MP-Ld**	**LD-DDCI**	**MP+DDCI**	**Placebo**	*vs. LD+DDCI*	*vs.. LD-DDCI*	*vs. MP-Ld*	*vs. MP+DDCI*	*vs. LD+DDCI*	*vs. LD-DDCI*	*vs. MP+DDCI*	*vs. LD+DDCI*	*vs. LD-DDCI*	*vs. LD+DDCI*
Levodopa Ratio	1 (reference)	5 : 1	3.5 : 1	5 : 1	1 : 1	0 : 1	-	-	-	-	-	-	-	-	-	-
Levodopa dose (mg) [b]	258 (52)	1311 (261)	917 (199)	1317 (263)	267 (61)	0	-	-	-	-	-	-	-	-	-	-
Levodopa (mg/kg) [b]	3.5 (0.2)	17.6 (1.1)	12.4 (0.9)	17.7 (1.1)	3.6 (0.2)	0	-	-	-	-	-	-	-	-	-	-
MP dose (g)	-	23.2 (4.9)	16.1 (3.7)	-	4.7 (1.1)	0	-	-	-	-	-	-	-	-	-	-
Latency to *Full* ON (min)	27 (13)	18 (5)	22 (11)	24 (11)	23 (5)	-	**0.008**	**0.042**	*0.092*	*0.085*	0.226	0.671	0.638	0.526	0.651	0.300
ON Duration [c] (min)	177 (36)	221 (32)	195 (41)	272 (44)	139 (37)	-	**<0.001**	**<0.001**	**0.022**	**<0.001**	0.154	**<0.001**	**0.015**	**0.046**	**<0.001**	**<0.001**
UPDRS part III																
OFF	38 (11)	37 (11)	38 (13)	38 (11)	40 (9)	39 (9)	0.586	0.372	0.612	0.784	0.853	0.757	0.498	0.497	0.497	0.649
ON at 90’	14 (7)	12 (8)	13 (7)	14 (8)	14 (8)	36 (7)	**0.037**	*0.061*	0.296	0.128	0.421	0.173	0.228	0.483	0.372	0.439
ON at 180’	26 (16)	15 (11)	19 (10)	16 (10)	35 (12)	38 (9)	**0.002**	0.538	*0.077*	**0.001**	*0.096*	0.301	**0.005**	0.313	**<0.001**	**0.006**
Change 90’ *vs.* OFF (%)	62 (19)	67 (19)	63 (20)	60 (21)	65 (19)	7 (5)	**0.014**	**0.045**	0.273	*0.094*	0.649	0.174	0.158	0.480	0.340	0.525
Change 180’ *vs.* OFF (%)	31 (33)	60 (27)	47 (25)	59 (21)	16 (21)	3 (3)	**0.001**	0.769	*0.058*	**<0.001**	0.103	0.123	**0.004**	0.255	**<0.001**	**0.005**
Wearing-Off index (%) [d]	32 (30)	7 (13)	16 (24)	2 (11)	50 (26)	4 (3)	**0.007**	0.183	0.183	**0.001**	*0.089*	**0.038**	**0.017**	0.376	**<0.001**	**0.001**
Involuntary Movements																
AIMS at 90’	5.6 (4.0)	3.9 (2.7)	2.8 (1.7)	4.0 (3.5)	3.7 (3.2)	0 (0)	**0.021**	0.909	*0.067*	0.928	**0.010**	0.133	0.403	0.238	0.888	*0.085*
AIMS at 180’	2.0 (3.0)	2.9 (2.0)	3.8 (2.7)	3.1 (2.5)	0.4 (1.1)	0 (0)	0.314	0.591	0.461	**0.009**	0.920	0.389	0.192	0.251	**0.008**	0.258

Abbreviations: **AIMS**, Abnormal Involuntary Movements Scale, **LD +/- DDCI**, levodopa with/without the dopa-decarboxylase inhibitor Benserazide; **Hd**, high dose; **Ld**, low dose; **LD**, Levodopa, **min**, minutes; **MP**, Mucuna pruriens; **UPDRS**, Unified Parkinson Disease rating Scale.
Significant results (p<0.05) in **bold**, trend to significance (p<0.1) in *italics*.
[a] p-values according to paired t-test. Data versus placebo are not shown.
[b] Levodopa content in Mucuna preparation is calculated as 5.7% of weight.
[c] Defined as duration from full ON state to the OFF state.
[d] Defined as relative worsening of motor performance at 180’ compared to 90’; calculated as: (UPDRS III at 180’ – UPDRS III at 90’) / UPDRS III in the OFF state)*100.

