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Effect of Opicapone Tablets on Levodopa and 3-O-Methyldopa Pharmacokinetics in Healthy Japanese Subjects: Phase 1 Study

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Abstract

This study evaluated the effect of a small-tablet formulation of opicapone for use in clinical trials in Japan on the pharmacokinetics of levodopa (L-dopa) and 3-O-methyldopa (3-OMD). In an open-label, 3-period, single-sequence crossover phase 1 study in 80 healthy Japanese males (aged 20-45 years; body mass index, 18.5 to <30.0 kg/m^2), 10 mg of L-dopa/carbidopa 100 was administered 3 times daily on day 0 (period 1) and day 12 (period 3), and opicapone tablets (5, 10, 25, or 50 mg; n = 20 each group) were administered once daily for 11 days (period 2). During periods 1 and 3, plasma concentrations of L-dopa and 3-OMD were measured and pharmacokinetic parameters (maximum observed plasma concentration, time at which maximum concentration was observed, area under the plasma concentration–time curve from time 0 to 5 hours [AUC_{5h}] and from time 0 to 24 hours [AUC_{24h}] following each dose, terminal half-life) of plasma L-dopa and 3-OMD were determined along with the geometric mean ratio (period 3/period 1) of AUC_{24h} for L-dopa and 3-OMD. Maximum concentration of L-dopa for the first, second, or third doses of L-dopa/carbidopa did not significantly increase with increasing opicapone dose. The AUC of L-dopa increased with increasing opicapone dose but tended toward a peak plateau with opicapone doses of 25 mg and higher. Geometric mean ratios (90% confidence intervals) of AUC_{24h} were 5 mg, 1.16 (1.10-1.21); 10 mg, 1.26 (1.23-1.30); 25 mg, 1.51 (1.44-1.57); 50 mg, 1.60 (1.54-1.66). Opicapone tablets were well tolerated. In Japanese healthy subjects, increases in plasma exposure to L-dopa appear to level off with opicapone doses of 25 mg and higher, which may be relevant for optimal dosing among Japanese patients with Parkinson disease.

Keywords

3-OMD, COMT inhibitor, Japanese, levodopa, opicapone, Parkinson disease, pharmacokinetic, phase 1

Wearing-off phenomenon, characterized by motor fluctuations at the end of levodopa (L-dopa) treatment intervals, are common complications in patients with Parkinson disease (PD).[1] A recent cross-sectional study in Japan found that 56% of enrolled patients with PD (overall disease duration of approximately 7 years)

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experienced wearing-off, which was more likely in female patients with young onset of disease.[2]

Wearing-off phenomenon relates to an intrinsic problem with L-dopa pharmacokinetics and metabolism. L-dopa undergoes rapid and extensive metabolism by peripheral aromatic L-dopa acid decarboxylase (AADC) and catechol-O-methyltransferase (COMT), reducing the bioavailable dose in the brain to approximately 1% of the ingested dose.[3] Addition of AADC inhibitors, such as carbidopa, are used routinely in combination with L-dopa to reduce the peripheral metabolism of L-dopa. However, even in the presence of AADC inhibitors, approximately 90% of L-dopa is metabolized in the periphery.[4] As a result, COMT inhibitors have the potential to further enhance the action of L-dopa by reducing the conversion of L-dopa to 3-O-methyldopa (3-OMD), which also competes with L-dopa at the blood-brain barrier.[5-7] Opicapone (Bial-Portela & Ca, S.A., S. Mamede do Coronado, Portugal) is a peripheral, long-acting, third-generation COMT inhibitor.[8] Opicapone is approved in Europe as an adjunctive therapy to combinations of L-dopa/DOPA decarboxylase inhibitors for improvement of wearing-off in PD.[9] Similar to previously approved COMT inhibitors, opicapone improves wearing-off phenomenon by inhibition of COMT in the periphery to reduce the conversion of L-dopa to the competitive 3-OMD metabolite and effectively enhancing the brain penetration and duration of action of L-dopa.[1,10] However, compared with other available COMT inhibitors, opicapone provides greater convenience via once-daily dosing, which also is thought to allow for improved independent titration of L-dopa doses.[10] Further, opicapone has been shown in a previous pharmacokinetic study to provide a superior response to entacopone in terms of increasing L-dopa trough levels and extent of exposure, which was attributed to a more pronounced, long-lasting, and sustained COMT inhibition by opicapone.[11]

The Japanese manufacturer of opicapone (ONO Pharmaceutical Co. Ltd., Osaka, Japan) plans to change the existing formulation used in previous clinical trials (size 1 capsules) to small tablets for trials in Japanese patients. This was considered necessary to reduce the potential for difficulties in swallowing opicapone among Japanese patients, especially those with dysphagia. Another part of this study protocol compared the pharmacokinetics of opicapone size 1 capsules with the proposed small-tablet formulation.

In response to this background and proposed changes to the formulation of opicapone for the Japanese market, this phase 1 study was designed to evaluate the effect of multiple oral doses of once-daily opicapone tablets on the pharmacokinetics of L-dopa.

