Clinical Pharmacology in Drug Development
2021, 10(2) 173–179

DOI: 10.1002/cpdd.802

Pharmacokinetic Comparison of Capsule and Tablet Formulations of Opicapone in Healthy Japanese Subjects: Phase 1 Study

Masahiro Nomoto[1,2], Atsushi Takeda[3,4], Katsuaki Iwai[5], Akihisa Nishimura[5], and Nobutaka Hattori[6]

Abstract

Opicapone, a peripheral, long-acting catechol-O-methyltransferase inhibitor has been shown to improve wearing-off phenomenon in randomized, double-blind studies. This study compared the pharmacokinetic characteristics of opicapone small-tablet and size 1 capsule formulations after single oral administration to healthy Japanese subjects. In this open-label, randomized, 2-way and 2-period crossover phase 1 study, 48 healthy male subjects (aged 20 to 45 years; body mass index, 18.5 to <30.0 kg/m^2) were randomly assigned to 2 cohorts (n = 24 each), which were administered opicapone 25 or 50 mg in a tablet-capsule or capsule-tablet sequence under fasted conditions. Blood samples were collected for pharmacokinetic analysis before opicapone capsule/tablet administration and at regular intervals over 24 hours after administration. Compared with capsules, tablets were associated with higher C_{max} and $AUC_{last/0-\infty}$ values. However, $t_{1/2}$ and t_{max} values were similar with opicapone 25- and 50-mg capsules/tablets. Geometric mean ratios (tablets/capsules) of C_{max}, AUC_{last}, and $AUC_{0-\infty}$ were 1.24, 1.18, and 1.19, respectively, for the 25-mg dose and 1.42, 1.28, and 1.27, respectively, for the 50-mg dose. Opicapone was well tolerated, and no serious adverse events occurred. A small tablet formulation of opicapone proposed for use in Japanese clinical trials was associated with apparent greater exposure compared with the existing hard capsule formulation, which should be considered when developing opicapone for Japanese patients.

Keywords

COMT inhibitor, Japanese, opicapone, Parkinson's disease, pharmacokinetic, phase 1

Globally, the burden of Parkinson's disease (PD) has more than doubled in the past generation and is estimated to affect approximately 250 000 Japanese people based on 2016 prevalence data.[1] Levodopa (L-dopa) is still considered the gold-standard treatment for PD, but its efficacy is substantially limited by a short half-life, poor penetration into brain tissue, and peripheral metabolism via 2 main enzymatic pathways: DOPA decarboxylase (DDC) and catechol-O-methyltransferase (COMT).[2,3] Typical motor complications of chronic L-dopa administration are dyskinesias at the peak of the dose concentration and motor fluctuations, characterized by reemergence of motor symptoms near the end of the treatment interval ("wearing-off").[3,4] Wearing-off increases in frequency over time and eventually affects most patients with long-standing PD (~75%-80% at >10 years).[5] Strategies to reduce wearing-off include modification of factors that affect gastrointestinal absorption of L-dopa, dose-adjusting strategies, and adjuvant treatment, including COMT inhibitors.[3]

[1]Department of Neurology and Clinical Pharmacology, Ehime University Graduate School of Medicine, Matsuyama, Japan
[2]Department of Neurology, Saiseikai Imabari Hospital, Imabari, Japan
[3]National Hospital Organization, Sendai-Nishitaga Hospital, Sendai, Japan
[4]Department of Cognitive & Motor Aging, Tohoku University, Graduate School of Medicine, Sendai, Japan
[5]Department of Clinical Development, Ono Pharmaceutical Co., Ltd., Osaka, Japan
[6]Department of Neurology, Juntendo University Graduate School of Medicine, Tokyo, Japan

Submitted for publication 21 January 2020; accepted 7 March 2020.