Table e-3. Cardiovascular response to interventions.

	Treatment Arm *					
	LD+DDCI	**MP-Hd**	**MP-Ld**	**LD-DDCI**	**MP+DDCI**	**Placebo**
OFF						
Supine						
Systolic BP, mmHg	138 (17)	137 (15)	137 (13)	140 (17)	133 (19)	136 (13)
Diastolic BP, mmHg	81 (8)	83 (8)	83 (8)	85 (10)	80 (10)	78 (7)
Mean BP value, mmHg	100 (9)	101 (8)	101 (8)	103 (11)	100 (12)	101 (8)
Heart Rate, bpm	81 (14)	78 (13)	83 (16)	82 (14)	81 (14)	84 (14)
Standing						
Systolic BP, mmHg	135 (16)	131 (18)	135 (13)	133 (14)	131 (10)	136 (16)
Diastolic BP, mmHg	84 (8)	82 (7)	83 (9)	82 (12)	81 (10)	83 (8)
Mean BP, mmHg	101 (9)	98 (9)	100 (10)	100 (11)	99 (12)	101 (10)
Heart Rate, bpm	84 (14)	81 (14)	85 (16)	85 (14)	83 (14)	86 (14)
ON 90 minutes						
Supine						
Systolic BP, mmHg	112 (13)	113 (10)	115 (10)	119 (16)	116 (12)	139 (16) [b]
Diastolic BP, mmHg	66 (8)	68 (7)	69 (8)	72 (10)	70 (9)	79 (8) [b]
Mean BP, mmHg	82 (9)	83 (7)	84 (8)	88 (12)	85 (9)	99 (9) [b]
Heart Rate, bpm	74 (7)	78 (11)	80 (12)	79 (9)	79 (9)	84 (14)
Standing						
Systolic BP, mmHg	110 (10)	111 (10)	115 (11)	116 (13)	114 (10)	135 (15) [b]
Diastolic BP, mmHg	68 (6)	67 (5)	69 (8)	72 (9)	70 (8)	80 (9) [b]
Mean BP, mmHg	82 (7)	82 (5)	84 (8)	87 (10)	85 (8)	99 (9) [b]
Heart Rate, bpm	77 (9)	81 (11)	82 (12)	81 (9)	80 (8)	86 (14)
Systolic BP change Standing *vs.* Supine, mmHg	2 (8)	0 (6)	0 (6)	3 (6)	2 (6)	4 (8)
Orthostatic Hypotension, N (%) [a]	1 (5.6)	1 (5.6)	0 (0)	2 (11.1)	0 (0)	0 (0)
Treatment-induced Changes						
Systolic BP decrease ON *vs.* OFF standing	25 (16)	20 (15)	20 (15)	18 (12)	19 (16)	1 (5) [b]
Diastolic BP decrease ON *vs.* OFF standing	16 (8)	15 (7)	14 (7)	11 (11)	12 (9)	3 (6) [b]

Abbreviations: **BP**, blood pressure; **bpm**, beat per minute; **DDCI,** dopa decarboxylase inhibitor (Benserazide); **Hd**, high dose; **HR**, heart rate; **LD**, Levodopa; **Ld**, Low dose; **MP**, Mucuna pruriens.

***** Data are reported as mean (and standard deviation) or counts [and percentage].

[a] Defined as decrease in systolic blood pressure ≥20 mmHg or a decrease in diastolic blood pressure ≥ 10 mmHg within 3 min of standing (Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology 1996; 46:1470)

[b] Significantly different from all other treatment arms according to t-test for paired data ($p<0.05$)

Table e-4. Pharmacokinetic measures and Pharmacodynamic response.

