

Appendix A – Supplementary Tables

SUPPLEMENTARY TABLE 1: Dosing schedule and post-dose blood draw times to obtain samples for pharmacokinetic analysis.

	Time of dosing – Cohort 1 (hours)					
	08:00	10:00	12:00	14:00	16:00	18:00
Post-dose	0, 20, 40,	0, 30, 60,	0, 30, 60,	0, 20, 40,	0, 30, 60,	0, 30, 60,
sampling times	60, 80,	90	90	60, 80,	90	90, 120
(minutes)	100			100		
	Time of dosing – Cohorts 2 and 3 (hours)					
	08:00	11:00	14:00	17:00		
Post-dose	0, 20, 40, 60,	0, 30, 60, 90,	0, 20, 40, 60,	0, 30, 60, 90,		
sampling times	80, 100, 120,	120, 150	80, 100, 120,	120, 150, 180		
(minutes)	140, 160		140, 160			

SUPPLEMENTARY TABLE 2: Demographic and baseline characteristics for all randomized patients.

	<b>Cohort 1</b>	<b>Cohort 2</b>	<b>Cohort 3</b>	<b>Total</b>
	<b>(n=7)</b>	<b>(n=10)</b>	<b>(n=8)</b>	<b>(n=25)</b>
Age, years	67.7 ± 6.78	69.8 ± 7.91	56.8 ± 14.58	65.0 ± 11.46
	(57-79)	(57-81)	(40-77)	(40-81)
Male, n (%)	5 (71.4)	5 (50.0)	4 (50.0)	14 (56.0)
Female, n (%)	2 (28.6)	5 (50.0)	4 (50.0)	11 (44.0)
Caucasian, n (%)	7 (100.0)	10 (100.0)	8 (100.0)	25 (100.0)
Height, cm	166.0 ± 4.04	167.1 ± 6.45	169.3 ± 12.43	167.5 ± 8.16
	(160-172)	(160-181)	(150-192)	(150-192)
Weight, kg	67.9 ± 6.84	68.0 ± 9.71	72.8 ± 16.60	69.5 ± 11.52
	(60-80)	(55-87)	(47-105)	(47-105)
BMI, kg/m <sup>2</sup>	24.64 ± 2.020	24.41 ± 2.868)	25.11 ± 3.204	24.70 ± 2.682
	(21.4-27.1)	(19.6-27.6)	(20.8-28.5)	(19.6-28.5)
Daily 'off' time, hours	3.8 ± 1.68	4.1 ± 1.01	4.4 ± 1.05	4.1 ± 1.22
	(2-6)	(3-6)	(3-6)	(2-6)
Time since diagnosis of PD, years*	11.57 ± 3.867	10.83 ± 6.663	4.08 ± 2.408	8.88 ± 5.784
	(4.0-15.0)	(3.7-24.0)	(0.7-8.0)	(0.7-24.0)
Hoehn & Yahr staging, n (%)				
1	0	0	0	0
2	4 (57.1)	5 (50.0)	4 (50.0)	13 (52.0)
3	3 (42.9)	4 (40.0)	4 (50.0)	11 (44.0)
4	0	1 (10.0)	0	1 (4.0)
5	0	0	0	0

Values are mean ± standard deviation (range), or number of patients (%).

BMI = body mass index; PD = Parkinson's disease. \*Calculated as the number of years from the date of diagnosis to the date of Visit 1.

SUPPLEMENTARY TABLE 3: Pharmacokinetic parameters for L-dopa: Cohort 1 (including all patients with data available for the pharmacokinetic analyses and excluding patients with significant violations that may have invalidated or biased the results of the pharmacokinetic evaluations).