Corresponding Author:
Masahiro Nomoto, MD, PhD, Department of Neurology, Saiseikai Imabari Hospital, 7-6-1 Kitamura, Imabari, Ehime 799–1592, Japan
(e-mail: m-nomoto@imabari.saiseikai.or.jp)

Opicapone (BIAL, Portela & Ca, S.A.) is a peripheral, long-acting, third-generation COMT inhibitor initially developed by BIAL (Portela & Ca, S.A.).[5,6] Opicapone was approved in June 2016 by the European Medicines Agency as an adjunctive therapy to combinations of L-dopa/DDC inhibitor for improvement of end-of-dose motor fluctuations (wearing-off) in PD (available at: https://wwwemaeuropaeu/en/medicines/human/EPAR/ongentys). Opicapone improves the wearing-off phenomenon by significantly reducing COMT activity and thereby enhancing the brain penetration and duration of action of L-dopa.[2] Previous animal and pharmacokinetic studies have demonstrated that opicapone has a sustained COMT inhibitory effect despite prompt circulatory elimination, which allows for less frequent and more convenient once-daily administration than other COMT inhibitors.[2] In terms of pharmacokinetics, opicapone exhibits linear, dose-dependent absorption following single or multiple doses with a time to maximal plasma concentration of 1.5 to 4 hours[5-8] and a short half-life of approximately 1.0 to 2.0 hours.[6,7] The metabolism of opicapone is primarily hepatic and leads to a small number of inactive metabolites, mainly via sulfation (BIA 9–1103) and glucuronidation (BIA 9–1106).[8] The main inactive metabolite, BIA 9–1103, has a relatively long half-life, especially following repeated dosing.[6] Opicapone has been shown to be a weak, reversible inhibitor of CYP2C8 an CYP2C9, and observed in vitro effects on these enzymes are thought to be highly unlikely to have any clinical impact.[8,9] Pharmacokinetic studies show that opicapone increases L-dopa peak concentrations and exposure compared with placebo associated with marked decreases in the extent of exposure to 3-O-methyldopa, a main metabolite of L-dopa.[7,10] Findings across key randomized, placebo-controlled clinical trials of opicapone also found dose-dependent increases in L-dopa exposure and improvements in off-time compared with placebo.[11-13] Key pharmacokinetic parameters have been previously found to be similar between Japanese and Caucasian populations, albeit with differences in the relative extent to which certain metabolic pathways are used.[14] The main elimination pathway for opicapone is via hepatobiliary excretion,[8] although the urine concentrations of opicapone and its metabolites have typically been found to be below the limit of quantification.[6,14] The pharmacokinetics of opicapone do not appear to be significantly affected by age or renal impairment, although the combination of opicapone and monoamine oxidase inhibitors could result in inhibition of catecholamine metabolism and is generally contraindicated.[8]

Clinical trials of opicapone conducted in countries outside Japan used a size 1 hard capsule, which is also the currently marketed formulation in approved countries. However, the size 1 capsule may not be suitable for many Japanese patients with PD, especially those with dysphagia and other difficulties with swallowing larger capsules. Thus, the planned formulation used in clinical trials of Japanese patients will be modified from size 1 capsules to small tablets, developed by ONO Pharmaceutical Co. Ltd., Osaka, Japan.

This phase 1 study was designed to compare the pharmacokinetic characteristics of the proposed tablet and hard capsule formulations of opicapone after single oral administration to healthy Japanese adult male subjects.

Methods

Study Design

This study (trial registration JapicCTI-173582) was an open-label, randomized, 2-way and 2-period crossover phase 1 study conducted at a single site in Japan (Sugioka Kinen Hospital, Fukuoka, Japan). This study represents one part of a study protocol that also examined the effect of multiple oral doses of opicapone tablets on the pharmacokinetics of L-dopa and has been reported separately.

A total of 48 healthy male subjects were randomly assigned to 2 cohorts of 24 subjects each, which were divided into 2 groups of 12 subjects each. Cohort 1 groups (A, B) were administered a single dose of a opicapone 25-mg tablet or capsule in a tablet-capsule (group A) or capsule-tablet (group B) sequence under fasted condition with a minimum 28-day washout period between each group. Similarly, cohort 2 groups (C, D) were administered a single dose of a 50-mg tablet or capsule under the same conditions. Justification of the study design and washout period were based on the Japanese *Pharmaceutical and Food Safety Bureau's Guideline for Bioequivalence Studies of Generic Products*, 2012 (available at http://wwwnihsgojp/drug/be-guide(e)/Generic/GL-E_120229_BEpdf).