Methods

Study Design

This study (trial registration JapicCTI-173582) was an open-label, 3-period, single-sequence crossover phase 1 study conducted at a single site in Japan (Sugioka Kinen Hospital, Fukuoka, Japan). This study represents 1 part of a study protocol that also compared the pharmacokinetics of opicapone tablets and capsules and has been reported separately. Justification of the study design was partly based on a US Food and Drug Administration draft guidance for drug interaction studies,[12] which suggested that a 3-period, single-sequence crossover design could separate interindividual variation effects and evaluate the effect of opicapone on the pharmacokinetics of L-dopa more sensitively.

Initially, a screening examination was completed 3 to 30 days before the first dose period to confirm the eligibility of subjects. At the screening examination, consent was obtained and subjects underwent a clinical interview, physical examination, 12-lead electrocardiogram (ECG), routine laboratory testing (including hematology, clinical biochemistry examination, coagulation, immunology), and urine screening as well as determination of height, weight, and body mass index (BMI). Healthy Japanese adult males 20 to 45 years of age with a BMI of 18.5 to <30.0 kg/m^2 at the screening examination who provided first-person written informed consent were considered eligible to participate in this study. Key exclusion criteria included history of major (eg, cardiovascular, respiratory) disease unless judged acceptable as a subject by investigators, serious allergy, drug or alcohol abuse, marked prolongation of QT/QTc interval or suggestive symptoms, and gastrointestinal symptoms on a routine basis or within 7 days of the first dosing period.

A total of 80 eligible subjects were assigned according to screening number to 1 of 4 opicapone dose-related cohorts (A-D) of 20 subjects each and entered 3 consecutive treatment periods (Figure S1). Subjects were admitted to the study site from 2 days before receiving their first dose of opicapone and remained until the morning of the second day of the study treatment. During period 1 (reference period), a combination tablet consisting of L-dopa 100 mg/carbidopa 10 mg was orally administered 3 times a day on the day before the first dose of opicapone. During period 2, opicapone tablets were orally administered once daily at bedtime for 11 days at doses of 5 mg (cohort A), 10 mg (cohort B), 25 mg (cohort C), and 50 mg (cohort D) under fasting conditions.

The first dose of opicapone was administered at the study site on day 1, after which subjects were discharged and instructed to self-administer opicapone on

days 2 to 6 until being readmitted to the study site at which they were administered opicapone from days 7 to 11 (Figure S1). During period 3 (test period), L-dopa 100 mg + carbidopa monohydrate 10 mg was again orally administered 3 times a day on day 12 (1 day after the last dose of opicapone), after which subjects were discharged on day 13 (Figure S1). Subjects underwent a follow-up assessment on day 18, including clinical interview, physical examination, 12-lead ECG, laboratory testing, and evaluation for adverse events.

This study was conducted in compliance with the Declaration of Helsinki and relevant articles of the Pharmaceutical Affairs Law and the Ministerial Ordinance on Good Clinical Practice for Drugs. This study was reviewed and approved by the relevant Investigational Review Board (Hakata Clinic, Fukuoka, Japan) of the participating study site, and written informed consent was obtained from each study subject.

Pharmacokinetic Assessments and Analyses

The pharmacokinetic analysis population was defined as the group of subjects who received at least 1 dose of opicapone or L-dopa/carbidopa and had plasma concentration measurement results required for the pharmacokinetic analyses. To enable plasma L-dopa and 3-OMD concentration measurements, blood was drawn by venipuncture in relation to each administration of L-dopa/carbidopa before the first dose of the day, and at 0.5, 1, 1.5, 2, 3, 4, and 5 hours after the first and second dose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 8, and 14 hours after the third dose. Concentrations of plasma L-dopa and 3-OMD were determined using the liquid chromatography–tandem mass spectrometry method (Nuvisan GmbH, Neu-Ulm, Germany). Pharmacokinetic parameters of L-dopa and 3-OMD were derived from the individual plasma concentration–time profiles and included maximum observed plasma concentration (C_{max}), time at which C_{max} was observed, terminal half-life, area under the plasma concentration–time curve from time 0 to 5 hours following each dose (AUC_{5h}) and from time 0 to 24 hours following each dose (AUC_{24h}).

Determination of the plasma concentrations of L-dopa and 3-OMD was carried out in compliance with Good Laboratory Practice at Nuvisan GmbH (Neu-Ulm, Germany) by liquid chromatography–tandem mass spectrometry using a validated method with a lower limit of quantification of 20.0 ng/mL and 75.0 ng/mL, respectively. The assay accuracy, expressed as percentage of bias, was between –2.0% and 1.5% for L-dopa and –0.9% and 0.6% for 3-OMD. The precision was between 6.5 and 6.6% coefficient of variation for L-dopa and 4.4 and 5.9 coefficient of variation for 3-OMD.

Safety and Tolerability

The safety analysis set was defined as the group of subjects who received at least 1 dose of opicapone or the L-dopa/carbidopa combination. Safety assessments were conducted by determining the presence of adverse events and reactions via clinical interview, physical examination, 12-lead ECG, and routine laboratory testing. Safety-related data by cohort and treatment group were collected on the number of subjects who experienced adverse events, serious adverse events, and discontinuations attributable to the study drug and the number of deaths. Adverse events were categorized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities, Version 17.0 (Japanese version).