Features		Patient 1	Patient 2	Patient 3	Patient 4
Gender		F	F	M	M
Age (years)		52	77	54	61
Disease duration (years)		10	11	10	24
Body Weight		68	40	70	87
UPDRS part II – Off		12	13	12	17
UPDRS part III – Off		28	37	28	49
Hoehn and Yahr stage – Off		3	3	2.5	4
Levodopa daily dose (mg/day)		475	200	400	500
Concomitant DA agonists (type, mg/day)		ROP, 16	PPX, 0.78	-	ROP, 16
Concomitant iMAO-B or iCOMT		ENT	-	ENT	SEL, ENT
Levodopa plus DDCI					
Levodopa dose (mg)		100	100	150	250
Weight adjusted levodopa dose (mg/kg)		1.5	2.5	2.1	2.9
Motor Response	Time to ON, min	30	15	40	30
	UPDRS III at 90’	11	13	8	13
	Change vs. OFF (%)	60.7	64.9	71.4	73.5
	UPDRS III at 180’	22	9	22	19
	Change vs. OFF (%)	21.4	75.7	21.4	61.2
	Time to Dyskinesias, min	53	15	39	30
	AIMS at 90’	10	23	5	5
	AIMS at 180’	11	19	0	3
	Time to OFF, min	220	260	180	200
	ON Duration, min	185	245	140	170
Levodopa Pharmacokinetics	Cmax (µg/mL)	0.92	1.41	0.81	2.43
	tmax (min)	45	15	45	15
	AUC (µg/mL) x min	55.3	94.12	102.7	156.2
Mucuna Pruriens					
MP dose (g)		7	9	13.5	18
Levodopa content in MP (mg) [a]		399	513	769	1026
Weight-adjusted levodopa content (mg/kg)		5.9	13.0	11.0	11.8
Levodopa Ratio: MP-to-LD with DDCI		4 : 1	5 : 1	5 : 1	4 : 1
Motor Response	Time to ON, min	15	15	30	15
	- Change vs LD+DDCI, min	-20	0	-10	-15
	UPDRS III at 90’	8	12	9	17
	Change vs. OFF (%)	71.4	67.6	67.8	65.3
	UPDRS III at 180’	11	9	9	16
	Change vs. OFF (%)	60.7	75.7	67.8	67.3
	Time to Dyskinesias, min	15	15	30	21
	AIMS at 90’	5	22	4	4
	- Change vs LD+DDCI	-5	-1	-1	-1
	AIMS at 180’	7	22	7	2
	Time to OFF, min	220	480	420	240
	ON Duration, min	205	465	390	225
	- Change vs LD+DDCI, min	+20	+220	+250	+55
Levodopa Pharmacokinetics	C_{max} (µg/mL)	1.53	2.82	2.87	5.35
	- Change vs LD+DDCI, µg/mL	+0.61	+1.41	+2.06	+2.92
	t_{max} (min)	30	15	15	15
	- Change vs LD+DDCI, min	-15	0	-30	0
	AUC (µg/mL) x min	95.5	126.15	263.4	288
	- Change MP-to-LD+DDCI (%)	+73%	+34%	+156%	+84%

Levodopa without DDCI					
Levodopa dose (mg)		400	400	600	1000
Weight adjusted levodopa dose (mg/kg)		5.9	10	8.6	11.5
Levodopa Ratio: LD without DDCI-to-LD with DDCI		4 : 1	4 : 1	4 : 1	4: 1
Levodopa Ratio: LD without DDCI-to-MP		1 : 1	0.8 : 1	0.8 : 1	1 : 1
Motor Response	Time to ON, min	25	15	30	15
	- Change vs MP	+10	0	0	0
	UPDRS III at 90'	8	19	9	18
	Change vs. OFF (%)	71.4	48.6	67.8	63.3
	UPDRS III at 180'	11	23	11	19
	Change vs. OFF (%)	60.7	37.8	60.7	61.2
	Time to Dyskinesias, min	10	15	30	90
	AIMS at 90'	4	24	4	3
	- Change vs MP	-1	+2	0	-1
	AIMS at 180'	7	22	6	2
	Time to OFF, min	295	315	250	270
	ON Duration, min	270	300	220	255
	- Change vs MP, min	+65	-165	-170	+30
Levodopa Pharmacokinetics	C_{max} (µg/mL)	1.74	(1.22) [b]	2.1	4.27
	- Change vs MP, µg/mL	+0.21	(-1.60) [b]	-0.77	-1.08
	t_{max} (min)	45	(30) [b]	15	15
	- Change vs MP, min	+15	(+15) [b]	0	0
	AUC (µg/mL) x min	149.5	n.a. [b]	231.3	347.7
	- Change MP-to-LD without DDCI	-36%	n.a. [b]	+14%	-17%

Abbreviations: **AUC**, Area under the plasma concentration-time curve; **C_{max}**, peak plasma levodopa concentration; **DDCI**, Dopa decarboxylase inhibitor (i.e. benserazide *or* carbidopa); **LD**, Levodopa; **min**, minutes; **n.a.**, not available; **t_{max}**, time to peak plasma levodopa concentration; **UPDRS III**, Unified Parkinson's Disease Rating Scale, motor examination.

[a] Levodopa concentration in MP is 5.7% of roasted seed powder weight (Cassani et al., 2016)
[b] Missing pharmacokinetic data at 45', 60', and 120' due to troublesome dyskinesias and inability of blood sampling.