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 electrogram (ECG), routine laboratory testing (including hematology, biochemistry examination, coagulation, immunology) and urine screening as well as determination of height, weight, and body mass index (BMI). For each dose period, subjects were admitted to the study site from 2 days before receiving the study drug and remained admitted until the second day of the study treatment.

Healthy Japanese adult men aged 20 to 45 years with a BMI of 18.5 to <30.0 kg/m^2 at the screening examination who provided first-person written in-

formed 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.

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 set was defined as the group of subjects who received at least 1 dose of opicapone and had plasma concentration measurement results required for the pharmacokinetic analyses. Following administration by capsule or tablet of the single dose of opicapone on day 1, blood was withdrawn by venipuncture at repeated intervals and plasma concentrations of opicapone were determined using the liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (CMIC, Inc., Tokyo, Japan). Blood samples were collected before study drug administration and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after study drug administration.

Pharmacokinetic parameters of opicapone were derived from the individual plasma concentration-time profiles and included maximum observed plasma concentration (C_{max}), time at which C_{max} was observed (t_{max}), area under the plasma concentration-time curve from time zero to time of last measurable concentration (AUC_{last}) and from time zero to infinity ($AUC_{0-\infty}$), terminal half-life ($t_{1/2}$), and apparent total clearance of the drug from plasma after oral administration (CL/F).

Determination of the plasma concentrations of opicapone was carried out in compliance with Good Laboratory Practice at CMIC, Inc., Japan, by liquid LC-MS/MS using a validated method with a lower limit of quantification of 10.0 ng/mL. The assay accuracy was between 97.0% and 105.0%, and the precision was $\leq$3.6% coefficient of variation.

Safety and Tolerability

The safety analysis set was defined as the group of subjects who received at least 1 dose of the study drug. Safety assessments were made by determining the presence of adverse events and reactions via clinical interview, physical examination, 12-lead ECG, and routine laboratory testing.

Table 1. Demographic and Other Baseline Characteristics

		Opicapone 25 mg (n = 24)	Opicapone 50 mg (n = 24)
Age (years)	Mean ± SD	24.5 ± 6.7	25.6 ± 8.4
	Median	21.0	22.0
	Min-Max	20-42	20-45
Height (cm)	Mean ± SD	172.7 ± 7.0	171.1 ± 6.3
	Median	170.7	172.9
	Min-Max	162.3-187.6	160.9-183.7
Body weight (kg)	Mean ± SD	64.9 ± 6.7	62.9 ± 7.2
	Median	65.8	63.8
	Min-Max	52.6-75.4	52.6-78.7
BMI (kg/m^2)	Mean ± SD	21.8 ± 2.1	21.5 ± 2.3
	Median	21.5	21.3
	Min-Max	18.5-25.8	18.5-27.1

BMI, body mass index.

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 study drug, and the number of deaths. Adverse events were categorized by System Organ Class and Preferred Term according to MedDRA version 17.0 (Japanese). 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, 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. The primary pharmacokinetic analysis compared pharmacokinetic parameters between the 2 formulations. After natural logarithmic transformation of each pharmacokinetic parameter, analysis of variance was performed in a mixed-effects model, with factors of effects of the tablet or capsule formulations, treatment periods, and groups as fixed effects and subjects as a random effect. No statistical tests, including tests of statistical significance, were performed for analyses regarding safety.

Results

Subject Disposition and Characteristics

A total of 48 subjects (n = 24 in the 25- and 50-mg cohorts each) received at least 1 dose of study drug and were included in both pharmacokinetic and safety analysis populations. One subject discontinued treatment in the 50-mg group and was not included in calculation of summary pharmacokinetic statistics for the tablet formulation.