For each adverse event occurring from the start of study treatment until the end of the follow-up assessment, features including severity (mild, moderate, severe), seriousness, action taken, whether or not study treatment was continued, and causal relationship with the investigational drug (definite, probable, possible, not related) were recorded.

Statistics

Summary statistics were developed for baseline characteristics of subjects, pharmacokinetic parameters, and adverse events. For the analysis of pharmacokinetic parameters, geometric mean ratios and 90% confidence intervals (CIs) of C_{max} and AUC_{24h} values of L-dopa and 3-OMD were calculated, and the effect of opicapone was evaluated on the pharmacokinetics of plasma L-dopa and 3-OMD. Periods 1 and 3 were used as reference and test groups, respectively, and analysis of variance via a mixed effects model was performed after natural logarithmic transformation of each pharmacokinetic parameter, with intervention effects (period 1 or period 3) as a fixed effect and subjects as a random effect. The residual mean square from the analysis of variance was used to calculate the 90%CIs of geometric mean ratios. The geometric mean ratios and their 90%CIs were calculated by exponential transformation of differences in arithmetic means and their 90%CIs derived from natural logarithmic transformation of each pharmacokinetic parameter. No statistical tests, including tests of statistical significance, were performed for analyses regarding safety.

Results

Subject Disposition and Characteristics

Overall, 20 subjects in each opicapone treatment cohort (5 mg, 10 mg, 25 mg, and 50 mg) started treatment and all were included in the pharmacokinetic and safety analysis populations. One subject in the opicapone 10 mg and 1 subject in the opicapone 50-mg treatment

Table 1. Demographic and Other Baseline Characteristics

		Cohort (Opicapone Dose, N)			
		A (5 mg, N = 20)	B (10 mg, N = 20)	C (25 mg, N = 20)	D (50 mg, N = 20)
Age, y	Mean ± SD	33.7 ± 7.4	31.5 ± 9.0	25.1 ± 5.5	26.0 ± 5.0
	Median	32.5	29.5	23.5	25.0
	Min-Max	23-45	20-45	20-44	20-40
Height, cm	Mean ± SD	173.35 ± 5.71	168.95 ± 5.00	169.54 ± 6.17	170.59 ± 4.86
	Median	174.20	170.00	168.75	170.55
	Min-Max	163.5-182.2	155.7-177.9	159.0-182.6	164.5-182.1
Body weight, kg	Mean ± SD	68.73 ± 9.28	66.44 ± 8.71	60.78 ± 7.97	62.99 ± 8.19
	Median	66.65	65.20	58.90	59.70
	Min-Max	55.2-89.4	51.4-81.3	52.1-75.4	50.4-81.8
BMI, kg/m^2	Mean ± SD	22.88 ± 3.00	23.29 ± 2.96	21.09 ± 1.99	21.6 ± 2.15
	Median	22.48	23.27	20.85	20.90
	Min-Max	18.8-29.3	18.5-28.4	18.5-25.2	18.5-25.1

BMI, body mass index.

