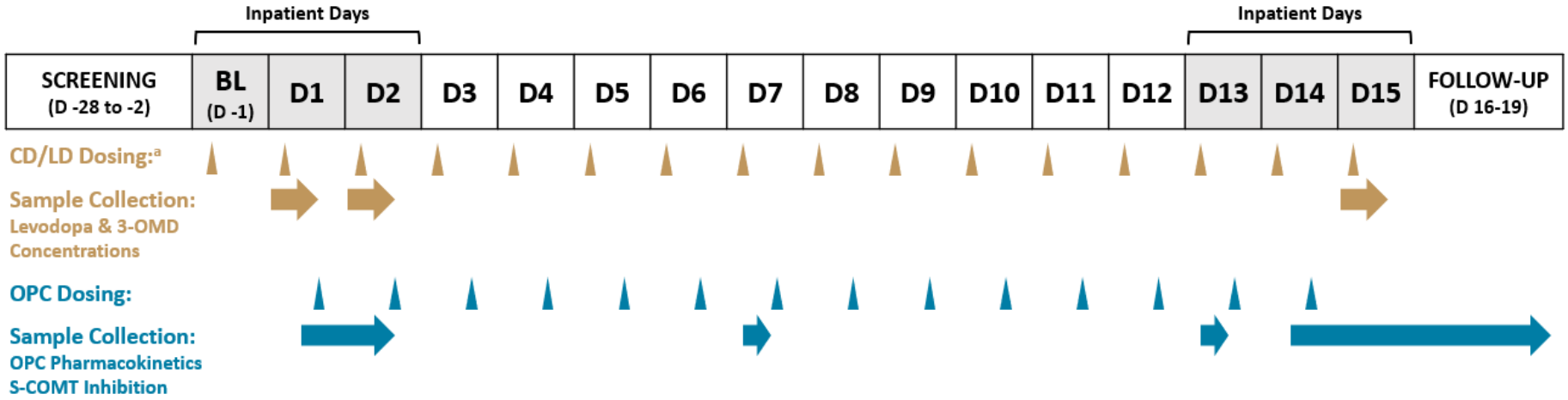
SUPPLEMENTARY MATERIALS

Figure S1. Study Design Overview



[a]Participants received Q3H or Q4H carbidopa/levodopa on Days 1, 2 and 15 and their usual carbidopa/levodopa regimen on other days. 3-OMD, 3-O-methyldopa; BL, baseline; CD/LD, carbidopa/levodopa; D, day; OPC, opicapone; S-COMT, soluble catechol-O-methyltransferase.

Table S1. Summary of Study Drug Dosing

	Study Day	Opicapone 50 mg	Carbidopa/Levodopa 25/100 mg
Inpatient stay at study center	Day -1 (baseline)	-----	Usual CD/LD regimen; no dosing after 19:00; no food or liquids after 23:00
	Day 1 (randomized to CD/LD 25/100 Q3H or Q4H)	Administered at ~20:00; no foods, liquids, or CD/LD intake within 1 hour of OPC dose (before or after)	First dose administered at ~07:00, then Q3H or Q4H; no food for 1 hour after each CD/LD dose (water allowed); no dosing after 19:00 hours; no food or liquids after 23:00
	Day 2	Administered at ~20:00; no foods, liquids, or CD/LD intake within 1 hour of OPC dose (before or after)	First dose administered at ~07:00, then same regimen as Day 1 (Q3H or Q4H); no food for 1 hour after each CD/LD dose (water allowed); resume usual stable regimen after 21:00
Outpatient	Days 3 to 12	Self-administered at ~20:00, except on Day 7 (administered at study center); no food, liquids, or CD/LD intake within 1 hour of OPC dose (before or after)	Usual stable regimen self-administered each day
Inpatient stay at study center	Days 13 and 14	Administered at ~20:00; no food, liquids, or CD/LD intake within 1 hour of OPC dose (before or after)	Usual stable regimen administered each day; no dosing after 19:00 on Day 14; no food or liquids after 23:00 on Day 14
	Day 15	-----	First dose administered at ~07:00, then same regimen as Days 1 and 2 (Q3H or Q4H); no food for 1 hour after each CD/LD dose (water allowed); usual stable regimen resumed after 21:00

CD/LD, carbidopa/levodopa 25/100 mg; OPC, opicapone 50 mg; Q3H, every 3 hours; Q4H, every 4 hours.

Table S2. Sample Collection Schedule

	Study Days	Blood Collection Timepoints[a]
For opicapone concentrations (plasma samples, PK analyses)	Day 1, 7, 13, 14	• 0.5 hours before OPC dose (at 20:00)
	Day 1-2	• 0.5, 1, 1.5, 2, 3, 4, 8, 10, 12, 16, and 24 hours post-dose (on Day 1)
	Day 14-19	• 0.5, 1, 1.5, 2, 3, 4, 8, 10, 12, 16, 24, 48, 72, 96, and 120 hours post-dose (on Day 14)
For levodopa and 3-OMD concentrations (plasma samples, PK analyses)	Day 1, 2, 15	For Q3H dosing • 0.5 hours before first CD/LD dose (at 07:00) • 0.5, 1, 1.5, 2, 2.5, and 3 hours after each CD/LD dose (at 07:00, 10:00, and 13:00), with last collection prior to the next CD/LD dose
		For Q4H dosing • 0.5 hours before first CD/LD dose (at 07:00) • 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours after each CD/LD dose (at 07:00, 11:00, and 15:00), with last collection prior to the next CD/LD dose
For S-COMT activity (erythrocyte samples, pharmacodynamic analysis)	Day 1, 7, 13, 14	• 0.5 hours before OPC dose (at 20:00)
	Day 1-2	• 1, 2, 4, 8, 12, 16, and 24 hours post-dose (on Day 1)
	Day 14-19	• 1, 2, 4, 8, 12, 16, 24, 48, 72, 96, and 120 hours post-dose (on Day 14)

[a]All CD/LD and opicapone dosing times are approximate.
3-OMD, 3-O-methyldopa; CD/LD, carbidopa/levodopa 25/100 mg; PK, pharmacokinetic; OPC, opicapone 50 mg, S-COMT, soluble catechol-O-methyltransferase.

Table S3. Geometric Mean Ratios for Levodopa Plasma Concentrations and Fluctuation Index[a]

Parameter	Geometric Mean Ratios (90% CI)	
	CD/LD Q3H (n=7)	CD/LD Q4H (n=8)
Total exposure ($AUC_{0\text{-}tlast}$)	1.62 (1.15–2.29)	1.94 (1.31–2.87)
Peak concentration (C_{max})	1.44 (0.99–2.08)	1.43 (0.95–2.15)
Trough concentration (C_{trough})	1.95 (1.35–2.82)	3.17 (2.07–4.84)
Peak-to-trough fluctuation (fluctuation index)	0.68 (0.45–1.02)	0.55 (0.41–0.74)

[a]Ratios calculated from geometric least squares means, based on pharmacokinetic profiles from after the third daily CD/LD dose on Day 15 (after last opicapone dose) versus Day 1 (before first opicapone dose) and estimated using an analysis of variance model for log-transformed values and main effect for study visit.

AUC, area under the concentration-time curve; CD/LD, carbidopa/levodopa 25/100 mg; CI, confidence interval; Q3H, every 3 hours; Q4H, every 4 hours.