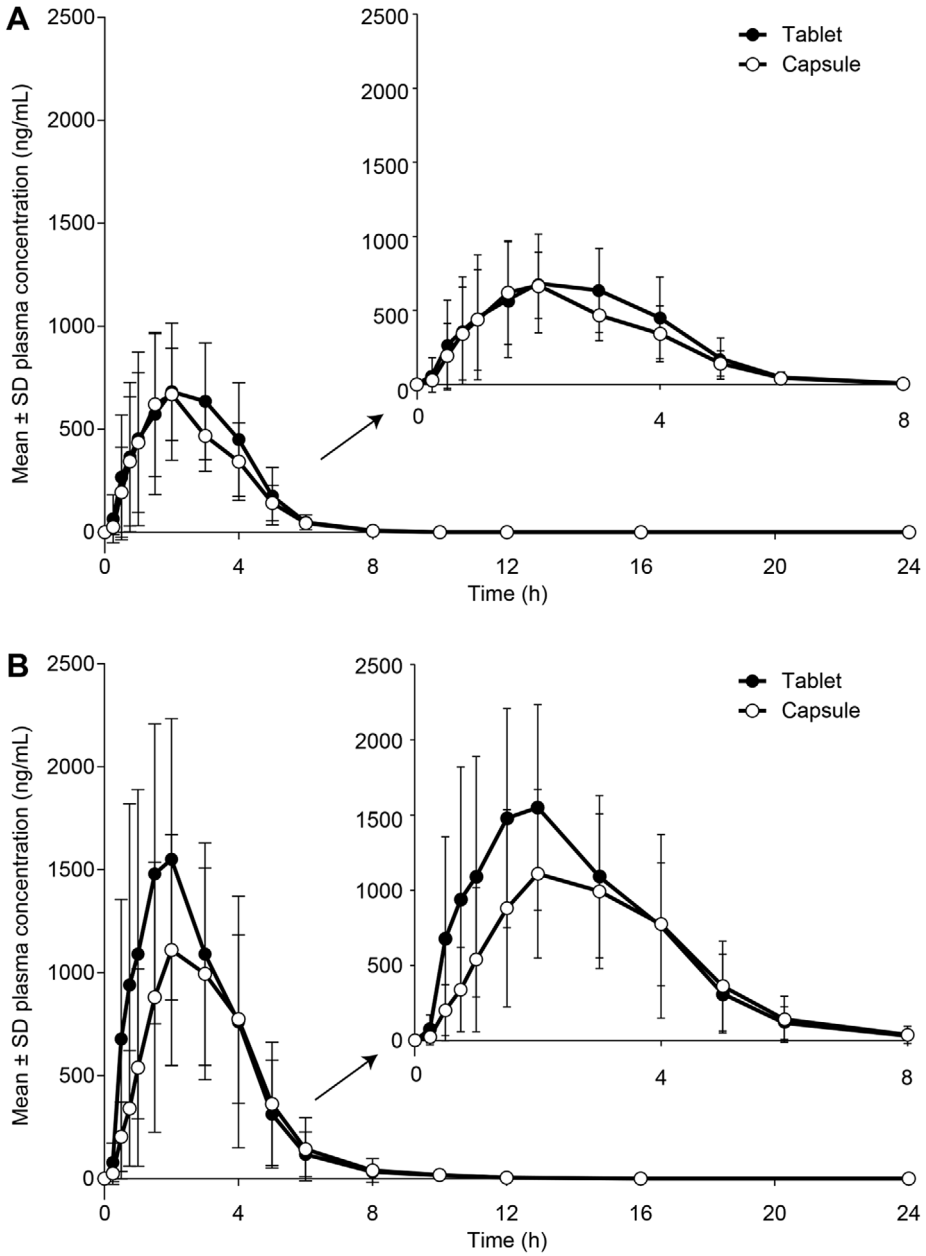

Figure 1. Mean (SD) plasma opicapone concentration-time profiles for the (A) 25-mg and (B) 50-mg doses.

Baseline characteristics of the subjects by treatment group are summarized in Table 1. No appreciable differences in any baseline characteristics were observable across the treatment groups.

Pharmacokinetic Evaluation

The mean plasma concentration-time profiles for the tablet and capsule formulations of opicapone for the 25- and 50-mg doses are shown in Figure 1. A notably higher concentration peak was evident for the 50-mg tablet formulation compared with the corresponding capsule formulation. In addition, the C_{max} and apparent plasma exposure based on the concentration-time profiles were higher at the 50-mg dose than the 25-mg dose for both formulations.