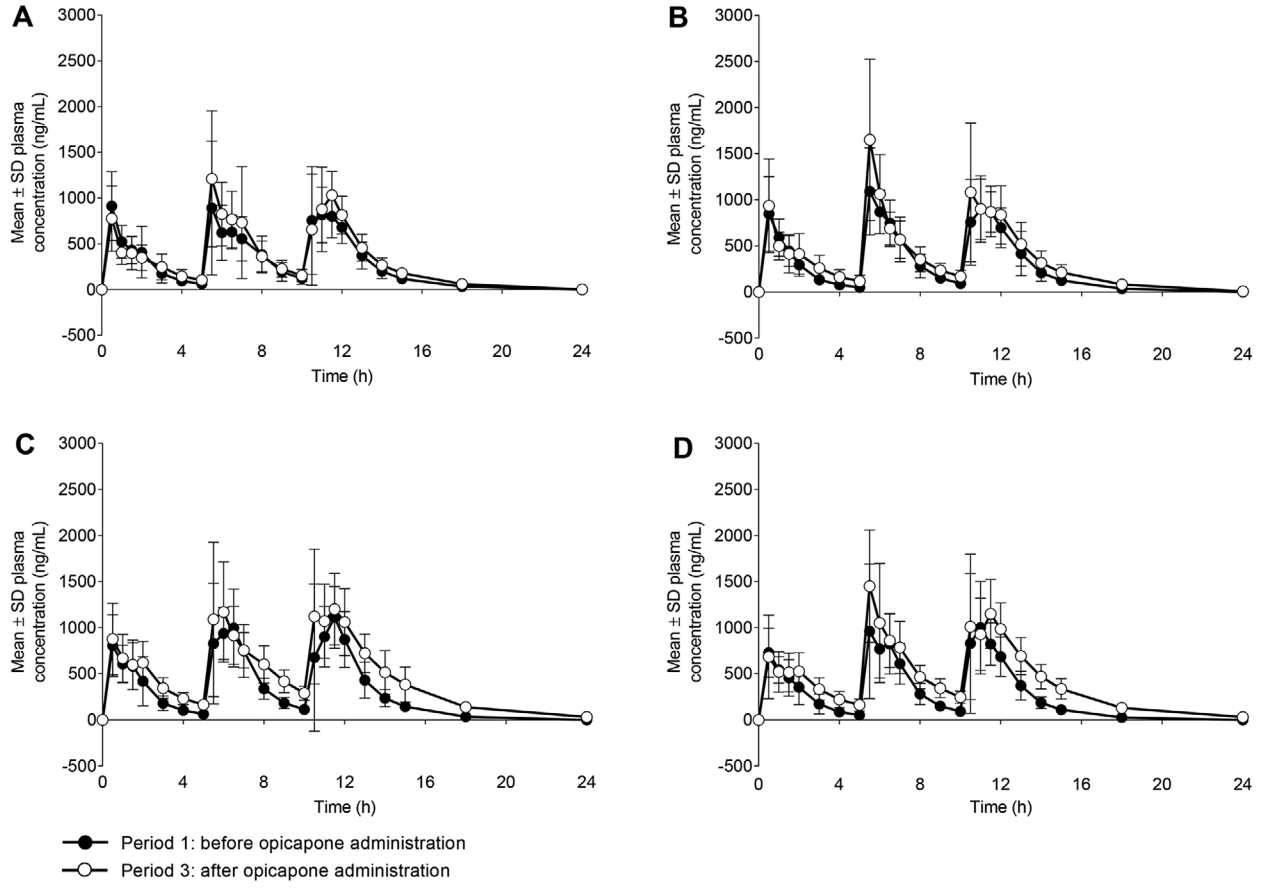

Figure 1. Mean plasma L-dopa concentration-time profiles. A, 5 mg; B, 10 mg; C, 25 mg; D, 50 mg. Error bars represent standard deviation.

cohort stopped treatment during the study due to patient request and adverse event (infectious enteritis), respectively.

Baseline characteristics of subjects are summarized in Table 1. There were no substantial differences between treatment cohorts in baseline characteristics, although subjects in the opicapone 25-mg and 50-mg dose cohorts tended to be slightly younger (median age, 23.5-25.0 years) and thinner (median BMI, 20.85-20.90 kg/m^2) than subjects in the 5-mg and 10-mg

Table 2. Pharmacokinetic Parameters of L-dopa in Plasma Following 3 Separate Doses of L-Dopa/Carbidopa Within a Day Before and After 11 Days of Once-Daily Administration of Opicapone Tablets

	Period 1 (Reference)			Period 3 (Test)		
Parameter by Cohort	First Dose	Second Dose	Third Dose	First Dose	Second Dose	Third Dose
A. 5 mg, N	20	20	20	20	20	20
C_{max}, ng/mL	989 ± 279	1180 ± 516	1180 ± 331	845 ± 246	1620 ± 576	1310 ± 417
t_{max},[a] h	0.50 (0.50-2.00)	1.25 (0.50-3.00)	1.00 (0.50-2.00)	0.50 (0.50-3.00)	0.50 (0.50-2.00)	1.00 (0.50-2.00)
AUC_{5h}, ng • h/mL)	1530 ± 371	2120 ± 361	2350 ± 375	1480 ± 277	2620 ± 573	2740 ± 444
AUC_{24h}, ng • h/mL			6230 ± 1000			7230 ± 1240
$t_{1/2}$, h	...	...	1.53 ± 0.194	...	...	1.86 ± 0.261
B. 10 mg, N	19[b]	19[b]	19[b]	19[b]	19[b]	19[b]
C_{max}, ng/mL	959 ± 289	1240 ± 332	1170 ± 262	1040 ± 423	1950 ± 581	1470 ± 424
t_{max},[a] h	0.50 (0.50-1.50)	0.50 (0.50-2.00)	1.00 (0.50-3.00)	0.500 (0.50-3.00)	0.500 (0.50-1.00)	0.50 (0.50-2.00)
AUC_{5h}, ng • h/mL)	1400 ± 301	2260 ± 400	2490 ± 409	1700 ± 373	2810 ± 586	3030 ± 509
AUC_{24h}, ng • h/mL)			6390 ± 1090			8110 ± 1700
$t_{1/2}$, h	...	...	1.59 ± 0.156	...	...	2.08 ± 0.279
C. 25 mg, N	20	20	20	20	20	20
C_{max}, ng/mL	949 ± 270	1400 ± 483	1450 ± 516	1050 ± 263	1610 ± 538	1640 ± 412
t_{max},[a] h	0.50 (0.50-2.00)	1.00 (0.50-2.00)	1.50 (0.50-2.00)	1.00 (0.50-2.00)	1.00 (0.50-3.00)	1.00 (0.50-4.00)
AUC_{5h}, ng • h/mL	1620 ± 425	2520 ± 500	2760 ± 507	2180 ± 356	3330 ± 589	3990 ± 697
AUC_{24h}, ng • h/mL			7170 ± 1400			10 800 ± 1760
$t_{1/2}$, h	...	...	1.46 ± 0.184	...	...	2.52 ± 0.312
D. 50 mg, N	20	20	20	19[b]	19[b]	19[b]
C_{max}, ng/mL	810 ± 186	1290 ± 518	1360 ± 543	855 ± 349	1730 ± 531	1580 ± 445
t_{max},[a] h	0.50 (0.50-2.00)	1.00 (0.50-3.00)	1.00 (0.50-2.00)	0.50 (0.50-3.00)	0.500 (0.50-2.00)	1.50 (0.50-3.00)
AUC_{5h}, ng • h/mL	1410 ± 384	2210 ± 487	2480 ± 477	1870 ± 389	3220 ± 698	3670 ± 562
AUC_{24h}, ng • h/mL			6300 ± 1200			9910 ± 1710
$t_{1/2}$, h	...	...	1.46 ± 0.160	...	...	2.53 ± 0.418