	Cohort 1: 2-hourly dosing regimen	
	V1512 (n=6)*	L-dopa/carbidopa (n=7)
$AUC_{0-t}$ , ng • h • mL <sup>-1</sup>		
Dose 1	1871 (32.7)	1706 (28.7)
Dose 2	2306 (32.8)	2505 (32.9)
Dose 3	2313 (19.2)	2480 (53.1)
Dose 4	2426 (29.9)	1946 (46.3)
Dose 5	2499 (27.4)	3151 (23.0)
Dose 6	2818 (21.8)	3275 (45.5)
$AUC_{0-12h}$ , ng • h • mL <sup>-1</sup>	14791 (24.0)	15887 (24.2)
$AUC_{0-6h}$ , ng • h • mL <sup>-1</sup>	6653 (25.9)	6880 (35.2)
$AUC_{6-12h}$ , ng • h • mL <sup>-1</sup>	8095 (25.2)	8918 (19.6)
$C_{max}$ , ng/mL		
Dose 1	1792 (35.1)	1624 (36.6)
Dose 2	2029 (39.3)	2190 (45.2)
Dose 3	1835 (22.6)	1990 (72.3)
Dose 4	1700 (27.7)	1524 (51.1)
Dose 5	1898 (39.9)	2531 (20.6)
Dose 6	2329 (13.4)	2662 (58.3)
$C_{max0-12h}$ , ng/mL	2674 (20.0)	3350 (26.6)
$t_{max}$ , h		
Dose 1	0.333 (0.233-0.667)	0.667 (0.317-1.33)
Dose 2	0.500 (0.417-0.500)	0.500 (0.467-1.50)

Dose 3	0.550 (0.500-1.00)	0.500 (0-1.00)
Dose 4	0.625 (0.333-1.00)	1.00 (0-1.98)
Dose 5	0.500 (0.467-1.00)	0.500 (0.467-1.50)
Dose 6	0.500 (0.500-1.00)	0.500 (0-0.500)

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Geometric mean (percentage coefficient of variation [CV%]) values shown for AUC and C<sub>max</sub>; median (range) values shown for t<sub>max</sub>.  
AUC = area under the curve; C<sub>max</sub> = maximum observed plasma concentration; t<sub>max</sub> = time to C<sub>max</sub>.  
\*One patient in this cohort prematurely withdrew from the study before receiving V1512.

SUPPLEMENTARY TABLE 4: Pharmacokinetic parameters for L-dopa: Cohort 2 (including all patients with data available for the pharmacokinetic analyses and excluding patients with significant violations that may have invalidated or biased the results of the pharmacokinetic evaluations).

	Cohort 2: 3-hourly dosing regimen	
	V1512 (n=8)	L-dopa/carbidopa (n=8)
<b>AUC<sub>0-t</sub>, ng • h • mL<sup>-1</sup></b>		
Dose 1	2061 (18.5)	1883 (53.2)
Dose 2	2551 (20.1)	2769 (26.8)
Dose 3	2588 (30.1)	2800 (26.8)
Dose 4	3089 (16.9)	3626 (20.2)
AUC <sub>0-12h</sub> , ng • h • mL <sup>-1</sup>	10445 (19.3)	11390 (18.9)
AUC <sub>0-6h</sub> , ng • h • mL <sup>-1</sup>	4677 (18.2)	4809 (26.5)
AUC <sub>6-12h</sub> , ng • h • mL <sup>-1</sup>	5756 (21.5)	6484 (21.6)
<b>C<sub>max</sub>, ng/mL</b>		
Dose 1	1502 (12.6)	1816 (24.8)
Dose 2	1668 (21.0)	1871 (30.8)
Dose 3	1326 (41.3)	1543 (34.4)
Dose 4	1711 (17.7)	2239 (26.5)
C <sub>max0-12h</sub> , ng/mL	1883 (11.8)	2543 (9.73)
<b>t<sub>max</sub>, h</b>		
Dose 1	0.333 (0.300-1.00)	0.650 (0.333-2.97)
Dose 2	0.500 (0-1.50)	0.500 (0-1.50)
Dose 3	1.00 (0.500-2.00)	1.32 (0.667-2.33)
Dose 4	0.500 (0.450-0.500)	0.983 (0.483-2.00)

Geometric mean (percentage coefficient of variation [CV%]) values shown for AUC and C<sub>max</sub>; median (range) values shown for t<sub>max</sub>.

AUC = area under the curve; C<sub>max</sub> = maximum observed plasma concentration; t<sub>max</sub> = time to C<sub>max</sub>.