Pharmacokinetic parameters for opicapone 25- and 50-mg capsules and tablets are summarized in Table 2. These results revealed notably higher C_{max}, and AUC values for the tablet formulation compared with the capsule formulation, especially at the 50-mg dose. In the opicapone 25-mg group, the geometric mean ratios (tablets/capsules) of C_{max}, AUC_{last}, and $AUC_{0-\infty}$ were 1.24, 1.18, and 1.19, respectively. In the opicapone 50-mg group, the corresponding ge-

Table 2. Summary Statistics of Plasma Opicapone Pharmacokinetic Parameters

	Opicapone 25 mg		Opicapone 50 mg	
	Capsule	Tablet	Capsule	Tablet
n	24	24	24	23[c]
C_{max} (ng/mL)	804 ± 255	970 ± 212	1460 ± 448	2070 ± 552
t_{max}[a] (h)	1.50 (0.50-4.00)	2.00 (1.00-5.00)	2.00 (1.50-4.00)	2.00 (0.75-4.00)
AUC_{last} (ng·h/mL)	2130 ± 618	2480 ± 586	4080 ± 1650	5170 ± 1520
$AUC_{0-\infty}$ (ng·h/mL)	2150 ± 617	2530 ± 581[b]	4210 ± 1620[b]	5200 ± 1530
$t_{1/2}$ (h)	0.748 ± 0.190	0.729 ± 0.173[b]	1.18 ± 0.477[b]	1.42 ± 0.664
CL/F (L/h)	12.9 ± 5.31	10.6 ± 3.50[b]	13.6 ± 5.09[b]	10.4 ± 3.20

$AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to time of last measurable concentration (ie, 24 hours); CL/F, apparent total clearance of the drug from plasma after oral administration; C_{max}, maximum observed plasma concentration; t_{max}, time at which C_{max} was observed; $t_{1/2}$, terminal half-life.
Values are presented as mean ± SD unless stated otherwise.
AUC_{last}: AUC_{24h}.
[a]Median (Min-Max).
[b]n = 23.
[c]One subject was not included in summary statistics calculation.

Table 3. Comparison of Plasma Opicapone Pharmacokinetic Parameters (C_{max}, AUC_{last}, $AUC_{0-\infty}$)

Opicapone Dose	Pharmacokinetic Parameter	Geometric Mean Ratio (Tablets/ Capsules)	*P*
25 mg	C_{max}[a]	1.24	.0013
	AUC_{last}[a]	1.18	.0005
	$AUC_{0-\infty}$[a]	1.19	.0002
50 mg	C_{max}[a]	1.42	.0001
	AUC_{last}[a]	1.28	.0006
	$AUC_{0-\infty}$[b]	1.27	.0008

$AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to time of last measurable concentration (ie, 24 hours); C_{max}, maximum observed plasma concentration.
AUC_{last}: AUC_{24h}.
[a]n = 24.
[b]n = 23.

ometric mean ratios were 1.42, 1.28, and 1.27, respectively. Consistent with this result, the geometric mean ratio for C_{max} and $AUC_{last}/AUC_{0-\infty}$ were significantly greater than unity, which is suggestive of higher plasma exposure associated with the tablet formulation (Table 3).

Safety and Tolerability

Opicapone was well tolerated, and no serious adverse events occurred during the study period in any group. Discontinuation was recorded during the washout period before period 2 in 1 subject who received opicapone 50 mg on the judgment of the investigator. Increased blood creatinine phosphokinase was detected in 1 subject during the follow-up examination in period 1, although this increase was considered mild and resolved 1 week later. This event was not considered related to the study drug.

Discussion

The objective of this phase 1 study was to compare the pharmacokinetic parameters of the proposed tablet for use in Japanese clinical trials and existing hard-capsule formulations of opicapone 25 and 50 mg. Both formulations were associated with similar plasma-time concentration profiles at each dose, although the tablet formulation produced higher plasma exposure than the capsule formulation, especially at the 50-mg dose.