AUC_{5h}, area under the plasma concentration–time curve from time 0 to 5 hours; AUC_{24h}, area under the plasma concentration–time curve from time 0 to 24 hours; C_{max}, maximum observed plasma concentration; t_{max}, time at which maximum concentration was observed; $t_{1/2}$, terminal half-life. Period 1 (reference): before the administration of opicapone. Period 3 (test): after the administration of opicapone.

[a]Median (Min-Max), all other values are expressed as arithmetic mean ± standard deviation.

[b]One subject was not included in calculation of summary statistics.

cohorts (median age, 29.5-32.5 years; median BMI, 22.48-23.27 kg/m^2).

Pharmacokinetic Evaluations

L-dopa concentration-time profile at different doses of opicapone (5, 10, 25, 50 mg) tablets for period 1 (before the first dose of opicapone) and period 3 (after the last dose of opicapone) are shown in Figure 1. Specific results for pharmacokinetic parameters related to L-dopa at these different doses of opicapone are shown in Table 2. Based on these results, there were no significant changes in the C_{max} of L-dopa in the first, second, or third doses of L-dopa/carbidopa when the dose of opicapone was increased. The AUC of L-dopa tended to increase with increasing opicapone dose except for a tendency toward a peak plateau at the highest opicapone dose (50 mg) relative to the 25-mg dose. Further, each of these parameters (C_{max}, AUC) were greater for period 3 (test) at each dose period relative to period 1 (reference).

Similarly, the 3-OMD concentration-time profile at different doses of opicapone (5, 10, 25, 50 mg) tablets (Figure 2) and the pharmacokinetic parameters for 3-OMD at these different doses of opicapone (Table 3) showed similar trends but, as expected, the concentration of 3-OMD decreased with each subsequent L-dopa/carbidopa dose. However, the C_{max} and AUC of 3-OMD decreased notably following opicapone administration, especially at the highest opicapone doses.

Figure 3 shows the dose-response effect of opicapone on the AUC_{24h} of plasma L-dopa and 3-OMD. The geometric mean ratio of the AUC_{24h} of L-dopa increased with increasing dose of opicapone, but when the dose of opicapone was 25 mg and higher, the plasma exposure to L-dopa seemed to be less than dose proportional. Similarly, the geometric mean ratio

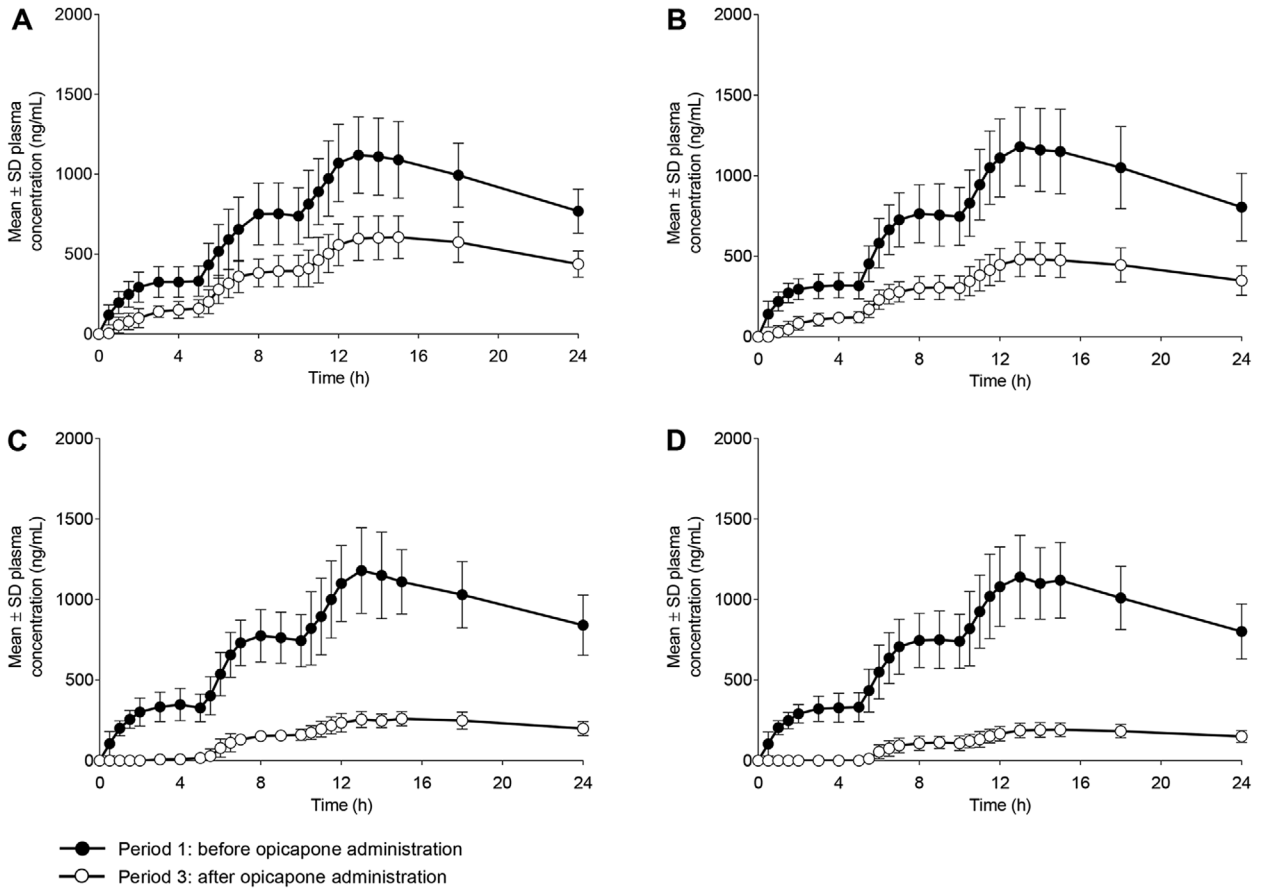

Figure 2. Mean plasma 3-OMD concentration-time profiles. A, 5 mg; B, 10 mg; C, 25 mg; D, 50 mg. Error bars represent standard deviation.

of the AUC_{24h} of 3-OMD decreased with increasing dose of opicapone, but the plasma exposure to 3-OMD appeared to be less than proportional with opicapone doses of 25 mg and higher.

Finally, the geometric mean ratios (90%CI) for post-/pre-opicapone administration of the AUC_{24h} of plasma L-dopa and 3-OMD at each opicapone dose also suggest a tendency for leveling off of the relative increase and decrease in L-dopa and 3-OMD, respectively, at 25 mg and 50 mg doses of opicapone (Table 4).

Safety

Overall, opicapone tablets were well tolerated at all doses with no major safety issues. Adverse events were infrequent at lower doses of opicapone but more common in the opicapone 50-mg cohort (Table 5). Adverse events thought to be possibly, probably, or definitely related to opicapone or L-dopa/carbidopa were assessed in periods 1, 2, and 3. In period 1, somnolence was reported by 1 subject (5%) in the opicapone 5-mg cohort and was determined at least possibly related to L-dopa/carbidopa. In period 2, one subject (5.3%) in the opicapone 10-mg cohort experienced enterocolitis, and 2 subjects (10.0%) in the opicapone 50-mg cohort had 1 event each of infectious enteritis and pharyngitis. However, no adverse events reported in period 2 were thought to be related to either opicapone or L-dopa/carbidopa. In period 3, adverse events were reported in 1 subject (5%), 3 subjects (15%), and 5 subjects (26.3%) in the opicapone 5-mg, 25-mg, and 50-mg cohorts, respectively. The most common events during this period across all dose groups were nausea (8 subjects; 10%), vomiting (3 subjects; 3.75%), and dizziness (2 subjects; 2.5%). All adverse events reported in period 3 were determined at least possibly related to opicapone or L-dopa/carbidopa.

Discussion

This phase 1 study aimed to evaluate the pharmacological efficacy of opicapone tablets at ascending doses (5-50 mg) via their effects on L-dopa. Opicapone doses <25 mg (ie, 5 mg, 10 mg) were added to the design of this study based on the results of the first part of this study, which showed a higher exposure after administration of opicapone tablets. This study found a plateau in the increase in L-dopa exposure after administration

Table 3. Pharmacokinetic Parameters of 3-OMD in Plasma Following 3 Separate Doses of L-dopa/Carbidopa Within a Day Before and After 11 Days of Once-Daily Administration of Opicapone Tablets