The cause of this result is not readily apparent but may relate to increased absorption of the smaller tablet formulation relative to the larger capsule formulation. Because of a lack of similar studies, this finding has not been observed in non-Japanese populations but is possibly related more to the physical characteristics of the different formulations than to specific characteristics of Japanese subjects. Regardless of the source of the observed differences, these results suggest a slightly greater potential for opicapone exposure in Japanese patients who receive the proposed tablet formulation during clinical trials. As a result of these findings and their implications, 2 smaller (5- and 10-mg) doses were added to a second part of this study protocol, which examined the effect of multiple oral doses of once-daily opicapone tablets on the pharmacokinetics of L-dopa and the 3-OMD metabolite and determined the dose-response effect of opicapone using L-dopa exposure as a surrogate marker.

Pharmacokinetic analyses showed a dose-dependent increase in plasma exposure of opicapone, which is consistent with findings from previous pharmacokinetic studies in non-Japanese subjects.[5] However, actual values for C_{max} and AUC tended to be higher in the present study than in pharmacokinetic studies among non-Japanese healthy subjects at comparable doses with the capsule formulation but particularly with the tablet formulation. This suggests the possibility of a difference in response in these healthy Japanese subjects based on a greater level of exposure despite the same or similar doses, which may be worth considering further in relevant studies to determine an optimal dose. The active metabolite (BIA 9–1079) of opicapone has been previously shown to have a similar dose-dependent increase in C_{max} and $AUC_{0-\infty}$ as well as a short half-life as that seen with opicapone, but this was not assessed in this study.[5]

This study demonstrated clinically acceptable safety of a single oral dose of opicapone whether in a tablet or capsule formulation. An extension of this phase 1 study will examine the effects of multiple opicapone dosing on L-dopa exposure in healthy Japanese subjects and further studies will provide information on efficacy and safety, including over long-term administration, in Japanese patients with PD.

Conclusion

Opicapone administered in both tablet and capsule formulations is well tolerated in healthy Japanese subjects. The finding of apparent greater exposure with the tablet compared with the existing hard-capsule formulation should be considered when developing opicapone for Japanese patients.

Acknowledgments

The authors thank all patients, investigators, volunteers, and staff who participated in this study. The authors also thank Yoshiko Okamoto, PhD, and Mark Snape, MBBS, CMPP, of inScience Communications, Springer Healthcare, who provided medical writing support. This medical writing assistance was funded by Ono Pharmaceutical Co. Ltd.

Conflicts of Interest

M.N. has received personal fees from Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eisai Co., Ltd., Hisamitsu Pharmaceutical Co., Inc., Meiji Seika Pharma Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd. and Kissei Pharmaceutical Co., Ltd. A.T. has received grants from Meiji Seika Pharma Co., Ltd., Hisamitsu Pharmaceutical Co., Inc., Pfizer Japan Inc., Sumitomo Dainippon Pharma Co., Ltd., and Kyowa Hakko Kirin Co., Ltd. and received personal fees from Sumitomo Dainippon Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and AbbVie Inc. N.H. has received a grant and other funding from Ono Pharmaceutical Co., Ltd., grants from the Japan Agency for Medical Research and Development (AMED), Japan Society for the Promotion of Science (JSPS), and Ministry of Education Culture, Sports, Science and Technology Japan (Grant-in-Aid for Scientific Research on Innovative Areas), personal fees from the International Parkinson and Movement Disorder Society, Acorda Therapeutics, Inc., Sanofi K.K., Pfizer Japan Inc., Alexion Pharmaceuticals, Inc., Mylan N.V., MSD K.K., and Lundbeck Japan K.K., personal fees and other funding from Sumitomo Dainippon Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., GlaxoSmithKline K.K., Nippon Boehringer Ingelheim Co., Ltd., FP Pharmaceutical Corporation, Eisai Co., Ltd., Kissei Pharmaceutical Co., Ltd., Nihon Medi-physics Co., Ltd., Novartis Pharma K.K., Biogen Inc., AbbVie Inc., Astellas Pharma Inc., and Daiichi Sankyo Co., Ltd., nonfinancial support from IBM Japan, Ltd., nonfinancial support and other support from Boston Scientific Japan K.K., and other support from Medtronic, Inc., Mitsubishi Tanabe Pharma Corporation, Hydrogen Health Medical Labo Co., Ltd., ABIST Co., Ltd., Melodian Co., Ltd., Daiwa Co., Ltd., Bayer Yakuhin, Ltd., Nihon Pharmaceutical Co., Ltd., Asahi Kasei Medical Co., Ltd., MiZ Co., Ltd., OHARA Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., and Hisamitsu Pharmaceutical Co., Inc. K.I. and A.N. are employees of Ono Pharmaceutical Co., Ltd.