	Period 1 (Reference)			Period 3 (Test)		
Parameter by Cohort	First Dose	Second Dose	Third Dose	First Dose	Second Dose	Third Dose
A. 5 mg, N	20	20	20	20	20	20
C_{max}, ng/mL	339 ± 95.9	782 ± 197	1150 ± 249	165 ± 43.2	407 ± 99.5	621 ± 137
t_{max},[a] h	4.00 (1.50-4.92)	4.00 (1.50-4.92)	3.00 (2.00-5.00)	4.92 (3.00-4.92)	4.00 (3.00-4.92)	4.00 (2.00-8.00)
AUC_{5h}, ng • h/mL	1290 ± 360	3160 ± 821	5100 ± 1110	502 ± 189	1650 ± 421	2710 ± 636
AUC_{24h}, ng • h/mL			18 000 ± 3840			9670 ± 2180
$t_{1/2}$, h	...	...	19.6 ± 6.35[b]	...	...	17.8 ± 4.99[c]
B. 10 mg, N	19[d]	19[d]	19[d]	19[d]	19[d]	19[d]
C_{max}, ng/mL	328 ± 78.9	779 ± 183	1190 ± 249	122 ± 34.9	311 ± 74.4	489 ± 104
t_{max},[a] h	4.00 (1.50-4.92)	3.00 (1.50-4.92)	3.00 (1.50-5.00)	4.92 (2.00-4.92)	4.00 (3.00-4.92)	4.00 (2.00-8.00)
AUC_{5h}, ng • h/mL	1310 ± 296	3310 ± 759	5340 ± 1160	376 ± 134	1310 ± 306	2180 ± 488
AUC_{24h}, ng • h/mL			18 800 ± 4270			7630 ± 1780
$t_{1/2}$, h	...	...	17.2 ± 3.22[e]	...	...	18.1 ± 3.37[f]
C. 25 mg, N	20	20	20	20	20	20
C_{max}, ng/mL	358 ± 101	811 ± 153	1230 ± 259	16.5 ± 33.8	165 ± 33.8	273 ± 48.9
t_{max},[a] h	4.00 (2.00-4.92)	3.00 (1.50-4.92)	4.00 (2.00-8.00)	4.92 (4.00-4.92)[h]	4.00 (3.00-4.92)	5.00 (1.50-8.00)
AUC_{5h}, ng • h/mL	1330 ± 305	3280 ± 640	5260 ± 1140	23.0 ± 53.7	587 ± 158	1140 ± 223
AUC_{24h}, ng • h/mL			18 700 ± 3720			3860 ± 785
$t_{1/2}$, h	...	...	25.7 ± 12.8[g]	...	...	20.1 ± 4.02[i]
D. 50 mg (N)	20	20	20	19[k]	19[k]	19[k]
C_{max}, ng/mL	342 ± 91.7	777 ± 173	1180 ± 251	0.00 ± 0.00	117 ± 38.3	197 ± 44.4
t_{max},[a] h	4.00 (2.00-4.92)	3.00 (2.00-4.92)	3.00 (1.50-5.00)	NC	4.00 (2.00-4.92)[l]	5.00 (2.00-8.00)
AUC_{5h}, ng • h/mL	1290 ± 275	3230 ± 749	5180 ± 1120	0.00 ± 0.00	407 ± 179	827 ± 217
AUC_{24h}, ng • h/mL			18 300 ± 3760			2790 ± 722
$t_{1/2}$, h	...	...	20.1 ± 6.26[j]	...	...	32.2 ± 24.6[m]

AUC_{5h}, area under the plasma concentration–time curve from time 0 to 5 hours; AUC_{24h}, area under the plasma concentration–time curve from time 0 to 24 hours; C_{max}, maximum observed plasma concentration; NC, not calculated; t_{max}, time at which maximum concentration was observed; $t_{1/2}$, terminal half-life.

Period 1: before the administration of opicapone. Period 3: after the administration of opicapone.

[a]Median (Min-Max), all other values are expressed as arithmetic mean ± standard deviation.

[b]N = 17.

[c]N = 11.

[d]One subject was not included in calculation of summary statistics.

[e]N = 17.

[f]N = 13.

[g]N = 17.

[h]N = 4.

[i]N = 8.

[j]N = 19.

[k]One subject was not included in calculation of summary statistics.

[l]N = 18.

[m]N = 9.

of opicapone 25 mg and higher. The geometric mean ratios of the AUC_{24h} of plasma L-dopa and 3-OMD generally increased and decreased, respectively, with increasing opicapone dose; however, both ratios showed a tendency toward leveling off at doses of opicapone 25 mg and higher.

In studies conducted in Europe and Canada, exposure to L-dopa increased and exposure to 3-OMD decreased with increasing doses of opicapone.[11,13,14] For example, a randomized, double-blind, study performed in 80 healthy subjects, demonstrated that the change in the AUC of 3-OMD between opicapone 50 mg and 75 mg was smaller than that between opicapone 25 mg and 50 mg.[11] Leveling off in pharmacokinetic exposure and pharmacodynamic effect with increased dose is to be expected in enzyme-mediated interactions and reflects the saturation of the enzyme at higher doses beyond which further dose increases have minimal

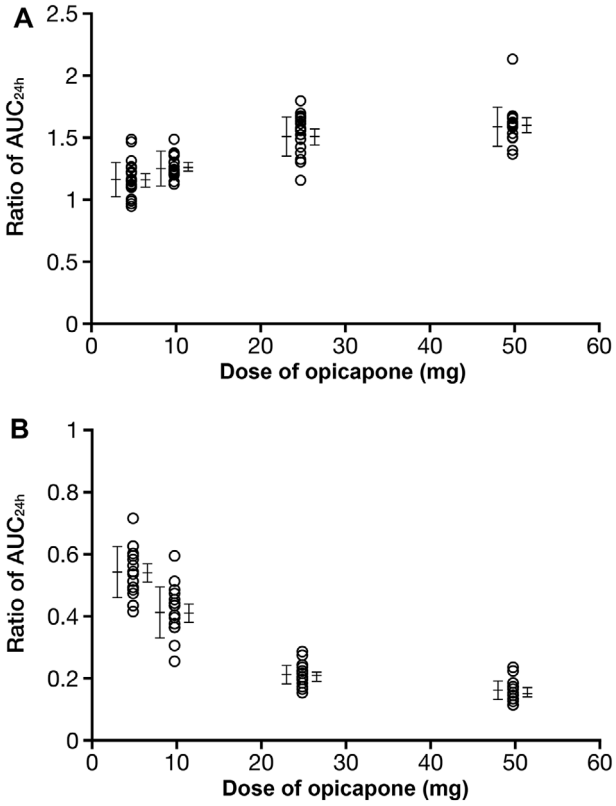

Figure 3. Dose response of the effect of opicapone on plasma (A) L-dopa and (B) 3-OMD pharmacokinetic parameter (AUC_{24h}). The ratios of AUC_{24h} in period 3 (after opicapone tablet administration) to that in period 1 (before opicapone tablet administration) for each subject are shown; left-hand side bars represent arithmetic mean and SD; right-hand side bars represent geometric mean ratios and their 90%CIs. 3-OMD, 3-O-methyldopa; AUC, area under the plasma concentration–time curve; CI, confidence interval; SD, standard deviation.

additional effect. However, in relation to the present study, the apparent leveling off of effect at even lower doses than those used in studies outside of Japan may reflect unique characteristics of the tablet formulation. This was found to lead to higher levels of exposure to opicapone than the existing capsule formulation in the other part of the study protocol reported elsewhere. Based on the higher exposure to opicapone with tablets compared with capsules noted in the first part of this study, these differences in exposure may lead to differences in dose-response relationships among ethnic groups.

This study suggests multiple oral doses of opicapone administered once daily at bedtime are associated with clinically acceptable safety and tolerability. The incidence of adverse events, especially nausea, vomiting, and dizziness, was higher in subjects who received opicapone 25 mg or 50 mg. These adverse events are all known reactions to L-dopa formulations, and their increased frequency in period 3 may be attributable to an increased exposure to L-dopa by opicapone.

Table 4. Evaluation of the Effect of Opicapone on Plasma L-dopa and 3-OMD Pharmacokinetic Parameter (AUC_{24h})

Opicapone Dose	N	Geometric Mean Ratio (90%CI)[a] for Period 3/Period 1	
		L-dopa	3-OMD
5 mg	20	1.16 (1.10-1.21)	0.54 (0.51-0.57)
10 mg	20	1.26 (1.23-1.30)	0.41 (0.38-0.44)
25 mg	20	1.51 (1.44-1.57)	0.21 (0.19-0.22)
50 mg	19	1.60 (1.54-1.66)	0.15 (0.14-0.17)

3-OMD, 3-O-methyldopa; AUC_{24h}, area under the plasma concentration–time curve from time 0 to 24 hours; CI, confidence interval; L-dopa, levodopa.
Period 1 (reference): before the administration of opicapone. Period 3 (test): after the administration of opicapone.

These results in Japanese healthy subjects extend those of the single-dose phase 1 study, which found that the tablet formulation was associated with greater opicapone exposure compared with the existing hard-capsule formulation. Future studies of the opicapone tablet formulation in Japanese patients with PD will provide information on clinical efficacy and safety, including long-term administration.

Conclusions

Opicapone tablets administered once a day for 11 days at doses of 5 mg to 50 mg were well tolerated with no safety issues. The geometric mean ratio (post/pre-opicapone dosing) of the AUC_{24h} of L-dopa increased with an increasing dose of opicapone up to 25 mg and higher, at which points plasma exposure to L-dopa appeared to level off. The results of the present study indicate that the dose at which leveling off of L-dopa exposure occurs is different in Japanese and non-Japanese populations, and this may be relevant when determining optimal opicapone dosing among Japanese patients with PD.

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Conflicts of Interest

M.N. has received personal fees from Ono Pharmaceutical Co., Ltd.; Takeda Pharmaceutical Co., Ltd.; Eisai Co., Ltd.;

Table 5. Incidence of Adverse Events

	Number (%) of Subjects Reporting Adverse Event											
Dose of Opicapone	5 mg			10 mg			25 mg			50 mg		
Period	1	2	3	1	2	3	1	2	3	1	2	3
N	20	20	20	20	19	19	20	20	20	20	20	19
All	1 (5.0)		1 (5.0)		1 (5.3)				3 (15.0)		2 (10.0)	5 (26.3)
Diarrhea			1 (5.0)									
Enterocolitis					1 (5.3)							
Nausea									3 (15.0)			5 (26.3)
Vomiting												3 (15.8)
Pharyngitis											1 (5.0)	
Enteritis, infectious											1 (5.0)	
Dizziness												2 (10.0)
Somnolence	1 (5.0)											
Cold sweat												1 (5.3)

The names of adverse events reported by the investigator were coded and classified using Medical Dictionary for Regulatory Activities, Version 17.0, Japanese version. Subjects who experienced the same event more than once in the same period were categorized in the highest intensity.

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Data Sharing

For data sharing, please contact the corresponding author.

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