Funding

This study was funded by Ono Pharmaceutical Co. Ltd., which contributed to the study design and data collection, analysis, and interpretation of data and the writing, review, and approval of the publication.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Data Sharing

For data sharing, please contact the corresponding author.

References

1. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden

of Disease Study 2016. *Lancet Neurol*. 2018;17(11):939-953.
2. Annus A, Vecsei L. Spotlight on opicapone as an adjunct to levodopa in Parkinson's disease: design, development and potential place in therapy. *Drug Des Devel Ther*. 2017;11:143-151.
3. Fackrell R, Carroll CB, Grosset DG, et al. Noninvasive options for 'wearing-off' in Parkinson's disease: a clinical consensus from a panel of UK Parkinson's disease specialists. *Neurodegener Dis Manag*. 2018;8(5):349-360.
4. Olanow CW, Obeso JA, Stocchi F. Drug insight: continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Nat Clin Pract Neurol*. 2006;2(7):382-392.
5. Almeida L, Rocha JF, Falcao A, et al. Pharmacokinetics, pharmacodynamics and tolerability of opicapone, a novel catechol-O-methyltransferase inhibitor, in healthy subjects: prediction of slow enzyme-inhibitor complex dissociation of a short-living and very long-acting inhibitor. *Clin Pharmacokinet*. 2013;52(2):139-151.
6. Rocha JF, Almeida L, Falcao A, et al. Opicapone: a short lived and very long acting novel catechol-O-methyltransferase inhibitor following multiple dose administration in healthy subjects. *Br J Clin Pharmacol*. 2013;76(5):763-775.
7. Rocha JF, Sicard E, Fauchoux N, et al. Effect of opicapone multiple-dose regimens on levodopa pharmacokinetics. *Br J Clin Pharmacol*. 2017;83(3):540-553.
8. Svetel M, Tomic A, Kresojevic N, Kostic V. Pharmacokinetic drug evaluation of opicapone for the treatment of Parkinson's disease. *Expert Opin Drug Metab Toxicol*. 2018;14(3):353-360.
9. Loureiro AI, Fernandes-Lopes C, Soares-da-Silva P. Potential for drug interaction of the novel COMT inhibitor opicapone. *The FASEB Journal*. 2017;31(1 Suppl):631.631.
10. Rocha JF, Ferreira JJ, Falcao A, et al. Effect of 3 single-dose regimens of opicapone on levodopa pharmacokinetics, catechol-O-methyltransferase activity and motor response in patients with Parkinson disease. *Clin Pharmacol Drug Dev*. 2016;5(3):232-240.
11. Ferreira JJ, Lees A, Rocha JF, et al. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. *Lancet Neurol*. 2016;15(2):154-165.
12. Ferreira JJ, Rocha JF, Falcao A, et al. Effect of opicapone on levodopa pharmacokinetics, catechol-O-methyltransferase activity and motor fluctuations in patients with Parkinson's disease. *Eur J Neurol*. 2015;22(5):815-825, e856.
13. Lees AJ, Ferreira J, Rascol O, et al. Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol*. 2017;74(2):197-206.
14. Falcao A, Rocha JF, Santos A, Nunes T, Soares-da-Silva P. Opicapone pharmacokinetics and pharmacodynamics comparison between healthy Japanese and matched white subjects. *Clin Pharmacol Drug Dev*. 2016;5(2):150-161.